

Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children

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Take home message

Children with true, severe therapy resistant asthma cannot be identified without electronic adherence monitoring.

List of abbreviations

ICS	Inhaled corticosteroids
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1sec
FVC	Forced vital capacity
BDR	Bronchodilator reversibility
STRA	Severe therapy resistant asthma
DA	difficult asthma
OCS	Oral corticosteroids
BL	Baseline
FU	Follow up
ACT	Asthma control test
PAQLQ	Pediatric quality of life questionnaire
MARS	Medicine adherence rating scale
BMQ	Beliefs in medicines questionnaires

Abstract

Rationale

International guidelines recommend that severe asthma can only be diagnosed after contributory factors, including adherence, have been addressed. Accurate assessment of adherence is difficult in clinical practice. We hypothesised that electronic monitoring in children would identify non-adherence thus delineating the small number with true severe asthma.

Methods

Asthmatic children already prescribed inhaled corticosteroids were prospectively recruited and persistence of adherence assessed using electronic monitoring devices. Spirometry, airway inflammation and asthma control were measured at start and end of the monitoring period.

Results

93 children (62 male) median age 12.4 years were monitored for a median of 92 days. Median monitored adherence was 74% (range 21-99%). We identified four groups: (1) good adherence during monitoring with improved control, 24% (likely previous poor adherence); (2) good adherence with poor control, 18% (severe therapy resistant asthma); (3) poor adherence with good control, 26% (likely over-treated); (4) poor adherence with poor control (32%). No clinical parameter prior to monitoring distinguished these groups.

Conclusions

Electronic monitoring is a useful tool for identifying children in whom a step up in treatment is indicated. Different approaches are needed in those who are controlled when adherent, or who are non-adherent. Electronic monitoring is essential in a paediatric severe asthma clinic.

Key words: adherence, asthma control, children

Introduction

Sub-optimal adherence to inhaled corticosteroids (ICS) is the most common reason for treatment failure in asthma (1). In children with apparently severe asthma referred to a tertiary centre, prescription pick up was <80% in over half the cohort (2). Previous studies have demonstrated a link between sub-optimal adherence and an increased risk of exacerbations, hospital admissions, asthma related deaths and reduced lung function (3, 4). Recent international guidelines for severe asthma recommend that non-adherence to treatment should be considered in all difficult to control patients. However, the authors acknowledge that detecting poor adherence can be challenging (5). Physician assessment is little better than chance (4) and self and parental reported adherence over-estimates treatment taken (6). Prescription pickup can act as a guide; those who pick up less prescriptions than they should are clearly not taking the intended dose. However, even when prescriptions are collected we do not know if the treatment is actually taken. Developing better tools for measuring adherence is important: firstly so that intervention strategies for adherence can be targeted to the appropriate patients (1) and secondly to avoid inappropriate investigations and escalation of treatment. Electronic monitoring devices can provide accurate data on medication usage including timing and number of doses taken. However, previously these devices were not widely commercially available. Newer generations of electronic monitoring devices (such as Smartinhalers™) can be used with a range of inhalers and the data downloaded remotely. This technology gives a clearer picture of adherence and how it impacts on asthma control and exacerbations. This information can potentially be used to guide asthma management

In this study we monitored adherence using electronic monitoring devices in children with a range of asthma severities followed up in a tertiary asthma centre.

We hypothesised that electronic monitoring could separate patients with persistent severe symptoms despite proven good adherence from patients with poor adherence and potential for optimisation of standard asthma therapy and secondly that electronically monitoring adherence would lead to improvements in asthma control.

Methods

Study population and design

This was a prospective observational cohort study. Participants were recruited from the Outpatient Department of the Royal Brompton Hospital, London between August 2014 and February 2015. All children were aged 5-17 years and had asthma diagnosed on the basis of evidence of one or more of the following:

- Documented bronchodilator reversibility ($\geq 12\%$)
- Recorded evidence of spontaneous variation in first second forced expired volume in 1 s (FEV_1) ($\geq 12\%$) in the past year
- Airway hyper-responsiveness confirmed by direct or indirect challenge tests

The children recruited were classified into three groups based on treatment levels and previous assessments: severe therapy resistant asthma (STRA), difficult asthma (DA) and mild-moderate asthma (see OLS Appendix A1).

