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Published in:
The Lancet. Respiratory Medicine

DOI:
10.1016/S2213-2600(22)00534-3

Publication date:
2023

Use of digital measurement of medication adherence and lung function to guide the management of uncontrolled asthma (INCA Sun): a multicentre, single-blinded, randomised clinical trial

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Summary

Background The clinical value of using digital tools to assess adherence and lung function in uncontrolled asthma is not known. We aimed to compare treatment decisions guided by digitally acquired data on adherence, inhaler technique, and peak flow with existing methods.

Methods A 32-week prospective, multicentre, single-blinded, parallel, randomly controlled trial was done in ten severe asthma clinics across Ireland, Northern Ireland, and England. Participants were 18 years or older, had uncontrolled asthma, asthma control test (ACT) score of 19 or less, despite treatment with high-dose inhaled corticosteroids, and had at least one severe exacerbation in the past year despite high-dose inhaled corticosteroids. Patients were randomly assigned in a 1:1 ratio to the active group or the control group, by means of a computer-generated randomisation sequence of permuted blocks of varying sizes (2, 4, and 6) stratified by fractional exhaled nitric oxide (FeNO) concentration and recruitment site. In the control group, participants were masked to their adherence and errors in inhaler technique data. A statistician masked to study allocation did the statistical analysis. After a 1-week run-in period, both groups attended three nurse-led education visits over 8 weeks (day 7, week 4, and week 8) and three physician-led treatment adjustment visits at weeks 8, 20, and 32. In the active group, treatment adjustments during the physician visits were informed by digital data on inhaler adherence, twice daily digital peak expiratory flow (ePEF), patient-reported asthma control, and exacerbation history. Treatment was adjusted in the control group on the basis of pharmacy refill rates (a measure of adherence), asthma control by ACT questionnaire, and history of exacerbations and visual management of inhaler technique. Both groups used a digitally enabled Inhaler Compliance Assessment (INCA) and PEF. The primary outcomes were asthma medication burden measured as proportion of patients who required a net increase in treatment at the end of 32 weeks and adherence rate measured in the last 12 weeks by area under the curve in the intention-to-treat population. The safety analyses included all patients who consented for the trial. The trial is registered with ClinicalTrials.gov, NCT02307669 and is complete.

Findings Between Oct 25, 2015, and Jan 26, 2020, of 425 patients assessed for eligibility, 220 consented to participate in the study, 213 were randomly assigned (n=108 in the active group; n=105 in the control group) and 200 completed the study (n=102 in the active group; n=98 in the control group). In the intention-to-treat analysis at week 32, 14 (14%) active and 31 (32%) control patients had a net increase in treatment compared with baseline (odds ratio [OR] 0·31 [95% CI 0·15–0·64], p=0·0015) and 11 (11%) active and 21 (21%) controls required add-on biological therapy (0·42 [0·19–0·95], p=0·038) adjusted for study site, age, sex, and baseline FeNO. Three (16%) of 19 active and 11 (44%) of 25 control patients increased their medication from fluticasone propionate 500 µg daily to 1000 µg daily (500 µg twice a day; adjusted OR 0·23 [0·06–0·87], p=0·026). 26 (31%) of 83 active and 13 (18%) of 73 controls reduced their medication from fluticasone propionate 1000 µg once daily to 500 µg once daily (adjusted OR 2·43 [1·13–5·20], p=0·022. Week 20–32 actual mean adherence was 64·9% (SD 23·5) in the active group and 55·5% (26·8) in the control group (between-group difference 11·1% [95% CI 4·4–17·9], p=0·0012). A total of 29 serious adverse events were recorded (16 [55%] in the active group, and 13 [45%] in the control group), 11 of which were confirmed as respiratory. None of the adverse events reported were causally linked to the study intervention, to the use of salmeterol–fluticasone inhalers, or the use of the digital PEF or INCA.

Interpretation Evidence-based care informed by digital data led to a modest improvement in medication adherence and a significantly lower treatment burden.

Lancet Respir Med 2023; 11: 591–601

Published **Online** March 21, 2023 https://doi.org/10.1016/S2213-2600(22)00534-3

This online publication has been corrected. The corrected version first appeared at thelancet.com/respiratory on April 18, 2023

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Funding **Health Research Board of Ireland, Medical Research Council, INTEREG Europe, and an investigator-initiated project grant from GlaxoSmithKline.**

Introduction

Of the 25 million US patients with asthma, roughly 10% are uncontrolled despite using both high-dose inhaled corticosteroids (ICS) and another controller medication.[1] Many of them have poor asthma control because they have inadequate adherence, poor inhaler technique, or untreated comorbid conditions. These patients have difficult-to-treat asthma and should improve when the interfering factors are addressed.[2]

However, the tools used to identify difficult-to-treat asthma vary in their sensitivity. For example, patients rarely report poor adherence but when it is assessed digitally, it is around 50%.[3–5] Pharmacy dispensing records, another measure of adherence, are only modestly related[6] to the values measured by digitally enabled inhalers and do not give any information on inhaler technique. Many patients with asthma also have conditions such as obesity, deconditioning, or gastro-oesophageal reflux, which have symptoms similar to asthma.[2,7–10] Use of symptoms to assess asthma control when a patient has one of these false-positive coexisting conditions can give the impression of poor asthma control. Thus, depending on the tools used, a patient with difficult-to-treat asthma might be misclassified as having severe asthma and prescribed add-on therapy, when it would be more appropriate to target the comorbid condition.

In this study we tested the hypothesis that objectively assessed medication adherence, inhaler technique, and lung function, incorporated into a structured, clinical decision support tool that delivered guideline treatment recommendations on the collected data, provides a safe and cost-effective way to manage patients with uncontrolled asthma (which might be either severe or difficult to treat). In the active group, inhaler use and technique were assessed with the validated digital acoustic recording device (Inhaler Compliance Assessment [INCA]).[6,11] Asthma control was assessed by means of both symptoms and concurrently recorded twice daily digital peak expiratory flow (ePEF). A control group had adherence and

Research in context

Evidence before this study

A systematic review of parallel and crossover, randomised controlled trials reported as full-text publications written in the English language were studied on the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and PsycINFO to identify studies published from Jan 1, 1995, to June 30, 2017, using the terms "adherence" and "randomised clinical trials of add-on therapy" showed that in none of the 67 clinical trials were digital devices used to assess adherence to inhaled corticosteroids before a biologic was added. However, studies have shown that adherence to inhaled corticosteoids is poor.

