British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

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

[R] Evidence reviews for smart inhalers

BTS/NICE/SIGN collaborative guideline NG245

Evidence reviews underpinning recommendations 1.6.9 and recommendations for research in the guideline

November 2024

Final

Developed by BTS, NICE and SIGN

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Contents

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. It should be noted that 'Smart Inhalers' terminology has been used throughout this review, but is synonymous with digital inhalers, which we refer to in the recommendations.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	People with a diagnosis of asthma.
Intervention	Preventer/maintenance therapy given via smart inhaler devices with feedback.
Comparisons	Usual care Device without feedback

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months, latest timepoint if more than one))
	• Mortality (dichotomous outcome at ≥6 months)
	• Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months)
	• Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months)
	• Hospital admissions (dichotomous outcome at ≥6 months)
	• Reliever/rescue medication use (continuous outcome at ≥3 months)
	• 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
	• Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 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.
	• Adverse events:
	  ○ linear growth (continuous outcome at ≥1 year)
	  ○ pneumonia frequency (dichotomous outcome at ≥3 months)

	○ adrenal insufficiency (as defined by study, including short synacthen test and morning cortisol, dichotomous outcome at ≥3 months) ○ bone mineral density (continuous outcome at ≥6 months) • Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
Study design	• RCTs • Systematic reviews of RCTs • Published Cochrane reviews, NMAs and IPDs will be considered for inclusion.

1.1.3. Methods and process

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

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

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

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

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

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

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

1.1.4.2. Excluded studies

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

1.1.5. Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Adejumo 2022	**Smart inhaler with feedback** via	*n=36* Adults (18-65 years) on BTS	Adherence Asthma control	Additional analysis excluding dysfunctional smart

Study	Intervention and comparison	Population	Outcomes	Comments
(Adejumo et al., 2022)	mobile application and with clinician **Device without feedback**	step 2-5 treatment with an MDI and at least one exacerbation in the previous 12 months **Age** ≥12 years **Exacerbations** At least one in past 12 months **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Mixed UK		inhalers included in appendix D.
Chan 2015 (Chan et al., 2015)	**Smart inhaler with audio**-visual function enabled **Device without feedback** - audio-visual function disabled	*n=220* Children (6-15y) prescribed regular twice-daily ICS after admission to ED with an asthma exacerbation **Age** 5-11 years **Exacerbations** Recruited patients admitted to ED with an exacerbation **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Not reported New Zealand	Adherence Asthma control Lung function Reliever use Severe asthma exacerbations	
Charles 2007 (Charles et al., 2007)	**Smart inhaler with adherence** monitoring and audio-visual reminders **Device without feedback** - adherence	*n=110* People aged 12-65 years required to take regular fixed dose ICS with no exacerbation in the previous month	Adherence	

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
Moore 2021 (Moore et al., 2021)	**Smart inhaler with feedback** via smartphone and clinician review at least once per month **Device without feedback**	*n=174* People (≥18y) with poor asthma control (ACT <20) on ICS/LABA for >3 months with no changes to treatment in previous 3 months **Age** ≥12 years **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported **Asthma control** ACT score <20 Europe and North America	Adherence Rescue medication use Asthma control	Five arms in trial, arms 3 and 5 included as most relevant to this review
Morton 2017 (Morton et al., 2017)	**Smart inhaler with reminders and adherence monitoring** with data reviewed at review every three months **Device without feedback** - no reminders or clinician reviews	*n=90* People with poorly controlled asthma (ACQ >1.5) on regular ICS with no change in medication in the past month **Age** Mixed: 6-16 years old (mean ~10.3 (2.9) years) **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported **Asthma control** ACQ score >1.5 UK	Asthma control Lung function	
Mosnaim 2021 (Mosnaim et al., 2021)	**Smart inhaler with reminders and data collection displayed on an app** available to	*n=100* Adults aged 25-65 years with uncontrolled asthma and	Adherence Rescue medication use	

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

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

See Appendix D for full evidence tables

1.1.6. Summary of the effectiveness evidence

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		Comments
				Risk with usual care	Risk difference with Smart inhaler	
Severe asthma exacerbations (final values, lower is better)	809 (4 RCTs) Mean follow-up: 7.5 months	⊕⊕◯◯ Low[a]	**RR 1.15** (0.72 to 1.82)	186 per 1,000	**28 more per 1,000** (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[b]	-	The mean Mini Asthma Quality of Life Questionnaire score was **5.4**	MD **0.39 higher** (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[b]	-	The mean Asthma Control Test score was **19.25**	MD **1.29 higher** (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[b]	-	The mean change in Asthma Control Questionnaire score was **0.06**	MD **0.36 lower** (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[b]	**RR 1.56** (1.00 to 2.43)	74 per 1,000	**41 more per 1,000** (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[a,c]	-	The mean adherence was **70.48%**	MD **2.22 higher** (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[b]	-	The mean FEV1 was **2.6L**	MD **0.01 lower** (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[b]	-	The mean change in FEV1 was **1.54%**	MD **2.73 higher** (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[b]	-	The mean change in FeNO inflammatory markers was **-1.7 ppb**	MD **3.3 higher** (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[a,d]	**RR 1.14** (0.85 to 1.51)	303 per 1,000	**42 more** per 1,000 (45 fewer to 154 more No clinical difference	MID=100 per 1000 (clinical importance), 0.8-1.25 (imprecision)

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 (I2=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)

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		Comments
				Risk with device without feedback	Risk difference with Smart inhaler	
Severe asthma exacerbations (final values, lower is better)	216 (1 RCT) Follow-up: 6 months	⊕⊕◯◯ Low[a]	**RR 1.04** (0.56 to 1.92)	155 per 1,000	**6 more per 1,000** (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 **6.25**	MD **0.06 lower** (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[b,c]	-	The mean Asthma Control Test score was **19.9**	MD **0.42 higher** (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[c,d]	-	The mean Childhood Asthma Control Test score was **20.49**	MD **0.38 higher** (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		Comments
				Risk with device without feedback	Risk difference with Smart inhaler	
Asthma control (Asthma Control Questionnaire, scale range 0-6, changes scores, lower is better)	89 (1 RCT) Follow-up: 12 months	⊕⊕◯◯ Low[e]	-	The mean change in Asthma Control Questionnaire score was **-0.95**	MD **0.19 lower** (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[d,f,g]	-	The mean proportion of SABA-free days was **18.6%**	MD **2.24 higher** (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[c]	-	The mean adherence was **54.94%**	MD **15.82 higher** (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 **97.2%**	MD **2.81 higher** (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[h]	-	0 per 1,000	**0 fewer** per 1,000 (0 fewer to 0 fewer) No clinical difference	Imprecision assessed on sample size due to zero events

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 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 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)

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)

See Appendix F for full GRADE tables.

1.1.7. Economic evidence

1.1.7.1. Included studies

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

1.1.7.2. Excluded studies

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

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

1.1.8. Summary of included economic evidence

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[a]	Potentially serious limitations[b]	• Within-RCT analysis (e-MATIC trial(Vasbinder et al., 2016)) • Cost-consequence analysis • Population: Children aged 4-11 years with doctor-diagnosed asthma • Comparators: 1. Device without feedback (current practice) 2. Smart inhaler using RTMM with SMS reminders on adherence • Follow up: 12 months	2-1: £83[c]	• Adherence: 12% (2-1) • c-ACT score: -1.07 (2-1) • PAQLQ score: -0.06 (2-1) • Asthma exacerbations: -0.14 (2-1)	Uncertainty around the point estimates was addressed using bootstrapping, generating confidence intervals for incremental costs and health outcomes (see Evidence Table).

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

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

(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 underestimated. The majority of the population had good asthma control at baseline, suggesting they were already taking 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.

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

1.1.9. Economic model

No health economic model was undertaken for this question.

1.1.10. Unit costs

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

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)

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

1.1.11. Evidence statements

1.1.11.1 Economic

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

1.2. The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

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

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

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

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

1.2.2. The quality of the evidence

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

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

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

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

1.2.3. Benefits and harms

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

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

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

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

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

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

1.2.4. Cost effectiveness and resource use

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

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

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

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

Nevertheless, the committee acknowledged that smart inhalers may be beneficial in a population with poor adherence and poor asthma control, and may be cost-effective if targeted at selected groups, for example people with severe asthma who are at, or are approaching, the point at which biologic agents might be considered. As a result, the committee agreed to make a research recommendation to explore clinical and cost-effectiveness on specific groups of people who may benefit from improved adherence.

1.2.5. Other factors the committee took into account

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

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

1.2.6. Recommendations supported by this evidence review

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

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Appendices

Appendix A – Review protocols

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	The following databases (from 2011 onwards) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies

		Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
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	RCTs Systematic reviews of RCTs Published Cochrane reviews, NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded Non-randomised studies
11.	Context	Smart inhalers could improve adherence to medication.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months, latest timepoint if more than one) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • 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 • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 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.
		• Adverse events:
		  ○ linear growth (continuous outcome at ≥1 year)
		  ○ pneumonia frequency (dichotomous outcome at ≥3 months)
		  ○ adrenal insufficiency (as defined by study, including short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
		  ○ bone mineral density (continuous outcome at 6 months)
		• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments 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.