1. Severe therapy resistant asthma (STRA): children in whom potentially modifiable factors had previously been addressed and who continued to have either or both of ongoing poor control and acute asthma attacks despite high dose ICS plus add on therapies (stage 4/5 BTS/SIGN guidelines)(7).
2. Difficult asthma (DA): children previously or currently prescribed high dose ICS who had been found to have modifiable factors (such as poor adherence) as a cause for ongoing poor asthma control
3. Mild-moderate asthma: well or partly controlled according to GINA guidelines (8) with a prescribed dose of ICS of $\leq 250\text{mcg FP}$ or $\leq 400\text{mcg BUD}$ (or equivalent) per day with the need for none or no more than one controller medication (long acting beta agonists, leukotriene receptor antagonists or theophylline).

Most children had previously been enrolled in our difficult asthma investigation protocol as previously described (2) (see OLS Appendix A2). All children attended a baseline visit at the start of the monitoring period and follow up visit 8-16 weeks later at the end of the monitoring period. Study visits were carried out as part of planned clinic visits hence the variability in follow up. Assessments carried out at the two study visits are shown in Figure 1. The study was approved by the Regional Ethical Committee (NRES Committee London-Westminster). All parents / legal guardians gave written informed consent prior to any study

procedures and the children gave age appropriate assent or consent. The study was registered with clinicaltrial.gov (NCT02252289).

Figure 1

Study procedures

Adherence monitoring

Inhaler technique competence was assessed by the specialist asthma nurses in clinic before the start of the study. Adherence was monitored using an electronic monitoring device Smartinhaler® (Adherium, New Zealand). Smartinhalers were available for Symbicort, Seretide and Flixotide. 1% of devices had to be exchanged before having been given out to a patient due to technical problems. In 5% of devices the battery died within a range of 2 weeks before the follow up visit so this period had to be deducted from the adherence calculation. Participants and their guardians were informed that the Smartinhaler would record the total number of actuations of their ICS per day. It was attached to the participant's own inhaler in clinic at the baseline visit. The devices contain a microchip which records the date and time each dose is taken. The data were downloaded at the follow up visit by the study physician who managed the Smartinhaler set up and software.

The Medicines Adherence Rating Scale (MARS-5) was used as a measure of self-reported adherence (9). The Beliefs about Medicines Questionnaire (BMQ) was used to elucidate determinants of adherence (10).

Adherence was defined as the percentage of controller medication doses taken relative to the number of doses prescribed. Adherence was defined a priori as a ratio of doses taken (based on previously published definitions): good adherence $\geq 80\%$ (11), moderate adherence 60-79% (12) and poor adherence $< 60\%$ (12).

The daily adherence was calculated with a maximum of 100%, to avoid falsely increased values due to dose dumping.

Assessments

Asthma control was measured using the Asthma Control Test (ACT) (13) for children aged ≥ 12 and the Childhood Asthma Control Test (cACT) for children < 12 years (14).

Baseline spirometry to measure FEV₁ and FVC was performed using a spirometer (Vitalograph Ltd, Buckingham, UK) in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (15). Bronchodilator reversibility (BDR) testing was performed 15 minutes after administration of 1000mcg salbutamol via a spacer. Exhaled nitric oxide (FENO) was measured using an online single breath chemiluminescence analyser (NIOX VERO, Aerocrine, Stockholm, Sweden) at an expiratory flow rate of 50ml/s (16).

Quality of life and psychological morbidity was assessed using the mini Paediatric Asthma Quality of Life Questionnaire (mPAQLQ) (17).

Exacerbations in the 3 months prior to the baseline visit and during the monitoring period were recorded from the interview with the patients and the hospital records. Severe exacerbations were defined as 3 or more days of oral prednisone prescription (18). Moderate exacerbations were defined as the presence of one or more of deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use, lasting for 2 days or more. Patients also noted their symptoms, any changes in medication and oral prednisolone courses in a symptom diary.

Atopy was defined as one or more positive skin prick tests to a panel of common aeroallergens: mixed grasses, cat, dog, house dust mite, *Aspergillus*, trees, *Alternaria*, *Cladosporium*, *Penicillium*, (wheal ≥ 3 mm) or serum specific IgE ≥ 0.34 kU/litre in the last three years.

No prescribed treatment changes were made in any patient until the end of the monitoring period.