Despite clinical trial evidence of effectiveness of inhaled corticosteroids in asthma, real-world data show that suboptimal adherence is common. Health-care professionals lack detailed and objective insight into their patients' medication adherence. Consequently, medication can be unnecessarily stepped-up resulting in higher treatment and economic burden to patients and society. Previous trials have shown that digital inhalers can help to enhance adherence in patients with asthma, an intermediate outcome. Consistent evidence on the effect of digital inhalers on hard clinical and economic outcomes is however lacking. Previous studies have not specifically focused on difficult-to-treat asthma, have not combined digital adherence data with digital peak expiratory flow data, and have not assessed the effect on treatment decisions and the economic implications of their intervention strategies.

Added value of this study

This study focused on patients with uncontrolled asthma using inhaled medication (corticosteroids), who were being considered for step-up therapy to Global Initiative for Asthma step 5. Patients' treatment was adjusted using digitally informed data (the active group) or self-reported data (the control group). Treatment burden and treatment adherence (primary endpoints) were measured by the final dose of treatment as recommended by a digital clinical decision tool. The economic implications of using a digitally enabled inhaler in combination with digital peak flow was also measured. The results show that patients who have their asthma digitally managed had considerably lower treatment and economic burden and better adherence compared with patients in the control group, and there was no difference between groups in terms of asthma control.

Implications of all the available evidence

To our knowledge this is the first randomised trial to evaluate the methods used to confirm that an individual has either severe or difficult-to-treat asthma. The results show that when digitally sourced data on adherence and digital peak flow is integrated in a clinical decision platform then medication doses are less likely to be increased. The implications of this work are that patients who are being considered for a biological agent should have a digital assessment of both inhaler adherence and lung function with the data integrated on a digital clinical decision platform.

exacerbations assessed by pharmacy records, inhaler technique by visual methods, and asthma control by a validated questionnaire.

Methods

Study design

This was an investigator-initiated, prospective, multicentre, single-blinded, parallel, randomised controlled trial (INCA Sun) carried out in ten severe asthma clinics across Ireland, Northern Ireland, and England. The trial design, sample size calculation, method of adherence assessment, and adherence promotion interventions were based on previous studies that the authors have done.[11,12] Ethical approval was granted by independent medical ethics committees for the individual hospitals involved. The protocol is included in the appendix.

Because of the COVID-19 pandemic, the collection of fractional exhaled nitric oxide (FeNO), blood tests, and spirometry data was suspended, and virtual visits were done. 36 patients (n=17 in the active group; n=19 in the control group) therefore did not have results for these tests available—data on the primary endpoint was collected for these patients. There were no other substantive changes in the protocol after trial commencement.

Participants

Eligible patients were aged at least 18 years with a clinical diagnosis of asthma according to Global Initiative for Asthma criteria, had been prescribed inhaled corticosteroids (≥500 µg per day of fluticasone propionate or equivalent to a maximum of 1000 µg per day) in combination with a twice daily ICS long-acting beta-agonist (LABA) for at least 12 months. Asthma diagnosis was confirmed as FEV_1/forced vital capacity of less than 70% and FEV_1 of less than 80%, a 12% change in FEV_1 following administration of a beta-agonist or spontaneously over a 1-year period, a positive bronchial provocation test, or at least a 10% variability in PEF within a 7-day period. Additionally, participants were required to have an asthma control test (ACT) score of no more than 19 and to have had one or more severe exacerbations in the past year (treatment with systemic corticosteroids, emergency department attendance, or admission to hospital). Patients who had a smoking history of at least 20 pack years, who were receiving any biological treatment or concurrent and ongoing treatment with a potent cytochrome P450 3A4 inhibitor, or who had reported a previous sensitivity to fluticasone propionate or salbutamol were excluded. Written informed consent was given by all patients before enrolment.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio into either the active or control study group. An independent statistician developed a computer-generated randomisation sequence that consisted of permuted blocks of varying sizes of 2, 4, and 6, stratified by FeNO concentration (high FeNO ≥45 ppb or low FeNO <45 ppb) and recruitment site. Randomisation was done by means of a concealed centralised, computerised web-based app, located at the sponsor's site, which the trial site accessed when they consented a patient. A statistician masked to the study allocation did the statistical analysis. In the control group, participants were masked to their adherence and errors in inhaler technique data that were recorded to the remote monitoring device.

Procedures

The 32-week trial had a 1-week run-in period, at the end of which participants were randomly assigned, three nurse-led education visits over 8 weeks, and three physician-led treatment adjustment visits (weeks 8, 20, and 32). Details of the technologies and the procedures are described below and in greater detail in the appendix (pp 2–12).

See Online for appendix

Remote monitoring technologies were used to assess inhaler technique and adherence and lung function. The INCA device was the source of data on treatment use and inhaler technique for both reliever and preventer medicines in both study groups (appendix p 2). This CE-marked, digitally enabled, audio-recording device is attached to the top of a diskus inhaler. Each time the inhaler is used, the device makes an audio recording. Analysis of the audio data by signal processing algorithms automatically processes and classifies the quality of each inhalation.[15–17] An inhalation error was classed as occurring if one of three major errors was detected: the inhaler was not primed, there was an exhalation into the inhaler before inhalation, or the inhalation flow peak inspiratory flow was less than 40 L/min. Adherence to