		Study investigators may be contacted for missing data where time and resources allow.
14.	Strategy for data synthesis	EndNote will be used for reference management, sifting, citations and bibliographies. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 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.
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:

		Age • <5 years • 5-11 years • ≥12 years Exacerbations • Frequent (2 or more per year) • Not frequent (including 1 per year) Exacerbators 2 (if heterogeneity not explained) • Less frequent (1 or more) • No exacerbations Adherence • Good >75% • Fair 50-75% • Poor <50% Control of asthma • Controlled • Uncontrolled	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative

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

		5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
24.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Qudsia Malik (Senior systematic reviewer) Clare Jones (Senior systematic reviewer) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager)
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

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 Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186	
28.	Other registration details	N/A	
29.	Reference/URL for published protocol	N/A	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	N/A	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	x	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Table 7: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • 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). • 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.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	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. 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) **Inclusion and exclusion criteria** • 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. • 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. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

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.

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/

41.	Meta-Analysis/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(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.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	29 and (39 or 50)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	conference:pt or (clinicaltrials or trialsearch):so
#5.	#3 not #4
#6.	MeSH descriptor: [Digital Technology] this term only
#7.	((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*) near/3 inhaler*):ti,ab,kw
#8.	((electric* or electronic*) near/4 (inhaler* or audio visual or audiovisual or device* or monitor* or adher*)):ti,ab,kw
#9.	((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*) near/3 (device* or track* or monitor* or adher*)):ti,ab,kw
#10.	(SmartTurbo* or SmartTouch or SmartInhaler or HeroTracker or CareTRx or Propeller system):ti,ab,kw
#11.	(or #6-#10)
#12.	#5 and #11

Epistemonikos search terms

1.	(title:((title:(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* OR electric* OR electronic* OR "audio visual" OR audiovisual OR SmartTurbo* OR SmartTouch OR SmartInhaler OR HeroTracker OR CareTRx OR Propeller) OR abstract:(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* OR electric* OR electronic* OR "audio visual" OR audiovisual OR SmartTurbo* OR SmartTouch OR SmartInhaler OR HeroTracker OR CareTRx OR Propeller)) AND (title:(inhaler*) OR abstract:(inhaler*))) OR abstract:((title:(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* OR electric* OR electronic* OR "audio visual" OR audiovisual OR SmartTurbo* OR SmartTouch OR SmartInhaler OR HeroTracker OR CareTRx OR Propeller) OR abstract:(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* OR electric* OR electronic* OR "audio

	visual" OR audiovisual OR SmartTurbo* OR SmartTouch OR SmartInhaler OR 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 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st 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 Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 Dec 2023	
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health	Inception - 29 Dec 2023	English language

Database	Dates searched	Search filters and limits applied
Technology Assessment (INAHTA)		

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

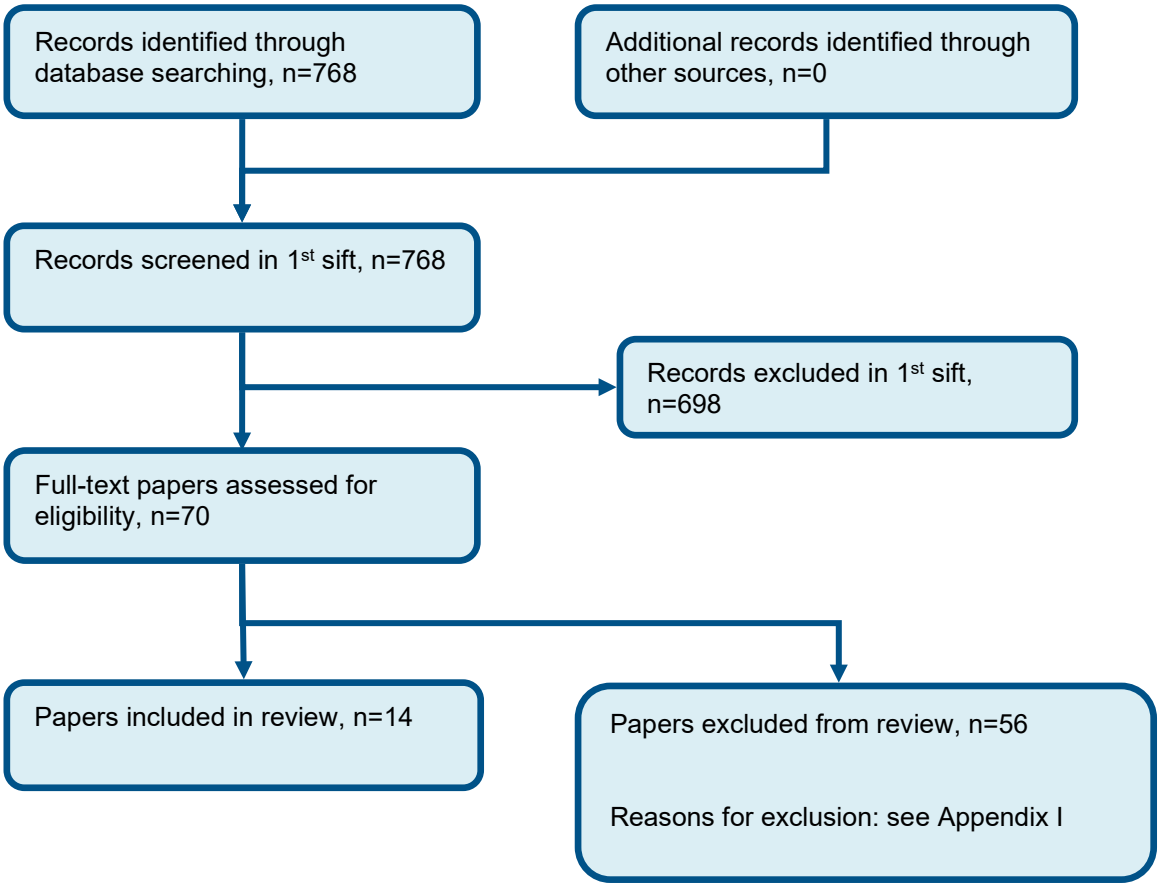
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

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

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

Inclusion criteria	Adults aged 18-65 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] Doctor's diagnosis of asthma for at least 12 months On BTS step 2-5 treatment via MDI Use of own internet-enabled and compatible mobile phone
Exclusion criteria	Diagnosis of COPD or onset of symptoms after the age of 40 in patients with ≥10 Pack Year History of smoking Other clinically significant coexisting respiratory disease e.g. fibrosis, bronchiectasis Patients on maintenance and reliever therapy ('SMART' or 'Fostair® MART')
Recruitment / selection of participants	No additional information
Intervention(s)	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
Population subgroups	**Age** ≥12 years

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

Additional comments	Complete case analysis

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 Sample size	n = 24 ; % = 67
Mean age (SD) Median (IQR)	48.3 (33.5 to 55.4)
Ethnicity Sample size	n = NR ; % = NR
Caucasian	n = 30 ; % = 83

Characteristic	Study (N = 36)
Sample size	
Comorbidities Nominal	NR

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

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
Adherence (Mean Percentage Daily) Final values Mean (SD)	NA (NA)	70.7 (32.1)	NA (NA)	59.4 (31.9)
Sensitivity Analysis 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) Mean (SD)	NA (NA)	74.4 (28.3)	NA (NA)	61.7 (34.8)

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
Asthma Control (Asthma Control Test) Scale range 5-25, change scores, Smart inhaler group n=17, feedback turned off group n=13 Mean (SD)	NA (NA)	2.12 (4.15)	NA (NA)	0.77 (4.94)

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 *(Outcome measured as % of prescribed doses actuated, not including timing of actuation)*

Adherence (Sensitivity Analysis)

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome measured as % of prescribed doses actuated, not including timing of actuation)*

Asthma Control

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

Secondary publication of another included study- see primary study for details	No additional information

Other publications associated with this study included in review	No additional information
Trial name / registration number	Australian New Zealand Clinical Trials Registry (ACTRN12613001353785)
Study type	Randomised controlled trial (RCT)
Study location	New Zealand
Study setting	No additional information
Study dates	May 2010 - February 2012
Sources of funding	Health Research Council of New Zealand and Cure Kids
Inclusion criteria	Aged 6-15 years Presenting with asthma to the regional ED in Auckland Physician-diagnosis of asthma and prescribed with a regular, twice-daily ICS
Exclusion criteria	Diagnosis with chronic lung disease other than asthma or congenital heart disease Resident outside of Auckland Diagnosis of a severe chronic medical condition leading to impaired immunity or increased morbidity
Recruitment / selection of participants	Children presenting at the ED diagnosed with asthma
Intervention(s)	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.
Population subgroups	**Age** 5-11 years **Exacerbations** Admitted to ED with an exacerbation **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Not reported
Comparator	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.
Number of participants	220 randomised, 113 completed (total) 110 randomised, 108 completed (smart inhaler) 110 randomised, 105 completed (feedback turned off)
Duration of follow-up	6 months
Indirectness	No additional information
Additional comments	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 Sample size	n = 55 ; % = 50	n = 52 ; % = 47
Mean age (SD) Mean (SD)	8.9 (2.5)	8.9 (2.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
European Sample size	n = 42 ; % = 38	n = 41 ; % = 37
Maori Sample size	n = 6 ; % = 5	n = 11 ; % = 10
Pacific Islander Sample size	n = 25 ; % = 23	n = 21 ; % = 19
Asian Sample size	n = 19 ; % = 17	n = 20 ; % = 18
Middle Eastern, Latin American or African Sample size	n = 2 ; % = 2	n = 6 ; % = 5

