

Draft for Consultation

# Asthma: diagnosis, monitoring and chronic asthma management (update)

## Smart inhalers

*BTS/NICE/SIGN collaborative guideline <number>*

*Evidence reviews underpinning recommendations 1.6.9 and  
recommendations for research in the BTS/NICE/SIGN guideline*

*June 2024*

*Draft for Consultation*

*These evidence reviews were developed by NICE*



## **Disclaimer**

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

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

This collaborative guideline covers health and care in England and Scotland. Decisions on how they apply in other UK countries are made by ministers in the [Welsh Government](#) and [Northern Ireland Executive](#). This collaborative guideline is subject to regular review and may be updated or withdrawn.

## **Copyright**

© NICE 2024. All rights reserved. Subject to [Notice of rights](#).

ISBN:

# Contents

<b>1. Smart preventer/maintenance inhalers</b> .....	<b>5</b>
1.1. Review question.....	5
1.1.1. Introduction.....	5
1.1.2. Summary of the protocol.....	5
1.1.3. Methods and process.....	6
1.1.4. Effectiveness evidence.....	6
1.1.5. Summary of studies included in the effectiveness evidence.....	6
1.1.6. Summary of the effectiveness evidence.....	13
1.1.7. Economic evidence.....	19
1.1.8. Summary of included economic evidence.....	20
1.1.9. Economic model.....	21
1.1.10. Unit costs.....	21
1.1.11. Evidence statements.....	21
1.2. The committee’s discussion and interpretation of the evidence.....	22
1.3. References.....	25
Appendix A – Review protocols.....	27
Appendix B – Literature search strategies.....	39
Appendix C – Effectiveness evidence study selection.....	48
Appendix D – Effectiveness evidence.....	49
Appendix E – Forest plots.....	147
Appendix F – GRADE tables.....	151
Appendix G – Economic evidence study selection.....	156
Appendix H – Economic evidence tables.....	157
Appendix I – Excluded studies.....	159
Appendix J – Research recommendation.....	167

# 1. Smart preventer/maintenance inhalers

## 1.1. Review question

What is the clinical and cost-effectiveness of smart preventer/maintenance inhalers for the management of asthma?

### 1.1.1. Introduction

Smart inhalers can be used to help people with asthma, and healthcare professionals involved in their care, monitor how regularly they take their treatment. The purpose of this review is to evaluate whether this intervention is effective at improving adherence to treatment, and more importantly whether this is effective, and cost-effective, at improving asthma control and preventing asthma attacks. This is an important question because widespread use of technologies like Smart Inhalers would have cost-implications for the NHS.

### 1.1.2. Summary of the protocol

For full details see the review protocol in 1.3.

**Table 1: PICO characteristics of review question**

<b>Population</b>	People with a diagnosis of asthma.
<b>Intervention</b>	Preventer/maintenance therapy given via smart inhaler devices with feedback.
<b>Comparisons</b>	Usual care Device without feedback
<b>Outcomes</b>	All outcomes are considered equally important for decision making and therefore have all been rated as critical: <ul style="list-style-type: none"><li>• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at <math>\geq 6</math> months, latest timepoint if more than one))</li><li>• Mortality (dichotomous outcome at <math>\geq 6</math> months)</li><li>• Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at <math>\geq 3</math> months)</li><li>• Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at <math>\geq 3</math> months)</li><li>• Hospital admissions (dichotomous outcome at <math>\geq 6</math> months)</li><li>• Reliever/rescue medication use (continuous outcome at <math>\geq 3</math> months)</li><li>• Adherence – prioritised as 1) % of puffs taken as prescribed (number of and timing of) could be reported as continuous or dichotomous and 2) Count of number times inhaler used</li><li>• Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at <math>\geq 3</math> months). Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.</li><li>• Adverse events:<ul style="list-style-type: none"><li>○ linear growth (continuous outcome at <math>\geq 1</math> year)</li><li>○ pneumonia frequency (dichotomous outcome at <math>\geq 3</math> months)</li><li>○ adrenal insufficiency (as defined by study, including short synacthen test and morning cortisol, dichotomous outcome at <math>\geq 3</math> months)</li></ul></li></ul>

	<ul style="list-style-type: none"> <li>○ months) <ul style="list-style-type: none"> <li>○ bone mineral density (continuous outcome at ≥6 months)</li> </ul> </li> <li>• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)</li> </ul>
<b>Study design</b>	<ul style="list-style-type: none"> <li>• RCTs</li> <li>• Systematic reviews of RCTs</li> <li>• Published Cochrane reviews, NMAs and IPDs will be considered for inclusion.</li> </ul>

### 1 1.1.3. Methods and process

2 This evidence review was developed using the methods and process described in  
3 [Developing NICE guidelines: the manual](#). Methods specific to this review question are  
4 described in the review protocol in 1.3 and the methods document.

5 Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

### 6 1.1.4. Effectiveness evidence

#### 7 1.1.4.1. Included studies

8 Fourteen randomised controlled trials were included in the review (Adejumo, et al., 2022,  
9 Chan, et al., 2015, Charles, et al., 2007, Chen, et al., 2020, Dierick, et al., 2023, Foster, et  
10 al., 2014, Gupta, et al., 2021, Moore, et al., 2021, Morton, et al., 2017, Mosnaim, et al., 2023,  
11 Mosnaim, et al., 2021, Otsuki, et al., 2009, Vasbinder, et al., 2016, Zairina, et al., 2016) these  
12 are summarised in Table 2 below. Evidence from these studies is summarised in the clinical  
13 evidence summary below (Table 3). Seven studies compared smart inhalers with feedback  
14 and/or reminders to smart inhalers with the smart functions disabled. The other seven  
15 studies compared smart inhalers to usual care.

16 Evidence was available for most outcomes. The outcomes for which there was no evidence  
17 were:

- 18 • Mortality
- 19 • Quality of life (smart inhaler vs device without feedback only)
- 20 • Hospital admissions (smart inhaler vs device without feedback only)
- 21 • Adverse events (linear growth, adrenal insufficiency, bone mineral density)
- 22 • Reliever medication use (smart inhaler vs usual care only)

23 See also the study selection flow chart in Appendix C, study evidence tables in Appendix D,  
24 forest plots in Appendix D and GRADE tables in Appendix F.

#### 25 1.1.4.2. Excluded studies

26 No Cochrane reviews were identified for this evidence review. See the excluded studies list  
27 in Appendix I.

### 28 1.1.5. Summary of studies included in the effectiveness evidence

29 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Adejumo 2022 (Adejumo et al., 2022)	Smart inhaler with feedback via mobile application and with clinician	n=36 Adults (18-65 years) on BTS step 2-5 treatment with an MDI and	Adherence Asthma control	Additional analysis excluding dysfunctional smart inhalers included in appendix D.

Study	Intervention and comparison	Population	Outcomes	Comments
	<b>Device without feedback</b>	at least one exacerbation in the previous 12 months  <b>Age</b> ≥12 years <b>Exacerbations</b> At least one in past 12 months <b>Exacerbators</b> Not reported <b>Adherence</b> Not reported <b>Asthma control</b> Mixed  UK		
Chan 2015 (Chan et al., 2015)	<b>Smart inhaler with audio-visual function enabled</b>  <b>Device without feedback</b> - audio-visual function disabled	<i>n</i> =220 Children (6-15y) prescribed regular twice-daily ICS after admission to ED with an asthma exacerbation  <b>Age</b> 5-11 years <b>Exacerbations</b> Recruited patients admitted to ED with an exacerbation <b>Exacerbators</b> Not reported <b>Adherence</b> Not reported <b>Asthma control</b> Not reported  New Zealand	Adherence Asthma control Lung function Reliever use Severe asthma exacerbations	
Charles 2007 (Charles et al., 2007)	<b>Smart inhaler with adherence monitoring and audio-visual reminders</b>  <b>Device without feedback</b> - adherence monitoring and audio-visual	<i>n</i> =110 People aged 12-65 years required to take regular fixed dose ICS with no exacerbation in the previous month  <b>Age</b>	Adherence	

Study	Intervention and comparison	Population	Outcomes	Comments
	reminders disabled	<p>≥12 years</p> <p><b>Exacerbations</b> Not reported</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> Not reported</p> <p>New Zealand</p>		
Chen 2020 (Chen et al., 2020)	<p><b>Smart inhaler with weekly feedback</b> based on data</p> <p><b>Device without feedback</b> – no weekly discussion</p>	<p>n=96</p> <p>Infants (6 months – 3y) with mild-moderate persistent asthma on regular ICS with no change in the past month</p> <p><b>Age</b> &lt;5 years</p> <p><b>Exacerbations</b> Not reported</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> Not reported</p> <p>China</p>	Adherence	
Dierick 2023 (Dierick et al., 2023)	<p><b>Smart inhaler with personalised education</b> based on inhaler data</p> <p><b>Usual care</b> – based on primary care guidelines</p>	<p>n=42</p> <p>Adults (≥18 years) diagnosed with asthma and treated in primary care receiving ICS with a spacer</p> <p><b>Age</b> ≥12 years</p> <p><b>Exacerbations</b> Not reported</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> Not reported</p> <p>The Netherlands</p>	Adherence Inflammatory markers (FeNO)	



Study	Intervention and comparison	Population	Outcomes	Comments
Foster 2014 (Foster et al., 2014)	<p><b>Smart inhaler with reminders or reminders plus personalised adherence discussions</b></p> <p><b>Usual care</b> – based on recent guidelines, including written asthma plans, reviewing inhaler technique</p>	<p><i>n</i>=119 People aged 14-65 years with suboptimal asthma control (ACT score ≤19) on twice-daily ICS/LABA for ≥1 month</p> <p><b>Age</b> ≥12 years</p> <p><b>Exacerbations</b> Not reported</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> Suboptimal control</p> <p>Australia</p>	<p>Asthma control Adherence Quality of life Lung function Severe asthma exacerbations</p>	
Gupta 2021 (Gupta et al., 2021)	<p><b>Smart inhaler with individualised feedback</b> provided via an app</p> <p><b>Usual care</b></p>	<p><i>n</i>=252 Children (4-17 years) with moderate-severe asthma on daily ICS for &gt;1 year and one exacerbation requiring oral corticosteroids in the past year</p> <p><b>Age</b> Mixed, ~80% aged 4-11 years, ~20% aged 12-17 years</p> <p><b>Exacerbations</b> At least one in the past year</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> Not reported</p> <p>USA</p>	<p>Asthma control Hospital admissions Severe asthma exacerbations</p>	
Moore 2021 (Moore et al.)	<p><b>Smart inhaler with feedback</b> via</p>	<p><i>n</i>=174 People (≥18y)</p>	<p>Adherence Rescue</p>	<p>Five arms in trial, arms 3 and 5</p>

Study	Intervention and comparison	Population	Outcomes	Comments
al., 2021)	<p>smartphone and clinician review at least once per month</p> <p><b>Device without feedback</b></p>	<p>with poor asthma control (ACT &lt;20) on ICS/LABA for &gt;3 months with no changes to treatment in previous 3 months</p> <p><b>Age</b> ≥12 years</p> <p><b>Exacerbations</b> Not reported</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> ACT score &lt;20</p> <p>Europe and North America</p>	<p>medication use</p> <p>Asthma control</p>	<p>included as most relevant to this review</p>
Morton 2017 (Morton et al., 2017)	<p><b>Smart inhaler with reminders and adherence monitoring</b> with data reviewed at review every three months</p> <p><b>Device without feedback</b> - no reminders or clinician reviews</p>	<p><i>n</i>=90</p> <p>People with poorly controlled asthma (ACQ &gt;1.5) on regular ICS with no change in medication in the past month</p> <p><b>Age</b> Mixed: 6-16 years old (mean ~10.3 (2.9) years)</p> <p><b>Exacerbations</b> Not reported</p> <p><b>Exacerbators</b> Not reported</p> <p><b>Adherence</b> Not reported</p> <p><b>Asthma control</b> ACQ score &gt;1.5</p> <p>UK</p>	<p>Asthma control</p> <p>Lung function</p>	
Mosnaim 2021 (Mosnaim et al., 2021)	<p><b>Smart inhaler with reminders and data collection displayed on an app</b> available to both participants and clinicians</p>	<p><i>n</i>=100</p> <p>Adults aged 25-65 years with uncontrolled asthma and receiving daily ICS with SABA</p>	<p>Adherence</p> <p>Rescue medication use</p>	

Study	Intervention and comparison	Population	Outcomes	Comments
	<b>Device without feedback</b> – no reminders or data feedback to either participants or clinicians	<b>Age</b> ≥12 years <b>Exacerbations</b> Mixed <b>Exacerbators</b> Mixed <b>Adherence</b> Not reported <b>Asthma control</b> Uncontrolled  USA		
Mosnaim 2023 (Mosnaim et al., 2023)	<b>Smart inhaler with reminders and application-given feedback on inhalation quality</b> , available to both participants and clinicians with treatment adjustments made based on smart inhaler data  <b>Usual care</b> , receiving care based on clinical judgement alone	<i>n</i> =427 Adolescents and adults aged ≥13 years with asthma that was uncontrolled (ACT <19) whilst receiving moderate-high dose ICS/LABA  <b>Age</b> ≥12 years <b>Exacerbations</b> Not reported <b>Exacerbators</b> Not reported <b>Adherence</b> Not reported <b>Asthma control</b> Uncontrolled  USA	Severe asthma exacerbations Hospital admissions Adverse events	
Otsuki 2009 (Otsuki et al., 2009)	<b>Smart inhaler with adherence monitoring and review sessions with asthma action plans and an education program</b> (five 30–45-minute sessions with an asthma educator) to improve adherence  <b>Usual care</b> – including an asthma education booklet and	<i>n</i> =166 Infants and children (2-12y) on maintenance therapy who had 2 ED visits or 1 hospitalisation due to asthma in the previous year  <b>Age</b> 5-11 years <b>Exacerbations</b> At least one in the past year <b>Exacerbators</b>	Hospital admissions Adherence	

Study	Intervention and comparison	Population	Outcomes	Comments
	resource guide	Not reported <b>Adherence</b> Not reported <b>Asthma control</b> Not reported  USA		
Vasbinder 2016 (Vasbinder et al., 2016)	<b>Smart inhaler with automated SMS reminders for missed doses</b>  <b>Device without feedback</b>	<i>n</i> =209 Children (4-11y) on ICS for ≥3 months  <b>Age</b> 5-11 years <b>Exacerbations</b> Not reported <b>Exacerbators</b> Not reported <b>Adherence</b> Not reported <b>Asthma control</b> Mixed - ~37% had uncontrolled asthma at baseline  The Netherlands	Adherence Quality of life Asthma control	
Zairina 2016 (Zairina et al., 2016)	<b>Smart inhaler with weekly feedback and asthma management plans</b> based on daily lung function measurements  <b>Usual care</b> – weekly to monthly reviews and information specific to asthma during pregnancy	<i>n</i> =72 Pregnant women (<20 weeks gestation) with any inhaled bronchodilator or anti-inflammatory agent in the past year  <b>Age</b> ≥12 years <b>Exacerbations</b> Not reported <b>Exacerbators</b> Not reported <b>Adherence</b> Not reported <b>Asthma control</b> Not reported  Australia	Asthma control Quality of life Lung function	

1 See Appendix D for full evidence tables

1 **1.1.6. Summary of the effectiveness evidence**

2 **Table 3: Clinical evidence summary: smart inhalers vs usual care**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care	Risk difference with Smart inhaler	Comments
Severe asthma exacerbations (final values, lower is better)	809 (4 RCTs) Mean follow-up: 7.5 months	⊕⊕○○ Low <sup>a</sup>	<b>RR 1.15</b> (0.72 to 1.82)	186 per 1,000	<b>28 more per 1,000</b> (52 fewer to 152 more)  No clinical difference	MID=30 per 1000 (clinical importance), 0.8-1.25 (imprecision)
Quality of life (Mini Asthma Quality of Life Questionnaire, scale range 1-7, mixed values, higher is better)	177 (2 RCTs) Mean follow-up: 6 months	⊕⊕⊕○ Moderate <sup>b</sup>	-	The mean Mini Asthma Quality of Life Questionnaire score was <b>5.4</b>	<b>MD 0.39 higher</b> (0.28 lower to 1.05 higher)  No clinical difference	MID=0.5 (established MID)
Asthma control (Asthma Control Test, scale range 0-25, final values, higher is better)	328 (2 RCTs) Mean follow-up: 9 months	⊕⊕⊕○ Moderate <sup>b</sup>	-	The mean Asthma Control Test score was <b>19.25</b>	<b>MD 1.29 higher</b> (0.41 higher to 2.17 higher)  No clinical difference	MID=3 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Smart inhaler	
Asthma control (Asthma Control Questionnaire-7, scale range 0-6, mixed values, lower is better)	69 (1 RCT) Follow-up: 6 months	⊕⊕⊕○ Moderate <sup>b</sup>	-	The mean change in Asthma Control Questionnaire score was <b>0.06</b>	MD <b>0.36 lower</b> (0.6 lower to 0.09 lower)  No clinical difference	MID=0.5 (established MID)
Hospital admissions (final values, lower is better)	783 (3 RCTs) Mean follow-up: 12 months	⊕⊕⊕○ Moderate <sup>b</sup>	<b>RR 1.56</b> (1.00 to 2.43)	74 per 1,000	<b>41 more per 1,000</b> (0 fewer to 105 more)  Clinically important benefit for usual care	MID=30 per 1000 (clinical importance), 0.8-1.25 (imprecision)
Adherence (% , mixed values, higher is better)	303 (3 RCTs) Mean follow-up: 8.7 months	⊕○○○ Very low <sup>a,c</sup>	-	The mean adherence was <b>70.48%</b>	MD <b>2.22 higher</b> (18.74 lower to 23.17 higher)  No clinical difference	MID=9.1 (median control group follow-up SD/2)
Lung function (FEV1, litres, final values, higher is better)	108 (1 RCT) Follow-up: 6 months	⊕⊕⊕○ Moderate <sup>b</sup>	-	The mean FEV1 was <b>2.6L</b>	MD <b>0.01 lower</b> (0.24 lower to 0.22 higher)  No clinical difference	MID=0.23 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Smart inhaler	
Lung function (% predicted FEV1, change scores, higher is better)	69 (1 RCT) Follow-up: 6 months	⊕⊕⊕○ Moderate <sup>b</sup>	-	The mean change in FEV1 was <b>1.54%</b>	<b>MD 2.73 higher</b> (2.23 lower to 7.69 higher)  No clinical difference	MID=5.16 (control group follow-up SD/2)
Inflammatory markers (FeNO, ppb, change scores, lower is better)	42 (1 RCT) Follow-up: 2 months	⊕⊕⊕○ Moderate <sup>b</sup>	-	The mean change in FeNO inflammatory markers was <b>-1.7 ppb</b>	<b>MD 3.3 higher</b> (3.27 lower to 9.87 higher)  No clinical difference	MID=5.2 (control group follow-up SD/2)
Adverse events (final values, lower is better)	409 (1 RCT) Follow-up: 6 months	⊕○○○ Very low <sup>a,d</sup>	<b>RR 1.14</b> (0.85 to 1.51)	303 per 1,000	<b>42 more</b> per 1,000 (45 fewer to 154 more)  No clinical difference	MID=100 per 1000 (clinical importance), 0.8-1.25 (imprecision)

- 1 a. Downgraded by two increments due to the 95%CI overlapping both MIDs
- 2 b. Downgraded by one increment due to the 95%CI overlapping one MID
- 3 c. Downgraded by two increments due to considerable heterogeneity indicating opposing benefits of the intervention (I<sup>2</sup>=94%) that cannot be explained by subgroup analysis or random effects model
- 4 d. Downgraded by two increments due to concerns arising from the randomisation method (method not reported) and deviations from the intended intervention (smart inhaler data uploaded on 73% of days, and checked by clinicians on 76% of weeks, indicating poor adherence)
- 5

1 **Table 4: Clinical evidence summary: smart inhalers vs device without feedback**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with device without feedback	Risk difference with Smart inhaler	Comments
Severe asthma exacerbations (final values, lower is better)	216 (1 RCT) Follow-up: 6 months	⊕⊕○○ Low <sup>a</sup>	<b>RR 1.04</b> (0.56 to 1.92)	155 per 1,000	<b>6 more per 1,000</b> (68 fewer to 142 more)  No clinical difference	MID=30 per 1000 (clinical importance), 0.8-1.25 (imprecision)
Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, final values, higher is better)	209 (1 RCT) Follow-up: 12 months	⊕⊕⊕⊕ High	-	The mean Paediatric Asthma Quality of Life Questionnaire score was <b>6.25</b>	<b>MD 0.06 lower</b> (0.41 lower to 0.29 higher)  No clinical difference	MID=0.5 (established MID)
Asthma control (Asthma Control Test, scale range: 5-25, mixed values, higher is better)	194 (2 RCTs) Mean follow-up: 6 months	⊕⊕○○ Low <sup>b,c</sup>	-	The mean Asthma Control Test score was <b>19.9</b>	<b>MD 0.42 higher</b> (0.70 lower to 1.54 higher)  No clinical difference	MID=3 (established MID)
Asthma control (Childhood Asthma Control Test, scale range 0-27, final values, higher is better)	220 (2 RCTs) Mean follow-up: 9 months	⊕○○○ Very low <sup>c,d</sup>	-	The mean Childhood Asthma Control Test score was <b>20.49</b>	<b>MD 0.38 higher</b> (1.88 lower to 2.64 higher)  No clinical difference	MID=2 (established MID)



Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with device without feedback	Risk difference with Smart inhaler	Comments
Asthma control (Asthma Control Questionnaire, scale range 0-6, changes scores, lower is better)	89 (1 RCT) Follow-up: 12 months	⊕⊕○○ Low <sup>e</sup>	-	The mean change in Asthma Control Questionnaire score was <b>-0.95</b>	MD <b>0.19 lower</b> (1.75 lower to 1.37 higher)  No clinical difference	MID=0.5 (established MID)
Reliever medication (SABA-free days, %, mixed values, higher is better)	264 (2 RCTs) Mean follow-up: 4.5 months	⊕○○○ Very low <sup>d,f,g</sup>	-	The mean proportion of SABA-free days was <b>18.6%</b>	MD <b>2.24 higher</b> (19.12 lower to 23.6 higher)  No clinical difference	MID=26.4 (follow-up control group SD/2)
Adherence (% daily doses administered, mixed values, higher is better)	583 (6 RCTs) Mean follow-up: 6.5 months	⊕⊕⊕○ Moderate <sup>c</sup>	-	The mean adherence was <b>54.94%</b>	MD <b>15.82 higher</b> (12.02 higher to 19.62 higher)  Clinically important benefit for Smart inhaler	MID=15.8 (median follow-up control group SD/2)
Lung function (% predicted FEV1, mixed values, higher is better)	309 (2 RCTs) Mean follow-up: 9 months	⊕⊕⊕⊕ High	-	The mean FEV1 was <b>97.2%</b>	MD <b>2.81 higher</b> (0.47 lower to 6.09 higher)  No clinical difference	MID= 8.9 (baseline control group SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with device without feedback	Risk difference with Smart inhaler	
Adverse events (final values, lower is better)	96 (1 RCT) Follow-up: 6 months	⊕⊕⊕○ Moderate <sup>h</sup>	-	0 per 1,000	<b>0 fewer</b> per 1,000 (0 fewer to 0 fewer) No clinical difference	Imprecision assessed on sample size due to zero events

- 1 a. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)
- 2 b. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)
- 3 c. Downgraded by one increment due to the 95%CI overlapping one MID
- 4 d. Downgraded by two increments due to substantial heterogeneity showing differing directions of benefit of the intervention that was not explained by a random effects model
- 5 e. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence to interventions) and missing outcome data
- 6 f. Downgraded by two increments due to concerns arising from the randomisation process (baseline data missing for 108 participants) and selection of the reported result (data reported was not in the format described in the pre-specified analysis)
- 7 g. Downgraded by two increments due to the 95%CI overlapping both MIDs
- 8 h. Downgraded by one increment due to zero events and inadequate sample size (70-350 participants= serious imprecision)
- 9
- 10 See Appendix F for full GRADE tables.