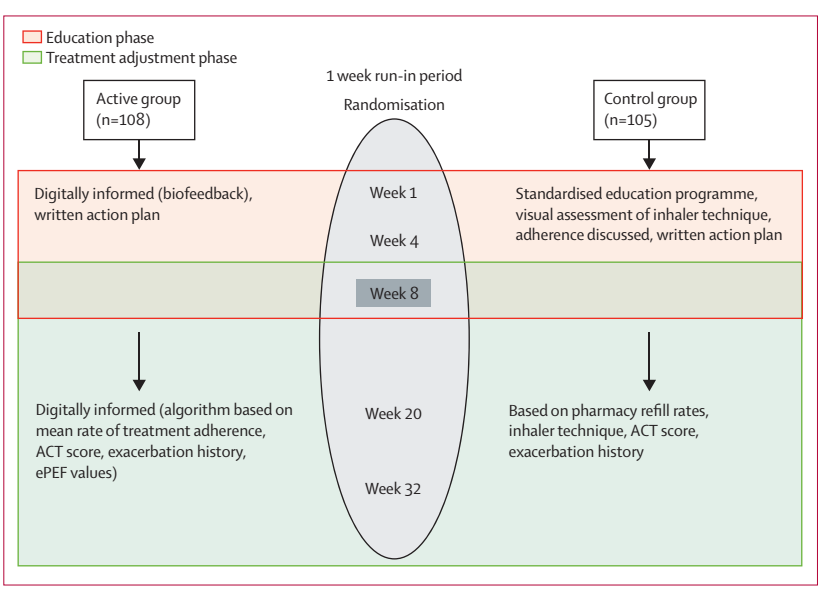

Figure 1: **Study flow**
Following consent, participants had a 1-week run-in period, followed by three education visits at day 7, week 4, and week 8. At weeks 8, 20, and 32 the participants in both groups had treatment adjustment visits, in which they had a structured visit, with the data and treatment recommendations hosted on a digital platform.

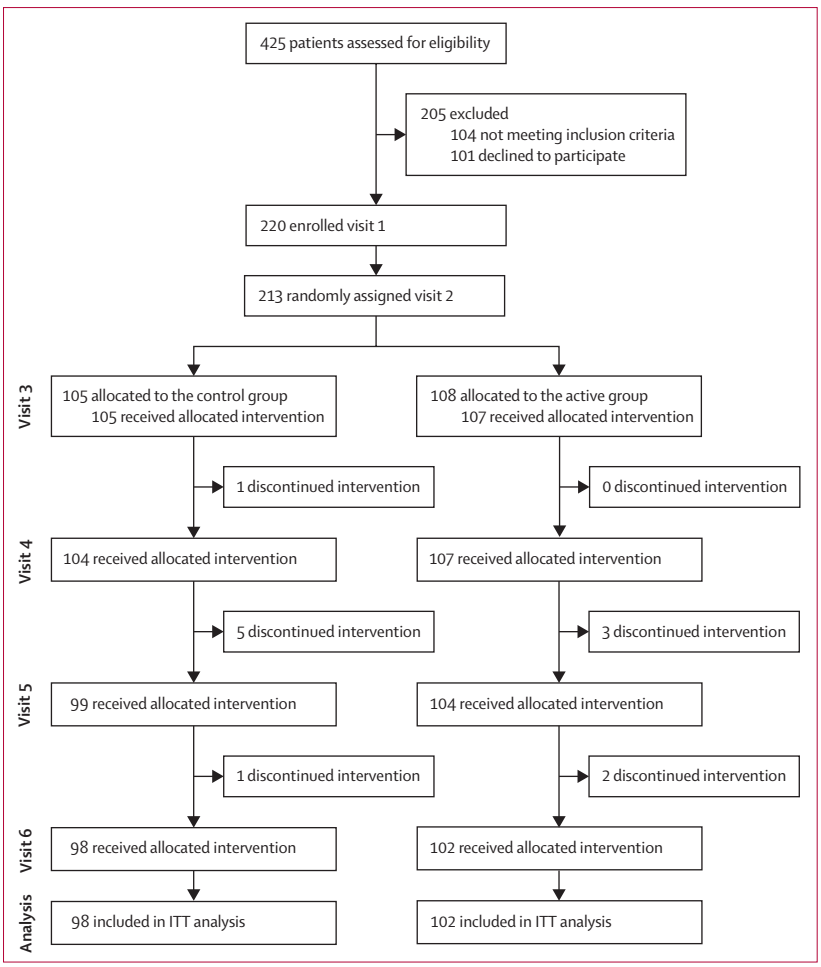

Figure 2: **Trial profile**
ITT=intention to treat.

the twice-daily ICS–LABA therapy (ie, ≥500 µg per day of fluticasone propionate or equivalent to a maximum of 1000 µg per day in combination with LABA) was then calculated, by means of an area under the curve (AUC) method (appendix p 3).[18] A CE-marked, digital PEF (ePEF; Vitalograph, Ennis, Ireland) was used to assess variations in airflow between visits.

To ensure standardisation of the clinical treatment decisions, the guideline recommendations for treatment adjustment were encoded in a clinical decision platform. The data from the remotely monitored adherence device, ePEF, patient-reported control, concurrent treatment, laboratory results of biomarkers of type-2 inflammation, and exacerbations were uploaded to a cloud-hosted system. In the education phase of the study, the data were displayed visually and provided in a patient-specific report (appendix p 4). In the medication management phase of the study, the decision tool suggested an intervention, but could be overruled by the clinician (appendix p 5).

Following consent and baseline data collection, to ensure equal stratification of persistently inflamed patients, a FeNO suppression test was done over the next 7 days.[14] The test required participants to continue their prescribed ICS–LABA therapy, along with an additional 1000 µg/day fluticasone propionate, and make a daily recording of FeNO (NIOX, Circassia, UK) in the run-in period. After 7 days, at visit 2, the participants returned, FeNO data were retrieved, and patients were randomly assigned with stratification based on the day 7 FeNO concentration.

Over the 8-week education phase, both groups had three separate nurse-led education visits (day 7, week 4, and week 8). The active group patients received visual biofeedback on their own adherence and errors in inhaler use (appendix p 4) and were shown the inter-relationships of treatment use and changes in their ePEF (appendix p 4). The taxonomy of the behavioural features of this biofeedback intervention has also been described previously.[6,18] Two previous multicentre, randomised trials, including one among patients with severe asthma, have shown that this biofeedback leads to sustained adherence.[11,19] They were also given a written asthma management plan.