Characteristic	Smart inhaler (N = 110)	Device without feedback (N = 110)
Other Sample size	n = 16 ; % = 15	n = 11 ; % = 10
Comorbidities Nominal	NR	NR

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
Asthma control (Childhood Asthma Control Test) Scale range 0-27, final values Mean (SD)	18.8 (4.5)	22.7 (3.7)	18.8 (4.2)	21.4 (4.2)
Lung Function (% predicted FEV1) (Percentage) Final values	92.1 (17.5)	100.8 (15.5)	89.5 (17.8)	97.2 (15.8)

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
Mean (SD)				

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
Severe Asthma Exacerbations (% of participants with at least 1 parent-reported exacerbation) Final values (months 4-6), smart inhaler n=106, device without feedback n=102 No of events	n = NA ; % = NA	n = 17 ; % = 17	n = NA ; % = NA	n = 17 ; % = 16

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

Section	Question	Answer
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

Severe Asthma Exacerbations

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

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

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	New Zealand
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by a research grant from GSK
Inclusion criteria	12-65 years old Diagnosis of asthma Required to take regular ICS at a fixed dose No exacerbation in the previous month or run-in period Not pregnant or lactating

	Using contraception if of child-bearing potential
Exclusion criteria	Diagnosis of COPD use of LABA History of other clinically significant disease
Recruitment / selection of participants	Recruited from research volunteer databases, newspaper adverts and informal contacts
Intervention(s)	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. 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.
Population subgroups	**Age** ≥12 years **Exacerbations** Not reported **Exacerbators**

	Not reported **Adherence** Not reported **Asthma control** Not reported
Comparator	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.
Number of participants	110 randomised, 90 completed (total) 55 randomised, 44 completed (Smart inhaler) 55 randomised, 46 completed (device without feedback)
Duration of follow-up	24 weeks
Indirectness	No additional information
Additional comments	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)
% Female Sample size	n = 27 ; % = 51	n = 33 ; % = 60
Mean age (SD) Median (range) Median (IQR)	39 (13 to 65)	35 (15 to 64)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Smart inhaler (N = 55)	Device without feedback (N = 55)
Lung function (Litres per minute) PEF Mean (SD)	434 (99)	444 (128)

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
Adherence (% medication taken from week 12-24) (Percentage) Final values Mean (SD)	NA (NA)	88 (16)	NA (NA)	66 (27)

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

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

Trial name / registration number	Clinicaltrials.gov: NCT03277664
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	No additional information
Study dates	September 2016 - January 2017
Sources of funding	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
Inclusion criteria	Aged 6 months - 3 years Mild or moderate persistent asthma Taking regular ICS with no change in medication in the last month
Exclusion criteria	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) Not living in Shanghai
Recruitment / selection of participants	Participants with a diagnosis of asthma were recruited from a children's medical center and community hospitals
Intervention(s)	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.
Population subgroups	**Age** <5 years **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Not reported
Comparator	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.

Number of participants	96 randomised, 86 completed (total) 46 randomised, 40 completed (smart inhaler) 50 randomised, 46 completed (device without feedback)
Duration of follow-up	6 months
Indirectness	No additional information
Additional comments	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

Characteristic	Smart inhaler (N = 46)	Device without feedback (N = 50)
Sample size		
Mean age (SD) Months Mean (SD)	25.8 (9.6)	27.3 (12.2)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Eczema Sample size	n = 25 ; % = 54.3	n = 26 ; % = 52
Rhinitis Sample size	n = 24 ; % = 52.2	n = 31 ; % = 62
Food allergy Sample size	n = 14 ; % = 30.4	n = 16 ; % = 32

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
Adherence (Percentage) Mean device-monitored in final month of study Mean (SD)	NA (NA)	72.3 (41.5)	NA (NA)	25 (36)

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
Adverse events Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

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
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

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	OUTERSPACE (OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE) Netherlands Trial Registry: NL9637
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Primary care
Study dates	No additional information
Sources of funding	Supported by Trudell Medical International
Inclusion criteria	Aged ≥18 years Physician diagnosed asthma treated in primary care Receiving ICS delivered via pMDI and a spacer with or without LABA or SABA
Exclusion criteria	Exacerbation, emergency department or hospital admission due to asthma within 30 days
Recruitment / selection of participants	Recruited from four primary care centres
Intervention(s)	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.
Population subgroups	**Age** ≥12 years **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported

	Asthma control Not reported
Comparator	Participants allocated to the usual care arm received usual care according to Dutch primary care asthma guidelines
Number of participants	42 randomised 21 allocated to smart inhalers 21 allocated to usual care
Duration of follow-up	8 weeks
Indirectness	None
Additional comments	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 Sample size	n = 15 ; % = 71	n = 12 ; % = 57
Mean age (SD) Mean (SD)	58.8 (18.1)	61.6 (12.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	86.2 (19)	79.4 (19.5)
Asthma control ACQ Mean (SD)	1.9 (0.8)	2.1 (1)

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
Adherence (%) Change scores Mean (SD)	NA (NA)	-5.1 (15.9)	NA (NA)	6.9 (18.2)
Inflammatory markers (FeNO) (ppb) Change scores Mean (SD)	NA (NA)	1.6 (11.3)	NA (NA)	-1.7 (10.4)

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

Secondary publication of	No additional information

another included study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Cluster randomised controlled trial randomised GP practitioners not patients
Study location	Australia
Study setting	Primary care GP practice
Study dates	2010 - 2013
Sources of funding	Funding for this study was provided by the National Health and Medical Research Council of Australia (ID571053).
Inclusion criteria	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 ≤19) Prescribed twice-daily ICS/LABA for at least 1-month
Exclusion criteria	Asthma exacerbation in the last month Use of budesonide/formoterol as maintenance and reliever therapy

	Major respiratory disease (eg, chronic obstructive pulmonary disease) Serious uncontrolled medical conditions Clinically important visual or auditory impairment Shift workers with a variable roster Pregnant or lactating women
Recruitment / selection of participants	GPs were recruited through 4 general practice organizational divisions in Sydney.
Intervention(s)	**Inhaler reminders plus adherence feedback (IRF):** 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. GPs received training on basic reminder device functions (5 min) and instructions on how to view Web-based medication feedback (5 min). **Inhaler reminders plus adherence feedback and personalised adherence discussions (IRF + PAD):** 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. 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. 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) *Two study arms containing adherence monitoring with/without personalised discussions combined for this review*
Population subgroups	**Age** ≥12 years **Exacerbations** Not reported **Exacerbators**

	Not reported **Adherence** Not reported **Asthma control** Suboptimal control
Comparator	**Usual care (UC):** 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).
Number of participants	Usual care: 15 GPS, 43 patients Monitoring without discussion: 15 GPS, 35 patients Monitoring with discussion: 13 GPs, 41 patients
Duration of follow-up	6 months
Indirectness	None
Additional comments	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 Sample size	n = 27 ; % = 63	n = 49 ; % = 64
Mean age (SD) Mean (SD)	40 (14.1)	39.8 (16)
Ethnicity Nominal	NR	NR
Comorbidities	NR	NR

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

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
Asthma Control (Asthma Control Test) scale range 5-25, final values Mean (SD)	15 (1.67)	18.6 (3.33)	14.61 (4.53)	19.14 (3.48)
Adherence (Percentage) final values Mean (SD)	NR (NR)	46 (30.1)	NA (NA)	73.39 (30.34)
Quality of Life (Mini Asthma Quality of Life Questionnaire) scale range 1-7, final values Mean (SD)	4.6 (1.17)	5.4 (1.11)	4.59 (1.56)	5.45 (1.04)
Lung Function (FEV1) (Litres) Final values Mean (SD)	2.5 (0.84)	2.6 (0.67)	2.65 (1.01)	2.59 (0.42)

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
Severe asthma exacerbations (requiring prednisone course) final values No of events	n = NA ; % = NA	n = 8 ; % = 18	n = NA ; % = NA	n = 7 ; % = 9

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

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

Continuousoutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Usual care-Smart inhalers-t6

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

Continuousoutcomes-Adherence-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

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

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

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

Study location	USA
Study setting	No additional information
Study dates	2016-2018
Sources of funding	Funded by UnitedHealth Group - lead author had received grants from UnitedHealth Group
Inclusion criteria	Aged 4-17 years Moderate-to-severe persistent asthma Prescription for daily ICS for 1 year before enrollment One exacerbation requiring oral corticosteroids in the year before trial enrollment
Exclusion criteria	Not English-speaking Participating in other asthma research Had respiratory conditions that would interfere with the assessment of asthma symptoms (eg, chronic lung disease, cystic fibrosis, and tracheostomy)
Recruitment / selection of participants	Participants were recruited from 5 medical clinics (3 primary care, 1 allergy, 1 pulmonary)
Intervention(s)	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.

