Inhaler reminders improve adherence with controller treatment in primary care patients with asthma

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Background: Poor adherence contributes to uncontrolled asthma. Pragmatic adherence interventions for primary care settings are lacking.

Objective: To test the effectiveness of 2 brief general practitioner (GP)-delivered interventions for improving adherence and asthma control.

Methods: In a 6-month cluster randomized 2 × 2 factorial controlled trial, with GP as unit of cluster, we compared inhaler reminders and feedback (IRF) and/or personalized adherence discussions (PADs) with active usual care alone; all GPs received action plan and inhaler technique training. GPs enrolled patients prescribed combination controller inhalers, with suboptimal Asthma Control Test (ACT) scores (ACT score ≤19). Inhaler monitors recorded fluticasone propionate/salmeterol adherence (covertly for non-IRF groups) and, in IRF groups, provided twice-daily reminders for missed doses, and adherence feedback. PAD GPs received communication training regarding adherence. Outcomes collected every 2 months included ACT scores (primary outcome) and severe exacerbations. Intention-to-treat mixed-model analysis incorporated cluster effect and repeated measures.

Results: A total of 43 GPs enrolled 143 patients with moderate-severe asthma (mean age, 40.3 ± 15.2 years; ACT score, 14.6 ± 3.8; fluticasone propionate dose, 718 ± 470 μg). Over 6 months, adherence was significantly higher in the IRF group than in non-IRF groups (73% ± 26% vs 46% ± 28% of prescribed daily doses; $P < .0001$), but not between PAD and non-PAD groups. Asthma control improved overall (mean change in ACT score, 4.5 ± 4.9; $P < .0001$), with no significant difference among groups ($P = .14$). Severe exacerbations were experienced by 11% of the patients in IRF groups and 28% of the patients in non-IRF groups ($P = .013$; after adjustment for exacerbation history; $P = .06$).

Conclusions: Inhaler reminders offer an effective strategy for improving adherence in primary care compared with a behavioral intervention or usual care, although this may not be reflected in differences in day-to-day asthma control. (J Allergy Clin Immunol 2014;134:1260-8.)

Key words: *Medication adherence, treatment effectiveness, intervention studies, antiasthmatic agents, asthma, ambulatory monitoring, health communication*

In asthma, adherence with inhaled controller medications, particularly inhaled corticosteroid (ICS)-containing medications, is important for achieving good asthma control, yet many studies report suboptimal adherence rates.[1] Poor adherence contributes to mortality and morbidity, including uncontrolled symptoms, impaired quality of life, exacerbations, and urgent health care

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Abbreviations used
ACT: Asthma Control Test
GP: General practitioner
ICS: Inhaled corticosteroid
IRF: Inhaler reminders and feedback
LABA: Long-acting β2-agonist
PAD: Personalized adherence discussion
T: Timepoint in months (eg, T2: Timepoint 2 months)
UC: Active usual care

utilization.[2-4] Without interruptions in ICS use, asthma-related hospitalizations could be reduced by 60%.[2]

General practitioners (GPs) identify poor adherence as 1 of the top 3 barriers to the delivery of effective asthma care.[5] Asthma guidelines recommend that GPs should assess and correct adherence at every visit[6,7] but provide few practical interventions. Furthermore, most published adherence interventions are too complex to be feasible for primary care, and some studies are nonrandomized or report no asthma outcomes.[8]

Models such as the Information-Motivation-Behavioral skills model theorize that health-related information, motivation, and behavioral skills are effective determinants of the extent to which a health behavior such as medication-taking will be performed.[9] Barriers to adherence may be "intentional" (eg, doubts or concerns about treatment effectiveness or side effects) and/or "unintentional" (eg, due to forgetting/chaotic lifestyles),[10] but no practical interventions have been developed to address these in primary asthma care.