1     **1.1.7. Economic evidence**

2     **1.1.7.1. Included studies**

3     One health economic study with the relevant comparison was included in this  
4     review(Vasbinder et al., 2016). This is summarised in the health economic evidence profile  
5     below (**Table 5**) and the health economic evidence table in Appendix H.

6     **1.1.7.2. Excluded studies**

7     No relevant health economic studies were excluded due to assessment of limited  
8     applicability or methodological limitations.

9     See also the health economic study selection flow chart in Appendix G.

1 **1.1.8. Summary of included economic evidence**

2 **Table 5: Health economic evidence profile: Smart inhaler with reminder vs device without feedback**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Uncertainty
Vasbinder 2016(Vasbinder et al., 2016) (Netherlands)	Partially applicable <sup>(a)</sup>	Potentially serious limitations <sup>(b)</sup>	<ul style="list-style-type: none"> <li>• Within-RCT analysis (e-MATIC trial(Vasbinder et al., 2016))</li> <li>• Cost-consequence analysis</li> <li>• Population: Children aged 4-11 years with doctor-diagnosed asthma</li> <li>• Comparators:                             <ol style="list-style-type: none"> <li>1. Device without feedback (current practice)</li> <li>2. Smart inhaler using RTMM with SMS reminders on adherence</li> </ol> </li> <li>• Follow up: 12 months</li> </ul>	2-1: £83 <sup>(c)</sup>	<ul style="list-style-type: none"> <li>• Adherence: 12% (2-1)</li> <li>• c-ACT score: -1.07 (2-1)</li> <li>• PAQLQ score: -0.06 (2-1)</li> <li>• Asthma exacerbations: -0.14 (2-1)</li> </ul>	Uncertainty around the point estimates was addressed using bootstrapping, generating confidence intervals for incremental costs and health outcomes (see Evidence Table).

3 Abbreviations: c-ACT = childhood asthma control test; ICS = inhaled corticosteroids; PAQLQ = paediatric asthma quality of life questionnaire; RCT = randomised controlled trial;  
4 RTMM = real-time medication monitoring; SMS = short message service.

5 (a) Dutch healthcare: social health insurance (SHI) system.

6 (b) Within-trial analysis with effectiveness data based on a single RCT. Baseline adherence was relatively high so the effectiveness of the intervention may have been  
7 underestimated. The majority of the population had good asthma control at baseline, suggesting they were already taking critical ICS dose even with imperfect adherence.  
8 Hence, the overall improvement in adherence was likely unnecessary and incapable of causing any clinical improvement. C-ACT questionnaire is likely overestimating asthma  
9 control levels in children with poor asthma control or poor symptoms perception.

10 (c) 2014 Dutch euros converted to UK pounds(OECD PPP).(Organisation for Economic Co-operation and Development (OECD), 2012) Cost components incorporated: RTMM  
11 device, medication, hospital and GP visits.  
12

1 **1.1.9. Economic model**

2 No health economic model was undertaken for this question.

3 **1.1.10. Unit costs**

4 Relevant unit costs are provided below to aid consideration of cost effectiveness.

5 **Table 6: Unit costs**

Resource	Unit costs	Source
Smartinhaler (SmartTouch, SmartTouch AV, SmartTurbo2)	£100	NICE Medtech innovation briefing[MIB90](National Institute for Health and Care Excellence, 2017)
SmarthinalerLive software access per each healthcare professional	£14.17 per month	NICE Medtech innovation briefing[MIB90] (National Institute for Health and Care Excellence, 2017)

6 *Note: all prices are VAT exclusive. Non-rechargeable devices will operate for at least 1 year and rechargeable*  
7 *devices have an expected service life of 2 years.*

8 **1.1.11. Evidence statements**

9 **Economic**

10

- 11 • One cost–consequence analysis found that a smart inhaler was more costly than a device  
12 without feedback for children with asthma (£83 more per patient) and had 12% better  
13 adherence and 0.14 fewer exacerbations per patient, but poorer asthma control (c-ACT  
14 score 1.07 lower per patient) and poorer quality of life (PAQLQ score 0.06 lower per  
15 patient). This analysis was assessed as partially applicable with potentially serious  
16 limitations.

17

1

## 2 **1.2. The committee’s discussion and interpretation of the** 3 **evidence**

### 4 **1.2.1. The outcomes that matter most**

5 The direct purpose of smart inhalers is to improve adherence to maintenance medication, with  
6 the expectation that this improved adherence would then improve symptom and quality of life  
7 and prevent exacerbations and asthma deaths. The occurrence of severe asthma  
8 exacerbations is of major importance as these are associated with an increased risk of death  
9 and have a significant deleterious effect on quality of life.

10 No evidence was identified for the following outcomes for either comparison:

- 11 • Mortality
- 12 • Adverse events (linear growth, adrenal insufficiency, bone mineral density)
- 13 • Inflammatory markers

14 No evidence was identified for quality of life for the comparison with devices without  
15 feedback, or for reliever medication use for the comparison with usual care.

### 16 **1.2.2. The quality of the evidence**

17 Fourteen randomised controlled trials were identified, the quality of which ranged from high  
18 to very low.

19 For the comparison with usual care, high quality evidence was identified for lung function,  
20 adherence and quality of life. Moderate quality evidence was identified for lung function,  
21 quality of life and asthma control. Low quality evidence was identified for severe asthma  
22 exacerbations, and very low quality evidence was identified for asthma control and hospital  
23 admissions. Evidence was generally deemed to be at low risk of bias, however when bias  
24 was identified it arose from deviations from the intended interventions due to participants  
25 failing to upload smart inhaler data, or clinicians not using the data as specified in the study  
26 design.

27 For the comparison with devices without feedback, high quality evidence was identified for  
28 lung function and moderate quality evidence for reliever medication use. All other identified  
29 evidence was low or very low quality. Where a risk of bias was identified, this arose due to  
30 the randomisation process used, missing outcome data and selective outcome reporting due  
31 to reporting values achieved through methods that did not match those specified in the  
32 statistical analysis section.

33 It was not possible to form subgroups in any of the analyses due to insufficient numbers of  
34 studies. This resulted in significant variability in the populations combined in each analysis,  
35 which was noted as a barrier to making recommendations by the committee, resulting in the  
36 research recommendation made above.

### 37 **1.2.3. Benefits and harms**

38 For the comparison with usual care, a clinically important harm of smart inhalers was seen  
39 with 41 more hospital admissions per 1,000 people based on moderate quality evidence from  
40 three RCTs containing 783 participants over a mean follow-up duration of 12 months. Whilst  
41 not reaching the clinical importance threshold of 30 events per 1,000 people, low quality  
42 evidence indicated that severe asthma exacerbations showed a similar trend, with 28 more

1 events per 1,000 people in the smart inhaler arm than with usual care seen in four RCTs  
2 containing 809 participants over a mean follow-up duration of 7.5 months.

3 When comparing smart inhalers to devices without feedback, the only clinically important  
4 difference was seen in adherence, based on very low-quality evidence from six RCTs,  
5 showing a 15.82% difference in favour of smart inhalers with feedback switched on.

6 When comparing between studies the committee noted that the entry criteria for the differed  
7 considerably, with a majority recruiting people who had some indication of poor asthma  
8 control (low asthma quality of life scores, recent exacerbations, or both) but several looking  
9 at people with more stable asthma. There was a pattern in the included studies whereby in  
10 the group of papers comparing smart inhalers with usual care, the baseline adherence, the  
11 asthma control, and quality of life scores were worse than in the set of papers comparing  
12 smart inhalers to devices with feedback switched off. These baseline differences provide a  
13 plausible explanation for the greater benefit shown for the comparison with devices without  
14 feedback. This is highlighted well in the data for adherence. The final adherence was ~70%  
15 with smart inhalers whether compared to usual care or to the inhaler with feedback switched  
16 off. However, final adherence was 70% in the usual care group vs 55% in the group using a  
17 smart inhaler with feedback switched off.

18 The evidence identified showed a clinically important harm of smart inhalers when looking at  
19 hospital admissions compared to usual care, with a risk difference also in favour of usual  
20 care approaching clinical significance for severe asthma exacerbations. These important  
21 clinical end points provided strong arguments against the recommendation of smart inhalers  
22 overall. However, the aforementioned benefit of smart inhalers on adherence when  
23 compared to devices without feedback was viewed as a promising finding by the committee,  
24 highlighting the potential utility of smart inhalers in some situations. A significant point of  
25 discussion among the committee was the time commitment required to set up and monitor  
26 smart inhalers. This is considerable, and the time investment adds to the high economic cost.  
27 Additionally, the variability in functionality of the smart inhaler devices was raised, with some  
28 devices simply monitoring number of actuations. The committee felt devices with only this  
29 feature would not be useful in practice and instead would want to see devices that provide  
30 feedback on the number and timing of actuations, as well as the technique of administration.

31 The committee concluded that smart inhalers can improve adherence, and this could in some  
32 people lead to benefits for asthma control and quality of life. However, this benefit is likely to  
33 be confined to those people with sub-optimal adherence and poor asthma control, and it is  
34 difficult from the data presented to define exactly how these people should be identified.

#### 35 **1.2.4. Cost effectiveness and resource use**

36 One health economic evaluation was included for this question. This was a cost-  
37 consequence analysis conducted alongside one of the trials included in the clinical review  
38 looking at a smart device with feedback compared to the device without feedback. The  
39 analysis was assessed as partially applicable with potentially serious limitations as it used a  
40 Dutch healthcare perspective and enrolled a population with relatively high adherence and  
41 asthma control. Despite finding considerable savings in hospitalisation with the smart device,  
42 the analysis found the intervention to be more expensive than usual care, mostly due to the  
43 high price of the device. In terms of outcomes, the smart device resulted in fewer  
44 exacerbations but poorer asthma control and quality of life compared to a device without  
45 feedback. These differences were not clinically or statistically significant. Adherence was  
46 higher in the smart device group compared to the device without feedback. This suggest that,  
47 although the intervention increases adherence to the treatment, this does not always  
48 translate into better clinical outcomes, especially if baseline asthma control and adherence  
49 were sufficiently high.

50 The committee were presented with the unit costs for smart devices in England. Devices  
51 were found to cost not less than £100 and to have a lifetime of around 1 year for non-

1 rechargeable devices and 2 years for rechargeable ones. The committee considered that the  
2 prices reported in NICE Medtech innovation briefing were in the lower bound of usual prices,  
3 as devices currently in the market are usually more expensive based on their knowledge.

4 The committee discussed the clinical findings in light of the economic evidence provided.  
5 Overall, the committee acknowledged that the evidence was not robust enough to make any  
6 recommendation that would change practice. Smart inhalers are not routinely used in current  
7 practice, they are only provided in specific cases. Smart inhalers were found to improve  
8 adherence and some clinical outcomes, but the economic evidence clearly indicates that the  
9 intervention is considerably more expensive than usual care.

10 Nevertheless, the committee acknowledged that smart inhalers may be beneficial in a  
11 population with poor adherence and poor asthma control, and may be cost-effective if  
12 targeted at selected groups, for example people with severe asthma who are at, or are  
13 approaching, the point at which biologic agents might be considered. A research  
14 recommendation was made to explore clinical and cost-effectiveness on specific groups of  
15 people who may benefit from improved adherence. Moreover, although smart inhalers were  
16 not recommended for routine use, a consensus recommendation to use clinical judgment to  
17 prescribe smart devices to people with poor adherence was made. This recommendation  
18 should not have a significant resource impact as it reflects current practice where smart  
19 inhalers are considered in specific cases. Furthermore, it may potentially prevent people to  
20 be escalated to expensive treatments with biologics.

#### 21 **1.2.5. Other factors the committee took into account**

22 From the lay members perspective, it was raised that not all people with asthma would be  
23 able to access smart inhalers due to the requirement for a smartphone and Bluetooth  
24 connectivity. This was a concern particularly for elderly persons and those with learning  
25 disabilities who may struggle to use the technology. The committee felt that whilst smart  
26 inhalers are relatively straightforward devices, this was a valid concern.

27 In summary the committee acknowledged that smart inhalers could be valuable but only if  
28 used selectively and did not feel able to recommend them for general use at present.  
29 Research is needed to identify the circumstances in which they would be most effective, and  
30 it was felt particularly important to include health economic analysis in such research.

#### 31 **1.2.6. Recommendations supported by this evidence review**

32 This evidence review supports recommendation 1.6.9 and the research recommendation on  
33 smart inhalers.  
34



### 1 1.3. References

- 2 Adejumo I, Patel M, McKeever TM, et al. (2022) Does inhaler technology improve adherence  
3 and asthma control? A pilot randomised controlled trial *Annals of Allergy, Asthma,*  
4 *and Immunology* 04: 04.
- 5 Chan AH, Stewart AW, Harrison J, et al. (2015) The effect of an electronic monitoring device  
6 with audiovisual reminder function on adherence to inhaled corticosteroids and school  
7 attendance in children with asthma: a randomised controlled trial *The Lancet*  
8 *Respiratory Medicine* 3 (3): 210-219.
- 9 Charles T, Quinn D, Weatherall M, et al. (2007) An audiovisual reminder function improves  
10 adherence with inhaled corticosteroid therapy in asthma *Journal of Allergy and*  
11 *Clinical Immunology* 119 (4): 811-816.
- 12 Chen J, Xu J, Zhao L, et al. (2020) The effect of electronic monitoring combined with weekly  
13 feedback and reminders on adherence to inhaled corticosteroids in infants and  
14 younger children with asthma: a randomized controlled trial *Allergy, Asthma, &*  
15 *Clinical Immunology : Official Journal of the Canadian Society of Allergy & Clinical*  
16 *Immunology* 16: 68.
- 17 Dierick BJH, Achterbosch M, Eikholt AA, et al. (2023) Electronic monitoring with a digital  
18 smart spacer to support personalized inhaler use education in patients with asthma:  
19 The randomized controlled OUTERSPACE trial *Respiratory Medicine* 218: 107376.
- 20 Foster JM, Usherwood T, Smith L, et al. (2014) Inhaler reminders improve adherence with  
21 controller treatment in primary care patients with asthma *Journal of Allergy and*  
22 *Clinical Immunology* 134 (6): 1260-1268.e1263.
- 23 Gupta RS, Fierstein JL, Boon KL, et al. (2021) Sensor-Based Electronic Monitoring for  
24 Asthma: A Randomized Controlled Trial *Pediatrics* 147 (1): 01.
- 25 Moore A, Preece A, Sharma R, et al. (2021) A randomised controlled trial of the effect of a  
26 connected inhaler system on medication adherence in uncontrolled asthmatic  
27 patients *European Respiratory Journal* 57 (6): 06.
- 28 Morton RW, Elphick HE, Rigby AS, et al. (2017) STAAR: a randomised controlled trial of  
29 electronic adherence monitoring with reminder alarms and feedback to improve  
30 clinical outcomes for children with asthma *Thorax* 72 (4): 347-354.
- 31 Mosnaim GS, Hoyte FCL, Safioti G, et al. (2023) Effectiveness of a Maintenance and  
32 Reliever Digihaler System in Asthma: 24-week Randomized Study (CONNECT2) *The*  
33 *journal of allergy and clinical immunology In practice*.
- 34 Mosnaim GS, Stempel DA, Gonzalez C, et al. (2021) The Impact of Patient Self-Monitoring  
35 Via Electronic Medication Monitor and Mobile App Plus Remote Clinician Feedback  
36 on Adherence to Inhaled Corticosteroids: A Randomized Controlled Trial *The Journal*  
37 *of Allergy & Clinical Immunology in Practice* 9 (4): 1586-1594.
- 38 National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. .  
39 London. National Institute for Health and Care Excellence, 2014. Available from:  
40 <http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview>
- 41 National Institute for Health and Care Excellence. Smartinhaler for asthma. London. National  
42 Institute for Health and Care Excellence, 2017. Available from:  
43 <https://www.nice.org.uk/advice/mib90/chapter/The-technology>
- 44 Organisation for Economic Co-operation and Development (OECD). Purchasing power  
45 parities (PPP). 2012. Available from: <http://www.oecd.org/std/ppp> Last accessed:  
46 15/03/2024.

- 1 Otsuki M, Eakin MN, Rand CS, et al. (2009) Adherence feedback to improve asthma  
2 outcomes among inner-city children: a randomized trial *Pediatrics* 124 (6): 1513-  
3 1521.
- 4 Vasbinder EC, Goossens LM, Rutten-van Molken MP, et al. (2016) e-Monitoring of Asthma  
5 Therapy to Improve Compliance in children (e-MATIC): a randomised controlled trial  
6 *European Respiratory Journal* 48 (3): 758-767.
- 7 Zairina E, Abramson MJ, McDonald CF, et al. (2016) Telehealth to improve asthma control in  
8 pregnancy: a randomized controlled trial *Respirology (Carlton, Vic)* 21 (5): 867-874.
- 9
- 10

## 1 Appendix A – Review protocols

### 2 Review protocol for smart inhalers

ID	Field	Content
0.	PROSPERO registration number	CRD42023443353
1.	Review title	Smart preventer/maintenance inhalers for the management of asthma
2.	Review question	What is the clinical and cost-effectiveness of smart preventer/maintenance inhalers for the management of asthma?
3.	Objective	To determine the effectiveness of smart preventer/maintenance inhalers for the management of asthma.
4.	Searches	<p>The following databases (from 2011 onwards) will be searched:</p> <ul style="list-style-type: none"> <li>• Cochrane Central Register of Controlled Trials (CENTRAL)</li> <li>• Cochrane Database of Systematic Reviews (CDSR)</li> <li>• Embase</li> <li>• MEDLINE</li> <li>• Epistemonikos</li> </ul> <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> <li>• English language studies</li> <li>• Human studies</li> </ul> <p>Other searches:</p>

		<ul style="list-style-type: none"> <li>• Inclusion lists of systematic reviews</li> </ul> <p>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.</p> <p>The full search strategies will be published in the final review.</p> <p>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).</p>
5.	Condition or domain being studied	Asthma
6.	Population	Inclusion: People with a diagnosis of asthma.
7.	Intervention	Preventer/maintenance therapy given via smart inhaler devices with feedback
8.	Comparator	Usual care Device without feedback

9.	Types of study to be included	<p>RCTs</p> <p>Systematic reviews of RCTs</p> <p>Published Cochrane reviews, NMAs and IPDs will be considered for inclusion.</p>
10.	Other exclusion criteria	<p>Non-English language studies.</p> <p>Conference abstracts will be excluded</p> <p>Non-randomised studies</p>
11.	Context	<p>Smart inhalers could improve adherence to medication.</p>
12.	Primary outcomes (critical outcomes)	<p>All outcomes are considered equally important for decision making and therefore have all been rated as critical:</p> <ul style="list-style-type: none"> <li>• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at <math>\geq 6</math> months, latest timepoint if more than one)</li> <li>• Mortality (dichotomous outcome at <math>\geq 6</math> months)</li> <li>• Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at <math>\geq 3</math> months)</li> <li>• Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at <math>\geq 3</math> months)</li> <li>• Hospital admissions (dichotomous outcome at <math>\geq 6</math> months)</li> <li>• Reliever/rescue medication use (continuous outcome at <math>\geq 3</math> months)</li> <li>• Adherence – prioritised as 1) % of puffs taken as prescribed (number of and timing of) could be reported as continuous or dichotomous and 2) Count of number times inhaler used</li> <li>• Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at <math>\geq 3</math> months). Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1</li> </ul>

		<p>%pred.</p> <ul style="list-style-type: none"> <li>• Adverse events:             <ul style="list-style-type: none"> <li>○ linear growth (continuous outcome at <math>\geq 1</math> year)</li> <li>○ pneumonia frequency (dichotomous outcome at <math>\geq 3</math> months)</li> <li>○ adrenal insufficiency (as defined by study, including short synacthen test and morning cortisol, dichotomous outcome at <math>\geq 3</math> months)</li> <li>○ bone mineral density (continuous outcome at 6 months)</li> </ul> </li> <li>• Inflammatory markers; exhaled nitric oxide (continuous outcome at <math>\geq 8</math> weeks)</li> </ul>
13.	Data extraction (selection and coding)	<p>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.</p> <p>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.</p> <p>A standardised form will be used to extract data from studies (see <a href="#">Developing NICE guidelines: the manual</a> section 6.4).</p> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> <li>• papers were included /excluded appropriately</li> <li>• a sample of the data extractions</li> <li>• correct methods are used to synthesise data</li> <li>• a sample of the risk of bias assessments</li> </ul> <p>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.</p>

		Study investigators may be contacted for missing data where time and resources allow.
14.	Strategy for data synthesis	<p>EndNote will be used for reference management, sifting, citations and bibliographies.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.</p> <p>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.</p> <p>An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.</p> <p>A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).</p>
15.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <p>For Intervention reviews the following checklist will be used according to study design being assessed:</p> <ul style="list-style-type: none"> <li>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)</li> <li>• Randomised Controlled Trial: Cochrane RoB (2.0)</li> </ul> <p>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.</p>
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:

		<p>Age</p> <ul style="list-style-type: none"> <li>• &lt;5 years</li> <li>• 5-11 years</li> <li>• ≥12 years</li> </ul> <p>Exacerbations</p> <ul style="list-style-type: none"> <li>• Frequent (2 or more per year)</li> <li>• Not frequent (including 1 per year)</li> </ul> <p>Exacerbators 2 (if heterogeneity not explained)</p> <ul style="list-style-type: none"> <li>• Less frequent (1 or more)</li> <li>• No exacerbations</li> </ul> <p>Adherence</p> <ul style="list-style-type: none"> <li>• Good &gt;75%</li> <li>• Fair 50-75%</li> <li>• Poor &lt;50%</li> </ul> <p>Control of asthma</p> <ul style="list-style-type: none"> <li>• Controlled</li> <li>• Uncontrolled</li> </ul>	
17.	Type and method of review	<input checked="" type="checkbox"/>	Intervention
		<input type="checkbox"/>	Diagnostic
		<input type="checkbox"/>	Prognostic
		<input type="checkbox"/>	Qualitative



		<input type="checkbox"/>	Epidemiologic	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	31 <sup>st</sup> March 2023		
21.	Anticipated completion date	30 <sup>th</sup> October 2024		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Piloting of the study selection process	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
23.	Named contact	5a. Named contact National Guideline Centre		

		<p>5b Named contact e-mail</p> <p><a href="mailto:asthmachronicmanagement@nice.org.uk">asthmachronicmanagement@nice.org.uk</a></p> <p>5e Organisational affiliation of the review</p> <p>National Institute for Health and Care Excellence (NICE) and National Guideline Centre</p>
24.	Review team members	<p>From the National Guideline Centre:</p> <p>Bernard Higgins (Guideline lead)</p> <p>Sharon Swain (Guideline lead)</p> <p>Qudsia Malik (Senior systematic reviewer)</p> <p>Clare Jones (Senior systematic reviewer)</p> <p>Toby Sands (Systematic reviewer)</p> <p>Alfredo Mariani (Senior health economist)</p> <p>Lina Gulhane (Head of information specialists)</p> <p>Stephen Deed (Information specialist)</p> <p>Amy Crisp (Senior project manager)</p>
25.	Funding sources/sponsor	<p>This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</p>
26.	Conflicts of interest	<p>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.</p>

27.	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 <a href="#">Developing NICE guidelines: the manual</a> . Members of the guideline committee are available on the NICE website: <a href="https://www.nice.org.uk/guidance/indevelopment/gid-ng10186">https://www.nice.org.uk/guidance/indevelopment/gid-ng10186</a>	
28.	Other registration details	N/A	
29.	Reference/URL for published protocol	N/A	
30.	Dissemination plans	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> <li>• notifying registered stakeholders of publication</li> <li>• publicising the guideline through NICE's newsletter and alerts</li> <li>• 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.</li> </ul>	
31.	Keywords	N/A	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	<input checked="" type="checkbox"/>	Ongoing
		<input type="checkbox"/>	Completed but not published
		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input type="checkbox"/>	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>	

1

2 **Health economic review protocol**3 **Table 7: Health economic review protocol**

<b>Review question</b>	<b>All questions – health economic evidence</b>
<b>Objectives</b>	To identify health economic studies relevant to any of the review questions.
<b>Search criteria</b>	<ul style="list-style-type: none"> <li>• Populations, interventions and comparators must be as specified in the clinical review protocol above.</li> <li>• Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).</li> <li>• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)</li> <li>• Unpublished reports will not be considered unless submitted as part of a call for evidence.</li> <li>• Studies must be in English.</li> </ul>
<b>Search strategy</b>	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
<b>Review strategy</b>	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). (National Institute for Health and Care Excellence)</p> <p><b>Inclusion and exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.</li> <li>• If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.</li> <li>• If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</li> </ul>

**Where there is discretion**

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

**Setting:**

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

**Health economic study type:**

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

**Year of analysis:**

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'.
- Studies published before 2006 be excluded before being assessed for applicability and methodological limitations.