Population subgroups	**Age** Mixed, ~80% aged 4-11 years, ~20% aged 12-17 years **Exacerbations** At least one in the past year **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Not reported
Comparator	Only information provided is that this is 'control'. Assumed usual care as no mention of sensor being given to all participants.
Number of participants	252 randomised, all completed (total)

	127 randomised (smart inhaler) 125 randomised (usual care)
Duration of follow-up	12 months
Indirectness	No additional information
Additional comments	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 Sample size	n = 38 ; % = 30.7	n = 47 ; % = 36.8
Mean age (SD) (years)	9.3 (3.2)	9.2 (3.5)

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

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
Asthma Control (Asthma Control Test) 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
Severe asthma exacerbations 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
Hospital admissions 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 Reference	Moore, A.; Preece, A.; Sharma, R.; Heaney, L. G.; Costello, R. W.; Wise, R. A.; Ludwig-Sengpiel, A.; Mosnaim, G.; Rees, J.; 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

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT03380429
Study type	Randomised controlled trial (RCT)
Study location	Europe and North America
Study setting	No additional information
Study dates	January 2018 - January 2019
Sources of funding	GlaxoSmithKline R&D (NCT03380429)
Inclusion criteria	Aged 18 years or older

	Documented physician diagnosis of asthma as their primary respiratory disease Asthma Control Test score <20 at screening visit 4 Non-smokers (never smoked or not smoking for >6 months with <10 pack years history 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 Able to read in a language supported by the smart phone app in their region 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 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 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
Exclusion criteria	Known or suspected alcohol or drug abuse History of life-threatening asthma Lower respiratory tract infection within 7 days 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

	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 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 Ever received treatment with biological based therapy (e.g. omalizumab, mepolizumab) for asthma 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
Recruitment / selection of participants	Recruited from 65 centres across Europe and North America
Intervention(s)	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). 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. 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.
Population subgroups	**Age**

	≥12 years **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported **Asthma control** ACT score <20
Comparator	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.

	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.
Number of participants	Smart inhaler: 88 allocated, Device without feedback: 86 allocated,
Duration of follow-up	6 months
Indirectness	None
Additional comments	Unclear

Study arms

Smart inhaler (N = 88)

Secondary publication of another included study- see primary study for details	n/a
Other publications associated with this study included in review	n/a
Study setting	Unclear: centres
Study dates	Between January 2018 and January 2019
Inclusion criteria	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 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 <20 at randomization visit (V2, 3, or 4).
Exclusion criteria	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.
Population subgroups	none
Number of participants	Smart feedback: 88 No feedback: 86
Indirectness	none
Additional comments	

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 Sample size	n = 59 ; % = 67	n = 47 ; % = 55
Mean age (SD)	48 (15)	47 (16)

Characteristic	Smart inhaler (N = 88)	Device without feedback (N = 86)
Mean (SD)		
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian % Sample size	n = 4 ; % = 5	n = 5 ; % = 6
Black or African % Sample size	n = 8 ; % = 9	n = 4 ; % = 5
American white % Sample size	n = 76 ; % = 86	n = 74 ; % = 86
Comorbidities Nominal	NR	NR
Asthma control ACT Mean (SD)	15 (3.07)	15.7 (2.72)

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	Smart inhaler, Baseline, N = 88	Smart inhaler, 6 month, N = 81	Device without feedback, Baseline, N = 86	Device without feedback, 6 month, N = 83
Adherence at 4-6 months (%) Mean (SD)	NA (NA)	78.2 (23.4)	NA (NA)	67 (31.6)
Rescue medication use (SABA-free days, months 4-6) (%) *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)	NA (NA)	9.8 (18.1)	NA (NA)	18.6 (52.8)
Asthma Control (Asthma Control Test) scale range 5-25, final values Mean (SD)	15 (3.07)	20.2 (3.8)	15.7 (2.72)	19.9 (4)

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

Outcome	Smart inhaler, Baseline, N = 88	Smart inhaler, 6 month, N = 88	Device without feedback, Baseline, N = 86	Device without feedback, 6 month, N = 86
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 1

Severe asthma exacerbations - 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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Rescue medication use (months 4-6)

Section	Question	Answer
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

Secondary publication of	No additional information

another included study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	ClinicalTrials.gov: NCT02451709
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	No additional information
Study dates	October 2013 - August 2014
Sources of funding	Funded by the Sheffield Children's Hospital Charity
Inclusion criteria	Taking regular inhaled steroids, with no change in their medication in the last month Asthma Control Questionnaire (ACQ) score of at least 1.5, indicating poorly controlled asthma BTS level 3 asthma
Exclusion criteria	Non-English speaking Had another significant chronic condition
Recruitment / selection of participants	Participants attending hospital clinics in Sheffield or Rotherham were screened for eligibility
Intervention(s)	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 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.
Population subgroups	**Age** Mixed: 6-16 years old (mean ~10.3 (2.9) years) **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported

	Asthma control ACQ score >1.5
Comparator	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.
Number of participants	90 randomised, 79 completed, 89 analysed (total) 47 randomised, 40 completed, 47 analysed (smart inhaler) 43 randomised, 39 completed, 42 analysed (device without feedback)
Duration of follow-up	12 months
Indirectness	No additional information
Additional comments	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)
% Female Sample size	n = 19 ; % = 40	n = 20 ; % = 48
Mean age (SD) (years) Mean (SD)	10.4 (2.9)	10.2 (2.9)
Ethnicity Sample size	n = NA	n = NA ; % = NA
White British Sample size	n = 30 ; % = 64	n = 24 ; % = 57
Black African Sample size	n = 3 ; % = 6	n = 6 ; % = 14
British Pakistani Sample size	n = 11 ; % = 23	n = 11 ; % = 26
British Indian Sample size	n = 0 ; % = 0	n = 1 ; % = 2
Asian (other)	n = 1 ; % = 2	n = 0 ; % = 0

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

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
Asthma control (Asthma Control Questionnaire) Scale range 0-6, change scores Mean (SD)	NA (NA)	-1.14 (1.44)	NA (NA)	-0.95 (4.99)

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
Lung Function (% predicted FEV1) (Percent of predicted) Change scores Mean (SD)	NA (NA)	3 (11.45)	NA (NA)	1.54 (14.13)

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

ContinuousOutcomes-Asthmacontrol(AsthmaControlQuestionnaire)-MeanSD-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

ContinuousOutcomes-LungFunction(%predictedFEV1)-MeanSD-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.; Szefler, 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

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

Inclusion criteria	Uncontrolled asthma Aged 25-65 years Receiving daily ICS and a SABA inhaler
Exclusion criteria	Using inhalers not compatible with smart devices Other severe comorbidities that could interfere (e.g., severe psychiatric disorder)
Recruitment / selection of participants	Recruited through electronic medical records from allergist/immunologist or pulmonologist practices and mailing potential participants
Intervention(s)	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. 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.
Population subgroups	**Age** ≥12 years **Exacerbations**

	Mixed **Exacerbators** Mixed **Adherence** Not reported **Control of asthma** Uncontrolled
Comparator	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.
Number of participants	100 randomised 75 allocated to smart inhalers, 73 completed 25 allocated to device without feedback, 24 completed
Duration of follow-up	3 months
Indirectness	None

Additional comments	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 Sample size	n = 60 ; % = 80	n = 20 ; % = 80
Mean age (SD) Mean (SD)	49.3 (11.63)	46.06 (14.29)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black/African American	n = 19 ; % = 25.3	n = 7 ; % = 28

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

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
Reliever/rescue medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	19 (30.93)	NA (NA)	6 (21.68)
Adherence (%) Change scores Mean (SD)	NA (NA)	-2 (22.09)	NA (NA)	-17 (22.96)

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; Safioti, 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

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

Study location	USA
Study setting	Conducted across 44 sites - no information on care setting
Study dates	February 2021 - March 2022
Sources of funding	Funded by Teva Branded Pharmaceutical Products R&D
Inclusion criteria	Aged ≥13 years Uncontrolled asthma (ACT score <19) Receiving moderate-high dose ICS/LABA maintenance medication with SABA as-needed
Exclusion criteria	Current or previous (>10 pack years) smoker Previous use of a digital inhaler Other clinically significant medical condition Hospitalised for severe asthma within 30 days COPD or COPD-asthma overlap Use of systemic corticosteroids within 30 days Use of biologic treatment within 90 days
Recruitment / selection of participants	Method not reported
Intervention(s)	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, were added as deemed necessary by the study investigator. 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.
Population subgroups	**Age** ≥12 years **Exacerbations** Not reported **Exacerbators** Not reported **Adherence** Not reported

	Asthma control Uncontrolled
Comparator	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. 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.
Number of participants	427 randomised 242 allocated to smart inhalers, 183 completed 185 allocated to usual care, 174 completed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	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

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

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

Outcomes

Study timepoints

- Baseline
- 24 week

Dichotomous Outcomes

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

Section	Question	Answer
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 checked by HCPs on 76% of weeks, indicating inadequate adherence with the intervention)*
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 *(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)*
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 *(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)*

Section	Question	Answer
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

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Clinicaltrials.gov (NCT00233181)
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information

Study dates	2001 - 2003
Sources of funding	Supported by National Heart, Lung, and Blood Institute grant HL063333
Inclusion criteria	Aged 2-12 years of age Physician-diagnosed asthma 2 ED visits or 1 hospitalization for asthma in the preceding year Resided in Baltimore city Prescribed an asthma controller medication
Exclusion criteria	No additional information
Recruitment / selection of participants	Children with asthma were recruited from the pediatric ED by weekly review of discharge records
Intervention(s)	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.
Population subgroups	**Age**

