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A randomised controlled trial of the effect of a connected inhaler system on medication adherence in uncontrolled asthmatic patients

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In individuals with uncontrolled asthma, data feedback on maintenance therapy use from a connected inhaler system led to increased maintenance adherence and feedback on rescue medication usage led to more rescue-free days but did not improve asthma control https://bit.ly/39kmVBA

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ABSTRACT Suboptimal adherence to maintenance therapy contributes to poor asthma control and exacerbations. This study evaluated the effect of different elements of a connected inhaler system (CIS), comprising clip-on inhaler sensors, a patient-facing app and a healthcare professional (HCP) dashboard, on adherence to asthma maintenance therapy.

This was an open-label, parallel-group, 6-month, randomised controlled trial in adults with uncontrolled asthma (asthma control test (ACT) score less than 20) on fixed-dose inhaled corticosteroids/long-acting β-agonist maintenance therapy (n=437). All subjects received fluticasone furoate/vilanterol ELLIPTA dry-powder inhalers for maintenance and salbutamol/albuterol metered-dose inhalers for rescue, with a sensor attached to each inhaler. Participants were randomised to one of five CIS study arms (allocation ratio 1:1:1:1:1) reflecting the recipient of the data feedback from the sensors, as follows: 1) maintenance use to participants and HCPs (n=87); 2) maintenance use to participants (n=88); 3) maintenance and rescue use to participants and HCPs (n=88); 4) maintenance and rescue use to participants (n=88); and 5) no feedback (control) (n=86).

For the primary endpoint, observed mean±SD adherence to maintenance therapy over months 4–6 was 82.2±16.58% (n=83) in the "maintenance to participants and HCPs" arm and 70.8±27.30% (n=85) in the control arm. The adjusted least squares mean±SE was 80.9±3.19% and 69.0±3.19%, respectively (study arm difference: 12.0%, 95% CI 5.2–18.8%; p<0.001). Adherence was also significantly greater in the other CIS arms *versus* the control arm. The mean percentage of rescue medication free days (months 4–6) was significantly greater in participants receiving data on their rescue use compared with controls. ACT scores improved in all study arms with no significant differences between groups.

A CIS can improve adherence to maintenance medication and reduce rescue medication use in patients with uncontrolled asthma.

Introduction

Asthma presents a significant burden for both patients and healthcare systems [1, 2]. Although most asthma patients can be effectively treated with available asthma therapies, many patients have uncontrolled asthma which puts them at increased risk of asthma exacerbations and failure to achieve the goals of asthma care [2–4]. Suboptimal adherence to maintenance therapy is a key contributor to uncontrolled asthma [2, 5] and is associated with substantial disease-associated morbidity and mortality [3, 6, 7]. It is estimated that at least 50% of asthma patients fail to take their daily maintenance therapy as directed [2, 4]. The reasons for patient non-adherence are multifaceted and factors include patient age, understanding of the disease and its severity, complexity of treatment, forgetfulness, inhaler technique, concerns about side-effects, medication costs and ineffective healthcare professional (HCP)–patient communication [6, 8–10]. Enhancing patients' adherence to their prescribed maintenance therapy is paramount for achieving and maintaining asthma control.

Historically, the assessment of adherence to asthma medication has depended on subjective or surrogate methods such as prescription records [11–13]. Electronic monitoring devices allow for objective, accurate, remote, digital collection of adherence data [14–18] and provide innovative research. Studies evaluating the effect of electronic monitoring devices using audio visual reminders or physician feedback (or both) have demonstrated improvements in adherence rates compared with control groups (no reminders or feedback) [14, 19–23]. An association between increased adherence rates and improved clinical outcomes in terms of increased asthma control [21] and reduction in exacerbations [21, 22] has been demonstrated, but is limited to paediatric populations.

The connected inhaler system (CIS) in this study comprises clip-on inhaler sensors for the ELLIPTA dry-powder inhaler (DPI) and for a salbutamol/albuterol metered-dose inhaler (MDI) (Propeller Health, Madison, WI, USA), with wireless data transfer that can be viewed by patients and HCPs through a mobile app or computer dashboard (supplementary figure E1). Sensors record the time and date that the ELLIPTA DPI cover is opened/closed and the MDI is actuated. The interactive app can help to inform patients about their asthma, including use of GPS data to identify triggers (*e.g.* high pollen counts) that may initiate an asthma attack. In terms of usability and perceived value, the CIS concept has been well received by patients with asthma [24] and can reliably inform HCPs if a patient's treatment failure is related to poor adherence. This may enable greater engagement between the patient and their HCP regarding the patient's asthma management.

The primary aim of this study was to evaluate the effect of the CIS on adherence to maintenance therapy in participants with uncontrolled asthma and was the first study to compare various data feedback options of the CIS to participants and/or HCPs.