In the control group, participants' adherence and errors in inhaler technique data were recorded to the remote monitoring device. At each of the visits, there was a standardised education programme, as described in our previous studies.[15,16] Inhaler technique was checked by means of visual assessment and errors were corrected by means of the teach-to-goal method. At each visit, education on the nature of asthma was provided, barriers to and promotion of medication adherence discussed, and a written asthma management plan provided.

All patients, regardless of allocation, were provided with both an INCA-enabled salmeterol–fluticasone inhaler and a salbutamol reliever inhaler, as well as an ePEF, at each visit to cover the period until the next scheduled visit. The ePEF data was available to the patient for use in their action plan.

Structured physician-delivered visits occurred at weeks 8, 20, and 32; each comprised a fully protocol-delivered structured assessment. In the active group, the structured assessment involved the collection of mean rate of ICS–LABA adherence, self-reported ACT questionnaire, exacerbation history (confirmed by participants physician and pharmacy dispensing records) and the mean ePEF values of the previous 12 weeks. These data were incorporated into a decision algorithm to adjust treatment (appendix pp 4–11, and published previously[20,21]). In the control group, the data used for assessment was the adherence based on pharmacy refill rates, and visual assessment of inhaler technique. Asthma control was measured by the ACT questionnaire and exacerbation history (confirmed by pharmacy dispensing records of oral corticosteroids). Thus, the sources of data used for treatment decisions were the only differences between the active and control groups. The full details of the treatment management procedures are outlined in the appendix (p 11).

At each visit, spirometry, FeNO, peripheral blood eosinophils, total serum IgE and specific IgE adverse events, changes in medications, update on patient selected goals, ACT score, Mini Asthma Quality-of-Life Questionnaire score (miniAQLQ), and European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) were measured.

Outcomes

There were two coprimary endpoints in the INCA Sun study. The first was the between-group difference in the proportion of patients recommended to have a net increase in treatment, through a combination of escalation of inhaled corticosteroid medication at weeks 8 and escalation or reduction at weeks 20 and 32 medication as adjusted by the physician. At the end of this period, a net value was calculated, which could have been a net increase or decrease in medication and then add-on biological treatment was considered.[14] The second co-primary endpoint was the between-group difference in mean rate of adherence to preventer medication in the last 12 weeks of the trial, calculated for each of the two groups by the AUC method.[22] Secondary endpoints were the comparison in change in patient-reported asthma control reported using ACT, quality of life (asthma, general, and work performance) by means of miniAQLQ, changes in lung function, rate of exacerbations over the study and treatment adjustment period, asthma-related type-2 biomarkers, and direct costs (medicines, digital devices, hospital, and emergency department costs). Full details of secondary outcomes are in the appendix pp 14–16).

Statistical analysis

The sample size was estimated on the basis of two coprimary endpoints and the study sample size was chosen as the larger of the two estimates. In all cases, a two-sided significance level of 0·05 was assumed. For sample size calculation of the first primary endpoint, the between-group difference in appropriate medication prescription at the end of the study (ie, treatment burden), was based on the findings of our previous study.[11] With a χ^2 test comparing two independent proportions, the sample size required to detect such a difference with 90% power is 82 per group. Allowing for a 10% dropout rate, this gave a total required sample size of 180.

For sample size calculation of the second primary endpoint, to compare adherence to ICS–LABA therapy, on the basis of the results of our previous study,[11] a between-groups difference in adherence rate at the end of the study of approximately 10% is expected (pooled SD 25%). The sample size required to detect this difference with 80% power in a two-sided *t* test is 100 per group. Allowing for 10% dropout rate, this gives a total required sample size of 220. On the basis of these calculations, we aimed to recruit 110 patients in each group for a total of 220 patients. Further details on sample size calculations can be found in the statistical analysis plan, which was published on clinicaltrials.gov. The analysis was done by means of Stata 16. For the first coprimary endpoint, the between-group difference in medication prescription at the end of the study, logistic regression models were used and adjusted for age, sex, FEV_1, and stratification variables (study site and FeNO concentration at day 7 [FeNO ≥45 ppb or FeNO <45 ppb]). Fixed effect models were used as appropriate to control for study site effects. For the second coprimary endpoint, linear regression models were used for the between-groups difference of actual adherence to ICS–LABA therapy in the last 12 weeks of the trial.

For the **statistical analysis plan** see https://clinicaltrials.gov/ct2/show/NCT02307669

	Active (n=108)	Control (n=105)
Age, years	46·6 (15·4)	47·9 (14·4)
Sex		
Female	66 (61%)	71 (68%)
Male	42 (39%)	34 (32%)
BMI, kg/m²	29·8 (7·2)	30·4 (7·5)
Asthma features		
Asthma control test score	12·3 (3·5)	13·0 (3·6)
Mini Asthma Quality-of-Life Questionnaire score	3·0 (1·0)	3·9 (1·2)
Exacerbations in the past year	5·1 (3·7)	4·3 (2·8)
Oral steroid courses in the past year*	4·2 (3·3)	3·4 (2·4)
Hospital admissions in past year*	0·6 (1·1)	0·4 (1·0)
Biomarkers		
FeNO at day 1, ppb	30·6 (28·5)	28·2 (35·4)
FeNO at day 7, ppb	17 (11·5)	18 (13·2)
Blood eosinophil count, 10^9/L	0·42 (0·39)	0·35 (0·42)
Serum IgE, kU/L	360 (779)	331 (545)
Elevated IgE to *Aspergillus fumigatus*	15 (14%)	11 (10%)
Elevated IgE to house dust mite	53 (49%)	48 (46%)
Elevated IgE to grass pollen	39 (36%)	32 (30%)
Elevated IgE to dog antigen	23 (21%)	22 (21%)
Elevated IgE to cat antigen	21 (19%)	22 (21%)
Physiological features		
FEV_1, L	2·27 (0·92)	2·26 (0·85)
FEV_1, % predicted	74·4 (23·0)	77·6 (25·0)
FEV_1 Z score	−2·14 (1·49)	−1·95 (1·67)
FVC, L	3·29 (1·01)	3·22 (1·01)
FVC, % predicted	90·9 (20·1)	92·7 (22·7)
FVC Z score	−1·31 (1·34)	−1·28 (1·58)
FEV_1/FVC	0·68 (0·13)	0·69 (0·12)
Peak expiratory flow, L/min	392 (155)	393 (133)
Medications		
Diskus salmeterol–fluticasone proprionate, 500 µg per day	28 (17%)	19 (26%)
Long-acting antimuscarinic	31 (30%)	30 (29%)
Previously smoked	51 (47%)	36 (34%)
Current smoker	2 (2%)	3 (3%)

Data are mean (SD) or n (%), unless stated otherwise. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. FVC=forced vital capacity. *There was a significantly greater number of oral steroid courses in the past year (mean) in the active group and also numbers of exacerbations in the past year were significantly different between groups.