Statistical analysis

Statistical analysis was carried out using the statistical software GraphPad Prism and R (19). Data were tested for normality using visual inspection, histograms and Kolmogorov-Smirnov testing. Parametric tests were used for normally distributed data. If the data were not normally distributed or there were only small numbers non-parametric tests were used. The significance level was set at <0.05 .

Differences over the monitoring period (for each of the parameters measured) were analysed using the Wilcoxon signed rank or paired t-test.

Comparative analysis of variance between 2 groups for continuous data were performed using the student's t test for normally distributed data and the Mann Whitney U test for non-normally distributed data and for more than 2 groups the ANOVA or Kruskal Wallis respectively. Conservative Bonferroni correction was applied for multiple comparisons. A comparison of proportions between groups was performed using the Pearson Chi² test.

Results

In total 108 children were recruited. Fifteen patients did not complete the study (Figure 1 OLS). The data for the 93 children who completed the study are presented. Those who dropped out were significantly older and had more comorbidities (including migraine, focal epilepsy and delayed puberty) than those who completed the study. There were no other significant differences in baseline characteristics between the two groups (Table1).

Table 1: Demographics

	Participants who completed the study (n=93)	Drop outs (n=15)
Male sex, n (%)	62 (67)	9 (60)
Age (years) $\pm$ SD	11.9 $\pm$ 3.1	14.1 $\pm$ 3.0*
STRA, n (%)	21 (23)	2 (13)
DA, n (%)	51 (55)	8 (53)
Mild/moderate asthmatics, n (%)	21 (23)	5 (33)
Atopic, n (%)	82 (88)	13 (87)
Comorbidity (%)	17 (18)	8 (53)*
Treatment		
Median ICS dose (BDP equivalent mcg/day)	800 (100-3200)	1000 (200-2000)
Leukotriene-receptor-antagonist, n (%)	55 (59)	8 (53)
Long-acting β -agonist, n (%)	91 (98)	14 (93)
Theophylline n (%)	10 (11)	2 (13)
Maintenance OCS n (%)	8 (9)	2 (13)
Omalizumab n (%)	4 (4)	0 (0)

ICS: inhaled corticosteroids, BDP: Budesonide propionate. OCS: oral corticosteroids, STRA: severe therapy resistant asthmatics, DA: difficult asthmatics. Data shown as median (range) unless stated otherwise. *p<0.05

Adherence data

The median duration of monitoring was 92 days (range 56-200). Median adherence for the whole population was 74% (range 21-99%). Good adherence was found in 39 patients (42%) who took $\geq 80\%$ of their prescribed medication, 25 patients (27%) took 60-79% and 29 patients (31%) took $< 60\%$ of their prescribed treatment (table E2 OLS). Suboptimal adherence (adherence $< 80\%$) was seen in 58% of all patients in the study despite knowing they were being monitored.

There was no significant difference observed between the adherence groups with $\geq 80\%$, 60-79% or $< 60\%$ adherence in the following parameters at the start of monitoring: FeNO, FVC, FEV₁, BDR, ACT, cACT, mPAQLQ, exacerbation rate or OCS courses. The proportion of STRA, DA or mild asthmatics was not significantly different between the adherence groups ($p=0.22$; data not shown).

All patients and families stated that they took their asthma medication most of the time and as instructed by their physician and the median MARS-5 score did not show any significant difference between the three adherence groups (24 vs. 23 vs. 23 – see OLS table E3).

The BMQ revealed a significantly higher score for the item relating to overuse and over-prescription by health care professionals in the non-adherent group than in the adherent group (median BMQ score 2.2/5 vs 2/5) (OLS table E3). There were no significant differences in the other domains (belief about necessity of medication, concern about medications or harm of medications). Prescription uptake data for the year prior to the start of the study were available for 51 patients (55%). Prescription uptake and electronically monitored adherence showed no significant correlation. Electronically monitored adherence varied between 27 and 99% in participants with a prescription uptake of 100% (OLS Figure E2).

Identification of clinically meaningful groups

At the end of the monitoring period four groups could be identified according to their adherence and asthma control (ACT/cACT score). Clinical characteristics of these 4 groups are shown in table 2a.

Group 1: Previous poor control, but during monitoring, good adherence and good control $n=22$ (24%); these patients most likely improved their control by being adherent when they knew they were being monitored. Over the monitoring period

there were significant improvements in FEV1, mPAQLQ and exacerbation rate after the Bonferroni correction for multiple testing.