Methods

Participants

Included participants were ⩾18 years of age with a primary respiratory diagnosis of asthma, ⩾3 months maintenance therapy with inhaled corticosteroids (ICS)/long-acting β-agonists (LABAs), an asthma control test (ACT) score of less than 20 (denoting uncontrolled asthma) [25] and were non-smokers (*i.e.* had never smoked or had not smoked for >6 months, with a history of <10 pack-years). Full inclusion/exclusion criteria are detailed in the supplementary material. All participants provided their written informed consent and the study was approved by the relevant ethics committee at each centre.

Study design

This was an open-label, randomised, multicentre, parallel group study conducted in 65 centres across Europe and North America between January 2018 and January 2019. 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), participants were randomised to one of five CIS study arms (allocation ratio 1:1:1:1:1) for the 6-month treatment period. The study arms reflected the type of data feedback from the sensors (participant/HCP; maintenance/rescue use) (table 1 and figure 1).

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This study is registered at www.clinicaltrials.gov with identifier number NCT03380429. Information on GlaxoSmithKline R&D data sharing commitments and requesting access can be found at www.clinicalstudydatarequest.com

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TABLE 1 Connected inhaler system study arms

Arm	Type of data and recipient of data feedback
1	Data on maintenance use supplied to participants and HCPs
2	Data on maintenance use supplied to participants only
3	Data on maintenance and rescue use supplied to participants and HCPs
4	Data on maintenance and rescue use supplied to participants only
5	No data from sensors supplied to participants or HCPs (control)

HCP: healthcare professional.

Participants were assigned to a study arm by the HCP or designee using an interactive web response system and the randomisation and medication ordering system. The randomisation schedule was generated by Clinical Statistics (GlaxoSmithKline, Brentford, UK) using validated internal software (RandAll NG).

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 in study arms 1–4. Participants in arm 5 (control) were provided with a home hub so that their data could be passively uploaded during the study, although neither they nor their HCP could see their medication usage.

After review of the participant's adherence to maintenance medication (arms 1 and 3 only) and rescue medication use (arm 3 only), 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. Further details on the study design can be found in the supplementary material.

Study outcomes

The primary endpoint was the comparison of adherence to ELLIPTA maintenance therapy over months 4–6 between study arm 1 (maintenance data provided to participants and HCPs) and arm 5 (no data provided). This was chosen as the primary comparison as arm 1 was regarded as the most likely model that would be used in clinical practice. Adherence was defined as participants taking the prescribed single

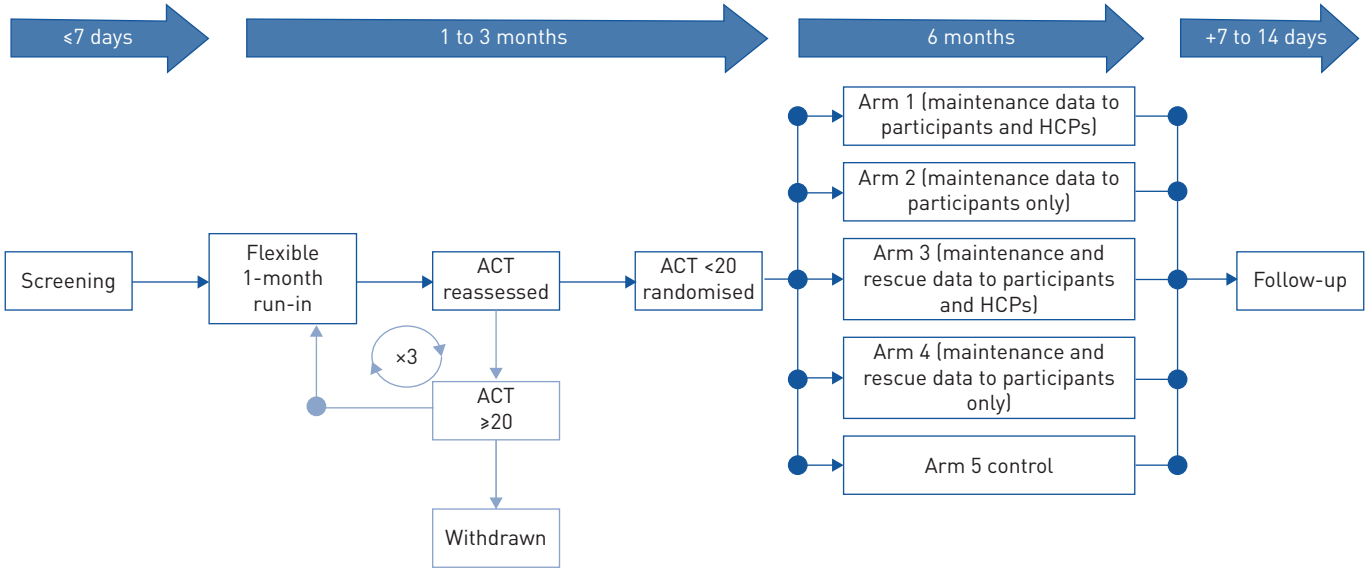

FIGURE 1 Study schematic. ACT: asthma control test; HCP: healthcare professional.