For intentional poor adherence, providing health professionals with communication training, for example, in empathic, nonconfrontational motivational interviewing techniques, can modify patients' beliefs and attitudes, leading to improved health behaviors[11-13] and medication adherence.[14,15] For unintentional poor adherence in chronic diseases due to forgetting, reminder packaging (eg, blister packaging for tablets) improves adherence by establishing medication-taking routines.[16,17] Interactive adherence reminders for inhaled medications are more technically complex, but reliable devices are now available.[18,19] Only 1 study of such devices has been reported in asthma, demonstrating higher adherence (93% vs 74%) in patients receiving reminders; the high adherence in the control group may reflect the controlled research environment and free medications.[20]

However, the effectiveness of such strategies in asthma has not been tested in real-life community settings. We designed 2 brief primary care interventions: (1) inhaler reminders with GP feedback and (2) personalized GP-patient discussions about adherence. Both incorporated the 3 components of the Information-Motivation-Behavioral skills model, with the goal of targeting intentional and unintentional barriers to medication adherence in asthma. The aim of this study was to measure the effect of these interventions, separately and together and compared with active usual care (UC), on adherence with combination ICS/long-acting β2-agonist (LABA) medications and asthma control in people with poorly controlled moderate-severe asthma.

METHODS

Study design

We conducted a 6-month pragmatic cluster 2 × 2 factorial parallel-group randomized controlled trial in general practices in Greater Sydney, Australia, during the period 2010 to 2013. GPs were randomized to either the active group or the control group for each intervention and trained to deliver the intervention(s) with patients from their practice. The interventions (detailed later) were as follows: personalized audiovisual inhaler reminders and feedback (IRF) and brief personalized adherence discussions (PADs). All GPs received brief training in UC including one-off checking and teaching inhaler technique and writing asthma action plans. The interventions were compared separately and together, and with UC alone.

To maximize relevance to clinical practice, prescribing was according to the GP's clinical judgment, only 2 study visits were required (1 for enrollment and initial delivery of the intervention to the patient and 1 for follow-up), and most outcome data were collected by telephone by study staff (T0, T2, T4, and T6 months). For more details of methods, see this article's Online Repository at www.jacionline.org.

Medications and inhaler monitoring

The GP gave each patient a SmartTrack device (Nexus6, Auckland, New Zealand; Fig 1) that clipped onto their ICS/LABA inhaler and asked 3 onscreen questions about asthma control each month. After the device was activated during the T0 call, it recorded the date/time of all actuations and uploaded the data each month to a secure Web site. Device reliability and accuracy have been reported.[18] For IRF groups, GPs and patients were shown how to customize ringtones/reminder times and view the medication feedback online. Patients also received 1 albuterol pressurized metered dose inhaler, 1 month's supply of fluticasone propionate/salmeterol pressurized metered dose inhaler (Seretide, GlaxoSmithKline, Boronia, Australia) at their GP-prescribed dose, and a miniWright Digital peak expiratory flow/FEV_1 meter.

Randomization, blinding, and allocation concealment

Randomization of GPs was by computer-generated random code, with a minimization algorithm to ensure balance of GP locations by socioeconomic area,[21] previous asthma/chronic obstructive pulmonary disease management training in the past 12 months, and GPs speaking a second language other than English. After randomization, GP allocation concealment was maintained until during the training workshop. As with any behavioral intervention, blinding of GPs and patients to their own intervention(s) was not possible, but the other interventions were not described, and to aid blinding, GPs in each group received UC training. To avoid bias, and with ethics approval, GPs in the UC and PAD-only groups, and their patients, were not advised about the SmartTrack recording function until study end, when all patients received a debriefing statement and were offered a confidential copy of their adherence record.

Recruitment and training of GPs

GPs were recruited through 4 general practice organizational divisions in Sydney. Inclusion criteria were access to computer and e-mail, and not currently participating in another adherence-promoting study. To minimize cross-contamination between intervention groups, only 1 GP from a practice could participate. Each randomized GP received his or her respective training modules (Table I) in a half-day workshop before enrolling patients. At workshop end, GPs recorded their rating of the usefulness of the study interventions on a visual analog scale ranging from 0 to 100 (0 = not at all useful, 100 = extremely useful). GPs were reimbursed $100 per patient enrolled.