Group 2: Poor control of asthma before and during monitoring, despite good adherence n=17 (18%); these children are likely to have true severe therapy resistant asthma requiring increased or add-on treatment. There were no significant improvements in this group.

Group 3: Good asthma control ($ACT/cACT \geq 20$) at the end of monitoring, despite suboptimal adherence in the monitoring period ($<80\%$): n= 24 (26%); it is likely that these patients are over-treated. Over the monitoring period mPAQLQ improved significantly (after Bonferroni correction).

Group 4: Suboptimal control and poor adherence n=30 (32%); these patients need the reasons for poor adherence explored. There were no significant improvements in any measure of asthma control over the monitoring period.

Changes in asthma control over the monitoring period are displayed in Table 2b. All the tests were adjusted for conservative Bonferroni multiple comparison test due to having analyzed a maximum of 8 asthma control parameters in each category ($0.05/8$ interaction tests = 0.00625). These four groups and potential management options are shown in Figure 2.

Table 2a: Baseline characteristics of four groups stratified according to adherence and asthma control at the end of the monitoring period

	Good adherence ($\geq 80\%$)		Suboptimal adherence ($< 80\%$)	
	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Asthma control at follow up	ACT ≥ 20	ACT < 20	ACT ≥ 20	ACT < 20
N: patients (% of population)	22 (24%)	17 (18%)	24 (26%)	30 (32%)
Age, mean in years $\pm$ SD	11.5 $\pm$ 2.8	11.6 $\pm$ 3.8	12.2 $\pm$ 2.5	12.2 $\pm$ 3.3
Sex: male	16/22	10/17	18/24	18/30
Ethnicity: Caucasian	13/22	12/17	10/24	16/30
Atopic	18/22 (82%)	16/17 (94%)	20/24 (83%)	28/30 (93%)
BMI	18 (14-29)	20 (14-30)	21 (15-39)	20 (14-32)
Smoke exposure: yes	6/22 (27%)	3/17 (18%)	3/24 (13%)	6/30 (20%)
FEV1, mean % predicted $\pm$ SD	88.3 $\pm$ 15.4	87.6 $\pm$ 24.7	83.7 $\pm$ 19.2	86.6 $\pm$ 17.3
BDR, %	7.4 (0-59)	6.1 (0-52)	9.2 (0-123)	8.5 (0-49)
FeNO, ppb	18 (5-111)	53 (6-175)	35.5 (13-122)	42.5 (6-118)
mPAQLQ	6.2 (3-7)	3.9 (2-6.9)	6.3 (2.3-7)	4.1 (2.2-7.0)*

Data are presented as medians (range) unless stated otherwise. BMI: body mass index, BL: baseline visit, BDR: bronchodilator reversibility, %, FeNO: fractional exhaled nitric oxide, mPAQLQ: median pediatric quality of life questionnaire score, FEV1: forced expiratory volume in 1s

Table 2b: Changes in asthma control over the monitoring period in the four groups stratified according to adherence and asthma control

	Visit	Good adherence ($\geq 80\%$)		Suboptimal adherence ($< 80\%$)	
		GROUP 1	GROUP 2	GROUP 3	GROUP 4
Asthma control at follow up		ACT ≥ 20	ACT < 20	ACT ≥ 20	ACT < 20
N patients (% of population)		22 (24%)	17 (18%)	24 (26%)	30 (32%)
FEV1, mean % pred $\pm$ SD	BL	88.3 $\pm$ 15.4	87.6 $\pm$ 24.7	83.7 $\pm$ 19.2	86.6 $\pm$ 17.3
	FU	98.9 $\pm$ 16.4	93.0 $\pm$ 18.4	89.9 $\pm$ 13.4	91.0 $\pm$ 15.5
	p-value	0.002*	0.158	0.134	0.060
BDR, %	BL	7.4 (0-59)	6.1 (0-52)	9.2 (0-123)	8.5 (0-49)
	FU	2.3 (0-12)	6.2 (0-18)	3.8 (0-42)	4.5 (0-20)
	p-value	0.014	0.2067	0.023	0.044
FeNO, ppb	BL	18 (5-111)	53 (6-175)	35.5 (13-122)	42.5 (6-118)
	FU	11 (5-85)	18 (8-155)	33.0 (9-96)	31.5 (8-193)
	p-value	0.029	0.280	0.015	0.419
mPAQLQ	BL	6.2 (3-7)	3.9 (2-6.9)	6.3 (2.3-7)	4.1 (2.2-7.0)
	FU	6.8 (5.5-7)	4.9 (1.9-6.2)	6.7 (4.8-7)	4.6 (2.6-6.7)
	p-value	0.0003*	0.015	0.006*	0.074
Exacerbations, n	BL	1 (0-10)	2 (0-8)	1 (0-10)	1 (0-8)
	FU	0 (0-2)	0 (0-2)	0 (0-2)	1 (0-4)
	p-value	0.005*	0.040	0.039	0.891