	5-11 years **Exacerbations** At least one in the past year **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Not reported
Comparator	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.
Number of participants	166 randomised, 153 completed (total) 83 randomised, 76 completed (smart inhaler)

	83 randomised, 77 completed (usual care)
Duration of follow-up	18 months
Indirectness	No additional information
Additional comments	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 Sample size	n = 29 ; % = 35	n = 34 ; % = 41
Mean age (SD) (years) Mean (SD)	6.54 (3.43)	7.35 (3.3)

Characteristic	Smart inhaler (N = 83)	Usual care (N = 83)
Ethnicity Black Sample size	n = 81 ; % = 98	n = 80 ; % = 96
Comorbidities Nominal	NR	NR

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
Hospital admissions (from month 12-18) final values No of events	n = NA ; % = NA	n = 12 ; % = 15.8	n = NA ; % = NA	n = 10 ; % = 13

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
Adherence (from month 12-18) (%) Final values Mean (SD)	83.16 (29.69)	87.33 (25.24)	84.87 (26.77)	94.96 (10.78)

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

ContinuousOutcomes-Adherence(frommonth12-18)-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

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Netherlands Trials Registry: NTR2583
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	No additional information
Study dates	January 2012 - December 2012
Sources of funding	Grants from The Netherlands Organization for Health Research and Development, GlaxoSmithKline and Evalan BV (providing inhalers at cost price)

Inclusion criteria	4-11 years old Diagnosed with asthma for ≥6 months ICS use for ≥3 months Using a pMDI (fluticasone, fluticasone/salmeterol or beclomethasone) Parent/caregiver has a mobile phone
Exclusion criteria	No additional information
Recruitment / selection of participants	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 ⩾6 months and who had visited the outpatient clinic in the past 12 months.
Intervention(s)	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.
Population subgroups	**Age** 5-11 years

	Exacerbations Not reported **Exacerbators** Not reported **Adherence** Not reported **Asthma control** Mixed - ~37% had uncontrolled asthma at baseline
Comparator	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.
Number of participants	219 randomised, 209 completed (total) 108 randomised, 101 completed (smart inhaler) 111 randomised, 108 completed (device without feedback)
Duration of follow-up	12 months

Indirectness	None
Additional comments	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

Characteristic	Smart inhaler (N = 101)	Device without feedback (N = 108)
% Female Sample size	n = 42 ; % = 41.6	n = 36 ; % = 33.3
Mean age (SD) Mean (SD)	7.8 (2.2)	7.7 (2.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Smart inhaler (N = 101)	Device without feedback (N = 108)
Dutch Sample size	n = 63 ; % = 62.4	n = 73 ; % = 67.6
Non-Dutch Sample size	n = 38 ; % = 37.6	n = 35 ; % = 32.4
Asthma control cACT Mean (SD)	20.6 (4.4)	20.4 (3.9)

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
Adherence (proportion of doses administered correctly) (Percentage) final values Mean (95% CI)	NA (NA to NA)	69.3 (65.5 to 73.4)	NA (NA to NA)	57.3 (52.8 to 61.7)

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
Quality of life (Paediatric Asthma Quality of Life Questionnaire) Scale range: 1-7, final values Mean (95% CI)	NA (NA to NA)	-0.06 (-0.41 to 0.15)
Asthma control (Childhood Asthma Control Test) Scale range: 0-27, final values Mean (95% CI)	NA (NA to NA)	-1.07 (-3.51 to 0.56)

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

ContrastOutcomes-Qualityoflife(PaediatricAsthmaQualityofLifeQuestionnaire)-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

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

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	ACTRN 12613000800729
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	No additional information
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Pregnant women with asthma aged ≥18 years <20 weeks gestation Able to communicate in English Self-reported use of any inhaled bronchodilator or anti-inflammatory agent for asthma within the previous 12 months
Exclusion criteria	Under specialist care for difficult asthma Not in possession of a smart phone
Recruitment / selection of participants	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.

Intervention(s)	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 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.
Population subgroups	**Age** ≥12 years **Exacerbations** Not reported **Exacerbators** Not reported

	Adherence Not reported **Asthma control** Not reported
Comparator	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.
Number of participants	72 randomised, 67 completed (total) 36 randomised, 32 completed (smart inhaler) 36 randomised, 35 completed (usual care)
Duration of follow-up	6 months
Indirectness	None
Additional comments	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)
% Female Sample size	n = 36 ; % = 100	n = 36 ; % = 100
Mean age (SD) Mean (SD)	31.1 (4.7)	31.8 (4.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 30 ; % = 84	n = 30 ; % = 84
Asian Sample size	n = 3 ; % = 8	n = 3 ; % = 8
Other Sample size	n = 3 ; % = 8	n = 3 ; % = 8
Comorbidities	NR	NR

Characteristic	Smart inhaler (N = 36)	Usual care (N = 36)
Nominal		
Lung function (% of predicted) FEV1 Mean (SE)	89.1 (2.3)	91.6 (0.1)
Asthma control ACQ Mean (SE)	1.1 (0.1)	1.2 (0.1)

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
Asthma Control (Asthma Control Questionnaire-7) scale range 0-6, change scores Mean (SE)	NA (NA)	-0.3 (0.11)	NA (NA)	0.06 (0.1)

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

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 Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 2 ; % = 1

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
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)

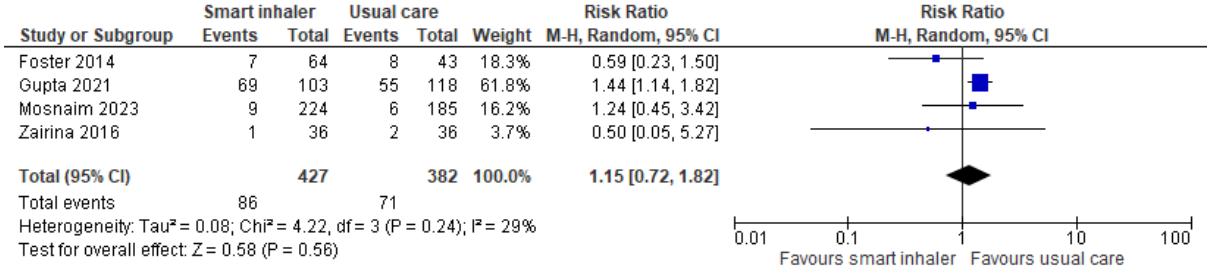


Figure 3: Quality of life (mini asthma quality of life questionnaire, scale range 1-7, mixed values, higher is better)

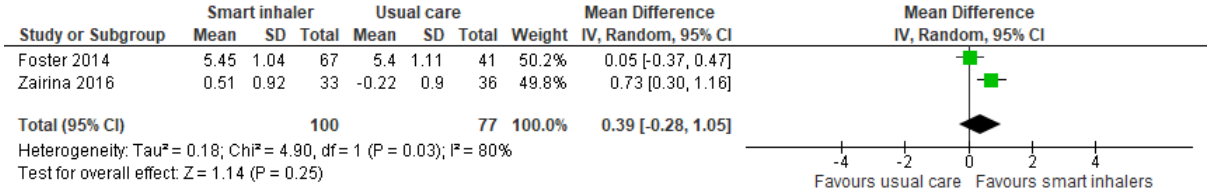


Figure 4: Asthma control (asthma control test, scale range 0-25, final values, higher is better)

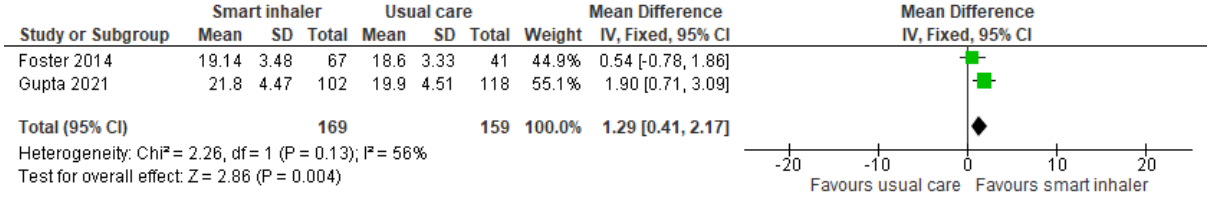


Figure 5: Asthma control (asthma control questionnaire-7, scale range 0-6, change scores, lower is better)

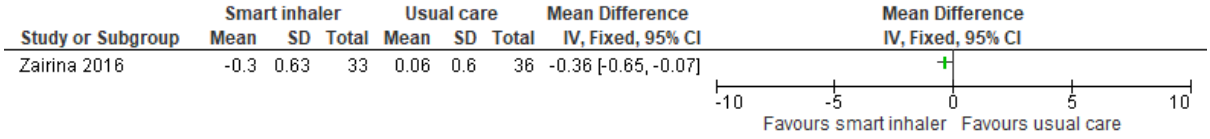


Figure 6: Hospital admissions (final values, lower is better)