Patient recruitment

Eligible participants were patients aged 14 to 65 years, with suboptimal asthma control (Asthma Control Test [ACT] score ≤19),[22] and prescribed twice-daily ICS/LABA for 1 month or more. Exclusion criteria were asthma exacerbation (defined by oral corticosteroid use, emergency department visit, or hospitalization) in the last month, use of budesonide/formoterol as maintenance and reliever therapy, major respiratory disease (eg, chronic obstructive pulmonary disease), serious uncontrolled medical conditions,

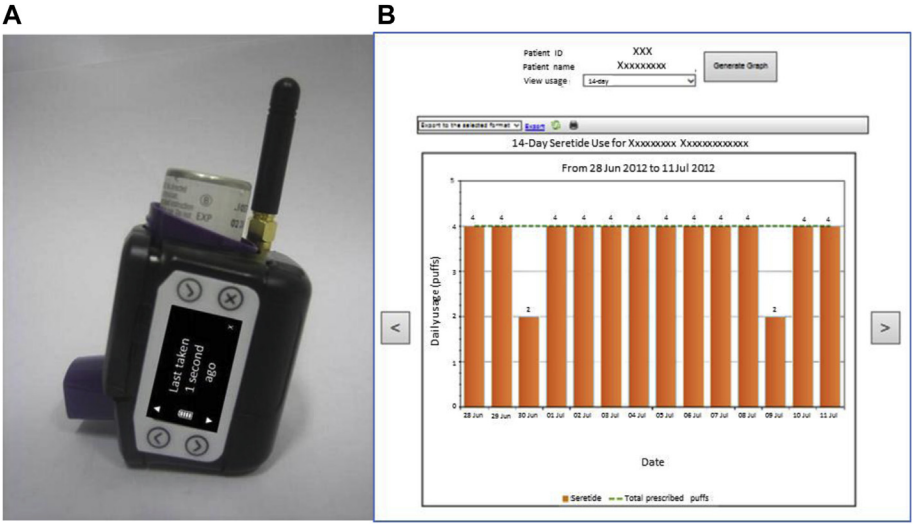


FIG 1. A, SmartTrack device installed on a fluticasone propionate/salmeterol inhaler. **B,** Example adherence feedback for IRF groups. The device electronically recorded the date/time of every actuation. The screen display (time since last dose taken) was seen only by patients in IRF groups. Feedback could be viewed by the IRF patient and his or her GP on a secure Web site. The graph showed the number of inhalations prescribed *(dotted line)* and the number of inhalations the patient took each day over a 14-day period. Patients and their GPs could access this graph on a password-protected Web site and a copy was e-mailed to them every 30 days.

clinically important visual or auditory impairment, shift workers with a variable roster, and pregnant or lactating women. Patients were not reimbursed for participation.

Interventions

UC (all GPs). All GPs received brief training on the delivery of active UC. This was based around the "Asthma Cycle of Care," an Australian government–incentivized primary care asthma management program that includes the provision of a written asthma action plan, inhaler technique review/education, and a follow-up appointment. In the study workshop, 10 minutes were allocated for training GPs in each of the action plans and inhaler technique (Table I).

Personalized adherence discussions. GPs asked patients to complete a short questionnaire about barriers to controller inhaler use.[23] They were trained to carry out a personalized discussion about the patient's key barrier(s) to adherence and to help the patient set goals and goal-achievement strategies[24] around an asthma issue that the patient wished to resolve, using patient-centered materials.

Inhaler reminders plus adherence feedback. Patients received twice-daily SmartTrack reminders for missed ICS/LABA doses. They could customize ringtones/ring times, cancel individual reminders, or switch reminders off completely. Each month, GPs received an automated e-mail to view a Web site graph of their patients' daily ICS/LABA use (Fig 1); the patient could log in to view his or her own graph at any time. GPs were asked to discuss the ICS/LABA-use graph with the patient at the study follow-up visit or at any subsequent appointments, at the GP's discretion. Only GPs in PAD groups were trained in specific communication strategies for discussing adherence.

The factorial design resulted in 4 randomization groups: UC, PAD, IRF, and IRF + PAD.

Outcome measures

Initial data (T0) were collected by telephone once the GP provided the patient's details (target <7 days), and at T2, T4, and T6 months. The primary outcome measure (assessed at the patient level) was the ACT score, collected by telephone by a researcher blinded to the patient's intervention group.

Secondary outcome measures were the Mini Asthma Quality of Life Questionnaire,[25] Hospital Anxiety and Depression Scale,[26,27] and Medication Adherence Report Scale for Asthma (MARS-A),[28] data for which were collected by postal questionnaire, and FEV_1. Patient-reported data for previous prednisone courses were collected from patients by telephone at T0 (prednisone course in past 12 months: yes/no). Data for severe exacerbations (defined by prednisone courses)[29] during the study period were obtained from GP records at study end.