**Quality and relevance of effectiveness data used in the health economic analysis:**

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

## Appendix B – Literature search strategies

### B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

**Table 8: Database parameters, filters and limits applied**

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 Dec 2023	Randomised controlled trials Systematic review studies  Exclusions (animal studies, letters, comments, editorials, case studies/reports)  English language
Embase (OVID)	1974 – 20 Dec 2023	Randomised controlled trials Systematic review studies  Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports)  English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 20 Dec 2023	Exclusions (Cochrane reviews)  English language

#### Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.

12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	Digital Technology/
25.	((smart or smarter or cloud or software or monitor* or adher* or technol* or digital* or mobile or app* or bluetooth or automatic or remind* or tablet* or sensor* or device* or track*) adj3 inhaler*).ti,ab,kf.
26.	((electric* or electronic*) adj4 (inhaler* or audio visual or audiovisual or device* or monitor* or adher*).ti,ab,kf.
27.	((smart or smarter or cloud or software or technol* or digital* or mobile or app* or bluetooth or automatic or remind* or tablet* or sensor*) adj3 (device* or track* or monitor* or adher*).ti,ab,kf.
28.	(SmartTurbo* or SmartTouch or SmartInhaler or HeroTracker or CareTRx or Propeller system).ti,ab,kf.
29.	or/24-28
30.	23 and 29
31.	Meta-Analysis/
32.	Meta-Analysis as Topic/
33.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
34.	((systematic* or evidence*) adj3 (review* or overview*).ti,ab.
35.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
36.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
37.	(search* adj4 literature).ab.
38.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
39.	cochrane.jw.
40.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
41.	or/31-40
42.	randomized controlled trial.pt.
43.	controlled clinical trial.pt.
44.	randomi#ed.ab.
45.	placebo.ab.
46.	randomly.ab.
47.	clinical trials as topic.sh.
48.	trial.ti.
49.	or/42-48
50.	30 and (41 or 49)



**Embase (Ovid) search terms**

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	Digital Technology/
24.	((smart or smarter or cloud or software or monitor* or adher* or technol* or digital* or mobile or app* or bluetooth or automatic or remind* or tablet* or sensor* or device* or track*) adj3 inhaler*).ti,ab,kf.
25.	((electric* or electronic*) adj4 (inhaler* or audio visual or audiovisual or device* or monitor* or adher*).ti,ab,kf.
26.	((smart or smarter or cloud or software or technol* or digital* or mobile or app* or bluetooth or automatic or remind* or tablet* or sensor*) adj3 (device* or track* or monitor* or adher*).ti,ab,kf.
27.	(SmartTurbo* or SmartTouch or SmartInhaler or HeroTracker or CareTRx or Propeller system).ti,ab,kf.
28.	or/23-27
29.	22 and 28
30.	random*.ti,ab.
31.	factorial*.ti,ab.
32.	(crossover* or cross over*).ti,ab.
33.	((doubl* or singl*) adj blind*).ti,ab.
34.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
35.	crossover procedure/
36.	single blind procedure/
37.	randomized controlled trial/
38.	double blind procedure/
39.	or/30-38
40.	Systematic Review/



	HeroTracker OR CareTRx OR Propeller)) AND (title:(inhaler*) OR abstract:(inhaler*)))))
--	--

## B.2 Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31<sup>st</sup> March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31<sup>st</sup> March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies and modelling.

**Table 9: Database parameters, filters and limits applied**

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling
	Quality of Life 1946 – 29 Dec 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports)
	Modelling 1946 – 29 Dec 2023	English language
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling
	Quality of Life 1974 – 29 Dec 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts)
	Modelling 1974 – 29 Dec 2023	English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception – 31 <sup>st</sup> March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31 <sup>st</sup> March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

**Medline (Ovid) search terms**

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

**Embase (Ovid) search terms**

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/

5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/
27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43

45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/
53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

#### NHS EED and HTA (CRD) search terms

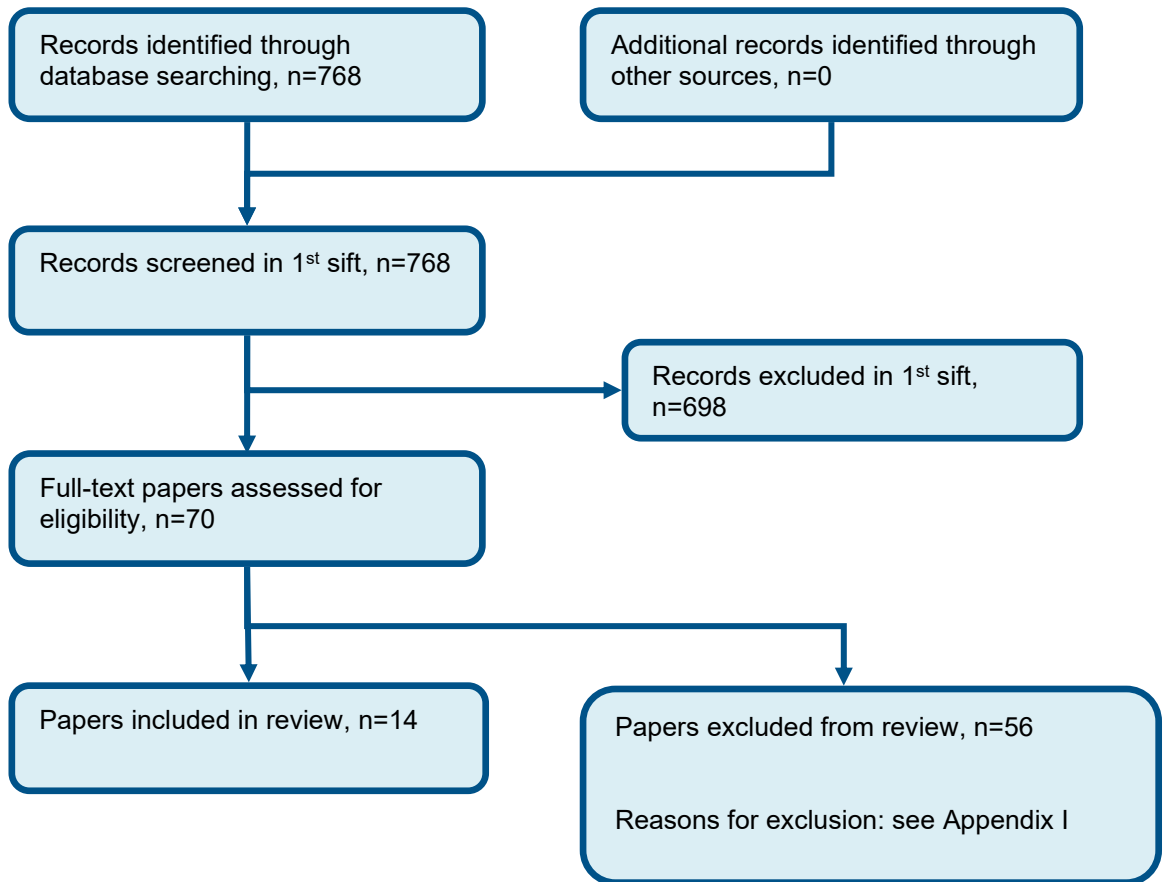
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

#### INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]
----	--

## Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of smart inhalers





## Appendix D – Effectiveness evidence

### Adejumo, 2022

**Bibliographic Reference** Adejumo, I.; Patel, M.; McKeever, T. M.; Shaw, D. E.; Does inhaler technology improve adherence and asthma control? A pilot randomised controlled trial; *Annals of Allergy, Asthma, & Immunology*; 2022; vol. 04; 04

#### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	clinicaltrials.gov (NCT02977078) and BioMed Central (ISRCTN90986892)
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	UK
<b>Study setting</b>	No additional information
<b>Study dates</b>	February 2017 - December 2018
<b>Sources of funding</b>	Funded by a grant from GSK

<b>Inclusion criteria</b>	<p>Adults aged 18-65</p> <p>Use of systemic corticosteroids for worsening asthma (or an increase from baseline dose in patients on long-term oral corticosteroids) in the prior 12 months [i.e. at least one asthma exacerbation requiring additional systemic corticosteroid in the prior 12 months]</p> <p>Doctor's diagnosis of asthma for at least 12 months</p> <p>On BTS step 2-5 treatment via MDI</p> <p>Use of own internet-enabled and compatible mobile phone</p>
<b>Exclusion criteria</b>	<p>Diagnosis of COPD or onset of symptoms after the age of 40 in patients with <math>\geq 10</math> Pack Year History of smoking</p> <p>Other clinically significant coexisting respiratory disease e.g. fibrosis, bronchiectasis</p> <p>Patients on maintenance and reliever therapy ('SMART' or 'Fostair® MART')</p>
<b>Recruitment / selection of participants</b>	<p>No additional information</p>
<b>Intervention(s)</b>	<p>Participants received Smartinhaler devices to remotely measure actuations, with feedback given via a mobile phone device and through discussion with the study investigator. If SABA overuse or ICS underuse were confirmed, clinical teams were notified and invited participants to a review meeting</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p><math>\geq 12</math> years</p>

	<p><b>Exacerbations</b></p> <p>At least one in past 12 months</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Mixed</p>
<b>Comparator</b>	Participants received Smartinhaler devices, but with no feedback from the mobile app
<b>Number of participants</b>	<p>36 randomised, 33 completed (total)</p> <p>18 randomised, 19 completed (Smart inhaler)</p> <p>18 randomised, 15 completed (feedback turned off)</p>
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	No additional information
<b>Additional</b>	Complete case analysis

**comments**

**Study arms**

**Smart inhaler (N = 18)**

Smart inhaler platform with feedback via mobile phone application and discussion with the study investigator

**Device without feedback (N = 18)**

Smart inhaler platform with no feedback

**Characteristics**

**Study-level characteristics**

Characteristic	Study (N = 36)
% Female	n = 24 ; % = 67
Sample size	
<b>Mean age (SD)</b>	48.3 (33.5 to 55.4)
Median (IQR)	
<b>Ethnicity</b>	n = NR ; % = NR
Sample size	
<b>Caucasian</b>	n = 30 ; % = 83
Sample size	

<b>Characteristic</b>	<b>Study (N = 36)</b>
<b>Comorbidities</b>	NR
Nominal	

## Outcomes

### Study timepoints

- Baseline
- 6 month

### Continuous Outcomes

<b>Outcome</b>	<b>Smart inhaler, Baseline, N = 18</b>	<b>Smart inhaler, 6 month, N = 18</b>	<b>Device without feedback, Baseline, N = 18</b>	<b>Device without feedback, 6 month, N = 15</b>
<b>Adherence (Mean Percentage Daily)</b> Final values	NA (NA)	70.7 (32.1)	NA (NA)	59.4 (31.9)
Mean (SD)				
<b>Sensitivity Analysis</b> Includes only devices which passed post-study testing or had demonstrated no major concerns (smart inhaler group n=13, feedback turned off group n=10)	NA (NA)	74.4 (28.3)	NA (NA)	61.7 (34.8)
Mean (SD)				
<b>Asthma Control (Asthma Control Test)</b> Scale range 5-25, change scores, Smart inhaler group n=17,	NA (NA)	2.12 (4.15)	NA (NA)	0.77 (4.94)

Outcome	Smart inhaler, Baseline, N = 18	Smart inhaler, 6 month, N = 18	Device without feedback, Baseline, N = 18	Device without feedback, 6 month, N = 15
feedback turned off group n=13				
Mean (SD)				
Adherence (Mean Percentage Daily) - Polarity - Higher values are better				
Asthma Control (Asthma Control Test) - Polarity - Higher values are better				

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### Adherence

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable <i>(Outcome measured as % of prescribed doses actuated, not including timing of actuation)</i>

#### Adherence (Sensitivity Analysis)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable <i>(Outcome measured as % of prescribed doses actuated, not including timing of actuation)</i>

## Asthma Control

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High <i>(Unblinded study design with subjective outcome measure with likely belief that the intervention is superior to the comparator)</i>
Overall bias and Directness	Overall Directness	Directly applicable

## Chan, 2015

**Bibliographic Reference** Chan, A. H.; Stewart, A. W.; Harrison, J.; Camargo, C. A., Jr.; Black, P. N.; Mitchell, E. A.; The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial; *The Lancet Respiratory Medicine*; 2015; vol. 3 (no. 3); 210-9

## Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information

<b>Trial name / registration number</b>	Australian New Zealand Clinical Trials Registry (ACTRN12613001353785)
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	New Zealand
<b>Study setting</b>	No additional information
<b>Study dates</b>	May 2010 - February 2012
<b>Sources of funding</b>	Health Research Council of New Zealand and Cure Kids
<b>Inclusion criteria</b>	<p>Aged 6-15 years</p> <p>Presenting with asthma to the regional ED in Auckland</p> <p>Physician-diagnosis of asthma and prescribed with a regular, twice-daily ICS</p>
<b>Exclusion criteria</b>	<p>Diagnosis with chronic lung disease other than asthma or congenital heart disease</p> <p>Resident outside of Auckland</p> <p>Diagnosis of a severe chronic medical condition leading to impaired immunity or increased morbidity</p>
<b>Recruitment / selection of participants</b>	Children presenting at the ED diagnosed with asthma
<b>Intervention(s)</b>	<p>Participants received an EMD attached to their ICS. The intervention group had the reminder function enabled. The EMD delivered twice-daily reminders for missed doses. Timings were set by investigators prior to each visit, as per participant preference. The reminder sounded until the correct dose was taken, or for up to 15 minutes, and did not sound if the correct dose was taken in the 6 hours preceding the reminder time. The EMD recorded the date and time of each actuation, ringtone initiation and sound and pMDI or battery removal/insertion. This information was stored on the device until data upload. Follow-up visits occurred every 2 months where investigators collected the EMD for performance checking and data upload. Participants were not aware that their usage was being monitored and were told that they were part of a study investigating the effect of a reminder inhaler.</p>



<b>Population subgroups</b>	<p><b>Age</b></p> <p>5-11 years</p> <p><b>Exacerbations</b></p> <p>Admitted to ED with an exacerbation</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Not reported</p>
<b>Comparator</b>	<p>Participants received an EMD attached to their ICS. The control group had the reminder function disabled. The EMD recorded the date and time of each actuation and pMDI or battery removal/insertion. This information was stored on the device until data upload. Follow-up visits occurred every 2 months where investigators collected the EMD for performance checking and data upload. Participants were not aware that their usage was being monitored and were told that they were part of a study investigating the effect of a reminder inhaler.</p>

<b>Number of participants</b>	220 randomised, 113 completed (total) 110 randomised, 108 completed (smart inhaler) 110 randomised, 105 completed (feedback turned off)
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	No additional information
<b>Additional comments</b>	Intention to treat

## Study arms

### Smart inhaler (N = 110)

Smart inhaler electrical monitoring device with audio visual function enabled

### Device without feedback (N = 110)

Smart inhaler electrical monitoring device with audio visual function disabled

## Characteristics

### Arm-level characteristics

Characteristic	Smart inhaler (N = 110)	Device without feedback (N = 110)
% Female	n = 55 ; % = 50	n = 52 ; % = 47
Sample size		

<b>Characteristic</b>	<b>Smart inhaler (N = 110)</b>	<b>Device without feedback (N = 110)</b>
<b>Mean age (SD)</b>	8.9 (2.5)	8.9 (2.6)
Mean (SD)		
<b>Ethnicity</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>European</b>	n = 42 ; % = 38	n = 41 ; % = 37
Sample size		
<b>Maori</b>	n = 6 ; % = 5	n = 11 ; % = 10
Sample size		
<b>Pacific Islander</b>	n = 25 ; % = 23	n = 21 ; % = 19
Sample size		
<b>Asian</b>	n = 19 ; % = 17	n = 20 ; % = 18
Sample size		
<b>Middle Eastern, Latin American or African</b>	n = 2 ; % = 2	n = 6 ; % = 5
Sample size		
<b>Other</b>	n = 16 ; % = 15	n = 11 ; % = 10
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		

## Outcomes

### Study timepoints

- Baseline
- 6 month

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 110	Smart inhaler, 6 month, N = 110	Device without feedback, Baseline, N = 110	Device without feedback, 6 month, N = 110
<b>Asthma control (Childhood Asthma Control Test)</b> Scale range 0-27, final values  Mean (SD)	18.8 (4.5)	22.7 (3.7)	18.8 (4.2)	21.4 (4.2)
<b>Lung Function (% predicted FEV1) (Percentage)</b> Final values  Mean (SD)	92.1 (17.5)	100.8 (15.5)	89.5 (17.8)	97.2 (15.8)

Asthma control (Childhood Asthma Control Test) - Polarity - Higher values are better

Lung Function (% predicted FEV1) - Polarity - Higher values are better

### Dichotomous Outcomes

Outcome	Smart inhaler, Baseline, N = 110	Smart inhaler, 6 month, N = 110	Device without feedback, Baseline, N = 110	Device without feedback, 6 month, N = 110
---------	----------------------------------	---------------------------------	--	---

Outcome	Smart inhaler, Baseline, N = 110	Smart inhaler, 6 month, N = 110	Device without feedback, Baseline, N = 110	Device without feedback, 6 month, N = 110
<b>Severe Asthma Exacerbations (% of participants with at least 1 parent-reported exacerbation)</b> Final values (months 4-6), smart inhaler n=106, device without feedback n=102	n = NA ; % = NA	n = 17 ; % = 17	n = NA ; % = NA	n = 17 ; % = 16
No of events				

Severe Asthma Exacerbations (% of participants with at least 1 parent-reported exacerbation) - Polarity - Lower values are better

#### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

##### Asthma control

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

##### Lung Function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

### Severe Asthma Exacerbations

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable <i>(Outcome measured as parent-reported exacerbations, not necessarily exacerbations require systemic corticosteroids)</i>

## Charles, 2007

**Bibliographic Reference** Charles, T.; Quinn, D.; Weatherall, M.; Aldington, S.; Beasley, R.; Holt, S.; An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma; Journal of Allergy & Clinical Immunology; 2007; vol. 119 (no. 4); 811-6

### Study details

<b>Secondary publication of another included study- see primary</b>	No additional information
---	---------------------------

<b>study for details</b>	
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	No additional information
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	New Zealand
<b>Study setting</b>	No additional information
<b>Study dates</b>	No additional information
<b>Sources of funding</b>	Supported by a research grant from GSK
<b>Inclusion criteria</b>	<p>12-65 years old</p> <p>Diagnosis of asthma</p> <p>Required to take regular ICS at a fixed dose</p> <p>No exacerbation in the previous month or run-in period</p> <p>Not pregnant or lactating</p> <p>Using contraception if of child-bearing potential</p>
<b>Exclusion criteria</b>	<p>Diagnosis of COPD</p> <p>use of LABA</p> <p>History of other clinically significant disease</p>
<b>Recruitment /</b>	Recruited from research volunteer databases, newspaper adverts and informal contacts

<b>selection of participants</b>	
<b>Intervention(s)</b>	<p>Participants received fluticasone propionate (250mcg twice daily) via the Smartinhaler MDI with covert adherence monitoring. The Smartinhaler incorporated an electronic monitoring device, which recorded the data and time of actuations. This information was uploaded onto a computer after the participant's visit to the study center. The intervention group Smartinhalers also contained an audiovisual reminder function. When the alarm was switched on, it generated a single beep which sounded every 30 seconds for 1 hour after the predesignated time that was programmed into the device. The alarm stopped if the MDI was actuated, or after 1 hour has passed. The device was programmed to emit the alarm twice per day at prespecified times. The device also had a colored light, which was green before actuation and turned red after. This served as an additional reminder to patients as to if they had taken their MDI as scheduled.</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p>≥12 years</p> <p><b>Exacerbations</b></p> <p>Not reported</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p>



	<b>Asthma control</b>  Not reported
<b>Comparator</b>	Participants received fluticasone proprionate (250mcg twice daily) via the Smartinhaler MDI with covert adherence monitoring. The Smartinhaler incorporated a electronic monitoring device, which recorded the data and time of actuations. This information was uploaded onto a computer after the participant's visit to the study center. Participants in the control group received no reminder from their inhaler.
<b>Number of participants</b>	110 randomised, 90 completed (total)  55 randomised, 44 completed (Smart inhaler)  55 randomised, 46 completed (device without feedback)
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	No additional information
<b>Additional comments</b>	No additional information

### Study arms

#### Smart inhaler (N = 55)

Smartinhaler MDI with covert adherence monitoring and audiovisual reminder function enabled

#### Device without feedback (N = 55)

Smartinhaler MDI with covert adherence monitoring and audiovisual reminder function disabled

## Characteristics

### Arm-level characteristics

Characteristic	Smart inhaler (N = 55)	Device without feedback (N = 55)
<b>% Female</b>	n = 27 ; % = 51	n = 33 ; % = 60
Sample size		
<b>Mean age (SD)</b>	39 (13 to 65)	35 (15 to 64)
Median (range)		
Median (IQR)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Lung function</b> (Litres per minute)	434 (99)	444 (128)
PEF		
Mean (SD)		

## Outcomes

### Study timepoints

- Baseline

- 24 week

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 55	Smart inhaler, 24 week, N = 44	Device without feedback, Baseline, N = 55	Device without feedback, 24 week, N = 46
<b>Adherence (% medication taken from week 12-24)</b> (Percentage) Final values	NA (NA)	88 (16)	NA (NA)	66 (27)
Mean (SD)				

Adherence (% medication taken from week 12-24) - Polarity - Higher values are better

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### Adherence

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

## Chen, 2020

**Bibliographic Reference** Chen, J.; Xu, J.; Zhao, L.; Zhang, J.; Yin, Y.; Zhang, F.; The effect of electronic monitoring combined with weekly feedback and reminders on adherence to inhaled corticosteroids in infants and younger children with asthma: a randomized controlled trial; *Allergy, Asthma, & Clinical Immunology : Official Journal of the Canadian Society of Allergy & Clinical Immunology*; 2020; vol. 16; 68

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	Clinicaltrials.gov: NCT03277664
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	China
<b>Study setting</b>	No additional information
<b>Study dates</b>	September 2016 - January 2017
<b>Sources of funding</b>	Funded by AstraZeneca, the Shanghai Shen Kang Hospital Development Center – Appropriate Technology Joint Development and Popularization Project, the Shanghai Shen Kang Hospital Development Center Projects for the Prevention and Control of Chronic Diseases, the key projects of the Shanghai Science and Technology Department of Medicine and Scientific research projects of Shanghai Science and Technology Commission

<b>Inclusion criteria</b>	<p>Aged 6 months - 3 years</p> <p>Mild or moderate persistent asthma</p> <p>Taking regular ICS with no change in medication in the last month</p>
<b>Exclusion criteria</b>	<p>Severe persistent asthma or another respiratory disease (eg, a chronic lung disease other than asthma, respiratory health impacted by cardiac conditions, or another medical co-morbidity)</p> <p>Not living in Shanghai</p>
<b>Recruitment / selection of participants</b>	<p>Participants with a diagnosis of asthma were recruited from a children's medical center and community hospitals</p>
<b>Intervention(s)</b>	<p>The SmartTrack Device which is attached to the surface of the nebulizer, monitored the daily use of the nebulizer (Budesonide). The device recorded the date, time, and number of actuations used. The usage data were saved in the smart device and automatically transferred to the central server via Bluetooth. All caregivers had their nebulizer technique checked by a qualified asthma nurse and received a brief asthma education session after randomization, emphasizing the importance of taking ICS regularly. All participants were reviewed in their routine asthma clinics 3-monthly, and all treatment decisions were made by the clinical team according to asthma guidelines. Data were collected and adherence rates were calculated weekly. All the device-monitored adherence data from the previous week were downloaded from the database and calculated by a qualified asthma nurse. Feedback was given through video chat consultation with the nurse on a weekly basis and reminded participants to keep taking the ICS.</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p>&lt;5 years</p> <p><b>Exacerbations</b></p> <p>Not reported</p>