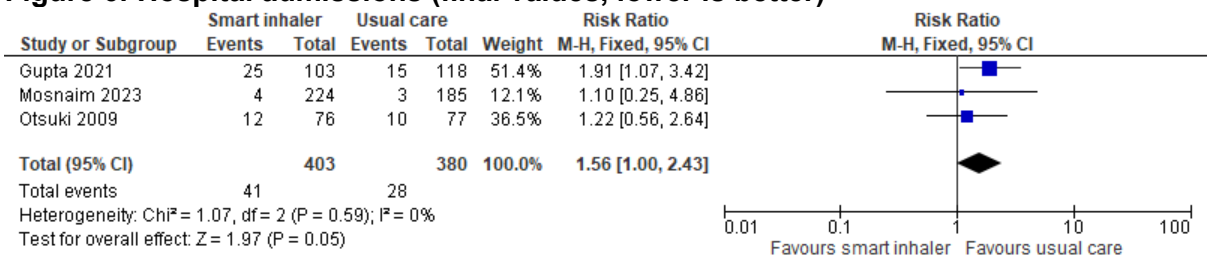


Figure 7: Adherence (%, mixed values, higher is better)

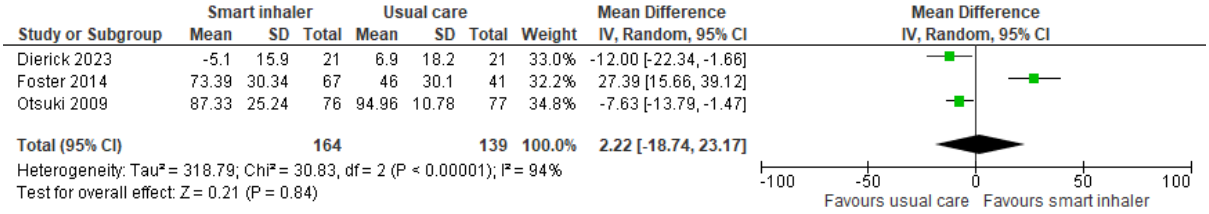


Figure 8: Lung function (FEV1, litres, final values, higher is better)

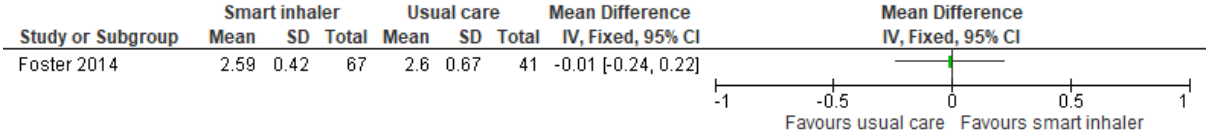


Figure 9: Lung function (% predicted FEV1, change scores, higher is better)

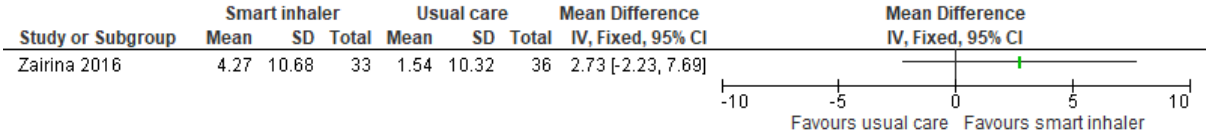


Figure 10: Inflammatory markers (FeNO, ppb, change scores, lower is better)

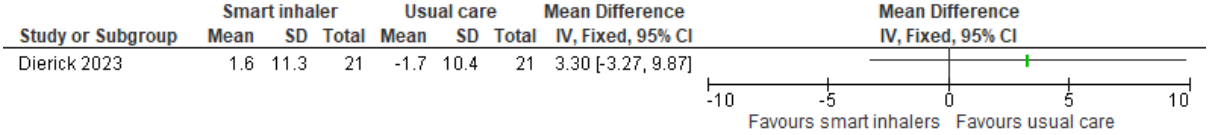
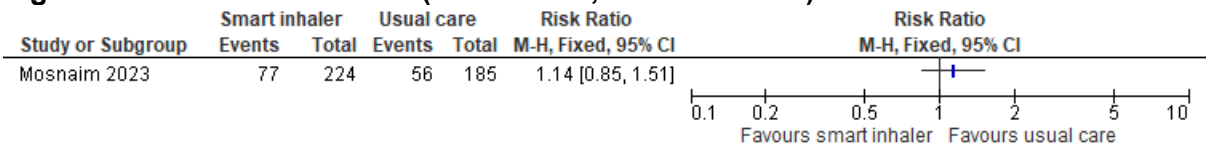


Figure 11: Adverse events (final values, lower is better)



Smart inhalers vs device without feedback

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

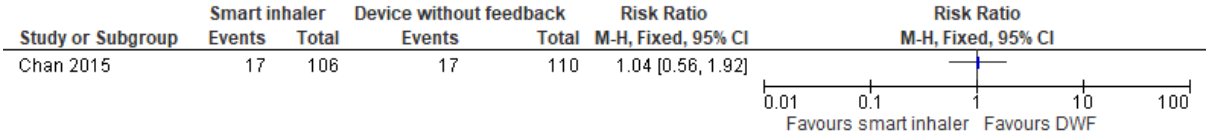


Figure 13: Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, final values, higher is better)

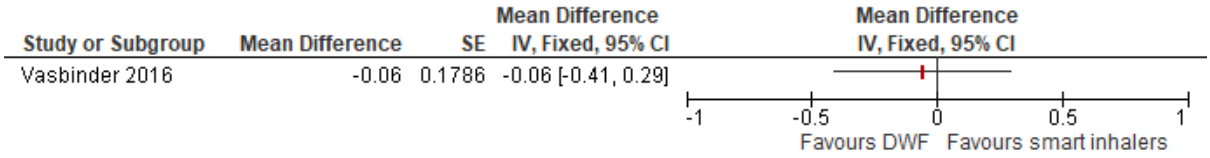


Figure 14: Asthma control (Asthma Control Test, scale range 5-25, mixed values, higher is better)

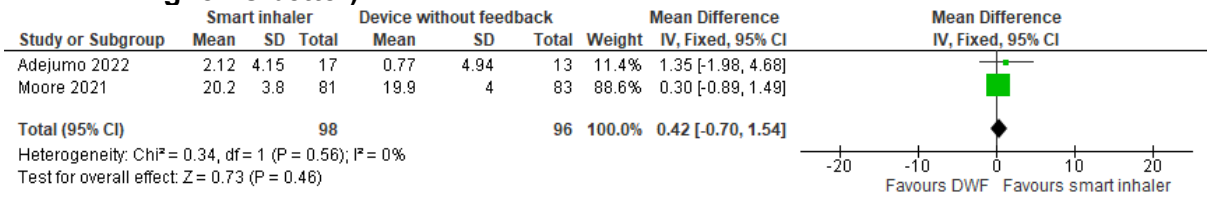


Figure 15: Asthma control (Childhood Asthma Control Test, scale range 0-27, final values, higher is better)

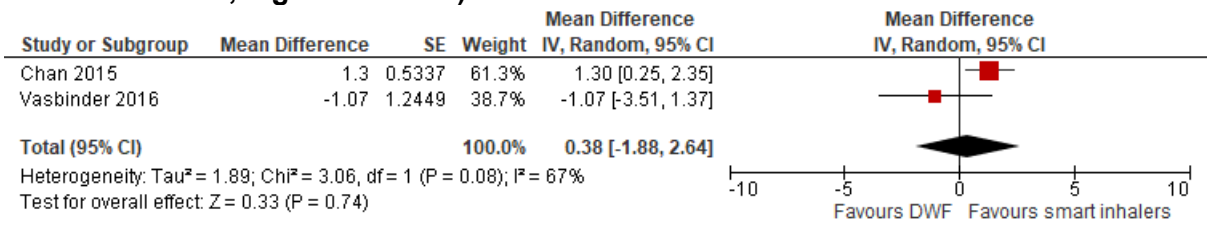


Figure 16: Asthma control (Asthma Control Questionnaire, scale range 0-6, changes scores, lower is better)

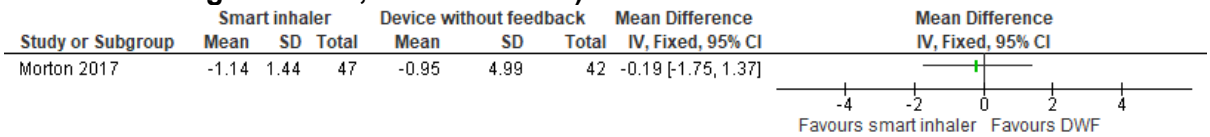


Figure 17: Reliever medication use (SABA-free days, %, mixed values, higher is better)

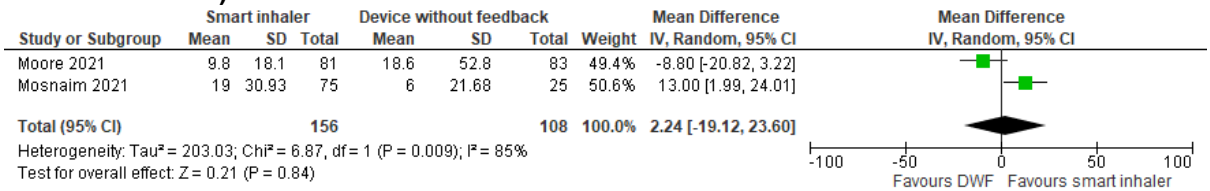


Figure 18: Adherence (% daily doses administered, mixed values, higher is better)