Sample size

The sample size calculation was based on CONSORT guidelines for cluster randomized trials[30] and data for ACT that were available at the time (significant change ≥1.5 points; SD, 3.1).[22] Allowing for 15% dropouts, the target sample size of 220 patients, with 44 GPs each contributing 5 patients, within-cluster correlation 0.1, and cluster effect of 1.4, had 80% power to show a difference among groups with significance level of less than .05. The minimal important difference for the ACT is now considered to be 3 or more points,[31] and this was used in our analyses.

Analysis

The primary analysis was by intention to treat. The effect on ACT of the 2 interventions separately, and of their interaction, was tested with a mixed-model analysis, with adjustment for T0 ACT and for clustering by GP, and including all available observations per patient over the 6-month study. A similar approach was taken for secondary outcomes; the binary variable "proportion of patients experiencing ≥1 severe exacerbation" was analyzed with a logistic regression model that used generalized estimating equations, with adjustment for exacerbation history (prednisone courses in past 12 months at baseline) and clustering by GP. Analyses were conducted using SAS statistical software (SAS Institute Inc, Cary, NC). For more details of analysis, see Online Repository.

Ethics approval and trial registration

The trial was approved by the Human Research Ethics Committee of the University of Sydney. All participants provided written informed consent.

TABLE I. GP training modules

Intervention module	GP training
UC	All GPs in all groups received UC training. This included advice on writing an asthma action plan (10 min), demonstrating and reviewing inhaler technique (10 min), and recent changes to asthma guidelines (15 min).
PAD	GPs received 2 h of small-group training on patient-centered communication around adherence. Training included an introduction to concepts of motivational interviewing, group assessment of video clips of good and bad communication, empathic discussion around adherence, including role play, and health goal-setting skills.
IRF	GPs received training on basic reminder device functions (5 min) and instructions on how to view Web-based medication feedback (5 min).

The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12610000854033).

RESULTS

GP participants

Sixty GPs were randomized, 55 attended training, and 43 were available to enroll patients. Five GPs withdrew before training while unaware of their allocation, 9 withdrew after training, and 3 were lost to follow-up (Fig 2). Of these 43 GPs (mean age, 54 ± 9 years; 56% men), more than half practiced in a socially disadvantaged location (Table II). The 17 GPs who withdrew differed from continuing GPs only with respect to having attended asthma or chronic obstructive pulmonary disease training in the past 12 months (71% of withdrawn GPs vs 41% of continuing GPs). At workshop end, GP-rated usefulness of the study interventions was high across all groups (visual analog scale 0-100, higher is better: UC, 80.8 ± 8.4; PAD, 82.5 ± 7.6; IRF, 82.0 ± 9.9; IRF + PAD, 81.9 ± 17.5; $P = .99$).

Patient participants

Forty GPs enrolled a total of 143 patients (62% women; mean age, 40.3 ± 15.2 years), half of whom lived in socially disadvantaged locations. Demographic and baseline characteristics were similar between groups, apart from a lower proportion of men in the IRF + PAD group and differences in the proportions of current smokers (Table II). At the first data collection timepoint (T0, 8.1 ± 7.5 days after enrollment), asthma was poorly controlled as indicated by an average ACT score of 14.6 ± 3.8 and FEV_1 77.1% ± 20.3% predicted, with 67 (52%) patients reporting 1 or more episode of asthma-related urgent health care utilization and/or prednisone use in the previous year.

Asthma control—Primary outcome

Of 143 enrolled patients, 129 completed the ACT at 2 or more time points and were included in the intention-to-treat analysis (Fig 2). At T2 months, average improvement in ACT score exceeded the minimal important difference (3 points) in all 4 groups (Fig 3, *A*); the proportions of patients with improved, unchanged, or worsened asthma control, based on the minimal important difference, were 68%, 28%, and 4%, respectively, similar among randomized groups (χ^2 $P = .64$). The improvement in ACT score was maintained in all groups at T6 months (overall mean change from T0, 4.5 ± 4.9; $P < .0001$). Significant within-group differences were observed in ACT score in all groups (Fig 3, *A*). Mixed-model analysis showed no significant difference in ACT score during the study among the 4 intervention groups ($P = .14$; Table III) nor between reminder versus nonreminder groups ($P = .27$).

