A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma

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On a period of monitored adherence only 27% of patients were refractory and adherent and thus need add-on therapy http://ow.ly/ddQr30gTpmb

Cite this article as: Sulaiman I, Greene G, MacHale E, *et al*. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *Eur Respir J* 2018; 51: 1701126 [https://doi.org/10.1183/13993003.01126-2017].

ABSTRACT In severe asthma, poor control could reflect issues of medication adherence or inhaler technique, or that the condition is refractory. This study aimed to determine if an intervention with (bio) feedback on the features of inhaler use would identify refractory asthma and enhance inhaler technique and adherence.

Patients with severe uncontrolled asthma were subjected to a stratified-by-site random block design. The intensive education group received repeated training in inhaler use, adherence and disease management. The intervention group received the same intervention, enhanced by (bio)feedback-guided training. The primary outcome was rate of actual inhaler adherence. Secondary outcomes included a pre-defined assessment of clinical outcome. Outcome assessors were blinded to group allocation. Data were analysed on an intention-to-treat and per-protocol basis.

The mean rate of adherence during the third month in the (bio)feedback group (n=111) was higher than that in the enhanced education group (intention-to-treat, n=107; 73% *versus* 63%; 95% CI 2.8%–17.6%; p=0.02). By the end of the study, asthma was either stable or improved in 54 patients (38%); uncontrolled, but poorly adherent in 52 (35%); and uncontrolled, but adherent in 40 (27%).

Repeated feedback significantly improved inhaler adherence. After a programme of adherence and inhaler technique assessment, only 40 patients (27%) were refractory and adherent, and might therefore need add-on therapy.

Introduction

Several new therapies are available for patients with severe uncontrolled asthma [1–3]. Practice guidelines recommend that in addition to profiling the phenotype of asthma, clinicians should also address adherence to therapy and inhaler technique before adding one of these treatments [4, 5]. Therefore, there is a need for clinicians to have a clear way to distinguish people who have poor asthma control due to issues related to adherence or inhaler technique, before using any add-on therapies.

Identifying inadequate adherence is difficult, as self-reporting is unreliable [6–11] and while pharmacy refill records may indicate that the patients have collected the prescriptions, this does not necessarily mean that they have used the inhaler either correctly or regularly. Even demonstrations of correct inhaler technique do not necessarily mean that the inhaler is used correctly when the individual is not being observed [12]. Electronic monitors provide objective measures of assessing adherence, and are therefore considered the gold standard [13]. However, most electronic devices do not indicate how well the inhaler has been used, *i.e.* they do not assess inhaler technique.

To address this problem, we developed a device, the INhaler Compliance Assessment (INCA), which could be attached to an inhaler to make a digital audio recording each time the inhaler is used. Automated analysis of the time and features of the audio provides objective assessment of both when and how the inhaler was used [14]. The technology has been validated *in vitro* and externally against other methods of assessing adherence [15–19]. Analysis of the audio and digital data graphically reports useful (bio) feedback: features of adherence such as time, habit and technique of use and the relationship of adherence to peak flow can be easily communicated to the patient by the clinicians. In addition, real-time information on inhaler adherence (including time of use and technique of use), peak expiratory flow and asthma control can be used to appropriately assess patients for step-up or even step-down therapy [4, 5].

To address the challenge of poor adherence in patients with severe unstable asthma, we devised an intensive, goal-orientated intervention, which includes several behaviour change techniques, as described by Michie *et al.* [20]. The details of the intervention have been described previously [21]. In this study, we tested the hypothesis that visual (bio)feedback to the patient on their specific components of adherence would improve adherence. To test this hypothesis, we studied patients with severe unstable asthma, who attended specialist asthma clinics, using the same enrolment criteria as those used in recent clinical trials that evaluated the use of additional bronchodilators [22, 23] and targeted biologics for uncontrolled asthma [1–3].

Methods

We followed the Consolidated Standards of Reporting Trials (CONSORT) and Template for Intervention Description and Replication (TIDIER) guidelines to report this nurse-led, patient education intervention with visual (bio)feedback of the individual's patterns of inhaler use. This was a prospective, multicentre, randomised, controlled, open-label clinical trial, conducted between February 7, 2012 and December 15, 2015. The protocol of the study and statistical plan has been published [21]. This study was sponsored by the Royal College of Surgeons in Ireland (RCSI), approved by the local hospitals Research Ethics Committees and registered on Clinicaltrials.gov, NCT01529697.