	<p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Not reported</p>
<b>Comparator</b>	Participants in the control group also had a SmartTrack device attached to their nebulizer. All the device-monitored adherence data were downloaded from the background database and calculated weekly. However, feedback and reminders were not given to the caregivers.
<b>Number of participants</b>	<p>96 randomised, 86 completed (total)</p> <p>46 randomised, 40 completed (smart inhaler)</p> <p>50 randomised, 46 completed (device without feedback)</p>
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	No additional information
<b>Additional comments</b>	No additional information

## Study arms

**Smart inhaler (N = 46)**  
SmartTrack Device

**Device without feedback (N = 50)**  
SmartTrack Device with feedback turned off

## Characteristics

### Arm-level characteristics

Characteristic	Smart inhaler (N = 46)	Device without feedback (N = 50)
% Female	n = 18 ; % = 39.1	n = 21 ; % = 62
Sample size		
<b>Mean age (SD)</b> Months	25.8 (9.6)	27.3 (12.2)
Mean (SD)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		

Characteristic	Smart inhaler (N = 46)	Device without feedback (N = 50)
<b>Eczema</b>	n = 25 ; % = 54.3	n = 26 ; % = 52
Sample size		
<b>Rhinitis</b>	n = 24 ; % = 52.2	n = 31 ; % = 62
Sample size		
<b>Food allergy</b>	n = 14 ; % = 30.4	n = 16 ; % = 32
Sample size		

## Outcomes

### Study timepoints

- Baseline
- 6 month

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 46	Smart inhaler, 6 month, N = 40	Device without feedback, Baseline, N = 50	Device without feedback, 6 month, N = 46
<b>Adherence</b> (Percentage) Mean device-monitored in final month of study	NA (NA)	72.3 (41.5)	NA (NA)	25 (36)
Mean (SD)				

Adherence - Polarity - Higher values are better



### Dichotomous Outcomes

Outcome	Smart inhaler, Baseline, N = 46	Smart inhaler, 6 month, N = 46	Device without feedback, Baseline, N = 50	Device without feedback, 6 month, N = 50
<b>Adverse events</b>	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Final values				
No of events				

Adverse events - Polarity - Lower values are better

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### Adherence

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

#### DichotomousOutcomes-Adverseevents-NoOfEvents-Smart inhaler-Device without feedback-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

## Dierick, 2023

**Bibliographic Reference** Dierick, Boudewijn J H; Achterbosch, Maria; Eikholt, Amber A; Been-Buck, Sandra; Klemmeier, Titia; van de Hei, Susanne J; Hagedoorn, Paul; Kerstjens, Huib A M; Kocks, Janwillem W H; van Boven, Job F M; Electronic monitoring with a digital smart spacer to support personalized inhaler use education in patients with asthma: The randomized controlled OUTERSPACE trial.; Respiratory medicine; 2023; vol. 218; 107376

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	OUTERSPACE (OUTcomes following Tailored Education and Retraining: Studying Performance and AdherenCE) Netherlands Trial Registry: NL9637
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	The Netherlands

<b>Study setting</b>	Primary care
<b>Study dates</b>	No additional information
<b>Sources of funding</b>	Supported by Trudell Medical International
<b>Inclusion criteria</b>	Aged ≥18 years  Physician diagnosed asthma treated in primary care  Receiving ICS delivered via pMDI and a spacer with or without LABA or SABA
<b>Exclusion criteria</b>	Exacerbation, emergency department or hospital admission due to asthma within 30 days
<b>Recruitment / selection of participants</b>	Recruited from four primary care centres
<b>Intervention(s)</b>	Participants allocated to the smart inhaler arm received usual care in addition to personalised inhalation education with detailed information about how and when they used their inhaled medication based on data from the smart spacer. Data was downloaded by nurses and discussed with the participant. Adherence interventions were generated using the TAI Toolkit.  The smart spacer used was a rechargeable device made up of the same components as a traditional spacer device. Visual feedback provided data on day-to-day inhaler use (day and time) as well as errors in inhaler use. A technique score out of 100 was generated that combined data from all inhalations and provided a visual summary for participant education.
<b>Population subgroups</b>	<b>Age</b>  ≥12 years  <b>Exacerbations</b>  Not reported

	<p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Not reported</p>
<b>Comparator</b>	Participants allocated to the usual care arm received usual care according to Dutch primary care asthma guidelines
<b>Number of participants</b>	<p>42 randomised</p> <p>21 allocated to smart inhalers</p> <p>21 allocated to usual care</p>
<b>Duration of follow-up</b>	8 weeks
<b>Indirectness</b>	None
<b>Additional comments</b>	Intention to treat

## Study arms

### Smart Inhaler (N = 21)

Personalised inhalation education with detailed information about how and when to use medication based on smart inhaler data

### Usual Care (N = 21)

Standard asthma care as per Dutch primary care guidelines

## Characteristics

### Arm-level characteristics

Characteristic	Smart Inhaler (N = 21)	Usual Care (N = 21)
% Female	n = 15 ; % = 71	n = 12 ; % = 57
Sample size		
<b>Mean age (SD)</b>	58.8 (18.1)	61.6 (12.3)
Mean (SD)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Lung function</b> (% of predicted) FEV1	86.2 (19)	79.4 (19.5)

Characteristic	Smart Inhaler (N = 21)	Usual Care (N = 21)
Mean (SD)		
<b>Asthma control</b> ACQ	1.9 (0.8)	2.1 (1)
Mean (SD)		

## Outcomes

### Study timepoints

- Baseline
- 8 week

### Continuous Outcomes

Outcome	Smart Inhaler, Baseline, N = 21	Smart Inhaler, 8 week, N = 21	Usual Care, Baseline, N = 21	Usual Care, 8 week, N = 21
<b>Adherence (%)</b> Change scores	NA (NA)	-5.1 (15.9)	NA (NA)	6.9 (18.2)
Mean (SD)				
<b>Inflammatory markers (FeNO)</b> (ppb) Change scores	NA (NA)	1.6 (11.3)	NA (NA)	-1.7 (10.4)
Mean (SD)				

Adherence - Polarity - Higher values are better

Inflammatory markers (FeNO) - Polarity - Lower values are better

**Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

**ContinuousOutcomes-Adherence-MeanSD-Smart Inhaler-Usual Care-t8**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**ContinuousOutcomes-Inflammatorymarkers(FeNO)-MeanSD-Smart Inhaler-Usual Care-t8**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**Foster, 2014**

**Bibliographic Reference**

Foster, J. M.; Usherwood, T.; Smith, L.; Sawyer, S. M.; Xuan, W.; Rand, C. S.; Reddel, H. K.; Inhaler reminders improve adherence with controller treatment in primary care patients with asthma; Journal of Allergy & Clinical Immunology; 2014; vol. 134 (no. 6); 1260-1268.e3

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	No additional information
<b>Study type</b>	Cluster randomised controlled trial  randomised GP practitioners not patients
<b>Study location</b>	Australia
<b>Study setting</b>	Primary care GP practice
<b>Study dates</b>	2010 - 2013
<b>Sources of funding</b>	Funding for this study was provided by the National Health and Medical Research Council of Australia (ID571053).
<b>Inclusion criteria</b>	Access to computer and e-mail  Not currently participating in another adherence-promoting study  Aged 14 to 65 years  Suboptimal asthma control (Asthma Control Test [ACT] score $\leq 19$ )  Prescribed twice-daily ICS/LABA for at least 1-month



<b>Exclusion criteria</b>	<p>Asthma exacerbation in the last month</p> <p>Use of budesonide/formoterol as maintenance and reliever therapy</p> <p>Major respiratory disease (eg, chronic obstructive pulmonary disease)</p> <p>Serious uncontrolled medical conditions</p> <p>Clinically important visual or auditory impairment</p> <p>Shift workers with a variable roster</p> <p>Pregnant or lactating women</p>
<b>Recruitment / selection of participants</b>	<p>GPs were recruited through 4 general practice organizational divisions in Sydney.</p>
<b>Intervention(s)</b>	<p><b>Inhaler reminders plus adherence feedback (IRF):</b></p> <p>Patients received twice-daily SmartTrack reminders for missed ICS/LABA doses. They could customize ringtones/ring times, cancel individual reminders, or switch reminders off completely. Each month, GPs received an automated e-mail to view a Web site graph of their patients' daily ICS/LABA use, the patient could log in to view his or her own graph at any time. GPs were asked to discuss the ICS/LABA-use graph with the patient at the study follow-up visit or at any subsequent appointments, at the GP's discretion.</p> <p>GPs received training on basic reminder device functions (5 min) and instructions on how to view Web-based medication feedback (5 min).</p> <p><b>Inhaler reminders plus adherence feedback and personalised adherence discussions (IRF + PAD):</b></p> <p>Patients received twice-daily SmartTrack reminders for missed ICS/LABA doses. They could customize ringtones/ring times,</p>

	<p>cancel individual reminders, or switch reminders off completely. Each month, GPs received an automated e-mail to view a Web site graph of their patients' daily ICS/LABA use, the patient could log in to view his or her own graph at any time. GPs were asked to discuss the ICS/LABA-use graph with the patient at the study follow-up visit or at any subsequent appointments, at the GP's discretion. GPs received training on basic reminder device functions (5 min) and instructions on how to view Web-based medication feedback (5 min). GPs asked patients to complete a short questionnaire about barriers to controller inhaler use. They were trained to carry out a personalized discussion about the patient's key barrier(s) to adherence and to help the patient set goals and goal-achievement strategies around an asthma issue that the patient wished to resolve, using patient-centred materials.</p> <p>All GPs in all groups received usual care training. This included advice on writing an asthma action plan (10 min), demonstrating and reviewing inhaler technique (10 min), and recent changes to asthma guidelines (15 min)</p> <p>*Two study arms containing adherence monitoring with/without personalised discussions combined for this review*</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p>≥12 years</p> <p><b>Exacerbations</b></p> <p>Not reported</p>

	<p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Suboptimal control</p>
<b>Comparator</b>	<p><b>Usual care (UC):</b></p> <p>All GPs received brief training on the delivery of active usual care. This was based around the “Asthma Cycle of Care,” an Australian government–incentivized primary care asthma management program that includes the provision of a written asthma action plan, inhaler technique review/education, and a follow-up appointment. In the study workshop, 10 minutes were allocated for training GPs in each of the action plans and inhaler technique. All GPs in all groups received usual care training. This included advice on writing an asthma action plan (10 min), demonstrating and reviewing inhaler technique (10 min), and recent changes to asthma guidelines (15 min).</p>
<b>Number of participants</b>	<p>Usual care: 15 GPs, 43 patients</p> <p>Monitoring without discussion: 15 GPs, 35 patients</p> <p>Monitoring with discussion: 13 GPs, 41 patients</p>
<b>Duration of follow-up</b>	6 months

<b>Indirectness</b>	None
<b>Additional comments</b>	Intention to treat

### Study arms

#### Usual care (N = 43)

Usual care delivered by GPs who had received recent training on asthma action planning, reviewing inhaler technique and current asthma guidelines

#### Smart inhalers (N = 76)

Smart inhaler with reminders and adherence feedback, either with or without personalised adherence discussions with the GP \*Two study arms combined for this review\*

### Characteristics

#### Arm-level characteristics

Characteristic	Usual care (N = 43)	Smart inhalers (N = 76)
% Female	n = 27 ; % = 63	n = 49 ; % = 64
Sample size		
Mean age (SD)	40 (14.1)	39.8 (16)
Mean (SD)		

Characteristic	Usual care (N = 43)	Smart inhalers (N = 76)
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Percentage current smokers</b>	n = 10 ; % = 23	n = 13 ; % = 17
Sample size		
<b>Percentage ex-smokers</b>	n = 10 ; % = 23	n = 24 ; % = 32
Sample size		
<b>Lung function</b> (% of predicted) FEV1	75.7 (22)	80.9 (17.6)
Mean (SD)		
<b>Asthma control</b> ACT	14.6 (3.4)	14.6 (3.9)
Mean (SD)		

## Outcomes

### Study timepoints

- Baseline
- 6 month

### Continuous outcomes

Outcome	Usual care, Baseline, N = 43	Usual care, 6 month, N = 41	Smart inhalers, Baseline, N = 76	Smart inhalers, 6 month, N = 76
<b>Asthma Control (Asthma Control Test)</b> scale range 5-25, final values	15 (1.67)	18.6 (3.33)	14.61 (4.53)	19.14 (3.48)
Mean (SD)				
<b>Adherence (Percentage)</b> final values	NR (NR)	46 (30.1)	NA (NA)	73.39 (30.34)
Mean (SD)				
<b>Quality of Life (Mini Asthma Quality of Life Questionnaire)</b> scale range 1-7, final values	4.6 (1.17)	5.4 (1.11)	4.59 (1.56)	5.45 (1.04)
Mean (SD)				
<b>Lung Function (FEV1) (Litres)</b> Final values	2.5 (0.84)	2.6 (0.67)	2.65 (1.01)	2.59 (0.42)
Mean (SD)				

Asthma Control (Asthma Control Test) - Polarity - Higher values are better

Adherence - Polarity - Higher values are better

Quality of Life (Mini Asthma Quality of Life Questionnaire) - Polarity - Higher values are better

Lung Function (FEV1) - Polarity - Higher values are better

### Dichotomous Outcomes

Outcome	Usual care, Baseline, N = 43	Usual care, 6 month, N = 43	Smart inhalers, Baseline, N = 76	Smart inhalers, 6 month, N = 76
---------	------------------------------	-----------------------------	----------------------------------	---------------------------------

Outcome	Usual care, Baseline, N = 43	Usual care, 6 month, N = 43	Smart inhalers, Baseline, N = 76	Smart inhalers, 6 month, N = 76
<b>Severe asthma exacerbations (requiring prednisone course)</b> final values	n = NA ; % = NA	n = 8 ; % = 18	n = NA ; % = NA	n = 7 ; % = 9
No of events				

Severe asthma exacerbations (requiring prednisone course) - Polarity - Lower values are better

#### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

##### Continuous outcomes - Asthma Control (Asthma Control Test) - Mean SD - Usual care - Smart inhalers - t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(Subjective outcome measure that was likely to be influenced by knowledge of the intervention received)</i>
Overall bias and Directness	Overall Directness	Directly applicable

##### Continuous outcomes - Adherence - Mean SD - Usual care - Smart inhalers - t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

**Continuousoutcomes-QualityofLife(MiniAsthmaQualityofLifeQuestionnaire)-MeanSD-Usual care-Smart inhalers-t6**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(Subjective outcome measure that was likely to be influenced by knowledge of the intervention received)</i>
Overall bias and Directness	Overall Directness	Directly applicable

**Continuousoutcomes-LungFunction(FEV1)-MeanSD-Usual care-Smart inhalers-t6**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**DichotomousOutcomes-Severeasthmaexacerbations(requiringprednisonecourse)-NoOfEvents-Usual care-Smart inhalers-t6**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low



Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

## Gupta, 2021

**Bibliographic Reference** Gupta, R. S.; Fierstein, J. L.; Boon, K. L.; Kanaley, M. K.; Bozen, A.; Kan, K.; Vojta, D.; Warren, C. M.; Sensor-Based Electronic Monitoring for Asthma: A Randomized Controlled Trial; Pediatrics; 2021; vol. 147 (no. 1); 01

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	Clinicaltrials.gov: NCT02994238
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	USA
<b>Study setting</b>	No additional information
<b>Study dates</b>	2016-2018

<b>Sources of funding</b>	Funded by UnitedHealth Group - lead author had received grants from UnitedHealth Group
<b>Inclusion criteria</b>	<p>Aged 4-17 years</p> <p>Moderate-to-severe persistent asthma</p> <p>Prescription for daily ICS for 1 year before enrollment</p> <p>One exacerbation requiring oral corticosteroids in the year before trial enrollment</p>
<b>Exclusion criteria</b>	<p>Not English-speaking</p> <p>Participating in other asthma research</p> <p>Had respiratory conditions that would interfere with the assessment of asthma symptoms (eg, chronic lung disease, cystic fibrosis, and tracheostomy)</p>
<b>Recruitment / selection of participants</b>	Participants were recruited from 5 medical clinics (3 primary care, 1 allergy, 1 pulmonary)
<b>Intervention(s)</b>	The intervention group received Propeller Health’s inhaler sensors for ICS and SABAs medications that allowed caregivers (through a mobile application) and clinicians involved in the trial (through a provider Web portal) to track the child’s SABA and daily ICS use, including the ICS–long-acting b-agonist Advair, throughout the study. The app also included features such as personalized insights, educational content, encouragement, surveys, and care team services. Sensors monitored inhaled medication use, capturing the date, time, and number of uses, and transmitted this information via Bluetooth to a paired smartphone and the provider portal in real-time. Providers from the 5 clinics received alerts via the Web portal to contact participants by telephone if they (1) missed ICS doses for 4 continuous days and/or (2) used >4 SABA doses per day. Participant-provider contact via phone call was initiated to help guide asthma management, which could include provider consultation, follow-up appointment scheduling, refilling medications, and/or addressing technical difficulties with the sensor.
<b>Population subgroups</b>	<p><b>Age</b></p> <p>Mixed, ~80% aged 4-11 years, ~20% aged 12-17 years</p>

	<p><b>Exacerbations</b></p> <p>At least one in the past year</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Not reported</p>
<b>Comparator</b>	Only information provided is that this is 'control'. Assumed usual care as no mention of sensor being given to all participants.
<b>Number of participants</b>	<p>252 randomised, all completed (total)</p> <p>127 randomised (smart inhaler)</p> <p>125 randomised (usual care)</p>
<b>Duration of follow-up</b>	12 months

<b>Indirectness</b>	No additional information
<b>Additional comments</b>	Intention to treat with mixed linear modeling

### Study arms

#### Smart inhaler (N = 125)

Smart inhaler attached to ICS and SABA inhalers that monitored usage and provided individual feedback through an app

#### Usual care (N = 127)

### Characteristics

#### Arm-level characteristics

Characteristic	Smart inhaler (N = 125)	Usual care (N = 127)
% Female	n = 38 ; % = 30.7	n = 47 ; % = 36.8
Sample size		
Mean age (SD) (years)	9.3 (3.2)	9.2 (3.5)
Mean (SD)		
Ethnicity	n = NA ; % = NA	n = NA ; % = NA
Sample size		

<b>Characteristic</b>	<b>Smart inhaler (N = 125)</b>	<b>Usual care (N = 127)</b>
<b>Non-hispanic white</b>	n = 30 ; % = 24	n = 30 ; % = 23.6
Sample size		
<b>Non-hispanic black</b>	n = 29 ; % = 23.2	n = 42 ; % = 33.1
Sample size		
<b>Hispanic</b>	n = 50 ; % = 40	n = 36 ; % = 28.4
Sample size		
<b>Other</b>	n = 9 ; % = 7.2	n = 10 ; % = 7.8
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		

## Outcomes

### Study timepoints

- Baseline
- 12 month

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 123	Smart inhaler, 12 month, N = 102	Usual care, Baseline, N = 126	Usual care, 12 month, N = 118
<b>Asthma Control (Asthma Control Test)</b> Scale range 5-25, final values  Mean (SD)	19.1 (3.4)	21.8 (4.5)	19.4 (3.4)	19.9 (4.5)

Asthma Control (Asthma Control Test) - Polarity - Higher values are better

### Dichotomous Outcomes

Outcome	Smart inhaler, Baseline, N = 103	Smart inhaler, 12 month, N = 103	Usual care, Baseline, N = 118	Usual care, 12 month, N = 118
<b>Severe asthma exacerbations</b> Courses of oral steroids prescribed due to asthma at emergency departments/hospitals, final values  No of events	n = NA ; % = NA	n = 69 ; % = 60.9	n = NA ; % = NA	n = 55 ; % = 50.9
<b>Hospital admissions</b> Due to an asthma attack, final values  No of events	n = NA ; % = NA	n = 25 ; % = 24.6	n = NA ; % = NA	n = 15 ; % = 12.3

Severe asthma exacerbations - Polarity - Lower values are better

Hospital admissions - Polarity - Lower values are better

Dichotomous data reported using available case analysis in supplementary material

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### ContinuousOutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Smart inhaler-Usual care-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

#### DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Smart inhaler-Usual care-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

#### DichotomousOutcomes-Hospitaladmissions(duetoanasthmaattack)-NoOfEvents-Smart inhaler-Usual care-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

## Moore, 2021

**Bibliographic** Moore, A.; Preece, A.; Sharma, R.; Heaney, L. G.; Costello, R. W.; Wise, R. A.; Ludwig-Sengpiel, A.; Mosnaim, G.; Rees, J.;

**Reference** Tomlinson, R.; Tal-Singer, R.; Stempel, D. A.; Barnes, N.; A randomised controlled trial of the effect of a connected inhaler system on medication adherence in uncontrolled asthmatic patients; European Respiratory Journal; 2021; vol. 57 (no. 6); 06

**Study details**

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	NCT03380429
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Europe and North America
<b>Study setting</b>	No additional information
<b>Study dates</b>	January 2018 - January 2019
<b>Sources of funding</b>	GlaxoSmithKline R&D (NCT03380429)
<b>Inclusion criteria</b>	Aged 18 years or older  Documented physician diagnosis of asthma as their primary respiratory disease  Asthma Control Test score <20 at screening visit 4



	<p>Non-smokers (never smoked or not smoking for &gt;6 months with &lt;10 pack years history)</p> <p>Male or Female participants: A female participant was eligible to participate if she was not pregnant, not breastfeeding, and at least one of the following conditions applied: (i) Not a woman of childbearing potential OR (ii) of childbearing potential who agreed to take adequate contraceptive precautions during the treatment period and for at least 5 days after the last dose of study treatment</p> <p>Able to read in a language supported by the smart phone app in their region</p> <p>Receiving therapy (fixed dose combination ICS/LABA) for 3 months, could not have changed dose in the month prior to 3 screening and was able to change to an equivalent dose of Relvar/Breo for the duration of the study. Other background asthma medication such as anti-leukotrienes and oral corticosteroids were permitted provided the dose had been stable for 1 month prior to screening</p> <p>Able to change to salbutamol/albuterol MDI rescue for the duration of the study and was judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits</p> <p>Owned a Android or IOS smart phone and a data package suitable for the installation and running of the App and sending and receiving data</p>
<b>Exclusion criteria</b>	<p>Known or suspected alcohol or drug abuse</p> <p>History of life-threatening asthma</p> <p>Lower respiratory tract infection within 7 days</p> <p>Concurrent diagnosis of COPD or other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases</p> <p>History of hypersensitivity/intolerance to any components of the study inhalers (e.g., lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy were also excluded</p> <p>Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or</p>

	<p>haematological abnormalities that were uncontrolled</p> <p>Ever received treatment with biological based therapy (e.g. omalizumab, mepolizumab) for asthma</p> <p>Received an investigational drug and/or medical device within 30 days of entry into the study, or within five drug half-lives of the investigational drug</p>
<b>Recruitment / selection of participants</b>	Recruited from 65 centres across Europe and North America
<b>Intervention(s)</b>	<p>Eligible participants received once daily fluticasone furoate/vilanterol via the ELLIPTA DPI and rescue medication such as salbutamol/ albuterol via the MDI during the run-in and treatment periods. Following a flexible 1-month run-in period (that could be repeated up to three times). At the screening and randomisation visits, participants received training on correct inhaler technique and how to attach the inhaler sensors. Adherence data were collected during the run-in but not fed-back to either the participants or the HCPs. Following randomisation, training on how to use the smartphone app was given to the participants. Data on maintenance and rescue use supplied to participants and healthcare providers (HCPs).</p> <p>After review of the participant's adherence to maintenance medication and rescue medication use, the HCP could e-mail or phone (utilising call or text options) the participant, or see them in clinic (at their discretion and as per their usual practice) to have an open, non-judgmental discussion concerning their adherence to treatment and/or rescue medication use. Over months 1–6 HCPs checked these data at least every 4 weeks.</p> <p>New medication was dispensed by a pharmacist or nurse not connected with the study. At these visits, which were always initiated by the participant as per the study protocol, the sensors were placed on the new inhalers and were synchronised to ensure proper functioning.</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p>≥12 years</p> <p><b>Exacerbations</b></p>