maintenance dose in any one day and the endpoint (percentage) was calculated as (number of days a participant was deemed adherent/number of days in the time period)×100. The endpoint was adjusted to how many days a participant contributed to the time period and for any device malfunctions or post-discontinuations of sensors (intercurrent events). Secondary endpoints included participant rescue medication usage and ACT score. Measurement of exhaled nitric oxide fraction (F_{eNO}) and peak expiratory flow (PEF) were included as clinical markers to characterise the participant population. Safety was assessed by incidence of adverse events (AEs). Complete details of the study endpoints can be found in the supplementary material.

Statistical analysis

The fixed sample size calculation was based on the primary endpoint, percentage of ELLIPTA doses taken (daily adherence) between months 4 and 6 as determined by the maintenance sensor and had approximately 90% power to detect an absolute difference of 15% in the primary comparison, with significance declared at the two-sided 5% level. A conservative standard deviation (SD) of 28% was chosen based on the control arm from a previous study (27%) [19] and with consideration of the technological uncertainty of variability in this type of data. A difference of 15% was selected based on expert clinical opinion sought during the design of the study and deemed a clinically meaningful improvement equating to approximately one extra dose per week of a once daily product. Using the above assumptions, the smallest observed effect predicted to result in a statistically significant difference between treatment groups (the minimum detectable difference) was 9%.

The primary and secondary adherence and rescue use endpoints were analysed using an ANCOVA model with randomised treatment (the study arm) entered as a five-level categorical predictor and adjusting for baseline maintenance adherence/rescue use, number of run-in visits, country, sex and age (in years). The pre-specified treatment arm comparisons (arm 1 *versus* arm 5, arm 2 *versus* arm 5, arm 3 *versus* arm 5 and arm 4 *versus* arm 5) were extracted from the full model.

In the run-in period, due to an oversight at some sites, the required manual syncing of inhaler sensors did not occur. As such, there were missing adherence data during the run-in period for 101 participants. However, the difficulty encountered in collecting baseline data was not due to participants' inability to use the devices correctly. For the statistical analyses the baseline data were imputed *via* the fully conditional specification regression method, adjusting for country, age, gender and number of run-in visits, as well as baseline and all post-baseline adherence measurements. A sensitivity analysis excluding these 101 participants showed results consistent with the primary analysis which included participants with imputed baseline adherence measurements. Due to this and not wanting to omit 101 participants' post-baseline adherence measurements, the results for the total population are presented. This issue did not impact recordings during the post-randomisation treatment period, as during this time all sensors were automatically synced daily to the mobile app or home hub. No adjustments for multiplicity were performed. Statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Full statistical methods are detailed in the supplementary material.

Results

Study population

Of the 483 participants enroled, 437 were randomised to a CIS study arm and 399 completed the study (supplementary figure E2). The main reasons for study withdrawal were "withdrawal by participant" (n=14) or "lost to follow-up" (n=10). The mean±SD age of participants was 47±15 years and 65% were female. The percentage of females was highest in arm 1 (74%) and lowest in arm 5 (55%) (table 2). Other baseline characteristics were similar across the study arms.

Adherence to maintenance therapy and rescue medication usage

Mean daily adherence rates were greater in all the CIS study arms (arms 1–4) compared with the control arm (arm 5) (figure 2, supplementary table E1 and supplementary figure E3). In all CIS study arms, an increase in mean adherence was observed during the first month which then decreased slightly over the following 5 months, compared with the control arm in which mean adherence rate was observed to decrease from months 4–6 (figure 2). For the primary endpoint, adjusted mean daily adherence over months 4–6 was greater in study arm 1 (80.9%) *versus* arm 5 (69.0%) (mean difference 12.0%, 95% confidence interval (CI) 5.2–18.8%; p<0.001) (table 3 and supplementary table E2 (sensitivity analysis)). Other intervention arms also resulted in significantly greater adherence to treatment *versus* the control arm (arm 5). There was no difference in mean adherence between the four CIS study arms. The largest change from baseline over months 4–6 was observed in the "maintenance and rescue data to participants and HCPs" arm (arm 3) (supplementary table E1).