Participants

Patients aged ⩾18 years with stage 3 to 5 asthma, according to the Global Initiative for Asthma (GINA) management strategy, were recruited from five specialist asthma clinics. Visits were performed at the clinical research centres of these university hospitals. Asthma diagnosis was based on one of the following: airflow obstruction with at least 12% reversibility, a >20% fall from baseline forced expiratory volume in 1 s (FEV_1) during a standard bronchial provocation challenge or variability in the diurnal peak expiratory flow of more than 15%.

This article has supplementary material available from erj.ersjournals.com

Received: June 21 2017 | Accepted after revision: Sept 29 2017

Support statement: This was a researcher-initiated study, funded by the Health Research Board of Ireland (HRA POR/2011/59). The authors acknowledge support from the Dublin Clinical Centre for Research. GSK provided the Diskus inhaler for this study (GSK Study Code 114882). The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

This study is registered at http://Clinicaltrials.gov with identifier NCT01529697.

Inclusion criteria: patients already attending the specialist clinic and using a prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines [4, 5] for more than 3 months, and who had at least one exacerbation that was treated with systemic glucocorticoids in the prior year, and whose condition was not controlled as per the GINA definition of uncontrolled asthma [4, 5].

Exclusion criteria included an unwillingness to participate in a clinical study or prior hypersensitivity to salmeterol/fluticasone. Prior to randomisation, all patients provided informed consent.

Interventions

All participants were asked to measure their peak expiratory flow (PEF) using an electronic monitor (ASMA-1, Vitalograph, Ireland) and to use their salmeterol/fluticasone Diskus inhaler, one puff, twice per day. Although they used the INCA device, the intensive education group did not receive (bio)feedback based on this device. Participants were not blinded to group assignment, but this group was blinded to INCA-(bio)feedback.

Specific behaviour change techniques for both groups are outlined in supplementary table S1. All intervention techniques were standardised using an intervention manual. Fidelity of the intervention was checked by timing the consultation, and in a sample cohort of 10%, by direct observation of the intervention being performed.

Outcomes

Adherence

The primary outcome was the rate of actual inhaler adherence, expressed as cumulative drug exposure for the last month of the intervention, calculated from INCA data.

The design, validation and use of the INCA have all been reported [14, 15, 17–19]. Proficiency of inhaler use was assessed using an automated signal processing based algorithm [14]. Our prior studies have identified that, in addition to not opening the inhaler, there are three critical errors in handling the Diskus [16–19]. These included: incorrect priming of the device; exhalation into the inhaler after priming, but before inhalation; or inhalation effort resulting in insufficient inspiratory flow. Analysis of the audio features recorded to the device can detect these critical errors. Critical errors in inhaler use, along with missed doses were combined into a single measure of adherence calculated as an area under the curve [24]. This was termed "actual adherence", and in prior studies we have shown that this method of analysis is more reflective of clinical outcomes than other standard methods of assessing adherence [25, 26]. Non-critical errors, such as short breath holds or multiple inhalations that do not affect medication delivery [27], were not included in the calculation of adherence. This measure incorporated the time of use, interval between doses and technique of use, and was calculated as a ratio of expected drug accumulation, if adherence could be matched to what was actually taken [26].

Clinical outcomes

At the end of the 3 months, data on PEF, asthma control (Asthma Control Test (ACT) and Asthma Quality of Life Questionnaire (AQLQ)) and inhaler adherence (from the INCA device) were combined to provide a clinically meaningful and personalised assessment of each patient's asthma. This provided a clinician with important information on aspects of uncontrolled severe asthma, as suggested by GINA [4, 5] as follows: 1) assess adherence (patient is uncontrolled and adherence is poor); 2) review comorbidities (patient is uncontrolled, adherence is good and PEF is stable); 3) step-up therapy (patient is uncontrolled, adherence is good and PEF is unstable); 4) consider reducing therapy, if the patient has both PEF >80% and is controlled.