ICS/LABA adherence

Adherence data were recorded throughout the study, starting from T0; 113 of 143 patients had analyzable SmartTrack data. No adherence data were available for 30 patients, but only for 6 patients (4% of those enrolled) this was due to device failure. Of the remaining 24 patients, 15 could not be contacted after enrollment to activate the device (UC, 2; PAD, 3; IRF, 0; IRF + PAD, 10), 8 patients reported losing the device (UC, 2; PAD, 2; IRF, 0; IRF + PAD, 4), and the GP changed 1 patient's ICS. Five SmartTracks failed in the field but were replaced and their data were retrieved.

Significant differences were observed in mean daily ICS/LABA adherence among the 4 groups during the study ($P = .0003$; Fig 3, *B*; Table III). Adherence was significantly higher in the 2 reminder/feedback groups than in the 2 nonreminder groups (73% ± 26% vs 46% ± 28% of daily prescribed doses; $P < .0001$). Adherence decreased over time in all groups, but after 6 months, adherence in the reminder/feedback groups was double that in the nonreminder/feedback groups (60% ± 38% vs 29% ± 33%; Fig 3, *C*).

Secondary outcomes

Over 6 months, severe exacerbations were experienced by 18% of UC, 48% of PAD, 7% of IRF, and 14% of IRF + PAD group patients (Table III). There were fewer patients with severe exacerbations in IRF than in non-IRF groups (7 of 64 [11%] vs 19 of 67 [28%]; $P = .013$), but this difference was not significant ($P = .06$) after adjustment for clustering and past self-reported prednisone use.

Mixed-model analysis showed no significant differences for any other secondary outcome among the 4 intervention groups, nor between reminder versus nonreminder groups (Table III). Overall, there were statistically significant and clinically important improvements from T0 to T6 months in asthma-related quality of life (mean change, 0.77 ± 1.15; $P < .0001$; Fig 3, *D*) and significant improvements in anxiety (−0.93 ± 3.18; $P = .022$) and self-reported adherence behavior (MARS-A, 0.28 ± 0.82; $P = .008$) (Table III). There were no significant changes in FEV_1% predicted or depression scores.

DISCUSSION

In this novel primary care–based intervention study of patients with moderate-severe asthma who were prescribed twice-daily

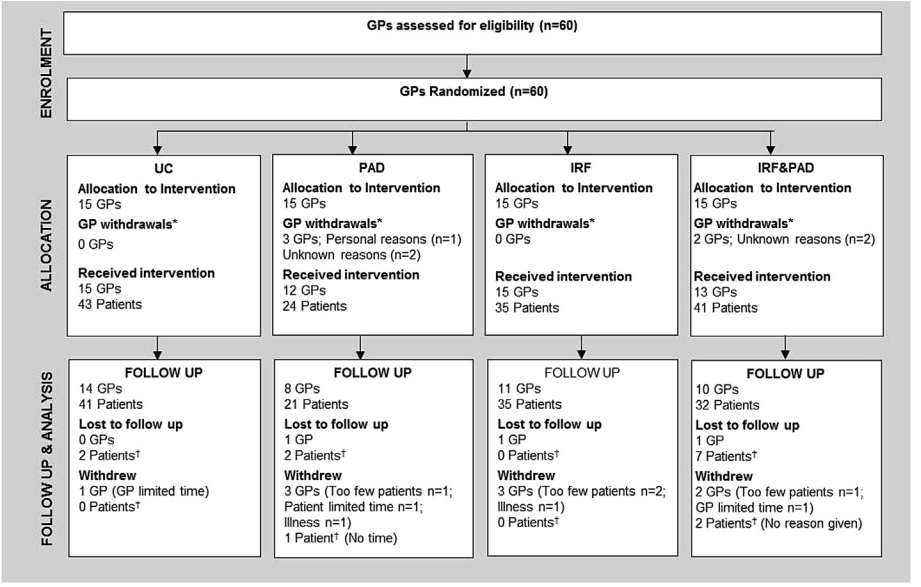


FIG 2. Flow of GPs and participants (intention-to-treat [ITT] population) through the study. The number of GPs in each intervention group who did not enroll a patient: UC = 0, PAD = 1, IRF = 1, IRF + PAD = 1. *GPs withdrew before allocation revealed and study training received. †Number of patients excluded from ITT analysis (asthma control) because of dropout or lost to follow-up before the completion of 2 or more study questionnaires.