TABLE 2 Baseline demographic and clinical characteristics

	Total population (n=437)	Arm 1 (n=87)	Arm 2 (n=88)	Arm 3 (n=88)	Arm 4 (n=88)	Arm 5 (n=86)
Age years						
Mean	47±15	47±16	47±15	48±15	48±13	47±16
18–64	380 (87)	74 (85)	79 (90)	75 (85)	80 (91)	72 (84)
65–84	56 (13)	13 (15)	8 (9)	13 (15)	8 (9)	14 (16)
⩾85	1 (<1)	0	1 (1)	0	0	0
Female sex	284 (65)	64 (74)	54 (61)	59 (67)	60 (68)	47 (55)
BMI kg·m^{-2}	31±8	30±7	30±7	32±9	31±7	30±8
Ethnicity						
Asian	22 (5)	4 (5)	5 (6)	4 (5)	4 (5)	5 (6)
Black or African American	34 (8)	10 (11)	3 (3)	8 (9)	9 (10)	4 (5)
White	373 (85)	72 (83)	76 (86)	76 (86)	75 (85)	74 (86)
Other	8 (2)	1 (1)	4 (5)	0	0	3 (3)
Baseline ACT score[#]	15.7±2.84[¶]	16.1±2.48	15.9±2.85	15.0±3.07	16.0±2.98	15.7±2.72

Data are presented as n (%) or mean±SD. Arm 1: maintenance data to participants and HCPs; arm 2: maintenance data to participants; arm 3: maintenance and rescue data to participants and HCPs; arm 4: maintenance and rescue data to participants; arm 5: no feedback (control). BMI: body mass index; ACT: asthma control test; HCP: healthcare professional. [#]: measured at the randomisation visit; [¶]: calculated *post hoc* (total population baseline only).

A numerical improvement in daily adherence was also observed over months 1–3 for arms 1–4 relative to arm 5 (a statistically significant difference for arms 1 and 2 *versus* arm 5), but these differences were smaller than those observed over the last 3 months of treatment (supplementary table E3). The magnitude of improvement in adherence (compared with arm 5) was greater in participants with poorer baseline asthma control (ACT score ⩽15 *versus* ACT score 16–19) and in those who were ⩽48 years of age *versus* those who were ⩾49 years old (table 4).

In our study, inclusion of HCPs in data feedback and their resulting actions (supplementary table E4) did not result in further benefit to participant adherence (table 3). Feedback from the rescue medicine sensor also did not demonstrate improvements in adherence to asthma controllers; however, it did result in reduced use of rescue medicines and increased rescue-free days (figure 3, supplementary tables E5–E7 and supplementary figure E4). The mean percentage of rescue-free days over months 4–6 was numerically

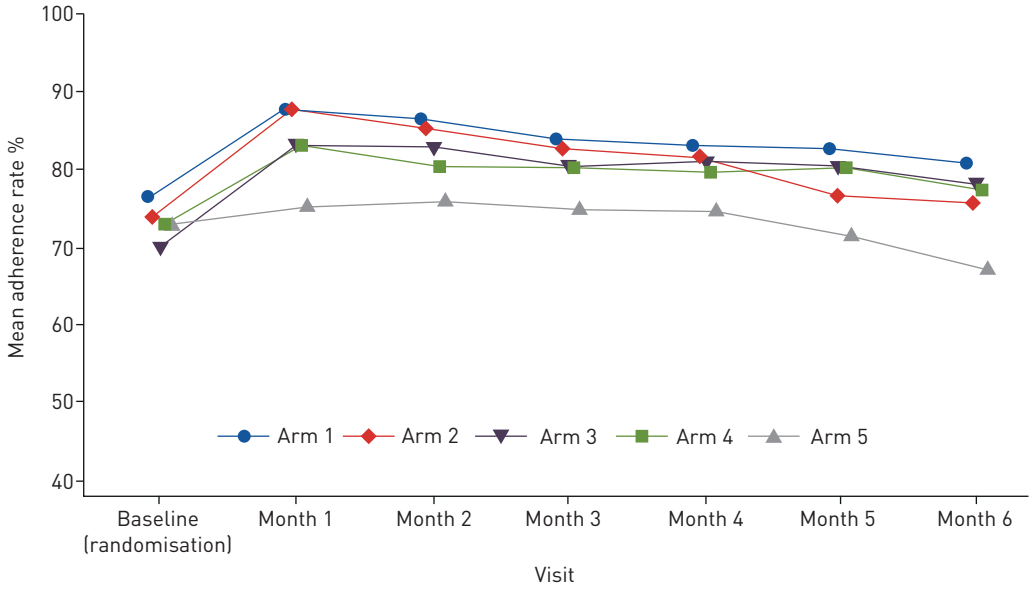

FIGURE 2 Monthly mean adherence rate (observed data). Arm 1: maintenance data to participants and healthcare professionals (HCPs); arm 2: maintenance data to participants; arm 3: maintenance and rescue data to participants and HCPs; arm 4: maintenance and rescue data to participants; arm 5: no feedback (control).