Data are presented as medians (range) unless stated otherwise. *Value significant after adjusting for Bonferroni multiple comparison test $p < 0.0065$. BL: baseline visit, FU: follow up visit, BDR: bronchodilator reversibility, %, FeNO: fractional exhaled nitric oxide, mPAQLQ: median pediatric quality of life questionnaire score, FEV1: forced expiratory volume in 1s

Only the group with good adherence and good asthma control had a significant improvement across a range of asthma control measures at the end of the monitoring

period. Those with good control at the end of monitoring despite suboptimal adherence also showed improvements across a range of measures but only the increase in mPAQLQ reached statistical significance after Bonferonni correction. The improvement in FEV1 has reached clinical significance according to the ATS definition. The ATS considers a minimally clinically significant difference (MCID) of 10% change in FEV1 relevant for adults (18). There is little data around about the MCID in FEV1 that children perceive. The ATS states that a change of 20% of FeNO indicates a significant change following an intervention (20). According to these recommendations a significant reduction was seen in the second group with good adherence and suboptimal control only. The MCID for ACT is 3 points which was achieved in the group with good and moderate adherence (table E2 OLS) (21). The minimal important difference for the PAQLQ is 0.5 points (22) which was reached in all groups except the group with suboptimal adherence and good asthma control.

Figure 2

Changes in asthma control over the monitoring period

FeNO, FVC, FEV1, GINA control, ACT, cACT, mPAQLQ, number of exacerbations and BDR improved significantly over the monitoring period for the cohort as a whole (Table E1 OLS). Those with adherence $\geq 80\%$ improved in all asthma control parameters, the group with 60-79% adherence improved in some but not all asthma control parameters. Those with adherence $< 60\%$ did not improve in any asthma control variable (Table E2 OLS). There was a significant but weak correlation between adherence and FeNO at the end of the monitoring period ($r=0.46$ $p<0.001$). No correlation was found between adherence and any other parameter.

Discussion

This study has demonstrated the importance of accurate adherence monitoring in children with asthma. Suboptimal adherence (<80%) was found in 58% of the children enrolled in this study despite knowing they were being monitored.

Asthma control improved following a period of monitoring in the cohort as a whole, however this was not the case for all and importantly we were able to identify clinically meaningful subgroups. We have shown that this technique delineates two groups with good recorded adherence. The first group in whom symptoms, lung function and exacerbation rate improved and who seemed to take more treatment after monitoring started since their control improved without any other intervention; and the second group who were adherent but whose control remained poor at the end of monitoring. This latter group are likely to have true severe asthma and merit further phenotyping of their airway disease. We identified a non-adherent group, in whom the reasons for poor adherence need to be explored sensitively. Within this group some had improved control despite suboptimal adherence and were presumably being prescribed more treatment than they actually needed. Electronic monitoring has only ensured good adherence in less than half the children in this study and therefore monitoring alone is not a sufficient intervention. However, we have demonstrated that electronic monitoring is an important tool to distinguish clinically important groups. Other factors that might have influenced improvement in asthma control cannot be excluded; however, the fact that the group with the worst adherence (<60%) did not improve in any measure of asthma control highlights the importance of adherence monitoring. Furthermore, even those previously thought to have severe therapy resistant asthma who had undergone a detailed nurse-led assessment of adherence, including prescription uptake and a home visit as part of our Difficult Asthma protocol, were no more adherent than the other groups. Therefore the distinction between difficult asthma and severe, therapy resistant asthma cannot be made with certainty in the absence of electronic monitoring. We suggest that the gold-standard definition for severe therapy resistant asthma must now include persistent poor control despite electronically recorded good adherence to treatment.

This study has again confirmed the inadequacy of self-reported adherence and the limitation of prescription uptake records. Using standard methods (exclusive of electronic monitoring) children with good adherence during the monitoring period were indistinguishable at

baseline from those with poor adherence. This highlights the difficulties in detecting poorly adherent patients in clinical practice.