TABLE II. GP and patients' demographic and baseline characteristics

GPs	UC (n = 14)	PAD (n = 8)	IRF (n = 11)	IRF + PAD (n = 10)	All GPs (N = 43)
Age (y), mean (range)	57.7 (45-75)	51.5 (46-65)	53.5 (32-68)	49.8 (35-65)	53.7 (32-75)
Sex: female	43	38	36	60	44
Years practicing as a GP, mean (range)	21.9 (2-42)	24.4 (5-48)	20.6 (4-40)	20.4 (9-40)	22 (2-48)
Language other than English spoken at home	43	63	64	40	51
Attended ≥1 asthma/COPD training events in past 12 mo*	50	38	36	30	41
Practicing in socially disadvantaged area†	57	50	64	50	56
Patients	**UC (n = 43)**	**PAD (n = 24)**	**IRF (n = 35)**	**IRF + PAD (n = 41)**	**All groups (N = 143)**
Sex: female	63	54	49	78	62
Age (y), mean ± SD	40.0 ± 14.1	42.3 ± 15.6	40.0 ± 13.7	39.7 ± 17.7	40.3 ± 15.2
ACT score, mean ± SD‡	14.6 ± 3.4	14.7 ± 4.2	15.1 ± 3.2	14.1 ± 4.4	14.6 ± 3.8
FEV_1 % predicted, mean ± SD	75.7 ± 22	67.3 ± 21.3	84.4 ± 19.4	78.0 ± 15.2	77.1 ± 20.3
ICS daily dose before study entry FP equivalent (μg), mean ± SD	683 ± 517	722 ± 500	704 ± 448	777 ± 426	718 ± 470
Proportion prescribed high-dose ICS§	44	54	40	66	51
Living in socially disadvantaged area†	63	45	37	54	51
Smoking: current/ex-smoker/never	23/23/55	0/27/73	11/26/63	22/37/41	15/28/57
Highest level of education: completed high school or lower	29	16	32	54	34
Language other than English spoken at home	40	40	32	36	37
Proportion with ≥1 prednisone course in last 12 mo	29	50	23	34	32

All variables % except where indicated. Total number of GPs with patients enrolled: 40.

COPD, Chronic obstructive pulmonary disease; *FP*, fluticasone propionate.

**P* value for difference between randomized (N = 17; 71% ≥1 events) and continuing (N = 43; 40% ≥1 events) GPs: χ^2 P = .045.

†Social disadvantage at GP practice location (GP)/home address (patients): "Disadvantaged" Socio-Economic Indexes For Area (SEIFA) quintile ≤3, "Advantaged" SEIFA quintile: 4-5.[21]

‡ACT (scored worst: 5; best: 25) score of 19 or less indicates suboptimal control.

§High dose >500 μg/d fluticasone propionate or equivalent.[6]

ICS/LABA, those who received electronic inhaler reminders for missed doses plus medication use feedback (IRF), on average, took 1.5 times more ICS/LABA over 6 months than did patients who received UC or PAD alone (73% vs 46%). At 6 months, mean adherence in reminder/feedback groups was double that in nonreminder/feedback groups (60% vs 29%). Clinically important improvements were seen in the primary outcome measure, asthma control (ACT score), in the total sample, and in asthma-related quality of life, but there were no significant differences among the 4 intervention groups nor between