TABLE 3 Daily adherence to maintenance therapy during months 4–6 and the difference in arms 1–4 *versus* arm 5

	Arm 1 (n=87)	Arm 2 (n=88)	Arm 3 (n=88)	Arm 4 (n=88)	Arm 5 (n=86)
Baseline					
n (observed)	63	69	66	65	72
Mean±SD %	76.5±24.4	73.7±28.6	69.7±33.8	73.1±27.4	73.2±30.2
Months 4–6[#]					
n (observed with baseline)	59	65	62	59	72
n (observed and imputed)	83	84	84	82	85
Least squares mean±SE[¶] %	80.9±3.19	77.2±3.04	78.3±3.11	77.1±3.25	69.0±3.19
CIS arm *versus* arm 5					
Difference %	12.0	8.2	9.3	8.1	
95% CI %	5.2–18.8	1.6–14.9	2.7–16.0	1.4–14.8	
p-value	<0.001	0.016	0.006	0.018	

Arm 1: maintenance data to participants and HCPs; arm 2: maintenance data to participants; arm 3: maintenance and rescue data to participants and HCPs; arm 4: maintenance and rescue data to participants; arm 5: no feedback (control). CIS: connected inhaler system; CI: confidence interval; HCP: healthcare professional. [#]: "observed with baseline" is the number of participants between the beginning of month 4 and the end of month 6 who have completely observed adherence, or partially observed adherence with intermittent missing data being imputed, and with no missing baseline adherence. "Observed and imputed" additionally includes participants who have missing baseline adherence imputed due to a device transmission failure or a human error, or who have no observed adherence for this time period and have all of their adherence data imputed. [¶]: adjusted for effects due to randomised treatment (study arm), baseline adherence, number of run-in visits, country, sex and age (in years).

greater for all arms compared with arm 5 and significantly greater in participants who received data on their amount of rescue use (arms 3 and 4) compared with participants who had no data fed back to them (arm 5). Study arm differences were 9.2% (95% CI 3.3–15.1%), p=0.002 (arm 3 *versus* arm 5) and 7.3% (95% CI 1.5–13.2%), p=0.015 (arm 4 *versus* arm 5) (supplementary table E7). This effect was not observed when data on maintenance therapy only was supplied (arms 1 and 2). There was no difference in rescue-free days between the four CIS study arms.

Asthma control

Mean ACT total score increased in all study arms during the 6-month treatment period (supplementary table E8) and ⩾65% of participants in each group were classified as a responder (ACT total score of 20 or more and/or a three-point or greater increase from baseline at month 6) (figure 4). There were no differences between arms with respect to change in ACT scores from baseline.

Exhaled nitric oxide fraction and peak expiratory flow

In all study arms, mean F_{eNO} decreased between the screening visit (mean±SD: 29.3±25.17 ppb) and the randomisation visit (mean±SD: 21.9±15.46 ppb); thereafter, few changes were observed over the 6-month study period (supplementary figure E5). A small clinical improvement in PEF between the screening and randomisation visits was also observed, again with no notable changes thereafter (supplementary figure E6).

Safety

During the treatment period, the incidence of AEs leading to withdrawal, as well as severe adverse events (SAEs) and adverse drug reactions, was low overall with no new or unexpected AEs reported. Four participants had a severe asthma exacerbation during the study (arm 1 (n=2), arm 2 (n=1) and arm 5 (n=1)); all resolved and none led to study withdrawal.

Discussion

This study demonstrated that the CIS significantly improved adherence to asthma maintenance therapy when participants and HCPs were provided with data on maintenance use compared with the control arm (no data feedback). All CIS intervention arms resulted in an improvement in participant adherence compared with the control group; however, provision of data on rescue medication use in addition to maintenance therapy use, or inclusion of HCPs in data feedback, did not result in further adherence benefit.

This study has some limitations reflecting the difficulties of carrying out randomised, controlled, clinical studies evaluating adherence. Although we experienced some difficulties in collecting baseline adherence at some sites, the results for the primary analysis (with imputed baseline data) and the sensitivity analysis (with these participants excluded) were consistent, suggesting that the approach taken for the primary

TABLE 4 Daily adherence to maintenance therapy over months 4–6 by baseline asthma control test (ACT) total score and by age group, with the difference in arms 1–4 *versus* arm 5