The improvements in asthma control over the monitoring period suggest that adherence improved over this time period since we made no changes in asthma treatment. We accept that we are not capturing the participant's "usual" adherence and that the electronic monitor is an intervention in itself even though it is not leading to improved adherence in all patients but just in a subgroup. However, the information gained is of vital importance in determining future management, including tailoring adherence interventions. For those with suboptimal asthma control who were poorly adherent during monitoring it is unlikely that a monitoring based system, even one which includes reminders will be beneficial (23). In this subgroup the individual patient barriers to adherence need to be explored and interventions tailored accordingly. Management needs to focus on the reasons for poor adherence and simply escalating the prescribed treatment will be futile. For those whose adherence improved due to monitoring, the challenge remains as to how to maintain good adherence beyond the monitoring period (or even during prolonged monitoring). Even in a comprehensive asthma care program 41% of children did not manage to reach good adherence despite frequent consultations (3). However, demonstrating that good control can be achieved may help to initiate a more sustained behaviour change. Further management in this group should focus on maintaining adherence and finding the optimal asthma treatment to maintain control.

Some of those with poor adherence had good control at the end of monitoring suggesting that, although remaining suboptimal, their adherence had probably improved. Their prescribed asthma treatment could potentially be reduced. It is likely that treatment had previously been escalated because poor asthma control may have been attributed to under-treatment instead of non-adherence. Finally those with on-going poor control despite monitored good adherence are either manipulating the devices (either deliberately by dose dumping or because of poor technique) or are truly steroid resistant. The next step would be a period of directly observed therapy before administering expensive additional treatments like omalizumab and other novel monoclonals.

We did not find a relationship between any of the measures of asthma control at baseline and monitored adherence. FeNO at the end of the monitoring period had the best correlation with adherence compared with other parameters measured. The relationship

between FeNO and adherence was similar to the recently published data from Klok et al. (24). FeNO differed significantly at the end of monitoring between those with good and poor adherence. In those with poor control despite good adherence there was no significant reduction in FeNO, again suggesting these are a truly steroid resistant group or adherence was over-estimated (25). FeNO is potentially a useful biomarker used in conjunction with adherence monitoring in determining management. In an exploratory analysis of participants with good adherence during electronic monitoring those whose FeNO remained high were prescribed a higher dose of ICS, had worse lung function and asthma control than those who had a fall of at least 10ppb over the monitoring. This suggests that changes in FeNO could be used to identify those with previously poor adherence whose adherence had improved because they were being monitored. As with the McNicholl study (26) in adults, FeNO suppression as a marker for improved adherence is most useful in those with high FeNO at baseline. This is potentially a useful clinical tool for monitoring adherence particularly as electronic monitoring devices are not widely available. However, 35% of our cohort had FeNO levels <25ppb at baseline and therefore FeNO suppression cannot be used as a guide in these patients.

There are a number of limitations with the devices used in this study. The Smartinhaler records actuations and not whether the dose was actually inhaled or whether the inhaler was used correctly. Newer devices are in development which measure inhalational flow or sound. However, the differential improvements in those with good, moderate and poor adherence suggest that the monitored adherence was accurate. The costs of these devices is not insignificant (~100-150€) and therefore funding was only available for the most common inhalers in our clinic (Symbicort, Seretide and Flixotide).

In this study 14 % of participants did not complete the study and mislaid their Smartinhaler or failed to attend follow up. Clearly no adherence information was available for these participants. It is possible that this is a reflection of a chaotic lifestyle which is likely to impact on adherence and therefore even a lost device can provide some useful information. Some may have felt that adherence monitoring was intrusive or unnecessary. Those who dropped out were older than those who completed the study and were more likely to have co-morbidities. Adolescents, particularly those with other health needs are a well-recognised risk group and the importance of meaningful engagement with this group and ensuring they

are not lost to follow up during transition to adult services cannot be stressed strongly enough.

The cut-points for adherence categories were based on previous studies (11, 12). The differential responses in asthma control between the three groups suggest that these are reasonable cut points for defining good, moderate and poor adherence. However, we accept that other studies have used other definitions for good and poor adherence and that these definitions are somewhat arbitrary. In some studies it has been shown that at least 80% of the prescribed dose needs to be taken to achieve optimal benefit (11). In our study even those with lower adherence (60 – 79%) showed some significant improvements (OLS table E3). The lack of improvement in those with adherence <60% suggests that this is a reasonable definition of poor or non-adherence and is keeping with the study by McNally et al which found a significant difference in healthcare utilization in those with adherence below 62% (12).