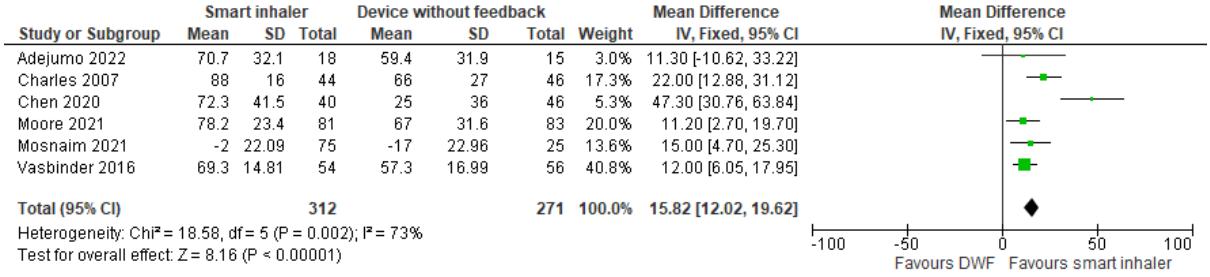


Figure 19: Lung function (% predicted FEV1, mixed values, higher is better)

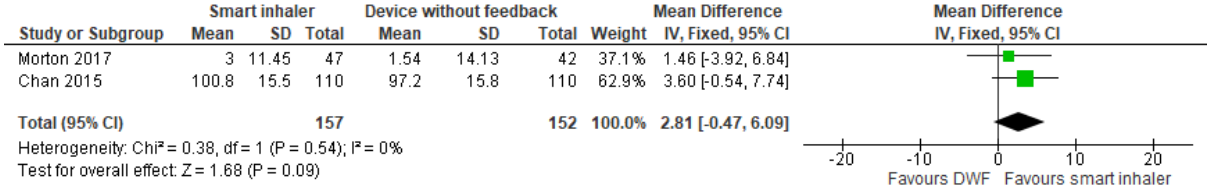
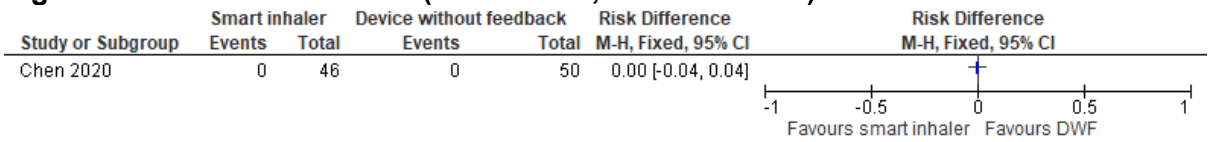


Figure 20: Adverse events (final values, lower is better)



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)		
Severe asthma exacerbations (final values, lower is better)												
4	randomised trials	not serious	not serious	not serious	very serious[a]	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
Quality of life (mini asthma quality of life questionnaire, scale range 1-7, mixed values, higher is better)												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	100	77	-	MD **0.39 higher** (0.28 lower to 1.05 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Asthma control (asthma control test, scale range 0-25, final values, higher is better)												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	169	159	-	MD **1.29 higher** (0.41 higher to 2.17 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Asthma control (asthma control questionnaire-7, scale range 0-6, change scores, lower is better)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	33	36	-	MD **0.36 lower** (0.65 lower to 0.07 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Hospital admissions (final values, lower is better)												

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)		
3	randomised trials	not serious	not serious	not serious	serious[b]	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
Adherence (%, mixed values, higher is better)												
3	randomised trials	not serious	very serious[c]	not serious	very serious[a]	none	164	139	-	MD **2.22 higher** (18.74 lower to 23.17 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, litres, final values, higher is better)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	67	41	-	MD **0.01 lower** (0.24 lower to 0.22 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (% predicted FEV1, change scores, higher is better)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	33	36	-	MD **2.73 higher** (2.23 lower to 7.69 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Inflammatory markers (FeNO, ppb, change scores, lower is better)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	21	21	-	MD **3.3 higher** (3.27 lower to 9.87 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	very serious[d]	not serious	not serious	very serious[a]	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 (I2=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[a]	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[b]	not serious	not serious	serious[c]	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[b]	not serious	not serious	serious[c]	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)												

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)		
2	randomised trials	not serious	very serious[d]	not serious	serious[c]	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)												
1	randomised trials	very serious[e]	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[a]	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[f]	not serious	very serious[g]	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[c]	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

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)		
Adverse events (final values, lower is better)												
1	randomised trials	not serious	not serious	not serious	serious[h]	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 (I2=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

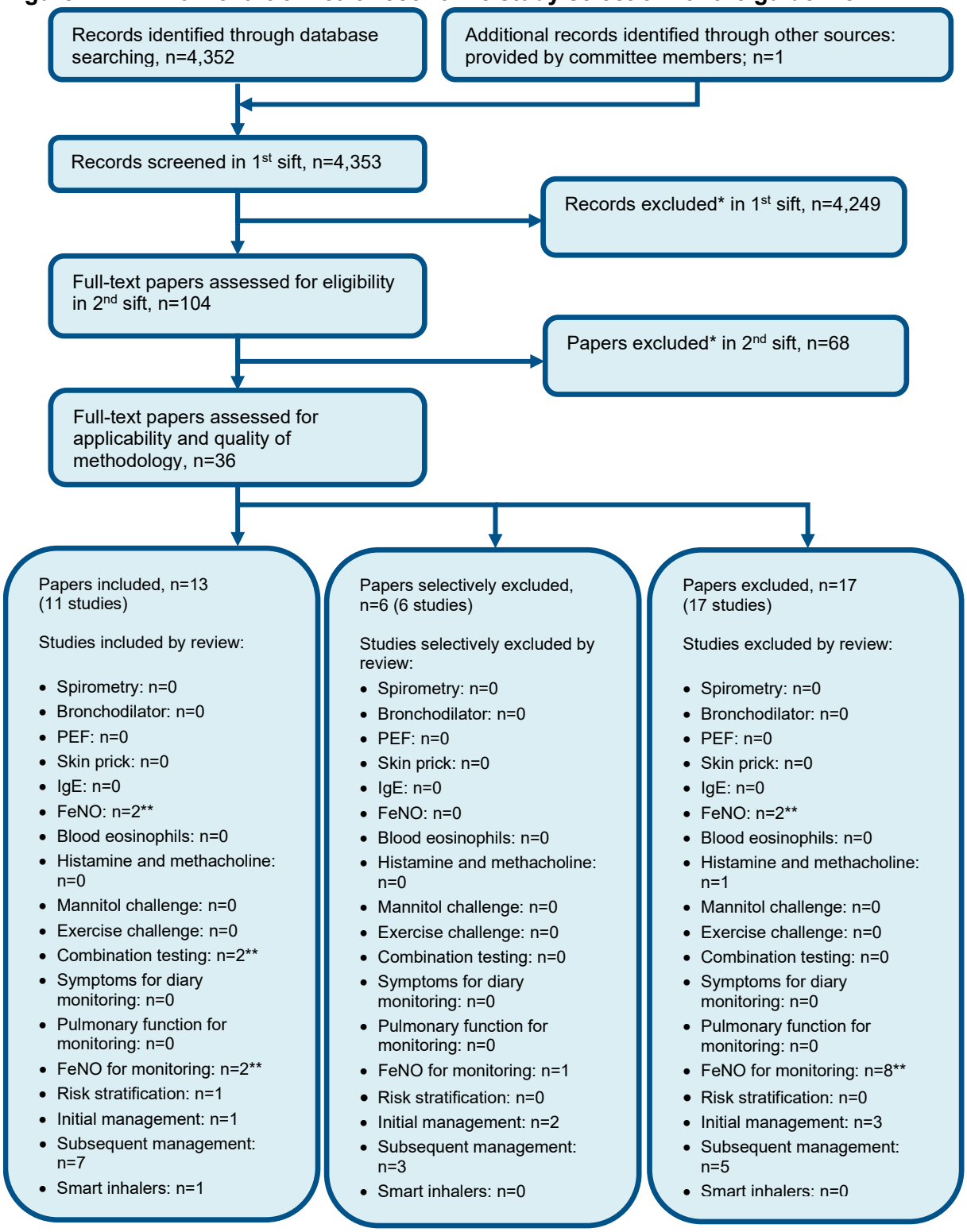
f. Downgraded by two increments due to considerable heterogeneity showing differing directions of benefit of the intervention (I2=85%) that was not explained by a random effects model

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**
Economic analysis: Cost-consequence analysis (health outcomes: adherence, asthma control, quality of life and exacerbations) **Study design:** Within-trial analysis **Approach to analysis:** 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. **Perspective:** Dutch healthcare perspective **Follow-up** 12 months **Discounting:** Costs: n/a ; Outcomes: n/a	**Population:** Children aged 4-11 years who had doctor-diagnosed asthma for >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. **Cohort settings:** Start age: 7.8 (5.6 to 10) Male: 66% **Intervention 1:** Device without feedback (current practice) **Intervention 2:** Smart inhaler using RTMM with SMS reminders on adherence	**Total costs (mean per patient):** Intervention 1: £549 Intervention 2: £631 Incremental (2−1): £83 (95% CI: -£47 to £234; p=NR) **Currency & cost year:** 2014 Dutch Euros (presented here as 2014 UK pounds[(a)]) **Cost components incorporated:** RTMM device, medication, hospital and GP visits	**Adherence:** Intervention 1: 57.3% Intervention 2: 69.3% Incremental (2−1): 12% (95% CI: 9.3% to 20.7%; p=NR) **Control** **c-ACT score:** Intervention 1: 22.17 Intervention 2: 21.10 Incremental (2−1): -1.07 (95% CI: -3.51 to 0.56; p=0.203) **Quality of life** **PAQLQ score:** Intervention 1: 6.25 Intervention 2: 6.19 Incremental (2−1): -0.06 (95% CI: -0.41 to 0.15; p=0.659) **Asthma exacerbations:** Intervention 1: 0.37	Smart inhaler using RTMM with SMS reminders improves adherence by 12% at an additional cost of £83. **Analysis of uncertainty:** Uncertainty around the point estimates was addressed using bootstrapping, generating confidence intervals for incremental costs and health outcomes.