Months 4–6	Arm 1 (n=87)	Arm 2 (n=88)	Arm 3 (n=88)	Arm 4 (n=88)	Arm 5 (n=86)
Baseline ACT total score: ⩽15					
n[#]	28	31	41	29	33
Least squares mean±SE %	82.7±4.61	82.4±4.51	75.5±3.99	75.6±4.61	64.5±4.36
CIS arm *versus* arm 5					
Difference %	18.3	18.0	11.0	11.2	
95% CI %	7.1–29.5	7.2–28.7	1.0–21.1	0.1–22.2	
Baseline ACT total score: 16–19					
n[#]	55	53	43	53	52
Least squares mean±SE %	80.7±3.66	74.8±3.45	81.7±3.90	78.5±3.70	72.7±3.76
CIS arm *versus* arm 5					
Difference %	8.0	2.1	9.0	5.8	
95% CI %	−0.5 to 16.5	−6.3 to 10.6	0.1 to 17.8	−2.6 to 14.3	
Age group: 18–35 years					
n[#]	23	21	21	13	28
Least squares mean±SE %	70.1±5.00	58.8±5.12	68.0±5.30	62.3±6.60	56.9±4.78
CIS arm *versus* arm 5					
Difference %	13.2	1.9	11.1	5.5	
95% CI %	0.9–25.6	−10.8 to 14.6	−1.4 to 23.6	−9.1 to 20.0	
Age group: 36–48 years					
n[#]	20	24	22	28	19
Least squares mean±SE %	82.0±5.38	82.3±4.90	74.7±5.05	76.3±4.68	65.6±5.47
CIS arm *versus* arm 5					
Difference %	16.5	16.8	9.1	10.8	
95% CI %	2.6–30.3	3.4–30.1	−4.4 to 22.6	−2.1 to 23.7	
Age group: 49–58 years					
n[#]	21	21	18	27	13
Least squares mean±SE %	85.1±5.30	84.6±5.21	79.2±5.52	82.1±4.70	76.4±6.47
CIS arm *versus* arm 5					
Difference %	8.7	8.2	2.8	5.7	
95% CI %	−6.8 to 24.2	−7.1 to 23.5	−13.1 to 18.6	−8.9 to 20.3	
Age group: >58 years					
n[#]	19	18	23	14	25
Least squares mean±SE %	88.0±5.56	82.8±5.53	91.6±5.05	87.4±6.42	81.6±4.90
CIS arm *versus* arm 5					
Difference %	6.4	1.2	10.0	5.8	
95% CI %	−6.9 to 19.7	−12.2 to 14.6	−2.6 to 22.6	−9.1 to 20.6	

Arm 1: maintenance data to participants and HCPs; arm 2: maintenance data to participants; arm 3: maintenance and rescue data to participants and HCPs; arm 4: maintenance and rescue data to participants; arm 5: no feedback (control). CIS: connected inhaler system; CI: confidence interval; HCP: healthcare professional. [#]: over months 4–6, n included the number of participants with observed and imputed data.

analysis was sufficiently robust. The high level of adherence in all study arms, including the control arm, may have limited the potential for demonstrating differences between the active study arms. This was possibly a result of a change in participant behaviour in response to having sensors on their inhalers even in the absence of data feedback, as was recently reported in an observational study [26]. The high levels of adherence may also result from the recruitment by interested centres of asthma patients who are engaged in their disease and therefore may not be completely representative of asthma patients in general. Another explanation for the high adherence may be the switch to once daily ICS/LABA from a twice daily combination, which was the case for the majority of participants. Furthermore, although symptomatic patients were randomised in this study, as defined by ACT score, mean F_{eNO} was relatively low at screening (mean 29.3 ppb) and further decreased between screening and randomisation (mean 21.9 ppb), indicating a "biomarker low" population with little residual ICS-responsive inflammation and therefore little room for clinical improvement with better adherence to maintenance therapy. This was borne out by the lack of change demonstrated in F_{eNO} and PEF over time. This suggests that perhaps not all participant symptoms were due to asthma and may have been related to other factors including being overweight/obesity (mean BMI $\geqslant 30\ kg{\cdot}m^{-2}$ across groups). Finally, the CIS sensors recorded the time that the maintenance inhaler was opened and closed as a surrogate for drug delivery, but did not capture data on a