Sample size

A sample size of 200 was estimated to have a power of 80% at the 0.05 significance level, with a 10% difference between the two study groups in the actual adherence rate and a 0.25 standard deviation, assuming that the rate of actual adherence was 0.65 in the first month. It was assumed that since the intensive education group was receiving enhanced care over the standard, that there would be improved adherence in this group compared to a 'true demonstration' group. The sample size baseline adherence rate was based on our preliminary findings in asthma patients [15], primary care [25], chronic obstructive pulmonary disease patients [28] and the relatively modest effect of adherence interventions generally described [29]. With an expected dropout rate of 10%, the target sample size to recruit was 220 patients.

Randomisation

Patients were block randomised by an electronic system and stratified by site. Block sizes were also random and varied from eight to 12, with a 1:1 allocation. The only blinding utilised was that of participants in the intensive education group not being provided (bio)feedback from the INCA, as described above.

Study implementation

The study design is summarised in a prior publication [21]. Each subsequent month, the patient was given a new inhaler with the INCA device attached, they were asked to demonstrate their inhaler use, and errors were corrected in the intensive education group using a checklist score [30, 31], or in the (bio)feedback group using visual feedback from the INCA device. Other data collected and recorded each month included: the AQLQ, ACT, reliever medication use, PEF and exacerbations.

Statistical analysis

All subjects who completed at least 1 month of the study were included in an intention-to-treat (ITT) analysis of the primary outcome (n=203), actual adherence at month 3. In order to include participants with missing data in the analysis, we used multiple imputation techniques [32]. Missing adherence data were multiply imputed (20 imputations) using chained linear regression equations. Variables used for imputation were age, sex, body mass index (BMI), FEV_1 (baseline) and any available adherence data. Imputation was performed separately for intensive education and (bio)feedback groups. A secondary per-protocol analysis was also conducted.

Results

Participants

Between February 2012 and December 2015, 218 patients were recruited and randomised (111 to (bio) feedback and 107 to intensive education). The flow of patients through the study is shown in figure 1. 50 patients (28 in the (bio)feedback group) were switched to the discus device from another inhaler device. The baseline characteristics of both groups are shown in table 1.

Inhaler adherence and technique

Including all consented participants who had at least 1 month of calculated adherence (n=206, 105 (bio) feedback and 101 intensive education) as part of an ITT analysis, a significant difference was observed in the primary outcome, favouring the (bio)feedback treatment group (table 2). The rate of actual adherence during the third month in the (bio)feedback group was 73% (95% CI 69–77%) *versus* 63% (95% CI 57–70%) in the intensive education group ($p \leqslant 0.01$). Comparing (bio)feedback and intensive education groups, a significant difference was observed in the change in adherence from month 1 to month 3 ($p=0.02$). In