***Table 1*: Baseline demographics**

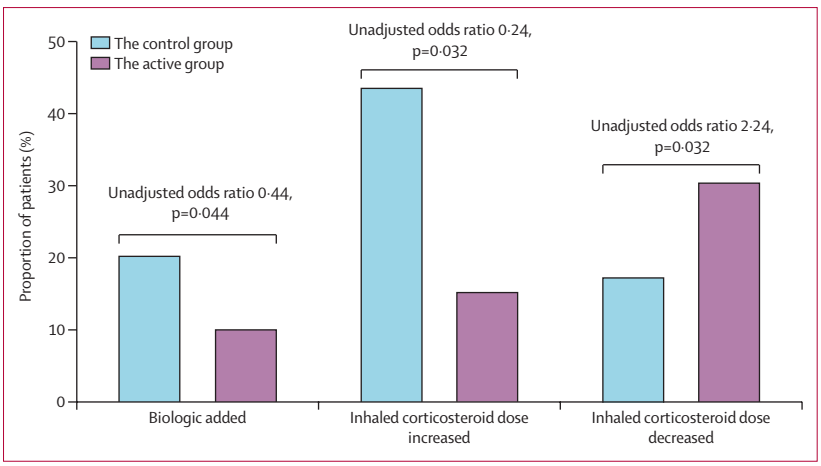

Figure 3: **Proportion of patients randomly assigned who were referred for add-on biological therapy**
At 32 weeks, patients were referred for add-on biological therapy (n=22 control; n=11 active); or over the treatment adjusted period, patients had inhaled corticosteroid dose increased from FP 500 µg once per day to 1000 µg once per day (3 [16%] of 19 active patients and 11 [44%] of 25 control patients), or reduced from FP 1000 µg once per day to 500 µg once per day (26 [31%] of 83 active patients and 13 [18%] of 73 control patients). The odds ratios for each of the changes in the active group, compared with the control group having these medication changes are per protocol analysis. FP=fluticasone propionate.

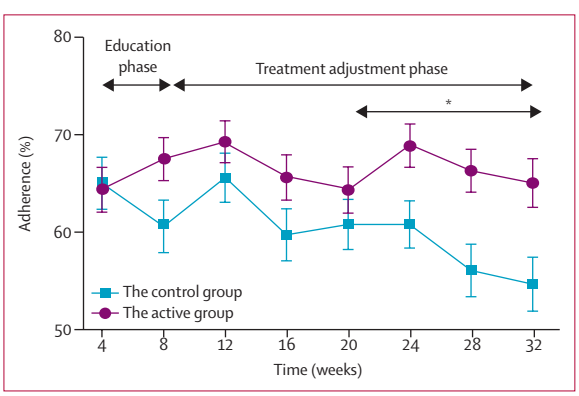

Figure 4: **The mean adherence in the active and control groups over the study period**
Adherence was calculated by means of the area under the curve method and expressed as a percentage of predicted per week. *Difference in adherence over the last 12 weeks of the study (coprimary endpoint of the study).

Primary analysis involved an intention-to-treat (ITT) analysis between two groups, with transformation as appropriate after examination of distributions and adjustment for age, sex, FEV_1, and stratification variables (study site and FeNO concentration at day 7 [FeNO ≥45 ppb or FeNO <45 ppb]). For the ITT analysis, missing data were imputed by means of multiple imputation by chained equations with 20 imputations implemented by means of the mi package in Stata. A per-protocol analysis, with adjustment for age, sex, FEV_1, and stratification variables is included in the appendix (p 13). The analyses of primary and secondary endpoints included all patients who were randomly assigned, whereas the safety analyses included all patients who consented for the trial. The trial was overseen by an independent data safety monitoring board, who met regularly and reviewed the safety data. The study and the statistical analysis plan were registered on clinicaltrials.gov, NCT02307669, and published previously.[24]

Role of the funding source

The funders played no role in the data analysis, data interpretation, or writing of the manuscript.

Results

Between Oct 25, 2015, and Jan 26, 2020, of 425 patients assessed for eligibility, 220 patients consented to participate in the study, and 213 patients were randomly assigned after the run-in period (n=108 in the active group; n=105 in the control group; figures 1 and 2). Patients were aged 47·2 years (SD 14·9; table 1), had a mean ACT score of 12 (3·5), and mean FEV_1 percent predicted of 76·0% (24·0). In the year before the study, there was a higher number of asthma exacerbations in the active group (5·1 [3·7]) than in the control group (4·3 [2·8]), and also numbers of exacerbations in the past year were significantly different between groups, but there were no other significant differences between the two groups.

The intention-to-treat (ITT) analysis was done on the 213 participants who were randomly assigned. The per-protocol analysis (appendix p 13) was done in the 200 patients who completed the study. 14 (14%) active and 31 (32%) controls had a net increase in treatment at week 32 compared with baseline (odds ratio [OR] 0·34 [95% CI 0·17–0·70], p=0·003; when adjusted for covariates and study site, OR 0·31 [0·15–0·64], p=0·0015). 11 (11%) of 102 active patients and 21 (21%) of 98 control patients needed add-on biological therapy (OR 0·45 [0·20–0·99], p=0·046; when controlling for age, sex, and baseline FeNO concentration, OR 0·42 [0·19–0·95], p=0·038).