	Not reported
	<b>Exacerbators</b>
	Not reported
	<b>Adherence</b>
	Not reported
	<b>Asthma control</b>
	ACT score <20
<b>Comparator</b>	<p>Eligible participants received once daily fluticasone furoate/vilanterol via the ELLIPTA DPI and rescue medication such as salbutamol/ albuterol via the MDI during the run-in and treatment periods. Following a flexible 1-month run-in period (that could be repeated up to three times). At the screening and randomisation visits, participants received training on correct inhaler technique and how to attach the inhaler sensors. Adherence data were collected during the run-in but not fed-back to either the participants or the HCPs. No data from sensors supplied to participants or HCPs.</p> <p>New medication was dispensed by a pharmacist or nurse not connected with the study. At these visits, which were always initiated by the participant as per the study protocol, the sensors were placed on the new inhalers and were synchronised to ensure proper functioning.</p>
<b>Number of participants</b>	<p>Smart inhaler: 88 allocated,</p> <p>Device without feedback: 86 allocated,</p>
<b>Duration of follow-</b>	6 months

<b>up</b>	
<b>Indirectness</b>	None
<b>Additional comments</b>	Unclear

### Study arms

#### Smart inhaler (N = 88)

<b>Secondary publication of another included study- see primary study for details</b>	n/a
<b>Other publications associated with this study included in review</b>	n/a
<b>Study setting</b>	Unclear: centres
<b>Study dates</b>	Between January 2018 and January 2019
<b>Inclusion criteria</b>	1. Participants aged 18 years or older, at the time of signing the informed consent. 2. Participants with documented physician diagnosis of asthma as their primary respiratory disease. 3. Asthma Control Test (ACT) score <20 at screening visit 4. Non-smokers (never smoked or not smoking for >6 months with <10 pack years history (Pack years = [cigarettes per day smoked/20] x number of years smoked) 5. Male or Female participants: A female participant was eligible to participate if she was not pregnant, not breastfeeding, and at least one of the following conditions applied: (i) Not a woman of childbearing potential (WOCBP) OR (ii) A WOCBP who agreed to take adequate contraceptive precautions during the treatment period and for at least 5 days after the last dose of study treatment. 6. Capable of giving signed informed consent which included compliance with the requirements and restrictions listed in the consent form and in this protocol. 7. Participant understood and was willing, able, and likely to comply with study procedures and restrictions. 8. Participant must have been able to read in a language supported by the smart phone app in their region. 9. Participant must have been on

	<p>maintenance therapy (fixed dose combination ICS/LABA) for 3 months, could not have changed dose in the month prior to 3 screening and was able to change to an equivalent dose of Relvar/Breo for the duration of the study. Other background asthma medication such as anti-leukotrienes and oral corticosteroids were permitted provided the dose had been stable for 1 month prior to screening. 10. Participant must have been able to change to salbutamol/albuterol MDI rescue for the duration of the study and was judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits. 11. Participant must have had their own Android or IOS smart phone and a data package suitable for the installation and running of the App and sending and receiving data. Data used by the CIS is approximately 1MB per month as a maximum; this is less data than a 1-minute video streamed from YouTube (2MB). 12. Participants must have been willing and able to download the app on to their personal smart phone and keep it turned on for the duration of the study. This also required Bluetooth to be turned on for the duration of the study. Participants also had to turn on mobile data for the app for the duration of study (unless travelling and when extra data roaming costs could be incurred). Inclusion criteria for randomization 1. Asthma Control Test (ACT) score &lt;20 at randomization visit (V2, 3, or 4).</p>
<b>Exclusion criteria</b>	<p>1. Participants with known or suspected alcohol or drug abuse which in the opinion of the investigator could interfere with the participant's proper completion of the protocol requirements. 2. History of life-threatening asthma, defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 6 months 4 3. A lower respiratory tract infection within 7 days of the screening visit. 4. Concurrent diagnosis of COPD or other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases. 5. History of hypersensitivity/intolerance to any components of the study inhalers (e.g., lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicated participation were also excluded. 6. Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that were uncontrolled. Significant was defined as any disease that, in the opinion of the investigator, would have put the safety of the participant at risk through participation, or which would have affected the analysis if the disease/condition exacerbated during the study. 7. Patients who had ever received treatment with biological based therapy (e.g. omalizumab, mepolizumab) for asthma. 8. Participants who had received an investigational drug and/or medical device within 30 days of entry into the study (screening), or within five drug half-lives of the investigational drug, whichever was longer. 9. A participant was not eligible for this study if he/she was an immediate family member of the participating investigator, sub-investigator, study coordinator, employee of the participating investigator, or any family member of a Propeller Health employee.</p>
<b>Population subgroups</b>	<p>none</p>

<b>Number of participants</b>	Smart feedback: 88 No feedback: 86
<b>Indirectness</b>	none
<b>Additional comments</b>	

Arm 3 of trial: Data on maintenance and rescue use supplied to participants and HCPs

**Device without feedback (N = 86)**

Arm 5 of trial: No data from sensors supplied to participants or HCPs (control)

**Characteristics**

**Arm-level characteristics**

Characteristic	Smart inhaler (N = 88)	Device without feedback (N = 86)
% Female	n = 59 ; % = 67	n = 47 ; % = 55
Sample size		
<b>Mean age (SD)</b>	48 (15)	47 (16)
Mean (SD)		
<b>Ethnicity</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Asian %</b>	n = 4 ; % = 5	n = 5 ; % = 6

Characteristic	Smart inhaler (N = 88)	Device without feedback (N = 86)
Sample size		
<b>Black or African %</b>	n = 8 ; % = 9	n = 4 ; % = 5
Sample size		
<b>American white %</b>	n = 76 ; % = 86	n = 74 ; % = 86
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Asthma control ACT</b>	15 (3.07)	15.7 (2.72)
Mean (SD)		

## Outcomes

### Study timepoints

- Baseline
- 6 month

**Continuous Outcomes**

<b>Outcome</b>	<b>Smart inhaler, Baseline, N = 88</b>	<b>Smart inhaler, 6 month, N = 81</b>	<b>Device without feedback, Baseline, N = 86</b>	<b>Device without feedback, 6 month, N = 83</b>
<b>Adherence at 4-6 months (%)</b>	NA (NA)	78.2 (23.4)	NA (NA)	67 (31.6)
Mean (SD)				
<b>Rescue medication use (SABA-free days, months 4-6) (%)</b>	NA (NA)	9.8 (18.1)	NA (NA)	18.6 (52.8)
*These values were scaled from a combined monthly total to a one-month total, for easier comparison with baseline and subsequent months. For participants who completed the study, the combined months total rescue value was calculated by adding the monthly total rescue use values and dividing by the number of months in the period. For participants who did not complete the study, the combined months total rescue values were weighted according to the observed time the participant was in the monthly periods, final values				
Mean (SD)				
<b>Asthma Control (Asthma Control Test)</b>	15 (3.07)	20.2 (3.8)	15.7 (2.72)	19.9 (4)
scale range 5-25, final values				
Mean (SD)				

Rescue medication use (SABA-free days, months 4-6) - Polarity - Lower values are better

Asthma Control (Asthma Control Test) - Polarity - Higher values are better

**Dichotomous Outcomes**

<b>Outcome</b>	<b>Smart inhaler, Baseline, N = 88</b>	<b>Smart inhaler, 6 month, N = 88</b>	<b>Device without feedback, Baseline, N = 86</b>	<b>Device without feedback, 6 month, N = 86</b>
<b>Severe asthma exacerbations</b>	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 1



<b>Outcome</b>	<b>Smart inhaler, Baseline, N = 88</b>	<b>Smart inhaler, 6 month, N = 88</b>	<b>Device without feedback, Baseline, N = 86</b>	<b>Device without feedback, 6 month, N = 86</b>
Final values				
No of events				

Severe asthma exacerbations - Polarity - Lower values are better

#### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

##### Adherence

<b>Section</b>	<b>Question</b>	<b>Answer</b>
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

##### Rescue medication use (months 4-6)

<b>Section</b>	<b>Question</b>	<b>Answer</b>
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

### Asthma control (Asthma Control Questionnaire)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

### DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Smart inhaler-Device without feedback-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

## Morton, 2017

**Bibliographic Reference** Morton, R. W.; Elphick, H. E.; Rigby, A. S.; Daw, W. J.; King, D. A.; Smith, L. J.; Everard, M. L.; STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma; Thorax; 2017; vol. 72 (no. 4); 347-354

### Study details

<b>Secondary publication of another included study- see primary</b>	No additional information
---	---------------------------

<b>study for details</b>	
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	ClinicalTrials.gov: NCT02451709
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	UK
<b>Study setting</b>	No additional information
<b>Study dates</b>	October 2013 - August 2014
<b>Sources of funding</b>	Funded by the Sheffield Children's Hospital Charity
<b>Inclusion criteria</b>	<p>Taking regular inhaled steroids, with no change in their medication in the last month</p> <p>Asthma Control Questionnaire (ACQ) score of at least 1.5, indicating poorly controlled asthma</p> <p>BTS level 3 asthma</p>
<b>Exclusion criteria</b>	<p>Non-English speaking</p> <p>Had another significant chronic condition</p>
<b>Recruitment / selection of participants</b>	Participants attending hospital clinics in Sheffield or Rotherham were screened for eligibility
<b>Intervention(s)</b>	<p>Prior to randomisation, all participants had their inhaler technique checked by a qualified asthma nurse, and received a brief asthma education session, emphasising the importance of taking inhaled steroids regularly. All participants were reviewed in their routine asthma clinics 3-monthly and all treatment decisions were made by the clinical team. A member of the study team downloaded data from the EMD at each visit. Participants in the intervention group had a commercially available EMD attached to their regular inhaler. The 'Smartinhalers' and 'Smartturbos' (Adherium, Auckland, New Zealand) were used. Participants were told the devices monitored the date and time of all actuations. At clinic visits, the adherence data from the</p>

	<p>previous 3 months were uploaded to a website, which displays the data graphically. These data were reviewed with the patient and parent/carer. Open, non-judgemental discussions were held about the adherence rate, barriers identified and, if necessary, personalised strategies for improvement were devised. Devices were set to play reminder alarms (music or character noises), with different times agreed for weekdays and weekends. Alarms sounded for 5s, every minute for 15 min (or until actuation), if the inhaler had not been actuated within the previous 6 hours of the specified time. The devices were locked to prevent tampering. Times were reviewed each study visit and changed if necessary.</p>
<p><b>Population subgroups</b></p>	<p><b>Age</b></p> <p>Mixed: 6-16 years old (mean ~10.3 (2.9) years)</p> <p><b>Exacerbations</b></p> <p>Not reported</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>ACQ score &gt;1.5</p>

<b>Comparator</b>	Prior to randomisation, all participants had their inhaler technique checked by a qualified asthma nurse, and received a brief asthma education session, emphasising the importance of taking inhaled steroids regularly. All participants were reviewed in their routine asthma clinics 3 monthly and all treatment decisions were made by the clinical team. A member of the study team downloaded data from the EMD at each visit. Control participants had the same EMDs attached to their regular inhaler, they were also told the devices monitored how much the inhalers were taken, but that these data would not be reviewed. Participants were seen in their standard asthma clinic and the data were downloaded, but not reviewed. The alarms were disabled, and the devices locked.
<b>Number of participants</b>	90 randomised, 79 completed, 89 analysed (total) 47 randomised, 40 completed, 47 analysed (smart inhaler) 43 randomised, 39 completed, 42 analysed (device without feedback)
<b>Duration of follow-up</b>	12 months
<b>Indirectness</b>	No additional information
<b>Additional comments</b>	Intention to treat

### Study arms

#### Smart inhaler (N = 47)

Smart inhaler devices attached to participants regular inhaler with reminders and reviews with clinicians

#### Device without feedback (N = 42)

Smart inhaler devices attached to participants regular inhaler with no reminders or clinician reviews

## Characteristics

### Arm-level characteristics

Characteristic	Smart inhaler (N = 47)	Device without feedback (N = 42)
<b>% Female</b>	n = 19 ; % = 40	n = 20 ; % = 48
Sample size		
<b>Mean age (SD) (years)</b>	10.4 (2.9)	10.2 (2.9)
Mean (SD)		
<b>Ethnicity</b>	n = NA	n = NA ; % = NA
Sample size		
<b>White British</b>	n = 30 ; % = 64	n = 24 ; % = 57
Sample size		
<b>Black African</b>	n = 3 ; % = 6	n = 6 ; % = 14
Sample size		
<b>British Pakistani</b>	n = 11 ; % = 23	n = 11 ; % = 26
Sample size		
<b>British Indian</b>	n = 0 ; % = 0	n = 1 ; % = 2
Sample size		
<b>Asian (other)</b>	n = 1 ; % = 2	n = 0 ; % = 0
Sample size		

Characteristic	Smart inhaler (N = 47)	Device without feedback (N = 42)
<b>Black Caribbean</b>	n = 2 ; % = 4	n = 0 ; % = 0
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		

## Outcomes

### Study timepoints

- Baseline
- 12 month

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 47	Smart inhaler, 12 month, N = 47	Device without feedback, Baseline, N = 42	Device without feedback, 12 month, N = 42
<b>Asthma control (Asthma Control Questionnaire)</b> Scale range 0-6, change scores	NA (NA)	-1.14 (1.44)	NA (NA)	-0.95 (4.99)
Mean (SD)				
<b>Lung Function (% predicted FEV1)</b> (Percent of predicted ) Change scores	NA (NA)	3 (11.45)	NA (NA)	1.54 (14.13)

Outcome	Smart inhaler, Baseline, N = 47	Smart inhaler, 12 month, N = 47	Device without feedback, Baseline, N = 42	Device without feedback, 12 month, N = 42
Mean (SD)				

Asthma control (Asthma Control Questionnaire) - Polarity - Lower values are better

Lung Function (% predicted FEV1) - Polarity - Higher values are better

#### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

##### Continuous Outcomes - Asthma control (Asthma Control Questionnaire) - Mean SD - Smart inhaler - Device without feedback - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

##### Continuous Outcomes - Lung Function (% predicted FEV1) - Mean SD - Smart inhaler - Device without feedback - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable



## Mosnaim, 2021

**Bibliographic Reference** Mosnaim, G. S.; Stempel, D. A.; Gonzalez, C.; Adams, B.; BenIsrael-Olive, N.; Gondalia, R.; Kaye, L.; Shalowitz, M.; Szeffler, S.; The Impact of Patient Self-Monitoring Via Electronic Medication Monitor and Mobile App Plus Remote Clinician Feedback on Adherence to Inhaled Corticosteroids: A Randomized Controlled Trial; The Journal of Allergy & Clinical Immunology in Practice; 2021; vol. 9 (no. 4); 1586-1594

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	NCT03860519
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	USA
<b>Study setting</b>	No additional information
<b>Study dates</b>	April 2018 - April 2019
<b>Sources of funding</b>	Funded by Propeller Health
<b>Inclusion criteria</b>	Uncontrolled asthma

	<p>Aged 25-65 years</p> <p>Receiving daily ICS and a SABA inhaler</p>
<b>Exclusion criteria</b>	<p>Using inhalers not compatible with smart devices</p> <p>Other severe comorbidities that could interfere (e.g., severe psychiatric disorder)</p>
<b>Recruitment / selection of participants</b>	<p>Recruited through electronic medical records from allergist/immunologist or pulmonologist practices and mailing potential participants</p>
<b>Intervention(s)</b>	<p>Both treatment groups had electronic medication monitors attached to their ICS and SABA inhalers to track date and time of inhaler use. Data was collected via a smartphone app that was available for participants and clinicians in the intervention arm.</p> <p>Participants in the smart inhaler arm received audio-visual ICS medication reminders for missed or late doses, and had access to their ICS and SABA usage via the app. Participants were contacted by study staff if poor adherence was noted (4 consecutive days of ICS missed) or worsening control was apparent (Expert Panel Report 3 guideline criteria). An asthma nurse called participants at months 1, 2 and 3 to review current asthma status and provide feedback on ICS and SABA usage.</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p>≥12 years</p> <p><b>Exacerbations</b></p> <p>Mixed</p>

	<p><b>Exacerbators</b></p> <p>Mixed</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Control of asthma</b></p> <p>Uncontrolled</p>
<b>Comparator</b>	Participants allocated to the device without feedback arm received no audio-visual reminders, had no access to the app, received no monthly calls from the asthma nurse or received any interventions beyond standard care. Participants were aware that they were using a smart monitor and that their adherence and SABA usage was being monitored by the study team.
<b>Number of participants</b>	<p>100 randomised</p> <p>75 allocated to smart inhalers, 73 completed</p> <p>25 allocated to device without feedback, 24 completed</p>
<b>Duration of follow-up</b>	3 months
<b>Indirectness</b>	None
<b>Additional comments</b>	Intention to treat

## Study arms

### Smart Inhaler (N = 75)

Smart inhaler that gave audio-visual reminders, collected data and displayed it on an app for both the participant and the clinician

### Device without feedback (N = 25)

Smart inhaler that collected data, but did not display any data or provide reminders to either the participant or clinician

## Characteristics

### Arm-level characteristics

Characteristic	Smart Inhaler (N = 75)	Device without feedback (N = 25)
% Female	n = 60 ; % = 80	n = 20 ; % = 80
Sample size		
Mean age (SD)	49.3 (11.63)	46.06 (14.29)
Mean (SD)		
Ethnicity	n = NA ; % = NA	n = NA ; % = NA
Sample size		
Black/African American	n = 19 ; % = 25.3	n = 7 ; % = 28
Sample size		

Characteristic	Smart Inhaler (N = 75)	Device without feedback (N = 25)
<b>Asian</b>	n = 3 ; % = 4	n = 3 ; % = 12
Sample size		
<b>White/Caucasian</b>	n = 53 ; % = 70.7	n = 15 ; % = 60
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Exacerbations</b> Requiring OCS in past year	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>one</b>	n = 22 ; % = 29.3	n = 5 ; % = 20
Sample size		
<b>more than one</b>	n = 30 ; % = 40	n = 17 ; % = 68
Sample size		

## Outcomes

### Study timepoints

- Baseline
- 3 month

### Continuous Outcomes

Outcome	Smart Inhaler, Baseline, N = 75	Smart Inhaler, 3 month, N = 75	Device without feedback, Baseline, N = 25	Device without feedback, 3 month, N = 25
<b>Reliever/rescue medication use (SABA-free days) (%)</b> Change scores	NA (NA)	19 (30.93)	NA (NA)	6 (21.68)
Mean (SD)				
<b>Adherence (%)</b> Change scores	NA (NA)	-2 (22.09)	NA (NA)	-17 (22.96)
Mean (SD)				

Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Adherence - Polarity - Higher values are better

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### ContinuousOutcomes-Reliever/rescuemedicationuse(SABA-freedays)-MeanSD-Smart Inhaler-Device without feedback-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**ContinuousOutcomes-Adherence-MeanSD-Smart Inhaler-Device without feedback-t3**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**Mosnaim, 2023**

**Bibliographic Reference** Mosnaim, Giselle S; Hoyte, Flavia C L; Safiotti, Guilherme; Brown, Randall; Hill, Tanisha; Li, Thomas; Sagalovich, Katja; DePietro, Michael; Wechsler, Michael E; Effectiveness of a Maintenance and Reliever Digihaler System in Asthma: 24-week Randomized Study (CONNECT2).; The journal of allergy and clinical immunology. In practice; 2023

**Study details**

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	CONNECT2 (NCT04677959)
<b>Study type</b>	Randomised controlled trial (RCT)

<b>Study location</b>	USA
<b>Study setting</b>	Conducted across 44 sites - no information on care setting
<b>Study dates</b>	February 2021 - March 2022
<b>Sources of funding</b>	Funded by Teva Branded Pharmaceutical Products R&D
<b>Inclusion criteria</b>	<p>Aged ≥13 years</p> <p>Uncontrolled asthma (ACT score &lt;19)</p> <p>Receiving moderate-high dose ICS/LABA maintenance medication with SABA as-needed</p>
<b>Exclusion criteria</b>	<p>Current or previous (&gt;10 pack years) smoker</p> <p>Previous use of a digital inhaler</p> <p>Other clinically significant medical condition</p> <p>Hospitalised for severe asthma within 30 days</p> <p>COPD or COPD-asthma overlap</p> <p>Use of systemic corticosteroids within 30 days</p> <p>Use of biologic treatment within 90 days</p>
<b>Recruitment / selection of participants</b>	Method not reported
<b>Intervention(s)</b>	Participants allocated to the intervention received a fluticasone propionate/salmeterol combination inhaler containing a dose of either 113 or 232 mcg FP and 14 mcg salmeterol, taken as one inhalation twice per day. Albuterol was used as-needed at a dose of 90 mcg per inhalation, 1-2 inhalations every 4-6 hours. Other maintenance medications, except ICS and LABAs,



	<p>were added as deemed necessary by the study investigator.</p> <p>Participants were trained in how to use the ICS/LABA and SABA smart inhalers, and the connected app. Objective information on device usage was provided to participants through the app, giving data such as peak inspiratory flow and corresponding inhalation quality, as well as providing reminders to take maintenance medication. This objective information was also available to study sites, and healthcare professionals were encouraged to check the data at least once per week. Healthcare professionals used data from the smart inhalers to adjust asthma according to their clinical judgement, with no pre-specified criteria for adjustment.</p>
<p><b>Population subgroups</b></p>	<p><b>Age</b></p> <p>≥12 years</p> <p><b>Exacerbations</b></p> <p>Not reported</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p>

	<p><b>Asthma control</b></p> <p>Uncontrolled</p>
<b>Comparator</b>	<p>Participants allocated to the comparator received a fluticasone propionate/salmeterol combination inhaler containing a dose of either 113 or 232 mcg FP and 14 mcg salmeterol, taken as one inhalation twice per day. Albuterol was used as-needed at a dose of 90 mcg per inhalation, 1-2 inhalations every 4-6 hours. Other maintenance medications, except ICS and LABAs, were added as deemed necessary by the study investigator.</p> <p>Participants in the usual care arm received vouchers to purchase their required maintenance and reliever medications, but continued to receive care managed based on clinical judgement, following local practice and asthma management guidelines. No objective data was available.</p>
<b>Number of participants</b>	<p>427 randomised</p> <p>242 allocated to smart inhalers, 183 completed</p> <p>185 allocated to usual care, 174 completed</p>
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	None
<b>Additional comments</b>	Modified ITT including all randomised participants who received at least one dose of study medication with at least one post-baseline asthma control measurement

## Study arms

### Smart inhaler (N = 242)

Digital inhaler with objective feedback provided to participants and healthcare professionals

**Usual care (N = 185)**

**Characteristics**

**Arm-level characteristics**

<b>Characteristic</b>	<b>Smart inhaler (N = 242)</b>	<b>Usual care (N = 185)</b>
<b>% Female</b>	n = 177 ; % = 73	n = 116 ; % = 63
Sample size		
<b>Mean age (SD)</b>	46.9 (18.4)	46.7 (17.7)
Mean (SD)		
<b>American-Indian/Alaska Native</b>	n = 0 ; % = 0	n = 1 ; % = 1
Sample size		
<b>Asian</b>	n = 6 ; % = 2	n = 7 ; % = 4
Sample size		
<b>Black or African American</b>	n = 45 ; % = 19	n = 37 ; % = 20
Sample size		
<b>Native Hawaiian or other Pacific Islander</b>	n = 1 ; % = 1	n = 1 ; % = 1
Sample size		