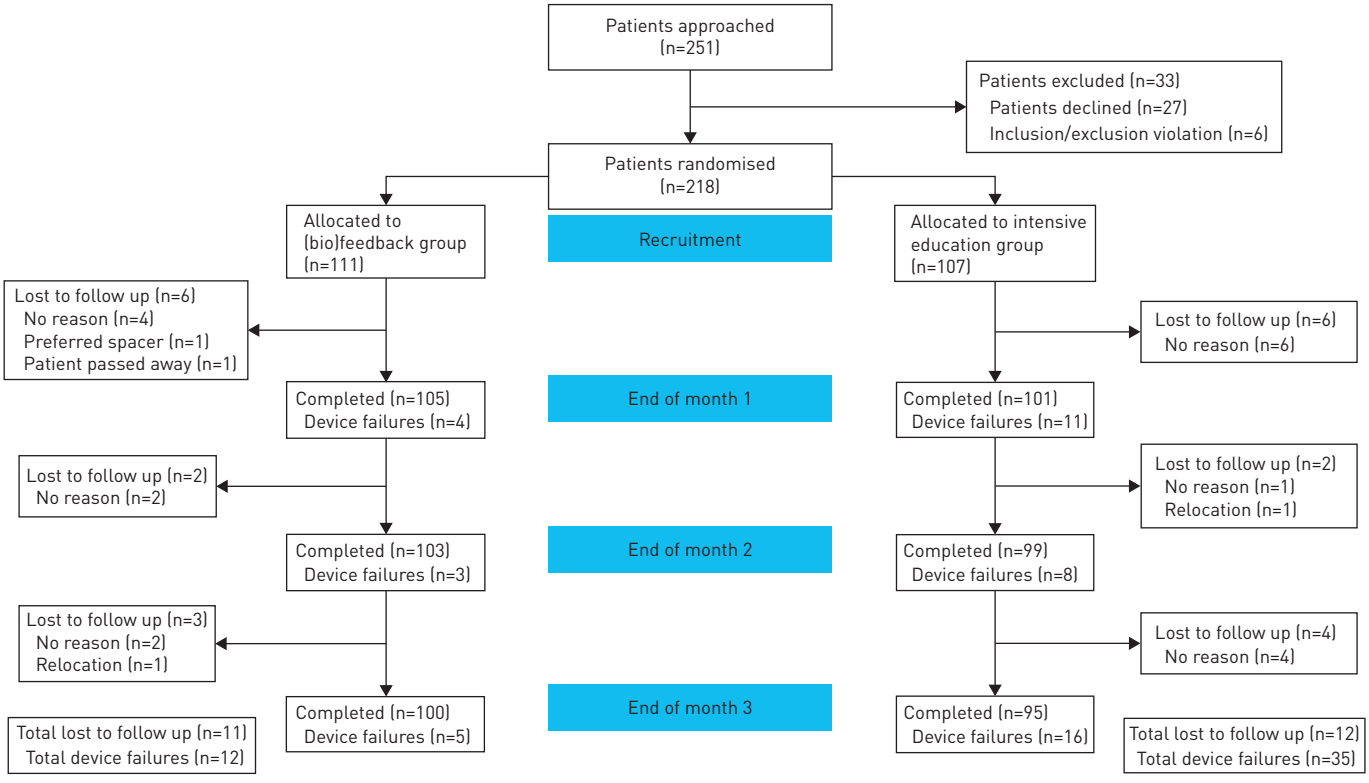

FIGURE 1 Study enrolment and outcomes: 218 patients were randomised to (bio)feedback and intensive education groups. A total of 23 patients were lost to follow-up and there were 47 device failures over the 3-month study protocol.

TABLE 1 Baseline characteristics of all recruited patients

	All	(Bio) feedback	Intensive education	p-value
Subjects n	218	111	107	
Age years	49.2±16.5	48.2±17.0	50.3±15.9	0.42
BMI	29.9±7.0	29.7±7.5	30.1±6.5	0.70
Females %	64	67	63	0.57
Smoking history %				0.29
Never smokers	56	60	52	
Ex-smokers	36	35	37	
Current smokers	8	5	11	
FEV_1 L	2.2±0.9	2.2±0.8	2.1±0.9	0.75
FEV_1 % predicted	73.0±22.1	75.1±20.8	70.8±23.3	0.23
FEV_1/FVC %	66.2±12	68.7±13	63.7±12	0.3
IgE $IU \cdot L^{-1}$	467.5±877.6	434.7±875.8	501.2±884.4	0.65
Serum eosinophils $cells \cdot mL^{-1}$	0.3±0.4	0.3±0.4	0.4±0.5	0.34
Atopy[#] % patients	57	55	59	0.76
Short oral steroid courses in the past year	3.9±3.4	4.1±3.7	3.8±3.2	0.60
Exacerbations in the past year n	4.5±3.5	4.5±3.7	4.5±3.3	0.94
Salmeterol/fluticasone dose % patients				0.83
250 µg	35	36	35	
500 µg	65	64	65	
Use of montelukast % patients	37	35	39	0.57
Use of LAMA % patients	17	16	17	0.93
GINA control % patients				0.64
Partly controlled	13	13	14	
Uncontrolled	87	87	86	
AQLQ	3.7±1.2	3.7±1.2	3.6±1.2	0.53
ACT	12.1±4.5	12.5±4.6	11.7±4.3	0.25
PEF $L \cdot min^{-1}$	376.1±135.5	378.8±128.2	373.2±143.3	0.37
PEF % expected	81.6±23.5	82.6±22.8	80.6±24.3	0.57
Inhaler Proficiency Score[¶]	7.5±2.7	7.6±2.6	7.5±2.8	0.70

Data presented as mean±SD, unless stated otherwise. [#]: atopy status was defined as a positive skin prick test response (wheal 3 mm larger than negative control) or a positive radioallergosorbent test (RAST) result to airborne allergens; [¶]: Inhaler Proficiency Score is an inhaler technique 10-point checklist, ranging from 0 to 10, where 10 represents the perfect inhaler technique. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LAMA: long-acting muscarinic antagonist; GINA: Global Initiative for Asthma, AQLQ: Asthma Quality of Life Questionnaire; ACT: Asthma Control Test; PEF: peak expiratory flow.