We next looked at changes in inhaled medications throughout the study period. Of those patients who started the study on fluticasone propionate 500 µg once daily, three (16%) of 19 active patients and 11 (44%) of 25 control patients had their fluticasone propionate dose increased to 1000 µg once daily (OR 0·24 [95% CI 0·06–0·89], p=0·032; when controlling for age, sex, and baseline FeNO concentration, OR 0·23 [0·06–0·87], p=0·026. Among those patients who entered the study on fluticasone propionate 1000 µg once per day, 26 (31%) of 83 active patients and 13 (18%) of 73 control patients had their dose reduced to 500 µg once per day (OR 2·23 [1·07–4·66], p=0·032, figure 3; when controlling for age, sex, and baseline FeNO concentration, OR 2·43 [1·13–5·20], p=0·022). There was no increase in the rate of exacerbations among patients who had their fluticasone propionate dose decreased (n=39; annualised adverse event rate predose reduction was 0·92 [SD 0·6] and after dose reduction was 0·82 [0·35], [95% CI –0·33 to 1·40], p=0·59).

The mean actual adherence (measured with the INCA inhaler) over the last 12 weeks of the study (ie,

weeks 20–32) was 55·5% (SD 26·8) in the control group and 64·9% (23·5) in the active group (between-group difference 9·4% [95% CI 2·31–16·4], p=0·010; figure 4). When controlling for age, sex, baseline FeNO concentration, and study site random effects in a linear regression model, the between groups difference was 11·1% (4·40–17·9, p=0·0012). There was a large variation in adherence between individuals (appendix p 24); in the last 12 weeks, 31 (31%) active patients and 17 (17%) control patients had an actual adherence rate of greater than 80% (OR 2·07 [95% CI 1·06–4·04], p=0·034). By contrast, 25 (25%) active and 35 (36%) control patients had an actual adherence in the last 12 weeks of less than 50% (OR 0·52 [0·28–0·97], p=0·039).

In the active group, at each adjustment visit, when ePEF was normal (mean PEF>80% predicted) and the patient had persisting symptoms, rather than increasing the ICS dose, comorbid conditions were addressed. Between 32% and 46% of decisions during the treatment adjustment visits were to address comorbidities in the active patient group (appendix pp 19, 32). For example, a total of 45 (46%) patients in the active group and 30 (29%) in the control group were treated for gastro-oesophageal disease (rate ratio 0·66 [95% CI 0·46–0·95], p=0·025; appendix p 19).

There were no significant differences in asthma control, quality-of-life scores, lung function, biomarkers for type-2 inflammation (eosinophil counts or FeNO), or exacerbation rates between the active and control groups (table 2; for the adjusted ITT analysis, in which baseline covariates have been accounted for, see appendix pp 14–16). Furthermore, there were no significant changes in FeNO, FEV_1, PEF, or exacerbation rates in either group over the treatment adjustment phase.

For the secondary outcome of direct cost, a comparison of the two types of intervention was done (figure 5). Given that there were no differences between the groups for secondary outcomes, this involved a cost-minimisation analysis. This analysis included the financial effect of the difference in rates of use of add-on biological therapy between groups, adherence to (medium-dose [500 µg or high-dose [1000 µg]) ICS–LABA treatment, the cost associated with exacerbation-associated resource use, and the costs of the digital devices and platform intervention. The cost of treating comorbid conditions was not included as low-cost generic drugs are available for these conditions. The individual costs per unit (appendix p 17) were based on a previous cost-effectiveness model.[23] On the basis of an Irish health-care payer perspective, the annual cost per person was €2759 per person lower in the active group (€5313) versus the control group (€8072; figure 5 and appendix p 17). For the study population who completed the study (n=200 patients) alone, this would mean overall annual cost saving of more than €500 000.

A total of 29 serious adverse events were recorded, 16 (55%) in the active group, and 13 (45%) in the control group (appendix p 20). None of the adverse events reported were causally linked to the study intervention, to the use of salmeterol–fluticasone inhalers, or to the

	Missing data, other than dropouts at the study end	Between group difference	p value
Between-group difference in the number of cases of oral candidiasis over total study period			
Control	11	6	0·13
Active	5	..	..
Missing data	0	..	..
Change in asthma control test over total study period			
Control	5·7 (4·4)	−0·58 (−1·96 to 0·79)	0·40
Active	5·0 (5·3)	..	..
Missing data	0	..	..
Change in Asthma Quality-of-Life Questionnaire score over total study period			
Control	1·3 (1·1)	−0·11 (−0·45 to 0·23)	0·53
Active	1·6 (1·3)	..	..
Missing data	0	..	..
Exacerbation rate over the total study period			
Control	0·81 (0·92)	IRR 1·18 (0·88 to 1·59)	0·28
Active	0·95 (1·11)		
Missing data	0	..	..
Exacerbation rate during treatment adjustment phase			
Control	0·551 (0·69)	IRR 1·16 (0·81 to 1·66)	0·43
Active	0·637 (0·90)	..	..
Missing data	0	..	..
Between-group difference in peak expiratory flow variability over total study period			
Control	−0·57% (15·15)	0·966 (−3·34 to 5·27)	0·66
Active	0·39% (13·42)	..	..
Missing data	0	..	..
Median number of reliever-free days in month 2			
Control	25 (29–41)	IRR 1·29	0·20
Active	19 (10–27)	..	..
Missing data	0	..	..
Median number of reliever-free days in month 8			
Control	25 (18–29)	IRR 1·29	0·18
Active	23 (14–29)	..	..
Missing data	0	..	..
Biomarkers for type-2 inflammation			
Change of FeNO over total study period, ppb			
Control	−10·5 (34·0)	−2·16 (−11·6 to 7·3)	0·65
Active	−10·7 (19·1)	..	..
Missing data for final visit	36	..	..
Relationship between difference in FeNO and mean adherence over total study period, ppb	..	r=0·173	0·028
Change in blood periostin over the total study period, pg/mL (exploratory outcome week 1–week 8)			
Control	−778 (−1437 to 1049)	−859	0·16
Active	−81 (−429 to 199)	..	..
Change in blood eosinophil count over total study period			
Control	−0·065 (0·452)	0·007 (−0·105 to 0·120)	0·88
Active	−0·056 (0·268)	..	..
Missing data for final visit	27	..	..