			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:[(b)] Partially applicable **Overall quality:**[(c)] 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

Appendix I – Excluded studies

Clinical studies

Table 10: Studies excluded from the clinical review

Study	Code [Reason]
Adejumo, I. and Shaw, D. E. (2018) Electronic monitoring devices as an intervention in Asthma: The story so far. Current Respiratory Medicine Reviews 14(1): 5-22	- Systematic review used as source of primary studies
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. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica tisiologica e malattie apparato respiratorio, Università di Napoli, Secondo ateneo 71(4): 161-9	- Systematic review used as source of primary studies
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. Current Therapeutic Research 61(2): 61-73	- Systematic review used as source of primary studies
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. BMJ open 13(8): e074127	- Review article but not a systematic review
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. Journal of Allergy & Clinical Immunology 128(3): 516-23.e1	- Comparator in study does not match that specified in this review protocol *Study compared smart inhalers to an intensive asthma education program not considered to be representative of usual care*
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. JAMA network open 5(3): e220615	- Systematic review used as source of primary studies

Study	Code [Reason]
Biblowitz, K.; Bellam, S.; Mosnaim, G. (2018) Improving Asthma Outcomes in the Digital Era: A Systematic Review. Pharmaceutical Medicine 32(3): 173-187	- Systematic review used as source of primary studies
Burgess, S. W., Sly, P. D., Cooper, D. M. et al. (2007) Novel spacer device does not improve adherence in childhood asthma. Pediatric Pulmonology 42(8): 736-9	- Study does not contain an intervention relevant to this review protocol *Study compares two spacer devices, not a smart inhaler against another method*
Burgess, S. W.; Sly, P. D.; Devadason, S. G. (2010) Providing feedback on adherence increases use of preventive medication by asthmatic children. Journal of Asthma 47(2): 198-201	- Data not reported in an extractable format or a format that can be analysed
Burkhart, P. V.; Dunbar-Jacob, J. M.; Rohay, J. M. (2001) Accuracy of children's self-reported adherence to treatment. Journal of Nursing Scholarship 33(1): 27-32	- Study does not contain an intervention relevant to this review protocol
Chan, A. H. Y., Stewart, A. W., Harrison, J. et al. (2017) Electronic adherence monitoring device performance and patient acceptability: a randomized control trial. Expert Review of Medical Devices 14(5): 401-411	- Duplicate reference
Chapman, K. R., Barnes, N. C., Greening, A. P. et al. (2010) Single maintenance and reliever therapy (SMART) of asthma: A critical appraisal. Thorax 65(8): 747-752	- Study does not contain an intervention relevant to this review protocol
Doshi, H., Hsia, B., Shahani, J. et al. (2021) Impact of Technology-Based Interventions on Patient-Reported Outcomes in Asthma: A Systematic Review. The Journal of Allergy & Clinical Immunology in Practice 9(6): 2336-2341	- Systematic review used as source of primary studies
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). American journal of respiratory and critical care medicine 189: a5368	- Conference abstract
Garin, Noe, Zarate-Tamames, Borja, Gras-Martin, Laura et al. (2023) Clinical Impact of Electronic Monitoring Devices of Inhalers in	- Systematic review used as source of primary studies

Study	Code [Reason]
Adults with Asthma or COPD: A Systematic Review and Meta-Analysis. Pharmaceuticals (Basel, Switzerland) 16(3)	
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	- Study protocol
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	- Conference abstract
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	- Study protocol
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)	- Conference abstract
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	- Systematic review used as source of primary studies
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	- Study does not contain an intervention relevant to this review protocol
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	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
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	- Study does not contain an intervention relevant to this review protocol
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	- Data not reported in an extractable format or a format that can be analysed *Qualitative data only*
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	- Conference abstract
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	- Conference abstract
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	- Study does not contain an intervention relevant to this review protocol
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 & Clinical Immunology in Practice 8(2): 635-644	- Study does not contain an intervention relevant to this review protocol
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	- Study does not contain an intervention relevant to this review protocol
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)	- Conference abstract
Onyirimba, F., Apter, A., Reisine, S. et al. (2003) Direct clinician-to-patient feedback discussion of	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
inhaled steroid use: its effect on adherence. Annals of Allergy, Asthma, & Immunology 90(4): 411-5	*Adherence data only provided for 2 weeks, not full study duration*
Ostrom, N. K., Raphael, G., Tillinghast, J. et al. (2018) Randomized trial to assess the efficacy and safety of beclomethasone dipropionate breath-Actuated inhaler in patients with asthma. Allergy and asthma proceedings 39(2): 117-126	- Study does not contain an intervention relevant to this review protocol
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. NPJ Primary Care Respiratory Medicine 25: 14099	- Study does not contain an intervention relevant to this review protocol
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. The Lancet Respiratory Medicine 1(1): 32-42	- Population not relevant to this review protocol
Patel, M., Pilcher, J., Reddel, H. K. et al. (2013) Metrics of salbutamol use as predictors of future adverse outcomes in asthma. Clinical & Experimental Allergy 43(10): 1144-51	- Study does not contain an intervention relevant to this review protocol
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. The Journal of Allergy & Clinical Immunology in Practice 2(6): 751-8	- Study does not contain an intervention relevant to this review protocol
Pilcher, J., Shirtcliffe, P., Patel, M. et al. (2015) Three-month validation of a turbuhaler electronic monitoring device: implications for asthma clinical trial use. BMJ open respiratory research 2(1): e000097	- Study design not relevant to this review protocol
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. Journal of Asthma 48(8): 839-47	- Study does not contain an intervention relevant to this review protocol
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. BMJ 344: e1756	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
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. Respiratory Care 65(3): 326-332	- Study does not contain an intervention relevant to this review protocol
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. Digital health 9: 20552076231216589	- Study design not relevant to this review protocol
Sobieraj, D. M., Weeda, E. R., Nguyen, E. et al. (2018) Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. JAMA 319(14): 1485-1496	- Systematic review used as source of primary studies
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. Trials 21(1)	- Study protocol
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. European Respiratory Journal 51(1): 01	- Study does not contain an intervention relevant to this review protocol
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. BMJ Open 6(1): e009350	- Study protocol
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. Journal of medical Internet research 25: e45896	- Review article but not a systematic review
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	- Study protocol

Study	Code [Reason]
Effectiveness Trial. JMIR research protocols 12: e45585	
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 correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. NPJ Primary Care Respiratory Medicine 26: 16079	- Study does not contain an intervention relevant to this review protocol
Vollmer, W. M., Feldstein, A., Smith, D. H. et al. (2011) Use of health information technology to improve medication adherence. 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-sympathicomimetics 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
Wang, G., Zhang, X., Zhang, H. P. et al. (2017) Corticosteroid plus β2-agonist in a single inhaler as reliever therapy in intermittent and mild asthma: a proof-of-concept systematic review and meta-analysis. Respiratory research 18(1): 203	- Study does not contain an intervention relevant to this review protocol
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. Thorax 65(1): 39-43	- Study does not contain an intervention relevant to this review protocol
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. The Journal of Allergy & Clinical Immunology in Practice 7(5): 1497-1506	- Study does not contain an intervention relevant to this review protocol *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*
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. Mayo Clinic Proceedings 91(4): 411-21	- Review article but not a systematic review

Study	Code [Reason]
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©). BMC Pulmonary Medicine 15: 84	- Study does not contain an intervention relevant to this review protocol
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 & adherence 12: 861-868	- Study does not contain an intervention relevant to this review protocol

Appendix J – Research recommendation

J.1 Research recommendation

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

J.2 Why this is important

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

1. British Lung Foundation. Asthma Statistics. https://statistics.blf.org.uk/asthma <accessed24th Nov 2023>
2. Vrijens, B et al. What we mean when we talk about adherence in respiratory medicine. J allergy clin immunol pract 2016; 4 (5):802-812
3. Holmes J, Heaney LG. Measuring adherence to therapy in airways disease. Breathe 2021; 17 (2): 1-8
4. Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. London: RCP 2014

J.3 Rationale for research recommendation

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

J.4 Modified PICO table

Population	Mild to moderate asthma • Stratified or inclusion/exclusion criteria to specify baseline adherence or asthma control: ▪ Participants with poor adherence at baseline ▪ Participants with sub-optimal asthma control
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.