Characteristic	Smart inhaler (N = 242)	Usual care (N = 185)
<b>Not reported</b>	n = 4 ; % = 2	n = 2 ; % = 1
Sample size		
<b>Other</b>	n = 1 ; % = 1	n = 1 ; % = 1
Sample size		
<b>White</b>	n = 185 ; % = 76	n = 136 ; % = 74
Sample size		
<b>Comorbidities</b>	NA	NA
Nominal		
<b>Asthma control ACT</b>	14.5 (2.9)	14.4 (3)
Mean (SD)		

## Outcomes

### Study timepoints

- Baseline
- 24 week

**Dichotomous Outcomes**

<b>Outcome</b>	<b>Smart inhaler, Baseline, N = 224</b>	<b>Smart inhaler, 24 week, N = 224</b>	<b>Usual care, Baseline, N = 185</b>	<b>Usual care, 24 week, N = 185</b>
<b>Severe asthma exacerbations</b> Final values No of events	n = NA ; % = NA	n = 9 ; % = 4	n = NA ; % = NA	n = 6 ; % = 3
<b>Hospital admissions</b> Final values No of events	n = NA ; % = NA	n = 4 ; % = 2	n = NA ; % = NA	n = 3 ; % = 2
<b>Adverse events</b> Final values No of events	n = NA ; % = NA	n = 77 ; % = 34	n = NA ; % = NA	n = 56 ; % = 30

Severe asthma exacerbations - Polarity - Lower values are better

Hospital admissions - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

**Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT****DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Smart inhaler-Usual care-t24**

<b>Section</b>	<b>Question</b>	<b>Answer</b>
Overall bias and Directness	Risk of bias judgement	High (No information on randomisation method used and smart inhaler data linked to cloud on 73% of days, and

Section	Question	Answer
		<i>checked by HCPs on 76% of weeks, indicating inadequate adherence with the intervention)</i>
Overall bias and Directness	Overall Directness	Directly applicable

#### DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Smart inhaler-Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High <i>(No information on randomisation method used and smart inhaler data linked to cloud on 73% of days, and checked by HCPs on 76% of weeks, indicating inadequate adherence with the intervention)</i>
Overall bias and Directness	Overall Directness	Directly applicable

#### DichotomousOutcomes-Adverseevents-NoOfEvents-Smart inhaler-Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High <i>(No information on randomisation method used and smart inhaler data linked to cloud on 73% of days, and checked by HCPs on 76% of weeks, indicating inadequate adherence with the intervention)</i>
Overall bias and Directness	Overall Directness	Directly applicable

## Otsuki, 2009

**Bibliographic Reference** Otsuki M; Eakin MN; Rand CS; Butz AM; Hsu VD; Zuckerman IH; Ogborn J; Bilderback A; Riekert KA; Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial.; Pediatrics; 2009; vol. 124 (no. 6)

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	Clinicaltrials.gov (NCT00233181)
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	USA
<b>Study setting</b>	No additional information
<b>Study dates</b>	2001 - 2003
<b>Sources of funding</b>	Supported by National Heart, Lung, and Blood Institute grant HL063333
<b>Inclusion criteria</b>	Aged 2-12 years of age  Physician-diagnosed asthma

	<p>2 ED visits or 1 hospitalization for asthma in the preceding year</p> <p>Resided in Baltimore city</p> <p>Prescribed an asthma controller medication</p>
<b>Exclusion criteria</b>	No additional information
<b>Recruitment / selection of participants</b>	Children with asthma were recruited from the pediatric ED by weekly review of discharge records
<b>Intervention(s)</b>	<p>Families who were randomly assigned to the AMF intervention received 5x 30-45 minute home visits by asthma educators at weeks 1, 2, 3, 4 and 8 after randomisation. Educators provided sessions based on 5 core components: review of prescribed asthma regimen and training in device technique, development of an asthma action plan, identification of barriers to accessing healthcare and problem solving to reduce them, discussion of beliefs and concerns about asthma and medication and provision of asthma educational materials. Additionally, participants received objective feedback of medication adherence via electronic medication monitors. Educators were trained to provide nonthreatening, supportive feedback on adherence to encourage a partnership with the family. Families were encouraged to set asthma control goals and weekly adherence goals with support from the educator who guided them based on the child's age and what to realistically expect. The importance of positive reinforcement, such as verbal praise and low-cost rewards, was discussed with the caregiver. When the child attained the adherence goal, the educator provided a small reward. When it was not achieved, the AE worked with the family to identify barriers and taught problem-solving skills. Families were taught to monitor adherence and asthma symptoms by using behavioural charts and symptom diaries. When possible, the educator highlighted the relationship between improvements in adherence and asthma outcomes.</p>
<b>Population subgroups</b>	<p><b>Age</b></p> <p>5-11 years</p> <p><b>Exacerbations</b></p> <p>At least one in the past year</p>



	<p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Not reported</p>
<b>Comparator</b>	Participants who were randomly assigned to the UC group received an asthma education booklet and resource guide that provided information about low-cost asthma care providers, social services, legal services, and other resources. Regardless of group assignment, participants were regularly encouraged to receive care from their primary care provider.
<b>Number of participants</b>	<p>166 randomised, 153 completed (total)</p> <p>83 randomised, 76 completed (smart inhaler)</p> <p>83 randomised, 77 completed (usual care)</p>
<b>Duration of follow-up</b>	18 months
<b>Indirectness</b>	No additional information
<b>Additional comments</b>	Intention to treat with full information maximum likelihood estimation

## Study arms

### Smart inhaler (N = 83)

Adherence monitoring with feedback from a healthcare professional following a structured asthma care plan

### Usual care (N = 83)

Asthma education booklet and resource guide

## Characteristics

### Arm-level characteristics

Characteristic	Smart inhaler (N = 83)	Usual care (N = 83)
% Female	n = 29 ; % = 35	n = 34 ; % = 41
Sample size		
Mean age (SD) (years)	6.54 (3.43)	7.35 (3.3)
Mean (SD)		
Ethnicity	n = 81 ; % = 98	n = 80 ; % = 96
Black		
Sample size		
Comorbidities	NR	NR
Nominal		

## Outcomes

### Study timepoints

- Baseline
- 18 month

### Dichotomous Outcomes

Outcome	Smart inhaler, Baseline, N = 83	Smart inhaler, 18 month, N = 76	Usual care, Baseline, N = 83	Usual care, 18 month, N = 77
<b>Hospital admissions (from month 12-18)</b> final values	n = NA ; % = NA	n = 12 ; % = 15.8	n = NA ; % = NA	n = 10 ; % = 13
No of events				

Hospital admissions (from month 12-18) - Polarity - Lower values are better

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 83	Smart inhaler, 18 month, N = 76	Usual care, Baseline, N = 83	Usual care, 18 month, N = 77
<b>Adherence (from month 12-18) (%)</b> Final values	83.16 (29.69)	87.33 (25.24)	84.87 (26.77)	94.96 (10.78)
Mean (SD)				

Adherence (from month 12-18) - Polarity - Higher values are better

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### Hospital admissions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

#### Continuous Outcomes-Adherence(from month 12-18)-MeanSD-Smart inhaler-Usual care-t18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

## Vasbinder, 2016

**Bibliographic Reference** Vasbinder, E. C.; Goossens, L. M.; Rutten-van Molken, M. P.; de Winter, B. C.; van Dijk, L.; Vulto, A. G.; Blankman, E. I.; Dahhan, N.; Veenstra-van Schie, M. T.; Versteegh, F. G.; Wolf, B. H.; Janssens, H. M.; van den Bemt, P. M.; e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC): a randomised controlled trial; European Respiratory Journal; 2016; vol. 48 (no. 3); 758-67

#### Study details

<b>Secondary</b>	No additional information
------------------	---------------------------

<b>publication of another included study- see primary study for details</b>	
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	Netherlands Trials Registry: NTR2583
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	The Netherlands
<b>Study setting</b>	No additional information
<b>Study dates</b>	January 2012 - December 2012
<b>Sources of funding</b>	Grants from The Netherlands Organization for Health Research and Development, GlaxoSmithKline and Evalan BV (providing inhalers at cost price)
<b>Inclusion criteria</b>	<p>4-11 years old</p> <p>Diagnosed with asthma for <math>\geq 6</math> months</p> <p>ICS use for <math>\geq 3</math> months</p> <p>Using a pMDI (fluticasone, fluticasone/salmeterol or beclomethasone)</p> <p>Parent/caregiver has a mobile phone</p>

<b>Exclusion criteria</b>	No additional information
<b>Recruitment / selection of participants</b>	Children were recruited from five outpatient clinics in the Netherlands. From the administration of each participating hospital, records were randomly selected of children aged 4–11 years who had doctor-diagnosed asthma for $\geq 6$ months and who had visited the outpatient clinic in the past 12 months.
<b>Intervention(s)</b>	All children, both in the intervention and in the control group, received a real time medication monitoring (RTMM) device for one year. ICS inhalations are registered by the RTMM-device which operates as follows: each time the pMDI is used, a data message containing patient-identification and time and date of administration is sent to the study database using the mobile telephone network. Only in the intervention group, time-tailored text message reminders are sent to the parents and, if the child has a mobile phone, also to the child, in order to warn that a dose is at risk of being forgotten. To ensure that text-messages are sent before the child goes to school (morning dose) or to bed (evening dose), a text-message is sent automatically if no ICS dose has been registered within 15 minutes after the individually planned time of inhalation.
<b>Population subgroups</b>	<p><b>Age</b></p> <p>5-11 years</p> <p><b>Exacerbations</b></p> <p>Not reported</p> <p><b>Exacerbators</b></p> <p>Not reported</p>

	<p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Mixed - ~37% had uncontrolled asthma at baseline</p>
<b>Comparator</b>	All children, both in the intervention and in the control group, received an real time medication monitoring (RTMM) device for one year. ICS inhalations are registered by the RTMM-device which operates as follows: each time the pMDI is used, a data message containing patient-identification and time and date of administration is sent to the study database using the mobile telephone network. No text reminders were given.
<b>Number of participants</b>	<p>219 randomised, 209 completed (total)</p> <p>108 randomised, 101 completed (smart inhaler)</p> <p>111 randomised, 108 completed (device without feedback)</p>
<b>Duration of follow-up</b>	12 months
<b>Indirectness</b>	None
<b>Additional comments</b>	Intention to treat with per protocol sensitivity analysis

## Study arms

### Smart inhaler (N = 101)

Smart inhaler device with SMS reminders

**Device without feedback (N = 108)**  
Smart inhaler device with no SMS reminders

**Characteristics**

**Arm-level characteristics**

<b>Characteristic</b>	<b>Smart inhaler (N = 101)</b>	<b>Device without feedback (N = 108)</b>
<b>% Female</b>	n = 42 ; % = 41.6	n = 36 ; % = 33.3
Sample size		
<b>Mean age (SD)</b>	7.8 (2.2)	7.7 (2.1)
Mean (SD)		
<b>Ethnicity</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Dutch</b>	n = 63 ; % = 62.4	n = 73 ; % = 67.6
Sample size		
<b>Non-Dutch</b>	n = 38 ; % = 37.6	n = 35 ; % = 32.4
Sample size		
<b>Asthma control cACT</b>	20.6 (4.4)	20.4 (3.9)
Mean (SD)		



## Outcomes

### Study timepoints

- Baseline
- 1 year

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 101	Smart inhaler, 1 year, N = 101	Device without feedback, Baseline, N = 108	Device without feedback, 1 year, N = 108
<b>Adherence (proportion of doses administered correctly)</b> (Percentage) final values	NA (NA to NA)	69.3 (65.5 to 73.4)	NA (NA to NA)	57.3 (52.8 to 61.7)
Mean (95% CI)				

Adherence (proportion of doses administered correctly) - Polarity - Higher values are better

### Contrast Outcomes

Outcome	Smart inhaler vs Device without feedback, Baseline, N2 = 108, N1 = 101	Smart inhaler vs Device without feedback, 1 year, N2 = 108, N1 = 101
<b>Quality of life (Paediatric Asthma Quality of Life Questionnaire)</b> Scale range: 1-7, final values	NA (NA to NA)	-0.06 (-0.41 to 0.15)
Mean (95% CI)		
<b>Asthma control (Childhood Asthma Control Test)</b> Scale range: 0-27, final values	NA (NA to NA)	-1.07 (-3.51 to 0.56)

Outcome	Smart inhaler vs Device without feedback, Baseline, N2 = 108, N1 = 101	Smart inhaler vs Device without feedback, 1 year, N2 = 108, N1 = 101
Mean (95% CI)		
Quality of life (Paediatric Asthma Quality of Life Questionnaire) - Polarity - Higher values are better		
Asthma control (Childhood Asthma Control Test) - Polarity - Higher values are better		

**Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

**Adherence (proportion of doses administered correctly)**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**Contrast Outcomes - Quality of life (Paediatric Asthma Quality of Life Questionnaire) - Mean Nine Five Percent CI - Smart inhaler - Device without feedback - t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**ContrastOutcomes-Asthmacontrol(ChildhoodAsthmaControlTest)-MeanNineFivePercentCI-Smart inhaler-Device without feedback-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

## Zairina, 2016

**Bibliographic Reference** Zairina, E.; Abramson, M. J.; McDonald, C. F.; Li, J.; Dharmasiri, T.; Stewart, K.; Walker, S. P.; Paul, E.; George, J.; Telehealth to improve asthma control in pregnancy: a randomized controlled trial; *Respirology* (Carlton, Vic.); 2016; vol. 21 (no. 5); 867-874

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information
<b>Other publications associated with this study included in review</b>	No additional information
<b>Trial name / registration number</b>	ACTRN 12613000800729
<b>Study type</b>	Randomised controlled trial (RCT)

<b>Study location</b>	Australia
<b>Study setting</b>	No additional information
<b>Study dates</b>	No additional information
<b>Sources of funding</b>	No additional information
<b>Inclusion criteria</b>	<p>Pregnant women with asthma aged <math>\geq 18</math> years</p> <p>&lt;20 weeks gestation</p> <p>Able to communicate in English</p> <p>Self-reported use of any inhaled bronchodilator or anti-inflammatory agent for asthma within the previous 12 months</p>
<b>Exclusion criteria</b>	<p>Under specialist care for difficult asthma</p> <p>Not in possession of a smart phone</p>
<b>Recruitment / selection of participants</b>	<p>Searched outpatient files and screened medical records of pregnant women with asthma scheduled to have a clinic visit on the following day by reviewing GP referral letters and/or notes from previous clinic consultations. At one of the sites, a letter of invitation including a brief explanation of the study together with their antenatal appointment letter was posted to all pregnant women newly registered with the antenatal clinic. Advertising posters were placed in the antenatal clinics of participating hospitals and on the websites of the National Asthma Council and the Asthma Foundation of Victoria. All interested participants were screened for eligibility by one of the researchers.</p>
<b>Intervention(s)</b>	<p>Women allocated to the intervention group were provided with a COPD-6 and a loaned smart mobile phone with the specifically designed Breathe-easy application installed on it. Each participant measured their lung function (FEV1 and FEV6) daily using the device and recorded asthma symptoms and asthma medication usage in the Breathe-easy application weekly. The daily lung function data were uploaded to a central server where the researchers, participants and their health professionals had secure access to the data. The participants' health professionals were contacted by one of the researchers if any medication changes or unscheduled asthma-related visits were needed. A written asthma work plan consistent with National guidelines was designed for each participant based on information obtained at baseline. The action plan contained instructions on which medications to take when feeling well, how to recognise worsening asthma, what to do when symptoms are getting worse and what to do in the event of an acute attack, including a first aid plan. Each participant received an automated weekly message regarding their asthma status based on the Breathe-easy algorithm. An automated weekly message of overall asthma control status was displayed as 'well-controlled' (score 0, green zone), or 'not well</p>

	controlled' (score 5, yellow zone and score 6, orange zone) to encourage participants to follow their agreed asthma action plan and/ or contact their health professional the next working day if there was no improvement. If the asthma control status was displayed as 'very poorly controlled' (score 7–15, red zone), patients were prompted to follow their agreed asthma action plan and contact their health professional on the same day.
<b>Population subgroups</b>	<p><b>Age</b></p> <p>≥12 years</p> <p><b>Exacerbations</b></p> <p>Not reported</p> <p><b>Exacerbators</b></p> <p>Not reported</p> <p><b>Adherence</b></p> <p>Not reported</p> <p><b>Asthma control</b></p> <p>Not reported</p>
<b>Comparator</b>	Women allocated to the control group received the usual medical care provided by the antenatal clinics and/or their health

	professionals. This included their regular weekly to monthly antenatal visits depending on their trimester and other complications. If during follow up, it was apparent that their asthma control deteriorated since prior assessment, the participant was advised by the research team to contact their health professional. The control group was also given a summarised version of the “Asthma and Pregnancy” brochure from the NAC which explained about asthma in pregnancy including first aid and emergency assistance number to use for any concerns regarding their asthma.
<b>Number of participants</b>	72 randomised, 67 completed (total) 36 randomised, 32 completed (smart inhaler) 36 randomised, 35 completed (usual care)
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	None
<b>Additional comments</b>	Available case analysis

### Study arms

#### Smart inhaler (N = 36)

Smart inhaler with application that showed daily lung function data

#### Usual care (N = 36)

## Characteristics

### Arm-level characteristics

Characteristic	Smart inhaler (N = 36)	Usual care (N = 36)
<b>% Female</b>	n = 36 ; % = 100	n = 36 ; % = 100
Sample size		
<b>Mean age (SD)</b>	31.1 (4.7)	31.8 (4.3)
Mean (SD)		
<b>Ethnicity</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Caucasian</b>	n = 30 ; % = 84	n = 30 ; % = 84
Sample size		
<b>Asian</b>	n = 3 ; % = 8	n = 3 ; % = 8
Sample size		
<b>Other</b>	n = 3 ; % = 8	n = 3 ; % = 8
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Lung function</b> (% of predicted) FEV1	89.1 (2.3)	91.6 (0.1)
Mean (SE)		

Characteristic	Smart inhaler (N = 36)	Usual care (N = 36)
<b>Asthma control ACQ</b>	1.1 (0.1)	1.2 (0.1)
Mean (SE)		

## Outcomes

### Study timepoints

- Baseline
- 6 month

### Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 36	Smart inhaler, 6 month, N = 33	Usual care, Baseline, N = 36	Usual care, 6 month, N = 36
<b>Asthma Control (Asthma Control Questionnaire-7)</b> scale range 0-6, change scores	NA (NA)	-0.3 (0.11)	NA (NA)	0.06 (0.1)
Mean (SE)				
<b>Quality of Life (Mini Asthma Quality of Life Questionnaire)</b> scale range 0-6, change scores	NA (NA)	0.51 (0.16)	NA (NA)	-0.22 (0.15)
Mean (SE)				
<b>Lung Function (% predicted FEV1)</b>	NA (NA)	4.27 (1.86)	NA (NA)	1.54 (1.72)



Outcome	Smart inhaler, Baseline, N = 36	Smart inhaler, 6 month, N = 33	Usual care, Baseline, N = 36	Usual care, 6 month, N = 36
change scores				
Mean (SE)				

Asthma Control (Asthma Control Questionnaire-7) - Polarity - Lower values are better

Quality of Life (Mini Asthma Quality of Life Questionnaire) - Polarity - Higher values are better

Lung Function (% predicted FEV1) - Polarity - Higher values are better

#### Dichotomous Outcomes

Outcome	Smart inhaler, Baseline, N =	Smart inhaler, 6 month, N = 36	Usual care, Baseline, N = 36	Usual care, 6 month, N = 36
Severe asthma exacerbations	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 2 ; % = 1
Final values				
No of events				

Severe asthma exacerbations - Polarity - Lower values are better

#### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

##### Asthma Control

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

### Quality of Life

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

### Lung Function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

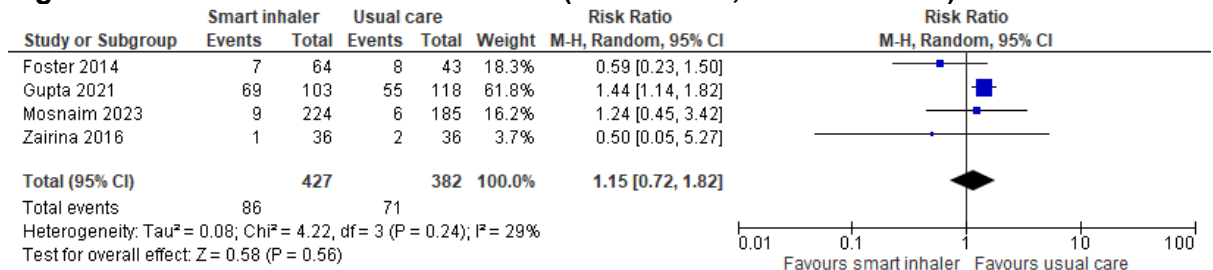
### DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Smart inhaler-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

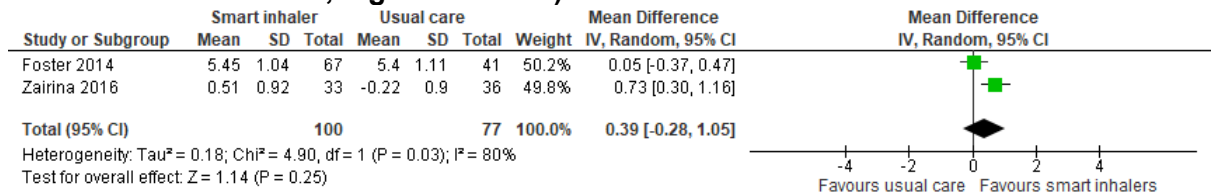
## Appendix E – Forest plots

### Smart inhalers vs usual care

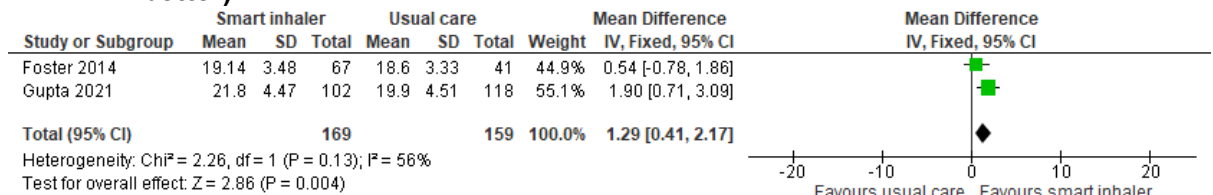
**Figure 2: Severe asthma exacerbations (final values, lower is better)**



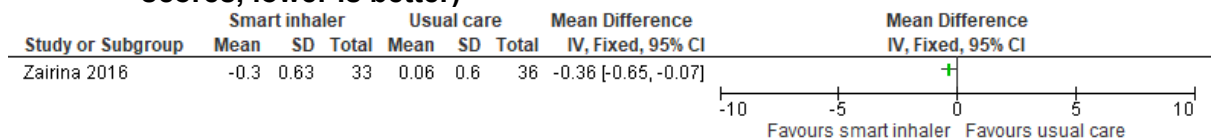
**Figure 3: Quality of life (mini asthma quality of life questionnaire, scale range 1-7, mixed values, higher is better)**



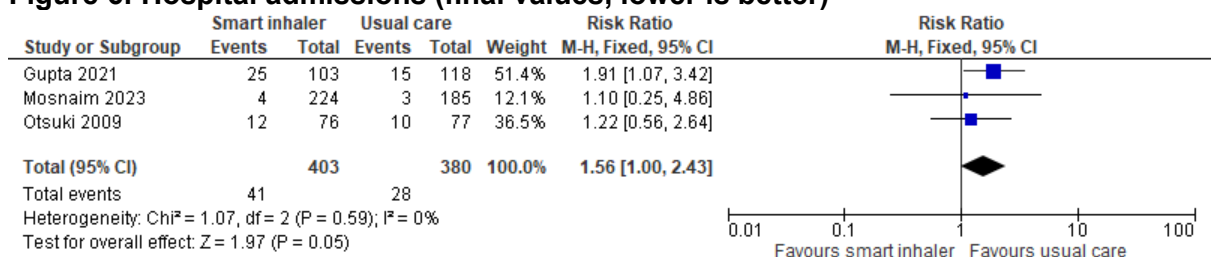
**Figure 4: Asthma control (asthma control test, scale range 0-25, final values, higher is better)**