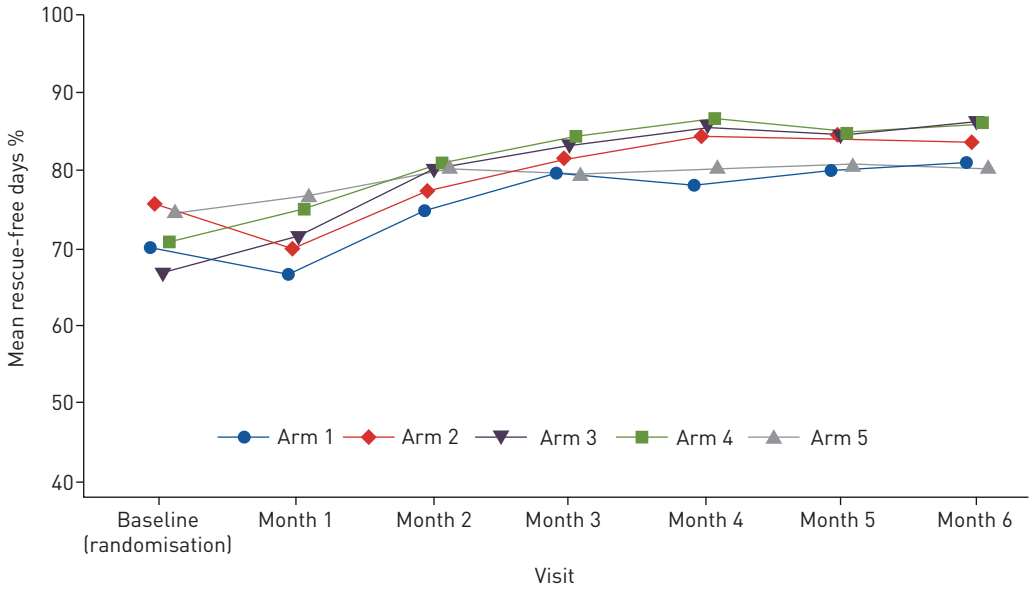

FIGURE 3 Monthly mean percentage of rescue-free days (observed data). Arm 1: maintenance data to participants and healthcare professionals (HCPs); arm 2: maintenance data to participants; arm 3: maintenance and rescue data to participants and HCPs; arm 4: maintenance and rescue data to participants; arm 5: no feedback (control).

participant's inhalation technique, the impact of which is unknown. Although common errors with inhaler technique have been reported for both DPIs [27, 28] and MDIs [27–29], the rate of errors with the ELLIPTA inhaler is reportedly low [30], suggesting that this would have been of relatively low impact in the present study. However, these results may not be generalisable to other inhalers. Sulaiman *et al.* [31] reported relatively good agreement between adherence measured by dose counter and attempted adherence (attempted inhalation) in patients with good adherence but less so in patients with poor adherence. In our study the baseline adherence data showed relatively good adherence amongst participants and therefore results may not be applicable to a broader population.

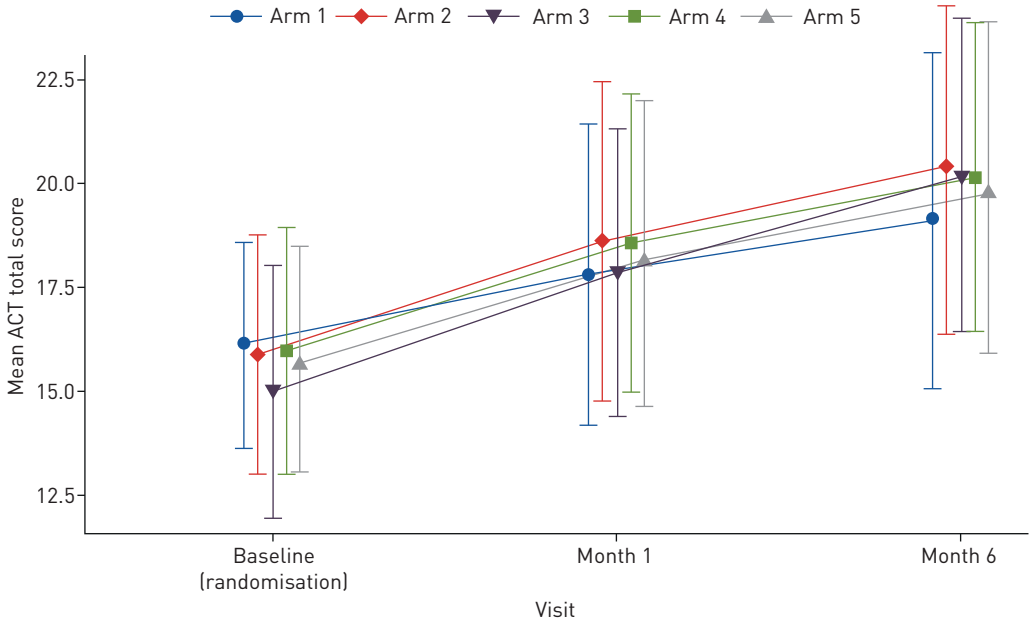

FIGURE 4 Mean±SD asthma control test (ACT) total score over the 6-month study period. Arm 1: maintenance data to participants and healthcare professionals (HCPs); arm 2: maintenance data to participants; arm 3: maintenance and rescue data to participants and HCPs; arm 4: maintenance and rescue data to participants; arm 5: no feedback (control).