(Table 2 continues on next page)

	Missing data, other than dropouts at the study end	Between group difference	p value
(Continued from previous page)			
Physiology (lung function)			
Between-group difference in FEV_1 during education phase (exploratory outcome week 1–week 8)			
Control	77·0% (22·6)	−4·15 (−11·99 to 1·68)	0·20
Active	72·8% (22·7)	..	..
Missing data for final visit	40	..	..
Between-group difference in FEV_1 at end of study (exploratory outcome week 1–week 8)			
Control	79·2% (19·7)	−5·12 (−11·92 to 1·72)	0·12
Active	74·1% (23·7)	..	
Between-group difference in PEF variability from month 1 to month 8 of the study (exploratory outcome)			
Control	−0·57 (15·153)	0·966 (−3·336 to 5·268)	0·66
Active	0·39 (13·424)	..	
Uncontrolled at end of education period (exploratory outcome)			
Active	13 (13%)	..	0·45
Control	16 (17%)	..	..
Uncontrolled at end of month 8 of the study (exploratory outcome)			
Active	18 (18%)	..	0·48
Control	14 (15%)	..	..

Data are mean (SD), median (IQR), n (%), or n, unless stated otherwise. IRR=incidence rate ratio. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. There were no differences between the two groups in this intention-to-treat analayis for any of the outcomes listed. Data missing are mostly due to the restrictions on data collection related to the COVID-19 pandemic.

Table 2: **Secondary endpoints**

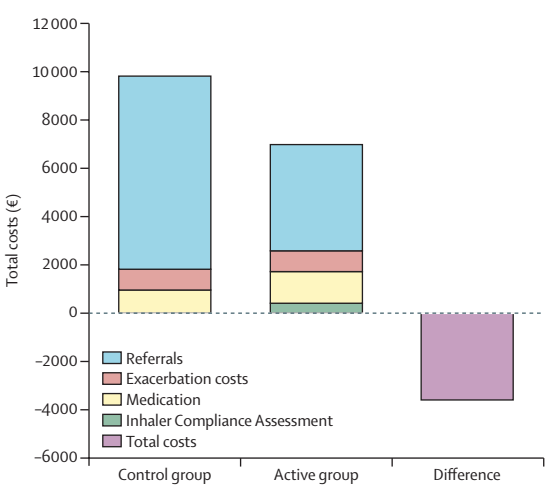

Figure 5: **Cost comparison between the active and control groups**
Costs are in euro. Full data are included in the appendix (p 17).

use of the ePEF or INCA device. 11 of these serious adverse events (38%) were confirmed as respiratory in nature (asthma exacerbations or infections), six of which occurred in two individuals, one of whom dropped out during the education phase of the study. Only one respiratory serious adverse event occurred in the active group after month 5; this participant did not have a dose reduction at any point during the study.

Among the adverse events, asthma attacks requiring oral corticosteroids were common and numerically higher in the active group (147 events in 72 individuals) than the control group (111 in 59). Other respiratory events, including chest infection, sinusitis episodes, and worsening of asthma symptoms (but not treated as an exacerbation) were common in both groups. There were no differences in the rates of adverse events between the two groups (appendix pp 22–23), although the study was not powered to detect differences. The number of people who had an exacerbation in the next 3 months after each treatment adherence is shown for each visit for the active and control patients in the appendix (p 32), as can be seen, there was no difference in the rates of exacerbation in any of the groups in whom an intervention was made.

The adherence to the protocol by physicians (post hoc) is shown in the appendix (p 31). There were 30 (5%) minor deviations across both groups mostly because of device failures, resulting in another pathway being followed, which did not affect the prescription of an additional medication, and in only 26 (4%) of cases did an investigator over-rule the decisions suggested by the clinical decision platform.

Discussion

Identifying patients with difficult-to-control asthma is one of the biggest clinical challenges respiratory physicians in practice have to attend to. Asthma guidelines advise that the modifiable factors of poor inhaler technique, insufficient adherence, or misdiagnosis of symptoms due to other co-existing conditions are excluded before additional therapy is prescribed. In this study, we implemented these recommendations in a digital decision support tool and incorporated data from a digital device that assessed adherence and inhaler technique and digital PEF. The importance of distinguishing difficult-to-control asthma from severe asthma is shown by finding that at the end of the study, despite all patients meeting the criteria for an add-on biological agent at the start of the study, at the end of the study 10% of the patients in the digitally informed group and 20% in the control group met the criteria for an add-on biological agent (table 2). Overall, 31% of participants in the active group had a dose reduction, without an increase in airway inflammation, symptoms, or exacerbations. These results indicate how asthma care can be digitally supported in an economically and clinically effective manner.

The choice of the co-primary endpoint asthma medication dose escalation, was chosen as a novel endpoint on the basis that, first, asthma control and risk of exacerbations are reduced by corticosteroids, but higher doses do not necessarily lead to additional benefits and they do carry the risk of side-effects. Second, the cost of medication is a concern and a cause of poor adherence for individual patients in countries

where they pay for their medicines. In countries where governments or private health care pay for patients' treatment, they can limit access to biological add-on therapy, which is costly to provide. Further, the patients were asked at each study visit about their goals for taking part in the study, and over 50% stated their primary goal was to reduce their medication burden.[24] As the aim of this study was to increase asthma treatment only when there was objective evidence of poor asthma control, it was expected that there would be no difference compared with the control group in asthma control, exacerbations, or airway type-2 inflammation among the patients in the active group who had their medications changed. Guidelines state that dose reduction should be the focus of care once asthma control has been achieved. In this study, over 20% of the patients treated with high-dose ICS–LABA therapy had features of adrenal gland suppression, indicating the risk of high-dose ICS.[25] Although the study was not powered to address the effect of dose reduction on exacerbation rates, at a patient level, the number of exacerbations did not increase after dose change. In other words, the reduction in treatment did not result in a loss of asthma control and exacerbation but did reduce the risk of the side-effects of inhaled corticosteroids.[25]

In this study, we focused on patients who had uncontrolled asthma and had repeated exacerbations, despite high-dose ICS–LABA therapy, because the next option for treatment escalation would be the effective but costly add-on biological therapies. In 10 000 patients across Australia, the UK, and the USA who were prescribed an add-on biologic, pharmacy ICS refill rates in the previous 6 months was less than 50%.[26–28] These data indicate the importance of assessing patients objectively before further therapies are prescribed. In this trial, all participants had 100% prescription refill rates, thus, in a more real-world setting the effects seen in this study might be more marked.