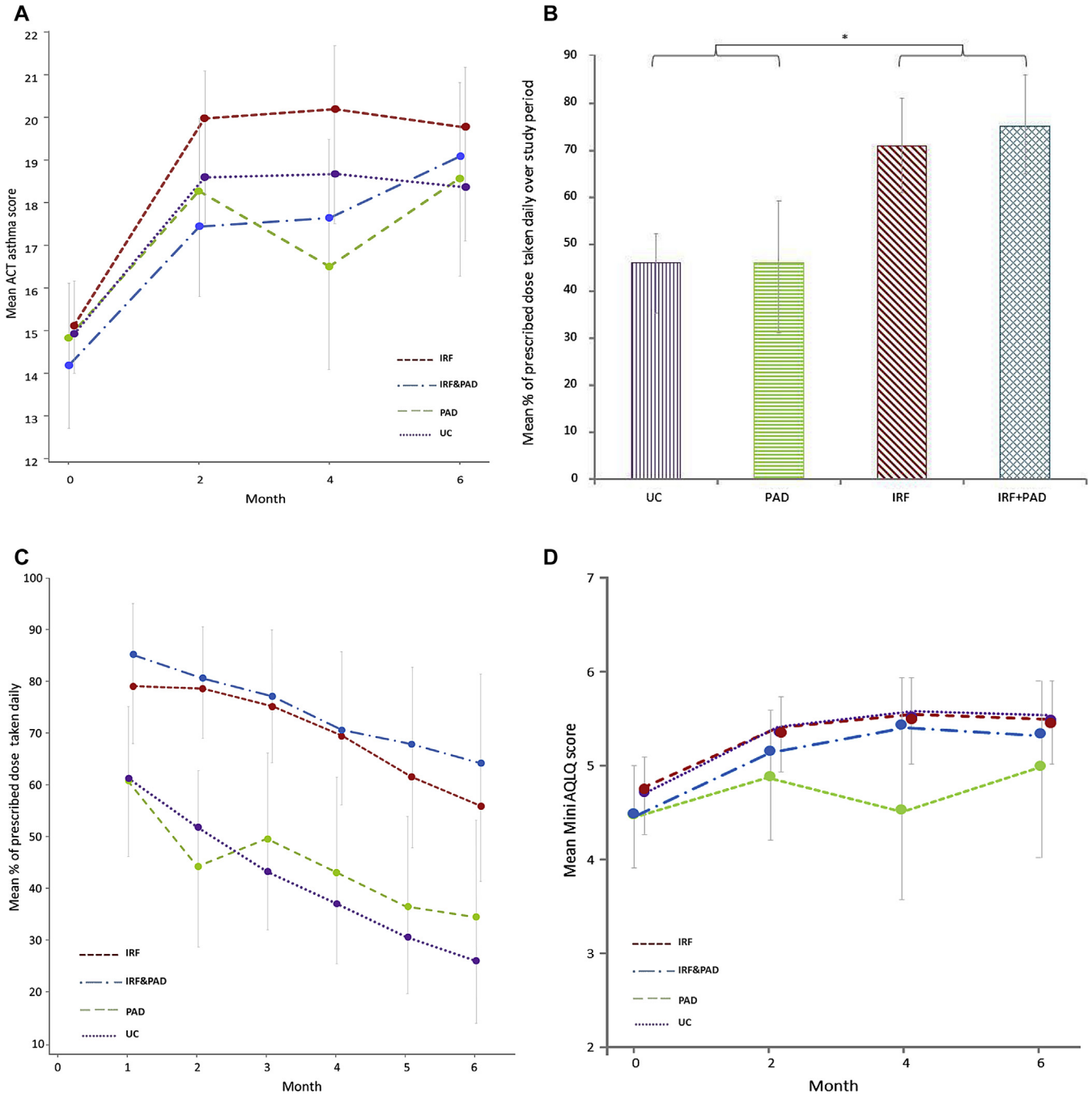


FIG 3. A, Mean asthma control (ACT score, primary outcome) by time point. **B,** Average ICS/LABA adherence over 6 months by intervention group. **C,** Mean ICS/LABA adherence by group and study month. **D,** Mean asthma quality of life (Mini AQLQ) by time point. *Mini AQLQ,* Mini Asthma Quality of Life Questionnaire. All GPs in all groups including UC received training in inhaler technique checking and writing an asthma action plan. All error bars 95% CIs. A change of 3 or more points in the ACT score represents a clinically important change; a score of more than 19 points represents good asthma control. Adherence monitors were activated at T0 (10.4 ± 7.3 days after patient enrolled and intervention delivered; no baseline adherence data available). A change of 0.5 or more in Mini AQLQ score represents a clinically important change. *$P < .0001$.

reminder or nonreminder groups. Fewer reminder/feedback patients than nonreminder patients experienced severe exacerbations during the study (11% vs 28%), but this difference did not remain significant after adjustment for clustering and exacerbation history (a predictor of future exacerbations).[32] With respect to psychological health, anxiety but not depression reduced significantly in the total sample although there were no differences among intervention groups.