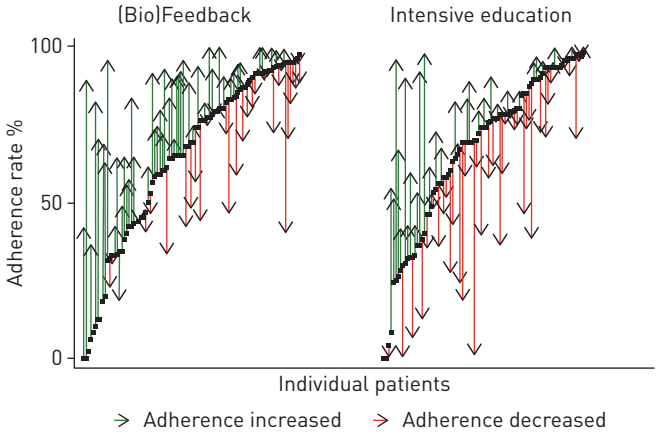

FIGURE 2 Adherence over time: Individual actual adherence rates of patients from month 1 to month 3. The overall month 3 actual adherence rate of intensive education patients was significantly lower than that of the (bio)feedback patients. Actual adherence, accounting for time of use, interval between doses and technique of use was calculated from INCA device data for each month.

TABLE 2 Different measures of adherence calculated over the 3-month study period with between group and within group comparisons.

Adherence rate	Month 1			Month 3		
	(Bio)feedback	Intensive education	p-value[#]	(Bio)feedback	Intensive education	p-value[¶]
Actual rate	63±27. 3	67±26.4	0.57	73±24*	63±26.0	<0.01
Average adherence from dose counter	86±24.7	92±46.8	0.27	92±15. 8	79±108.4	0.20
Attempted rate	82±18.7	78±22.5	0.11	73±26.2	82±18.1	0.01
Overdoses	6±8.7	7±10.4	0.55	3±5.2*	6±9.0	0.02
Missed doses	18±15.6	20±18.0	0.39	13±13.1	18±16.7	0.22
Technique error rate	11±19.2	8±18.9	0.36	11±13.9*	15±22.5	0.12

Data are presented as mean±SD, unless stated otherwise. [#]: comparing (bio)feedback and intensive education for month 1; [¶]: comparing (bio)feedback and intensive education for month 3. *: p<0.05, comparing month 1 to month 3. Actual rate incorporates time of use, interval between doses and technique of use. Average adherence is the conventional method of calculating adherence with the dose counter. Attempted rate accounts for the number of times a patient tried to use the inhaler, whereas overdoses and missed doses represent the rates of overdoses and missed doses, respectively, for each month. Technique error rate is the rate of inhaler errors made per month.

the (bio)feedback group, the rate of adherence rose from month 1 to the end of the study by 7.5% (95% CI 2.6–12.5%; p<0.01), but this rate fell in the intensive education group −3.4% (95% CI −10.2–3.3; p<0.01).

Per-protocol analysis, excluding patients with missing data, showed similar findings (75% *versus* 64% in the (bio)feedback and intensive education groups, respectively; p<0.007). An ordinary least squares regression model, controlling for age, BMI, gender, FEV_1, smoking history, previous salmeterol/fluticasone Diskus use and GINA classification at recruitment, showed a significant difference in actual adherence at month 3, between (bio)feedback and intensive education groups ($p \leqslant 0.01$). Changes in individual patient data are shown in figure 2.

The rates of technique errors, missed doses, overdoses and habit of use are shown in table 2. The most common critical errors were low peak inspiratory flow (n=460; 50% of all errors) and exhalation into the Diskus before inhalation (n=359; 39% of all errors). There were 14 separate episodes of dose dumping (more than 10 drug blisters within one audio file) in the intensive education group and none in the (bio)feedback group. 20 cases (20%) in the (bio)feedback group and 27 (28%) in the demonstration group showed <50% adherence in month 3.