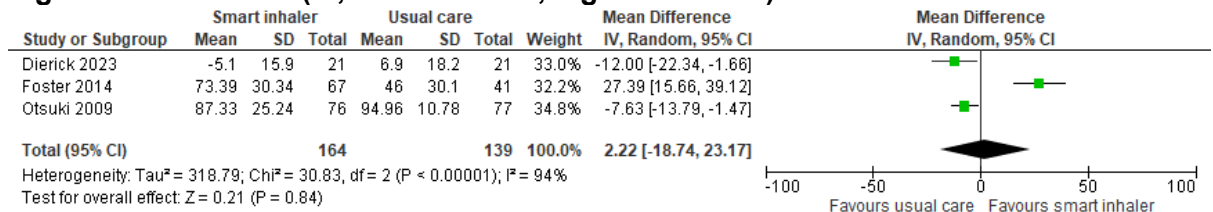
**Figure 5: Asthma control (asthma control questionnaire-7, scale range 0-6, change scores, lower is better)**



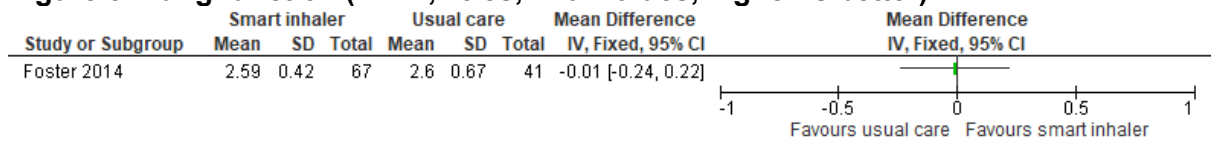
**Figure 6: Hospital admissions (final values, lower is better)**



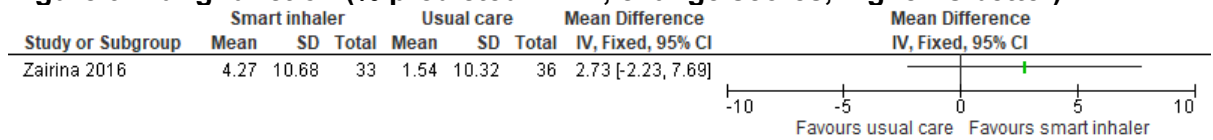
**Figure 7: Adherence (% , mixed values, higher is better)**



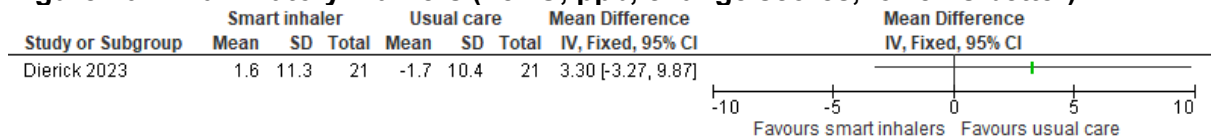
**Figure 8: Lung function (FEV1, litres, final values, higher is better)**



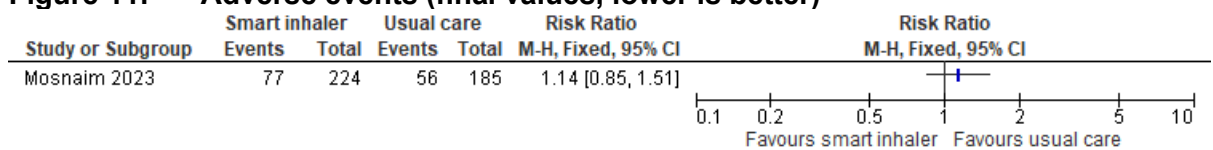
**Figure 9: Lung function (% predicted FEV1, change scores, higher is better)**



**Figure 10: Inflammatory markers (FeNO, ppb, change scores, lower is better)**

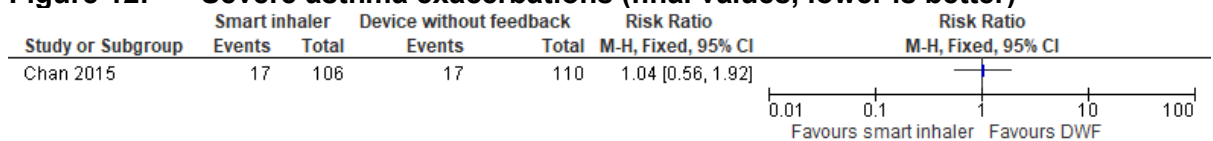


**Figure 11: Adverse events (final values, lower is better)**

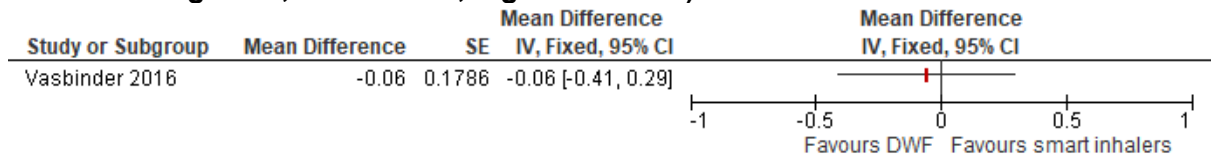


## Smart inhalers vs device without feedback

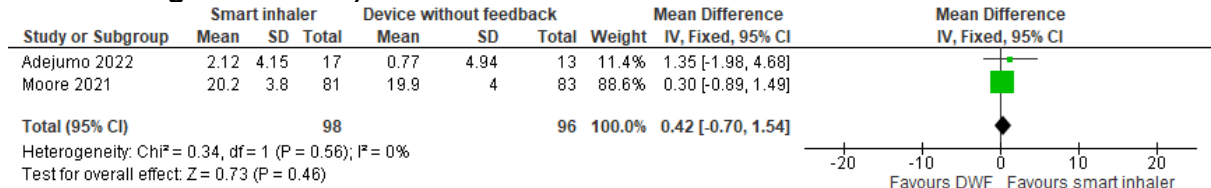
**Figure 12: Severe asthma exacerbations (final values, lower is better)**



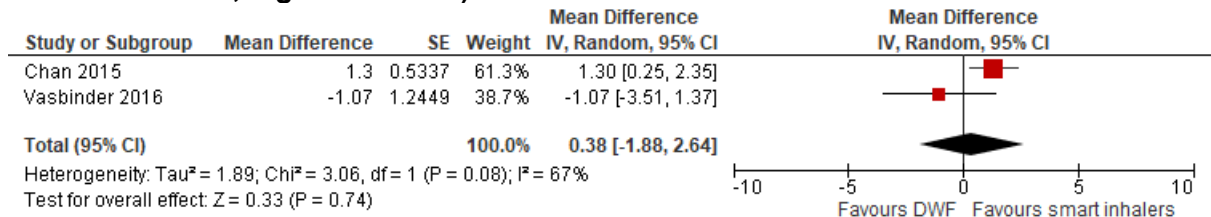
**Figure 13: Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, final values, higher is better)**



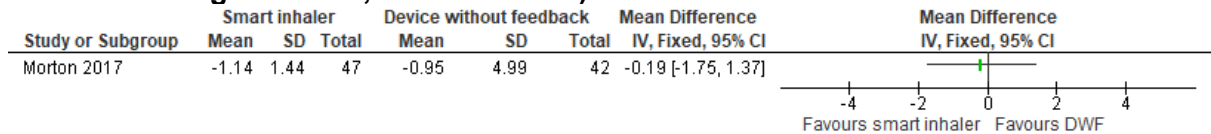
**Figure 14: Asthma control (Asthma Control Test, scale range 5-25, mixed values, higher is better)**



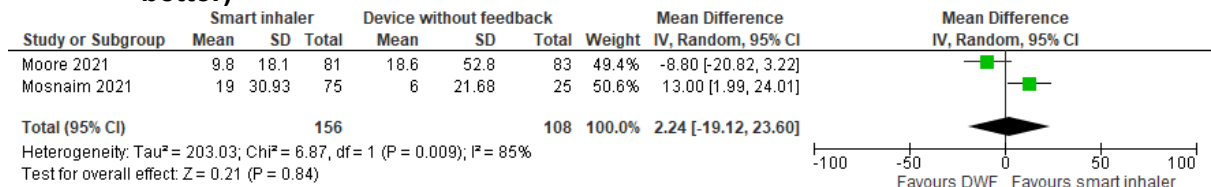
**Figure 15: Asthma control (Childhood Asthma Control Test, scale range 0-27, final values, higher is better)**



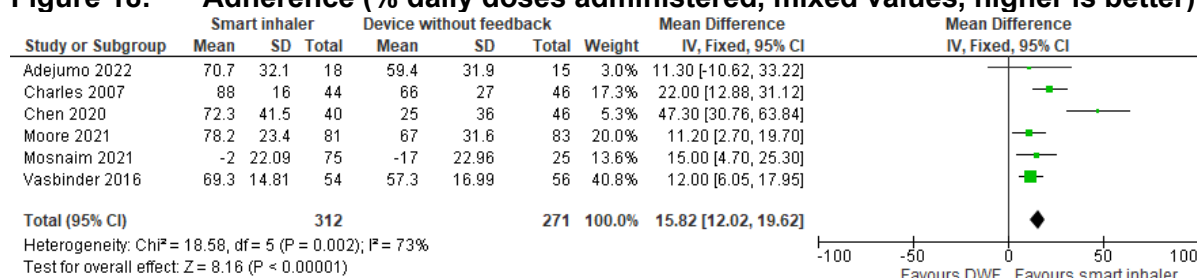
**Figure 16: Asthma control (Asthma Control Questionnaire, scale range 0-6, changes scores, lower is better)**



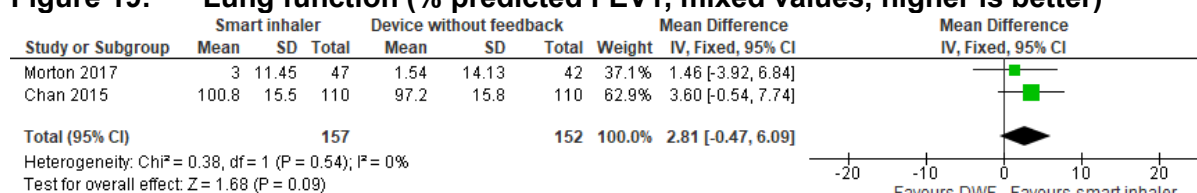
**Figure 17: Reliever medication use (SABA-free days, %, mixed values, higher is better)**



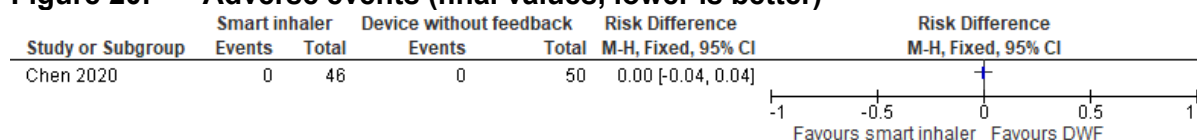
**Figure 18: Adherence (% daily doses administered, mixed values, higher is better)**



**Figure 19: Lung function (% predicted FEV1, mixed values, higher is better)**



**Figure 20: Adverse events (final values, lower is better)**



## Appendix F – GRADE tables

### Smart inhalers vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smart inhaler	usual care	Relative (95% CI)	Absolute (95% CI)		
<b>Severe asthma exacerbations (final values, lower is better)</b>												
4	randomised trials	not serious	not serious	not serious	very serious <sup>a</sup>	none	86/427 (20.1%)	71/382 (18.6%)	RR 1.15 (0.72 to 1.82)	28 more per 1,000 (from 52 fewer to 152 more)	⊕⊕○○ Low	CRITICAL
<b>Quality of life (mini asthma quality of life questionnaire, scale range 1-7, mixed values, higher is better)</b>												
2	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	100	77	-	MD 0.39 higher (0.28 lower to 1.05 higher)	⊕⊕⊕○ Moderate	CRITICAL
<b>Asthma control (asthma control test, scale range 0-25, final values, higher is better)</b>												
2	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	169	159	-	MD 1.29 higher (0.41 higher to 2.17 higher)	⊕⊕⊕○ Moderate	CRITICAL
<b>Asthma control (asthma control questionnaire-7, scale range 0-6, change scores, lower is better)</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	33	36	-	MD 0.36 lower (0.65 lower to 0.07 lower)	⊕⊕⊕○ Moderate	CRITICAL
<b>Hospital admissions (final values, lower is better)</b>												
3	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	41/403 (10.2%)	28/380 (7.4%)	RR 1.56 (1.00 to 2.43)	41 more per 1,000 (from 0 fewer to 105 more)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smart inhaler	usual care	Relative (95% CI)	Absolute (95% CI)		
<b>Adherence (% , mixed values, higher is better)</b>												
3	randomised trials	not serious	very serious <sup>a</sup>	not serious	very serious <sup>a</sup>	none	164	139	-	MD 2.22 higher (18.74 lower to 23.17 higher)	Very low	CRITICAL
<b>Lung function (FEV1, litres, final values, higher is better)</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	67	41	-	MD 0.01 lower (0.24 lower to 0.22 higher)	Moderate	CRITICAL
<b>Lung function (% predicted FEV1, change scores, higher is better)</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	33	36	-	MD 2.73 higher (2.23 lower to 7.69 higher)	Moderate	CRITICAL
<b>Inflammatory markers (FeNO, ppb, change scores, lower is better)</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	21	21	-	MD 3.3 higher (3.27 lower to 9.87 higher)	Moderate	CRITICAL
<b>Adverse events (final values, lower is better)</b>												
1	randomised trials	very serious <sup>d</sup>	not serious	not serious	very serious <sup>a</sup>	none	77/224 (34.4%)	56/185 (30.3%)	RR 1.14 (0.85 to 1.51)	42 more per 1,000 (from 45 fewer to 154 more)	Very low	CRITICAL

a. Downgraded by two increments due to the 95%CI overlapping both MIDs

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by two increments due to considerable heterogeneity indicating opposing benefits of the intervention (I<sup>2</sup>=94%) that cannot be explained by subgroup analysis or random effects model

d. Downgraded by two increments due to concerns arising from the randomisation method (method not reported) and deviations from the intended intervention (smart inhaler data uploaded on 73% of days, and checked by clinicians on 76% of weeks, indicating poor adherence)



## Smart inhalers vs device without feedback

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smart inhaler	device without feedback	Relative (95% CI)	Absolute (95% CI)		

### Severe asthma exacerbations (final values, lower is better)

1	randomised trials	not serious	not serious	not serious	very serious <sup>a</sup>	none	17/106 (16.0%)	17/110 (15.5%)	RR 1.04 (0.56 to 1.92)	6 more per 1,000 (from 68 fewer to 142 more)	⊕⊕○○ Low	CRITICAL
---	-------------------	-------------	-------------	-------------	---------------------------	------	----------------	----------------	---------------------------	---	-------------	----------

### Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, final values, higher is better)

1	randomised trials	not serious	not serious	not serious	not serious	none	101	108	-	MD 0.6 lower (0.41 lower to 0.29 higher)	⊕⊕⊕⊕ High	CRITICAL
---	-------------------	-------------	-------------	-------------	-------------	------	-----	-----	---	---	--------------	----------

### Asthma control (Asthma control test, scale range: 5-25, mixed values, higher is better)

2	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	98	96	-	MD 0.42 higher (0.7 lower to 1.54 higher)	⊕⊕○○ Low	CRITICAL
---	-------------------	----------------------	-------------	-------------	----------------------	------	----	----	---	--	-------------	----------

### Asthma control (Asthma control test, asthma control questionnaire, scale range 5-25, mixed values, higher is better)

2	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	99	98	-	MD 0.43 higher (0.68 lower to 1.55 higher)	⊕⊕○○ Low	CRITICAL
---	-------------------	----------------------	-------------	-------------	----------------------	------	----	----	---	---	-------------	----------

### Asthma control (childhood asthma control test, scale range 0-27, final values, higher is better)

2	randomised trials	not serious	very serious <sup>d</sup>	not serious	serious <sup>c</sup>	none	110	110	-	MD 0.38 higher (1.88 lower to 2.64 higher)	⊕○○○ Very low	CRITICAL
---	-------------------	-------------	---------------------------	-------------	----------------------	------	-----	-----	---	---	------------------	----------

### Asthma control (asthma control questionnaire, scale range 0-6, changes scores, lower is better)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smart inhaler	device without feedback	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious <sup>a</sup>	not serious	not serious	not serious	none	47	42	-	MD 0.19 lower (1.75 lower to 1.37 higher)	⊕⊕○○ Low	CRITICAL

Hospital admissions (asthma related emergency department visits, final values, lower is better)

1	randomised trials	not serious	not serious	not serious	very serious <sup>a</sup>	none	10/106 (9.4%)	13/110 (11.8%)	RR 0.80 (0.37 to 1.74)	24 fewer per 1,000 (from 74 fewer to 87 more)	⊕⊕○○ Low	CRITICAL
---	-------------------	-------------	-------------	-------------	---------------------------	------	---------------	----------------	---------------------------	--	-------------	----------

Reliever medication use (SABA-free days, %, mixed values, higher is better)

2	randomised trials	not serious	very serious <sup>f</sup>	not serious	very serious <sup>a</sup>	none	156	108	-	MD 2.24 higher (19.12 lower to 23.6 higher)	⊕○○○ Very low	CRITICAL
---	-------------------	-------------	---------------------------	-------------	---------------------------	------	-----	-----	---	--	------------------	----------

Adherence (% daily doses administered, mixed values, higher is better)

6	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none	312	271	-	MD 15.82 higher (12.02 higher to 19.62 higher)	⊕⊕⊕○ Moderate	CRITICAL
---	-------------------	-------------	-------------	-------------	----------------------	------	-----	-----	---	---	------------------	----------

Lung function (% predicted FEV1, mixed values, higher is better)

2	randomised trials	not serious	not serious	not serious	not serious	none	157	152	-	MD 2.81 higher (0.47 lower to 6.09 higher)	⊕⊕⊕⊕ High	CRITICAL
---	-------------------	-------------	-------------	-------------	-------------	------	-----	-----	---	---	--------------	----------

Adverse events (final values, lower is better)

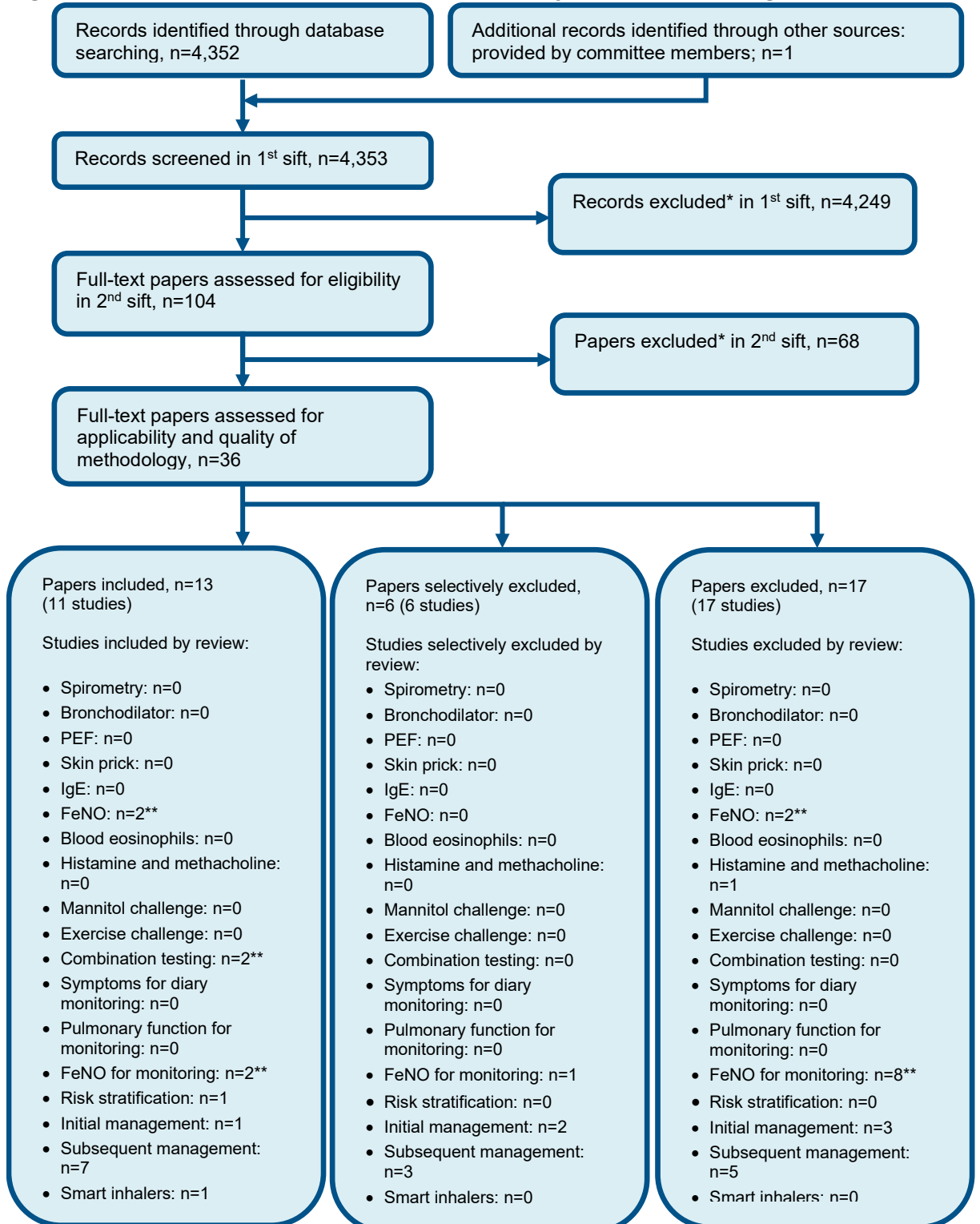
1	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	0/46 (0.0%)	0/50 (0.0%)	not estimable	0 fewer per 1,000 (from 40 fewer to 40 more)	⊕⊕⊕○ Moderate	CRITICAL
---	-------------------	-------------	-------------	-------------	----------------------	------	-------------	-------------	---------------	---	------------------	----------

a. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

- b. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)
- c. Downgraded by one increment due to the 95%CI overlapping one MID
- d. Downgraded by two increments due to substantial heterogeneity showing differing directions of benefit of the intervention ( $I^2=67\%$ ) that was not explained by a random effects model
- e. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence to interventions) and missing outcome data
- f. Downgraded by two increments due to considerable heterogeneity showing differing directions of benefit of the intervention ( $I^2=85\%$ ) that was not explained by a random effects model
- g. Downgraded by two increments due to the 95%CI overlapping both MIDs
- h. Downgraded by one increment due to zero events and inadequate sample size (70-350 participants= serious imprecision)

## Appendix G – Economic evidence study selection

**Figure 21: Flow chart of health economic study selection for the guideline**



\* Non-relevant population, intervention, comparison, design or setting; non-English language

\*\* Includes studies that are in multiple reviews

## Appendix H – Economic evidence tables

Study	Vasbinder 2016(Vasbinder et al., 2016)			
Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
<p><b>Economic analysis:</b> Cost-consequence analysis (health outcomes: adherence, asthma control, quality of life and exacerbations)</p> <p><b>Study design:</b> Within-trial analysis</p> <p><b>Approach to analysis:</b> Cost were calculated per 3-month using Dutch unit costs and resource use collected alongside the other clinical outcomes of e-MATIC trial(Vasbinder et al., 2016). A multilevel regression was used to calculate regression coefficients.</p> <p><b>Perspective:</b> Dutch healthcare perspective</p> <p><b>Follow-up</b> 12 months</p> <p><b>Discounting:</b> Costs: n/a ; Outcomes: n/a</p>	<p><b>Population:</b> Children aged 4-11 years who had doctor-diagnosed asthma for &gt;6 months and who had visited the outpatient clinic in the past 12 months. Other inclusion criteria were the use of ICS and having one caregiver with a mobile phone.</p> <p><b>Cohort settings:</b> Start age: 7.8 (5.6 to 10) Male: 66%</p> <p><b>Intervention 1:</b> Device without feedback (current practice)</p> <p><b>Intervention 2:</b> Smart inhaler using RTMM with SMS reminders on adherence</p>	<p><b>Total costs (mean per patient):</b> Intervention 1: £549 Intervention 2: £631 Incremental (2–1): £83 (95% CI: -£47 to £234; p=NR)</p> <p><b>Currency &amp; cost year:</b> 2014 Dutch Euros (presented here as 2014 UK pounds<sup>(a)</sup>)</p> <p><b>Cost components incorporated:</b> RTMM device, medication, hospital and GP visits</p>	<p><b>Adherence:</b> Intervention 1: 57.3% Intervention 2: 69.3% Incremental (2–1): 12% (95% CI: 9.3% to 20.7%; p=NR)</p> <p><b>Control c-ACT score:</b> Intervention 1: 22.17 Intervention 2: 21.10 Incremental (2–1): -1.07 (95% CI: -3.51 to 0.56; p=0.203)</p> <p><b>Quality of life PAQLQ score:</b> Intervention 1: 6.25 Intervention 2: 6.19 Incremental (2–1): -0.06 (95% CI: -0.41 to 0.15; p=0.659)</p> <p><b>Asthma exacerbations:</b> Intervention 1: 0.37</p>	<p>Smart inhaler using RTMM with SMS reminders improves adherence by 12% at an additional cost of £83.</p> <p><b>Analysis of uncertainty:</b> Uncertainty around the point estimates was addressed using bootstrapping, generating confidence intervals for incremental costs and health outcomes.</p>

			Intervention 2: 0.23 Incremental (2-1): -0.14 (95% CI: -0.61 to 0.25; p=0.432)	
--	--	--	---	--

**Data sources**

**Health outcomes:** Health outcomes were estimated from the e-MATIC trial (Vasbinder et al., 2016) using a multilevel regression model for repeated measures. **Quality-of-life weights:** n/a **Cost sources:** Standard unit costs from Dutch *Manual for Costing Studies* adjusted for inflation. Medication prices were based on the official list prices of drugs published on the internet, including VAT and increased by a standard prescription reimbursement for the pharmacists. The cost of RTMM devices were provided by the manufacturer.