The monitoring period in this study was relatively short and the impact of monitoring as an intervention is likely to wane with time (27). Furthermore, we acknowledge that this was not an interventional study as there was no control group so improvement cannot be attributed solely to adherence monitoring. Unmeasured influences or regression to the mean might have an effect as well.

Although one would hope that the demonstration of improved control with good adherence would help to initiate behaviour change in the individual this is perhaps an over optimistic view and the design of this study does not enable us to answer that question. Electronic monitoring studies which have used feedback and reminders have shown impressive differences in adherence in the intervention group but more modest improvements in asthma control (27, 28) This may be because the monitoring devices used measured actuations and not inhalation and participants in the intervention arm may have been manipulating the devices or had poor technique. Furthermore, interventions for those whose adherence remains poor when monitored are likely to be different to those who do well during a period of monitoring. For example, using reminders will help those who frequently forget (29) but will have little impact on those who are concerned about side effects or think the inhalers are ineffective and for whom an educational intervention would be more appropriate (30-32).

Further research is needed to assess the utility of combining electronic monitoring devices and tailored adherence interventions. However, this study has clearly demonstrated that electronic monitoring is essential if poor adherence is to be excluded as a cause of poor asthma control. Furthermore, the technique can be used to identify clinically meaningful subgroups whose ongoing management could be determined by a combination of adherence assessment and clinical control. We conclude that it is not possible to optimally manage severe asthma without the availability of objective monitoring of adherence.

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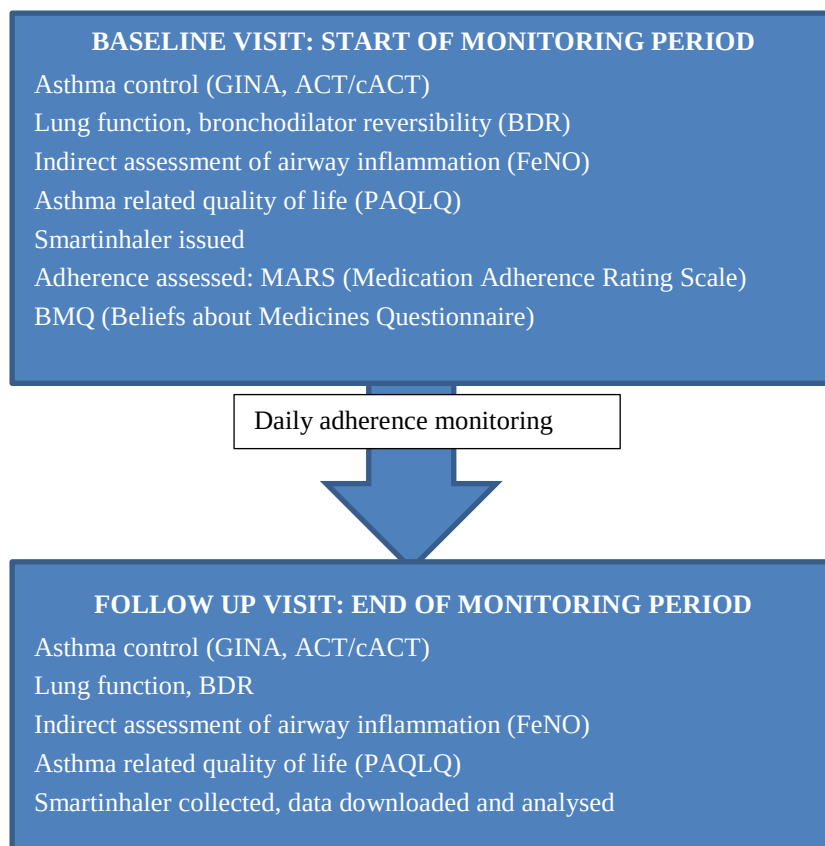
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Figures

Figure 1: Assessments at each study visit



GINA: Global Initiative for Asthma, (c)ACT: (childhood) asthma control test, FeNO: fractional exhaled nitric oxide, PAQLQ: pediatric quality of life questionnaire

Figure 2: Management strategies based on asthma control and adherence during monitoring