Clinical outcomes, refractory and difficult-to-manage asthma

At the end of the third month, as defined in the per-protocol analysis plan [21], general clinical outcomes were assessed (figure 3). Of these 146 participants, 54 were controlled and 92 patients still had some persisting issue related to asthma control. Among these, 52 (35%) were uncontrolled and had an actual adherence rate <80% (mean 51.8%), and could therefore be considered "difficult to manage", requiring more attention on adherence. 40 patients (27%) were uncontrolled with an adherence >80% (figure 3). There was no difference in clinical allocation between the (bio)feedback and demonstration groups.

Discussion

Monitored adherence, including inhaler technique and regularity of use, with (bio)feedback to the individual on their inhaler use, significantly increased and sustained adherence in patients with severe uncontrolled asthma. Further, relative to the (bio)feedback group, adherence fell significantly over time in the intensive education group, highlighting the value of personalised (bio)feedback in maintaining adherence. Monitored adherence also identified that over half of the patients who remained poorly controlled during the study were also poorly adherent. Thus, a monitoring programme can both improve adherence for many patients, as well as identify the cause of poor asthma control in others.

The intensive education received by our comparator group is far superior to what occurs in routine clinical practice, which could explain why adherence in both groups was far higher than we have reported in observational studies of patients using this technology [33, 34]. The intensive education approach in both groups used several key behaviour change approaches [15, 21], which might be the reason for the relatively high levels of adherence observed. Understanding how to use an inhaler, a major feature of poor adherence [20], was addressed by repeatedly reinforcing the key messages on regular habit formation, and correcting inhaler technique errors and asthma education at each visit. Opportunities to access asthma medications [20], another cause of poor adherence, were optimised, as all patients were given salmeterol/fluticasone inhalers at each visit. Motivation [20], a key aspect of behaviour change, was addressed at each

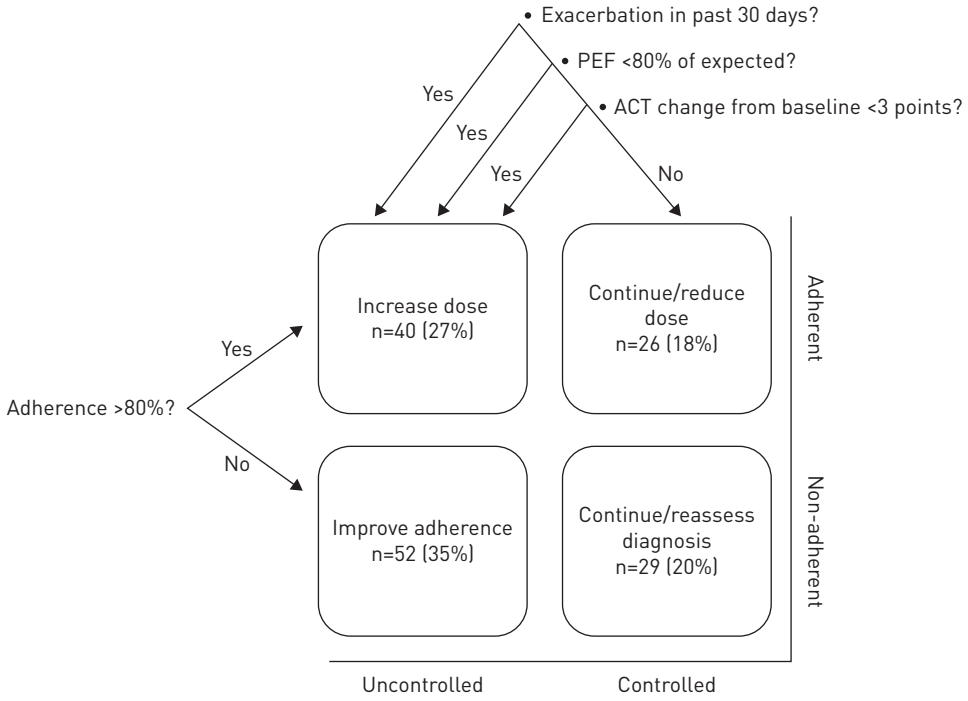

FIGURE 3 Clinical outcomes at the end of the study. After 3 months, patient data on peak expiratory flow (PEF), asthma control (Asthma Control Test (ACT) and Asthma Quality of Life Questionnaire) and inhaler adherence (from the INCA device) were combined to provide an assessment of each patient's asthma, as suggested by Global Initiative for Asthma. These included: 1) assess adherence (patient is uncontrolled and adherence is poor); 2) review comorbidities (patient is uncontrolled, adherence is good and PEF is stable); 3) step-up therapy (patient is uncontrolled, adherence is good and PEF is unstable); 4) consider reducing therapy if the patient has both good control and PEF >80%. Results of the decision tool are shown and indicate that after the monitored adherence programme, 40 (27%) patients needed additional medication as the next step.