Nonetheless, the primary aim of this study was to assess the effect of an adherence intervention and we demonstrated that the CIS was associated with a significant improvement in adherence to asthma controller therapy. A spike in total adherence observed during the first month for all active arms, but not seen in the control group, probably reflects the "new toy" effect of the asthma app. In addition, whilst adherence dropped off over time in the control arm, as participants reverted to their normal behaviour, adherence improvements were maintained in the CIS arms, demonstrating the utility of the system. The primary comparison exceeded the minimum detectable difference of 9% but did not meet the pre-specified difference of 15%. Considering the high mean adherence in the control arm, there was still an increase in absolute adherence of 12% in the primary intervention arm, equivalent to one additional dose of maintenance medication per week and a relative increase of approximately 17%. Adherence increased in all four CIS arms with no observed differences between arms. Although the largest change from baseline was observed in the "maintenance and rescue data to participants and HCPs" arm (arm 3), this group had the lowest baseline adherence and most room for improvement. As baseline adherence was included as a covariate in the model, this is taken into account and adjusts the least squares mean values accordingly, resulting in the largest difference in adherence over months 4–6 between a CIS arm and the control arm being seen in the "maintenance data to participants and HCPs" arm (arm 1). The baseline characteristics of age and ACT score at randomisation both had an impact on improvement in adherence to maintenance medication, with younger (18–48 years old) *versus* older participants and those with an ACT score $\leqslant$15 (worse asthma control) showing the greatest improvements. Consistent with our findings, the relationship between poor asthma control and non-adherence is well documented [2, 5, 6]. The positive response in our study shown by younger participants and those with worse asthma control is encouraging and may indicate subsets of patients who would particularly benefit from the CIS. These findings may also be pertinent when designing future studies to evaluate the CIS. Of note, these participants also had the greatest room for improvement. Identifying an ICS responsive population in terms of biomarkers such as F_{eNO} would also more likely result in the observed effects on adherence translating to improved clinical outcomes, as recently shown in a severe asthma population [32].

Although covert monitoring with the CIS could not be achieved practically in this study, several measures were incorporated to try and mimic real-world conditions. Minimising the number of clinic visits over the 6-month study period, study-independent medication dispensing visits that were initiated by the participant and the primary measurement period being over months 4–6 were all designed to result in participants reverting to their usual behaviour, as previously noted [33]. The largest improvements in adherence in the active CIS arms *versus* the control arm were observed over the last 3 months of treatment, compared with the first 3 months, supporting the benefit of this approach. The failure to demonstrate a relationship between higher adherence to maintenance treatment and lower short-acting β-agonist (SABA) use may be due to relatively low mean use of SABAs in the study or because patients with greater disease burden may use both more controller medication and more rescue medication. Whilst the provision of data on rescue medication use in addition to maintenance therapy use, or inclusion of HCPs in maintenance use data feedback, did not lead to additional benefits from the CIS in terms of maintenance adherence, results of mean data should not preclude the fact that, for some individual patients and/or HCPs, these features could provide further advantages in optimising patient adherence with treatment. On the other hand, it also suggests that a basic CIS, providing only feedback on maintenance treatment use to the patient, is a good workable system and HCPs need not view the dashboard system as an extra burden.

Clinically relevant improvements in asthma control scores were shown in all study arms, but no differences were observed between groups. This may have been due to the switch to once daily fluticasone furoate/vilanterol; however, the study was not powered on this or other secondary endpoints. The increase in the number of rescue-free days in participants who received data on their amount of rescue use suggests that their behaviour changed in response to seeing their rescue medication usage, possibly due to increased engagement in their asthma self-management. Although patients often overestimate how much maintenance medication they use [11, 34, 35], they may also underestimate how much rescue medication they use (due to misperceptions about their airway obstruction) [36]. In our study, seeing objective data for their rescue use appeared to affect this. Numerous surveys and reports have highlighted the serious consequences of under-using asthma maintenance therapy and over-using rescue medications [4, 37–39] and both have been identified as contributory risk factors for asthma deaths [38]. The problem of non-adherence is also significant in more severe disease. Approximately 65% of "difficult to control" patients with asthma referred for specialist care in the UK filled less than 80% of their inhaled maintenance medication prescriptions [40, 41]. In a US study of over 10 000 omalizumab users, 49% had very low adherence to ICS or ICS/LABA treatment (a medicine possession ratio of $\leqslant$50%) prior to initiation of biologic therapy [42]. The use of technology such as the CIS could provide a valuable tool for physicians to diagnose, monitor and support the way patients use their inhalers and ensure appropriate treatment escalation (including biologic therapy) by confirming adherence to background treatment.

In conclusion, in this first study to evaluate the impact of different components of a CIS (by comparing four different types of feedback on both maintenance and rescue medication use in participants with uncontrolled asthma), data feedback on maintenance therapy led to increased maintenance adherence and data feedback on rescue medication usage resulted in a greater number of rescue-free days, but not in additive benefits in controller adherence.

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