**Comments**

**Source of funding:** The study was supported by a non-conditional grant from the Netherlands Organization for Health Research and Development. The study was also partially sponsored by the pharmaceutical company GlaxoSmithKline, which is the manufacturer of the RTMM devices. **Limitations:** Within-trial analysis with effectiveness data based on a single RCT. Baseline adherence was relatively high so the effectiveness of the intervention may have been underestimated. The majority of the population had good asthma control at baseline, suggesting they were already taking a critical ICS dose even with imperfect adherence. Hence, the overall improvement in adherence was likely unnecessary and incapable of causing any clinical improvement. C-ACT questionnaire is likely overestimating asthma control levels in children with poor asthma control or poor symptoms perception. **Other:**

**Overall applicability:**<sup>(b)</sup> Partially applicable      **Overall quality:**<sup>(c)</sup> Potentially serious limitations

Abbreviations: c-ACT = childhood asthma control test; ICS = inhaled corticosteroids; n/a = not available; NR= not reported; PAQLQ = paediatric asthma quality of life questionnaire; RCT = randomised controlled trial; RTMM = real-time medication monitoring; SMS = short message service.

(a) Converted using 2014 purchasing power parities(OECDPPP)(Organisation for Economic Co-operation and Development (OECD), 2012)

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

# 1 Appendix I – Excluded studies

## 2 Clinical studies

3 **Table 10: Studies excluded from the clinical review**

Study	Code [Reason]
<a href="#">Adejumo, I. and Shaw, D. E. (2018) Electronic monitoring devices as an intervention in Asthma: The story so far.</a> Current Respiratory Medicine Reviews 14(1): 5-22	- Systematic review used as source of primary studies
<a href="#">Agarwal, R., Khan, A., Aggarwal, A. N. et al. (2009) Is the SMART approach better than other treatment approaches for prevention of asthma exacerbations? A meta-analysis.</a> Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica fisiologica e malattie apparato respiratorio, Università di Napoli, Secondo ateneo 71(4): 161-9	- Systematic review used as source of primary studies
<a href="#">Ahonen, A.; Leinonen, M.; Ranki-Pesonen, M. (2000) Patient satisfaction with EASYHALER compared with other inhalation systems in the treatment of asthma: a meta-analysis.</a> Current Therapeutic Research 61(2): 61-73	- Systematic review used as source of primary studies
<a href="#">Almutairi, Mohammed; Marriott, John F; Mansur, Adel (2023) Effect of monitoring adherence to regular inhaled corticosteroid (ICS) alone or in combination with a long-acting beta2-agonist (LABA) using electronic methods on asthma outcomes: a narrative systematic review.</a> BMJ open 13(8): e074127	- Review article but not a systematic review
<a href="#">Apter, A. J., Wang, X., Bogen, D. K. et al. (2011) Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial.</a> Journal of Allergy & Clinical Immunology 128(3): 516-23.e1	- Comparator in study does not match that specified in this review protocol  <i>Study compared smart inhalers to an intensive asthma education program not considered to be representative of usual care</i>
<a href="#">Beasley, R., Harrison, T., Peterson, S. et al. (2022) Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients With Poorly Controlled Asthma: A Systematic Review and Meta-analysis.</a> JAMA network open 5(3): e220615	- Systematic review used as source of primary studies
<a href="#">Biblowitz, K.; Bellam, S.; Mosnaim, G. (2018) Improving Asthma Outcomes in the Digital Era: A</a>	- Systematic review used as source of primary studies

Study	Code [Reason]
<p><a href="#">Systematic Review</a>. <i>Pharmaceutical Medicine</i> 32(3): 173-187</p>	
<p>Burgess, S. W., Sly, P. D., Cooper, D. M. et al. (2007) Novel spacer device does not improve adherence in childhood asthma. <i>Pediatric Pulmonology</i> 42(8): 736-9</p>	<p>- Study does not contain an intervention relevant to this review protocol</p> <p><i>Study compares two spacer devices, not a smart inhaler against another method</i></p>
<p><a href="#">Burgess, S. W.; Sly, P. D.; Devadason, S. G. (2010) Providing feedback on adherence increases use of preventive medication by asthmatic children.</a> <i>Journal of Asthma</i> 47(2): 198-201</p>	<p>- Data not reported in an extractable format or a format that can be analysed</p>
<p><a href="#">Burkhart, P. V.; Dunbar-Jacob, J. M.; Rohay, J. M. (2001) Accuracy of children's self-reported adherence to treatment.</a> <i>Journal of Nursing Scholarship</i> 33(1): 27-32</p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">Chan, A. H. Y., Stewart, A. W., Harrison, J. et al. (2017) Electronic adherence monitoring device performance and patient acceptability: a randomized control trial.</a> <i>Expert Review of Medical Devices</i> 14(5): 401-411</p>	<p>- Duplicate reference</p>
<p><a href="#">Chapman, K. R., Barnes, N. C., Greening, A. P. et al. (2010) Single maintenance and reliever therapy (SMART) of asthma: A critical appraisal.</a> <i>Thorax</i> 65(8): 747-752</p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">Doshi, H., Hsia, B., Shahani, J. et al. (2021) Impact of Technology-Based Interventions on Patient-Reported Outcomes in Asthma: A Systematic Review.</a> <i>The Journal of Allergy &amp; Clinical Immunology in Practice</i> 9(6): 2336-2341</p>	<p>- Systematic review used as source of primary studies</p>
<p>Foster, J. M., Smith, L., Usherwood, T. et al. (2014) A cluster randomised controlled trial of inhaler reminders and/or personalised adherence discussions for improving adherence and asthma control demonstrates the effectiveness and acceptability of reminders in primary care settings (Abstract). <i>American journal of respiratory and critical care medicine</i> 189: a5368</p>	<p>- Conference abstract</p>
<p><a href="#">Garin, Noe, Zarate-Tamames, Borja, Gras-Martin, Laura et al. (2023) Clinical Impact of Electronic Monitoring Devices of Inhalers in Adults with Asthma or COPD: A Systematic Review and Meta-Analysis.</a> <i>Pharmaceuticals (Basel, Switzerland)</i> 16(3)</p>	<p>- Systematic review used as source of primary studies</p>



Study	Code [Reason]
<p><a href="#">Gregoriano, C., Dieterle, T., Durr, S. et al. (2017) Impact of an Electronic Monitoring Intervention to Improve Adherence to Inhaled Medication in Patients with Asthma and Chronic Obstructive Pulmonary Disease: Study Protocol for a Randomized Controlled Trial. JMIR Research Protocols 6(10): e204</a></p>	<p>- Study protocol</p>
<p><a href="#">Harris, B., Silberman, J., Sarlati, S. et al. (2023) DIGITAL ASTHMA SELF-MANAGEMENT TOOL REDUCED EMERGENCY VISIT RATES IN A MEDICAID POPULATION. Annals of Allergy, Asthma and Immunology 131(5supplement2): 230-s231</a></p>	<p>- Conference abstract</p>
<p><a href="#">Hollenbach, J., Simoneau, T., Sun, Y. et al. (2021) Design, methods, and baseline characteristics of a pilot, randomized, controlled trial of the effects of an electronic monitoring device on medication adherence in children with asthma. Contemporary Clinical Trials Communications 21: 100706</a></p>	<p>- Study protocol</p>
<p><a href="#">Hoyte, F., Mosnaim, G., Rogers, L. et al. (2022) Data from a reliever-based Digital System supports patient-clinician interactions in asthma. European Respiratory Journal 60(supplement66)</a></p>	<p>- Conference abstract</p>
<p><a href="#">Lee, J. R., Leo, S., Liao, S. et al. (2021) Electronic adherence monitoring devices for children with asthma: A systematic review and meta-analysis of randomised controlled trials. International Journal of Nursing Studies 122: 104037</a></p>	<p>- Systematic review used as source of primary studies</p>
<p><a href="#">Lipworth, B. J. and Wilson, A. M. (1998) Dose response to inhaled corticosteroids: Benefits and risks. Seminars in Respiratory and Critical Care Medicine 19(6): 625-646</a></p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">Louis, R., Joos, G., Michils, A. et al. (2009) A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. International Journal of Clinical Practice 63(10): 1479-88</a></p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">Malmberg, L. P., Everard, M. L., Haikarainen, J. et al. (2014) Evaluation of in vitro and in vivo flow rate dependency of budesonide/formoterol easyhaler®. Journal of aerosol medicine and pulmonary drug delivery 27(5): 329-340</a></p>	<p>- Study does not contain an intervention relevant to this review protocol</p>

Study	Code [Reason]
<p><a href="#">Merchant, R., Inamdar, R., Henderson, K. et al. (2018) Digital Health Intervention for Asthma: Patient-Reported Value and Usability. JMIR MHealth and UHealth 6(6): e133</a></p>	<p>- Data not reported in an extractable format or a format that can be analysed <i>Qualitative data only</i></p>
<p><a href="#">Michaelchuk, W., Quach, S., Benoit, A. et al. (2023) Systematic review and meta-analysis of interactive digital self-management interventions for chronic respiratory disease. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 7(supplement1): 35-36</a></p>	<p>- Conference abstract</p>
<p>Morton, R.; Everard, M.; Elphick, H. (2015) Randomised control trial to investigate whether electronic adherence monitoring with reminder alarms and feedback can improve clinical outcomes in childhood asthma. European respiratory journal 46</p>	<p>- Conference abstract</p>
<p>O'Connor, R. D., Nelson, H., Borker, R. et al. (2004) Cost effectiveness of fluticasone propionate plus salmeterol versus fluticasone propionate plus montelukast in the treatment of persistent asthma. Pharmacoeconomics 22(12): 815-25</p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">O'Dwyer, S., Greene, G., MacHale, E. et al. (2020) Personalized Biofeedback on Inhaler Adherence and Technique by Community Pharmacists: A Cluster Randomized Clinical Trial. The Journal of Allergy &amp; Clinical Immunology in Practice 8(2): 635-644</a></p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p>O'Sullivan, S. (1999) On the role of PGD2 metabolites as markers of mast cell activation in asthma. Acta Physiologica Scandinavica, Supplement 166(644): 1-74</p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">Onnis, C., Ferri, S., Van Der Palen, J. et al. (2022) Effect of pharmacy-supported digital medicine program on asthma control. European Respiratory Journal 60(supplement66)</a></p>	<p>- Conference abstract</p>
<p>Onyirimba, F., Apter, A., Reisine, S. et al. (2003) Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence. Annals of Allergy, Asthma, &amp; Immunology 90(4): 411-5</p>	<p>- Data not reported in an extractable format or a format that can be analysed <i>Adherence data only provided for 2 weeks, not full study duration</i></p>
<p>Ostrom, N. K., Raphael, G., Tillinghast, J. et al. (2018) Randomized trial to assess the efficacy</p>	<p>- Study does not contain an intervention relevant to this review protocol</p>

Study	Code [Reason]
and safety of beclomethasone dipropionate breath-Actuated inhaler in patients with asthma. Allergy and asthma proceedings 39(2): 117-126	
<a href="#">Patel, M., Pilcher, J., Hancox, R. J. et al. (2015) The use of beta2-agonist therapy before hospital attendance for severe asthma exacerbations: a post-hoc analysis.</a> NPJ Primary Care Respiratory Medicine 25: 14099	- Study does not contain an intervention relevant to this review protocol
<a href="#">Patel, M., Pilcher, J., Pritchard, A. et al. (2013) Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial.</a> The Lancet Respiratory Medicine 1(1): 32-42	- Population not relevant to this review protocol
<a href="#">Patel, M., Pilcher, J., Reddel, H. K. et al. (2013) Metrics of salbutamol use as predictors of future adverse outcomes in asthma.</a> Clinical & Experimental Allergy 43(10): 1144-51	- Study does not contain an intervention relevant to this review protocol
<a href="#">Patel, M., Pilcher, J., Reddel, H. K. et al. (2014) Predictors of severe exacerbations, poor asthma control, and beta-agonist overuse for patients with asthma.</a> The Journal of Allergy & Clinical Immunology in Practice 2(6): 751-8	- Study does not contain an intervention relevant to this review protocol
<a href="#">Pilcher, J., Shirtcliffe, P., Patel, M. et al. (2015) Three-month validation of a turbuhaler electronic monitoring device: implications for asthma clinical trial use.</a> BMJ open respiratory research 2(1): e000097	- Study design not relevant to this review protocol
<a href="#">Quirce, S., Barcina, C., Plaza, V. et al. (2011) A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in Spain.</a> Journal of Asthma 48(8): 839-47	- Study does not contain an intervention relevant to this review protocol
<a href="#">Ryan, D., Price, D., Musgrave, S. D. et al. (2012) Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial.</a> BMJ 344: e1756	- Study does not contain an intervention relevant to this review protocol
<a href="#">Saeed, H., Abdelrahim, M. E., Rabea, H. et al. (2020) Impact of Advanced Patient Counseling Using a Training Device and Smartphone Application on Asthma Control.</a> Respiratory Care 65(3): 326-332	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
<p><a href="#">Smith, Mary Jane, Gao, Zhiwei, Chafe, Roger et al. (2023) A mobile health intervention for improving the technique of inhaled medications among children with asthma: A pilot study.</a> Digital health 9: 20552076231216589</p>	<p>- Study design not relevant to this review protocol</p>
<p><a href="#">Sobieraj, D. M., Weeda, E. R., Nguyen, E. et al. (2018) Association of Inhaled Corticosteroids and Long-Acting <math>\beta</math>-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis.</a> JAMA 319(14): 1485-1496</p>	<p>- Systematic review used as source of primary studies</p>
<p><a href="#">Sportel, E. T., Oude Wolcherink, M. J., Van Der Palen, J. et al. (2020) Does immediate smart feedback on therapy adherence and inhalation technique improve asthma control in children with uncontrolled asthma? A study protocol of the IMAGINE i study.</a> Trials 21(1)</p>	<p>- Study protocol</p>
<p><a href="#">Sulaiman, I., Greene, G., MacHale, E. et al. (2018) A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma.</a> European Respiratory Journal 51(1): 01</p>	<p>- Study does not contain an intervention relevant to this review protocol</p>
<p><a href="#">Sulaiman, I., Mac Hale, E., Holmes, M. et al. (2016) A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma.</a> BMJ Open 6(1): e009350</p>	<p>- Study protocol</p>
<p><a href="#">van der Kamp, Mattienne R, Hengeveld, Vera S, Brusse-Keizer, Marjolein G J et al. (2023) eHealth Technologies for Monitoring Pediatric Asthma at Home: Scoping Review.</a> Journal of medical Internet research 25: e45896</p>	<p>- Review article but not a systematic review</p>
<p><a href="#">van der Kamp, Mattienne, Hengeveld, Vera, Willard, Nico et al. (2023) Remote Patient Monitoring and Teleconsultation to Improve Health Outcomes and Reduce Health Care Utilization of Pediatric Asthma (ALPACA Study): Protocol for a Randomized Controlled Effectiveness Trial.</a> JMIR research protocols 12: e45585</p>	<p>- Study protocol</p>
<p><a href="#">van der Palen, J., Thomas, M., Chrystyn, H. et al. (2016) A randomised open-label cross-over study of inhaler errors, preference and time to achieve</a></p>	<p>- Study does not contain an intervention relevant to this review protocol</p>

Study	Code [Reason]
<a href="#">correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices</a> . NPJ Primary Care Respiratory Medicine 26: 16079	
<a href="#">Vollmer, W. M., Feldstein, A., Smith, D. H. et al. (2011) Use of health information technology to improve medication adherence</a> . American Journal of Managed Care 17(12specno): SP79-87	- Study does not contain an intervention relevant to this review protocol
Völkl, K. P., Kroll, V. M., Wiesemann, H. G. et al. (1991) Clinical efficacy of two beta 2-sympathomimetics in different inhalers in children with asthma. Comparison of pirbuterol in a breath-actuated inhaler and salbutamol in a customary metered-dose inhaler. Arzneimittel-Forschung 41(5): 533-536	- Study does not contain an intervention relevant to this review protocol
<a href="#">Wang, G., Zhang, X., Zhang, H. P. et al. (2017) Corticosteroid plus <math>\beta</math>2-agonist in a single inhaler as reliever therapy in intermittent and mild asthma: a proof-of-concept systematic review and meta-analysis</a> . Respiratory research 18(1): 203	- Study does not contain an intervention relevant to this review protocol
<a href="#">Weatherall, M., Wijesinghe, M., Perrin, K. et al. (2010) Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy</a> . Thorax 65(1): 39-43	- Study does not contain an intervention relevant to this review protocol
<a href="#">Weinstein, A. G., Singh, A., Laurenceau, J. P. et al. (2019) A Pilot Study of the Effect of an Educational Web Application on Asthma Control and Medication Adherence</a> . The Journal of Allergy & Clinical Immunology in Practice 7(5): 1497-1506	- Study does not contain an intervention relevant to this review protocol  <i>Study compared an intense adherence improvement intervention, including smart inhaler monitoring, with usual care with no adherence improvement aspects included - intervention deemed to contain elements beyond smart inhalers</i>
<a href="#">Yawn, B. P., Rank, M. A., Cabana, M. D. et al. (2016) Adherence to Asthma Guidelines in Children, Tweens, and Adults in Primary Care Settings: A Practice-Based Network Assessment</a> . Mayo Clinic Proceedings 91(4): 411-21	- Review article but not a systematic review
<a href="#">Zairina, E., Abramson, M. J., McDonald, C. F. et al. (2015) Study protocol for a randomised controlled trial evaluating the efficacy of a telehealth program--management of asthma with supportive telehealth of respiratory function in pregnancy (MASTERY©)</a> . BMC Pulmonary Medicine 15: 84	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
<a href="#">Zhou, Y., Lu, Y., Zhu, H. et al. (2018) Short-term effect of a smart nebulizing device on adherence to inhaled corticosteroid therapy in Asthma Predictive Index-positive wheezing children. Patient preference &amp; adherence 12: 861-868</a>	- Study does not contain an intervention relevant to this review protocol

1  
2

## 1 Appendix J – Research recommendation

### J.2.1 Research recommendation

3 Can digital inhaler monitors cost effectively improve adherence to preventer inhalers in  
4 asthma, does this lead to improved asthma control and which patients would benefit most  
5 from this intervention?

### J.6.2 Why this is important

7 Asthma affects 5.4 million people in the UK and results in 75,000 emergency hospital  
8 admissions a year (1). Steroid ‘preventer’ inhalers reduce swelling and sensitivity in the lungs  
9 in asthma and using them every day lowers the risk of an asthma attack. Despite this, half of  
10 asthma patients do not take their inhaler as prescribed by their doctor. This is called non-  
11 adherence, and can cause poorly controlled asthma, damage to the lungs, time off work,  
12 hospitalisation, and death (2-4). Asthma patients may be non-adherent for several reasons,  
13 such as not knowing how to use the inhaler correctly, forgetting to take it, not thinking it helps  
14 or fear of side-effects. Adherence is one of the most important factors that we could improve  
15 to increase treatment effectiveness in asthma. Digital inhaler monitors or “smart” inhalers  
16 have existed for over 20 years but little is known about the feasibility and cost effectiveness  
17 of their use in clinical practice and which asthma patients would benefit from them most.

- 18 1. British Lung Foundation. Asthma Statistics. <https://statistics.blf.org.uk/asthma> <accessed 24th Nov  
19 2023>
- 20 2. Vrijens, B et al. What we mean when we talk about adherence in respiratory medicine. *J allergy clin  
21 immunol pract* 2016; 4 (5):802-812
- 22 3. Holmes J, Heaney LG. Measuring adherence to therapy in airways disease. *Breathe* 2021; 17 (2): 1-8
- 23 4. Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD)  
24 Confidential Enquiry report. London: RCP 2014

### J2.3 Rationale for research recommendation

26

Importance to ‘patients’ or the population	The current evidence is mixed and not sufficient to show which patients would benefit most from smart inhalers. Further research could help identify which patients to prioritise smart inhalers for and how it could improve their asthma control.
Relevance to NICE guidance	Digital or “smart” inhalers have been considered in this guideline and there is a lack of data on impact on adherence and asthma control and cost-effectiveness to adopt them into clinical practice.
Relevance to the NHS	Non-adherence in asthma can lead to increased unplanned secondary care, use of the provision of oral corticosteroids, and in some cases, death. This places significant clinical and financial pressure on the NHS. A better understanding of the health economic and clinical benefits of smart inhalers as well as sense of which patients would benefit most would enable the NHS to create guidance of how to implement this digital intervention effectively.
National priorities	High
Current evidence base	Minimal long-term data, minimal comparative data and minimal health economic data.

1

Equality considerations	Research should consider how to minimise digital exclusion.
-------------------------	---

## J.24 Modified PICO table

3

Population	Mild to moderate asthma <ul style="list-style-type: none"> <li>Stratified or inclusion/exclusion criteria to specify baseline adherence or asthma control: <ul style="list-style-type: none"> <li>Participants with poor adherence at baseline</li> <li>Participants with sub-optimal asthma control</li> </ul> </li> </ul>
Intervention	Digital inhaler or “smart” inhaler, patient smart phone app and healthcare professional data portal.
Comparator	Usual asthma care without digital monitoring
Outcome	Adherence to preventer inhaler (percentage of prescribed doses used) and asthma control (over a 12 month period: number of asthma exacerbations requiring steroids; healthcare utilisation; use of reliever inhaler; changes in FeNO; asthma control and quality of life scores)
Study design	Cross-sectional study design
Timeframe	12-24 months
Additional information	Study should include a health economic analysis and embedded process evaluation.

4

5