visit by focusing on the patient's individual goals for asthma outcomes. The scripted intervention used in this study took less than 20 minutes to perform, was delivered by clinical research nurses and required little specific training.

There have been major developments in the field of monitored adherence in the last few years, with two notable recent studies. Chan *et al.* [35] showed clinically relevant outcomes in a group of children with asthma, who were given audio-visual reminders, as did Foster *et al.* [36], who studied poorly controlled patients attending primary care. As in the present study, both studies achieved significant improvements in clinical outcomes. The present study is different in a number of ways. Firstly, the source of recruitment differed, in that we enrolled patients who were attending specialist clinics, where inhaler training and adherence had been previously or concurrently addressed. The nature of feedback was also different, as one-on-one patient education was given that included information on inhaler technique and patient-identified routines to develop habit of use. Finally, a major difference in the present study is the clinical outcome of distinguishing refractory from difficult-to-control asthma.

The GINA guidelines indicate that assessment of uncontrolled asthma includes the assessment of adherence, management of comorbidities and consideration of step-up treatment [4, 5]. However, before considering comorbidities or step-up treatment, it is clear that adherence needs to be assessed first and deemed adequate. With monitored inhaler adherence, including inhaler technique, overall adherence can be appropriately assessed in real-time, thereby providing clinicians with crucial information to guide treatment that is in line with GINA recommendations.

Even within this short, focused study, adherence was not perfect, as 20% of the intensive education patients had adherence <50% during the third month. Identifying poor adherence as the potential cause of poor control is another outcome of the study, as this suggests that such patients might benefit from more specific interventions, such as motivational interviewing, rather than additional or further therapy. This finding also indicates that patient adherence within clinical trials or in clinical practice cannot be assumed

to be good. Therefore, prior to starting an advanced biological therapy, an assessment of adherence with electronic devices could be beneficial to patients with severe asthma.

Limitations of the present study include the relatively short follow-up, which prevented an assessment of the impact of the intervention on exacerbations, and the restriction to one, albeit commonly used, inhaler. This will be addressed in a follow-on study (NCT02307669). That study will incorporate information on adherence along with a biomarker profile of the patients. A longer observation period might lead to further improvements, such as reduced hyper-responsiveness and improved outcomes, as reported in the Gaining Optimal Asthma ControL (GOAL) study [37]. Furthermore, the enhanced education group received an intervention that comprised multiple behaviour change techniques, which are proven to change behaviour, over multiple visits. This "control" group received far beyond usual care, and this could have served to mask some of the effects of the intervention. It is not known how many behaviour change techniques, or indeed whether a certain mixture of them, is optimal. Notwithstanding, a significant difference in the primary outcome was seen when the INCA (bio)feedback was incorporated, suggesting a robust effect of the device.

In summary, the results of this study suggest (bio)feedback of adherence, leads to both significant clinical improvements in adherence and facilitates clinicians in directing future care, either towards additional treatments for refractory patients or towards specific interventions to address medication adherence.

Acknowledgements

Author contributions are as follows. I. Sulaiman and R.W. Costello were involved in all aspects required for this manuscript, including patient recruitment, data management and data analysis. E. MacHale, A.S. Bhreathnach, D.M. Murphy, E. Hunt and S.J. Lane were primarily involved in patient recruitment. S. D'Arcy, G. Greene, T. Taylor and R.B. Reilly were primarily involved in the audio analysis. F. Boland and G. Greene were primarily involved in the statistical analysis. B. Cushen, J. Seheult, G.B. Diette, J.M. FitzGerald, F. Doyle and M. Mokoka were involved in data analysis and all authors were involved in writing the manuscript.

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