The strengths of this study include the novel use of digital measurements of medication adherence and inhaler technique, as well as the use of this information in personalised biofeedback. Another strength of this study is the use of digital peak flow to more precisely assess asthma. The digital clinical decision support tool was a particular strength of the study as there was very good compliance by the clinicians to the recommended treatment suggestions. The potential effect on health-care systems of this digital approach to asthma management is considerable; the total annual cost of asthma in the USA is estimated to be US$65 billion, with much of the cost arising from patients with uncontrolled asthma.[29] The very substantial cost reduction achieved in this study represents how digital technology might reduce costs. The use of digital technology integrated into a clinical decision platform provides an additional step in managing patients; however, the benefits of individual care are also considerable. In interpreting these data, it is not suggested that access to an add-on biological therapy be restricted on the basis of previous adherence. Instead, a clinician who is precisely aware of an individual's degree of adherence can both address the drivers of adherence and make better treatment decisions for management.

There are several limitations to this study. Alterations to the trial protocol were made owing to COVID-19 restrictions, which did lead to loss of spirometry and biomarker data; however, this did not affect the data used for the primary endpoints. The pandemic has accelerated the use of remote monitoring tools, which makes the results of this study more clinically relevant. We could have used another biomarker, such as FeNO, to guide ICS dosing, but evidence for this approach was absent at the time of study design. The difference in adherence rates between the two study groups is modest but significant, at around 10%, and is similar to the degree of adherence generally reported in adherence intervention trials.[30] However, at an individual patient level, there was a good deal of variation in adherence, which was reflected in the differences in treatments prescribed for individual patients. We chose 80% as the degree of adherence for treatment adjustment as this figure is often quoted as the usual degree of adherence in clinical trials.[31] Given such a high degree of adherence, it could be argued that pharmacy refill records provide adequate information. In this study, all patients were provided with digitally enabled inhalers, so in effect refill rates were 100%. Hence, refill rates alone do not provide enough information, as they do not indicate how and when the treatment was taken. An important limitation of this study is that we used two separate methods of data collection to decide on treatment adjustment: traditional and digital methods. By necessity, this limitation has to be taken into consideration when interpreting these data. Many patients are prescribed inhaled corticosteroids both in reliever and preventer therapy, rendering the assessment of adherence even more complex.[32] Rather than setting a threshold of medication adherence as is traditionally done in clinical trials, future studies might include a summary measure of total corticosteroid exposure, as we have previously described.[25]

Implementation of evidence-based asthma management strategies by use of objective digital data led to significant reductions in high-dose asthma treatments and less escalation to biological agents compared to more traditional methods. This study has cost implications for patients with a reduction in high-dose inhaled corticosteroid treatment, which also leads to a reduction in the risk of side-effects. Clinicians can also use this digital approach to distinguish between severe and difficult-to-manage asthma which might require add-on biological therapy.

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Contributors
RWC conceptualised the study. RWC, LGH, and EM contributed to funding acquisition, resources, and validation. RBR, CH, RWC, and IS developed the software and visualisation. CM, EM, RWC, GG, DMM, LL, LGH, JMF, JFMvB, and VB were responsible for the data curation, formal analysis, software, visualisation, project administration, and writing of the original draft. RWC, GG, and EM had access to and verified the underlying data for analysis. RWC, LGH, DJJ, GG, JFMvB, BC, IS, PJK, BDK, MB, AMNK, DJJ, IC, JH, JF, MK, DMM, LL, JW, SP, TAM, and MCM contributed to the methodology, investigation, review, and editing of the manuscript. RWC supervised the research.

Declaration of interests
DJJ reports grants from AstraZeneca and personal fees from Sanofi Regeneron, AstraZeneca, and GlaxoSmithKline. BDK report personal fees from AstraZeneca and GlaxoSmithKline. GG reports patents to quantify adherence and to predict exacerbations. CH reports fees from Alphabet, granted as part of employment by Google. DMM reports personal fees from AstraZeneca, Teva, GlaxoSmithKline, Sanofi, and Novartis. RBR reports a patent for the use of acoustics to assess inhaler adherence. JFMvB reports institutional grants from Aardex, AstraZeneca, Chiesi, European Commission COST Action 19132 ENABLE, Lung Alliance Netherlands, Novartis, Trudell Medical and personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, Teva, Trudell Medical, and Vertex. LGH was academic lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma—Industrial Pharma partners Amgen, AstraZeneca, Medimmune, Janssen, Novartis, Roche–Genentech, GlaxoSmithKline, and Boehringer Ingelheim; grants or contracts from GlaxoSmithKline, Schering Plough, Synairgen, Novartis and Roche–Genentech MedImmune, Novartis UK, Roche–Genentech and GlaxoSmithKline; and lectures supported by AstraZeneca, Novartis, Roche–Genentech, Sanofi, Circassia, GlaxoSmithKline, Chiesi, and Teva. RWC reports institutional grants from GlaxoSmithKline, Aerogen, and Enterprise Ireland; personal fees from AstraZeneca, Teva, GlaxoSmithKline, PMD solutions, and Novartis; and a patent for the use of acoustics to assess inhaler adherence, to quantify adherence and to predict exacerbations. EM, CM, MCM, BC, IS, VB, PJK, MB, IC, JF, JH, MK, RC, LL, JW, SP, TAM, and AMNK declare no competing interests.

Data sharing
Data are available on reasonable request from the authors.

Acknowledgments
Grant funding: Health Research Board DI59, Medical Research Council, MR/M016579/1 (RASP), and ILP-HSR-2017-005 2210, INTEREG Europe (CHITIN CHI5436/18), and investigator-initiated project grant from GSK, with salary and provision of salmeterol–fluticasone medication. Thanks to Brigid Byrne for illustrations and Frank Keane for provision of INCA devices. The sponsor was the principal investigator's host institution, RCSI University, Dublin, Ireland.

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