The level of preintervention adherence was unknown because to maintain a real-world primary care context, there was no run-in

TABLE III. Primary and secondary outcomes: baseline values, average over the 6-month study period, and differences among groups

	UC		PAD		IRF		IRF + PAD		All	*P**	*P*†
Outcome	BL (CI)	Study period LSM (CI)	BL (CI)	Study period LSM (CI)	BL (CI)	Study period LSM (CI)	BL (CI)	Study period LSM (CI)	BL (CI)	Change from BL (all)	Difference among groups
Asthma control: ACT score	15 (14.0-15.9)	18.6 (17.6-19.7)	14.6 (13.0-16.2)	18.0 (16.6-19.5)	15.1 (14.1-16.2)	19.9 (18.8-21.0)	14.2 (12.6-15.9)	18.3 (17.1-19.5)	14.8 (14.1-15.4)	.0001	.14
Adherence (%), mean	—	46 (36-55)	—	46 (32-60)	—	71 (61-81)	—	76 (65-86)	—	—	.0003
mAQLQ	4.6 (4.3-5.0)	5.4 (5.1-5.8)	4.43 (3.9-5.0)	4.9 (4.5-5.4)	4.7 (4.3-5.1)	5.5 (5.1-5.8)	4.5 (3.9-5.0)	5.4 (5.0-5.7)	4.6 (4.4-4.8)	.0001	.26
Anxiety: HADSA	6.3 (4.9-7.7)	5.9 (4.9-7.0)	7.7 (5.8-9.6)	5.6 (4.0-7.1)	5.8 (4.4-7.3)	5.0 (3.9-6.1)	6.6 (4.8-8.3)	6.3 (5.1-7.5)	6.5 (5.7-7.3)	.022	.46
Depression: HADSD	4.4 (2.9-5.9)	3.8 (2.8-4.7)	6.2 (4.3-8.1)	4.4 (3.0-5.8)	3.5 (2.6-4.5)	3.3 (2.4-4.3)	4.3 (3.1-5.6)	4.0 (2.9-5.1)	4.5 (3.8-5.2)	.11	.65
MARSA-10	3.6 (3.4-3.7)	3.8 (3.6-4.0)	3.6 (3.5-3.8)	4.1 (3.8-4.4)	3.7 (3.4-4.0)	4.0 (3.7-4.2)	3.4 (3.1-3.8)	4.1 (3.8-4.3)	3.6 (3.4-3.7)	.008	.32
FEV_1 (L)	2.51 (2.28-2.75)	2.60 (2.48-2.73)	2.36 (1.91-2.81)	2.56 (2.40-2.73)	2.97 (2.65-3.28)	2.60 (2.47-2.72)	2.37 (2.07-2.67)	2.58 (2.43-2.72)	2.58 (2.42-2.74)	.42	.98
Patients with ≥1 severe exacerbation, n/N (%)		8 of 44 (18%)		11 of 23 (48%)		2 of 29 (7%)		5 of 35 (14%)		—	.06‡

All data except for severe exacerbations are mean (CI). For each treatment group, the first column shows the BL value and 95% CI for the outcome variable and the second column shows the LSM value and CI over the 6-month study period. The final 2 columns show significance levels for change from BL (all groups combined) and for differences among groups.
BL, Baseline; *HADS*, Hospital Anxiety and Depression Scale; *LSM*, least squares mean; *mAQLQ*, Mini Asthma Quality of Life Questionnaire; *MARSA-10*, Medication Adherence Report Scale for Asthma.
*One-way ANOVA.
†Intention-to-treat mixed-model analysis adjusted for clustering by GP, repeated measures and BL score (BL data for adherence % were not collected).
‡Generalized estimating equation model adjusted for exacerbation history (prednisone courses in past 12 months [yes/no] at BL) and clustering by GP. Total number of patients analyzed: ACT (scored 5 = poor, 25 = good) n = 129[22]; adherence (% of daily prescribed dose taken, recorded by electronic monitor) n = 113; mAQLQ (asthma-related quality of life; scored 1 = poor, 7 = good) n = 98[25]; HADS (scored 0 = low, 21 = high [scores ≥11 indicate probable mood disorder][26]): HADSA (anxiety subscale) n = 94; HADSD (depression subscale) n = 93; FEV_1 (L) (adjusted for age, sex, height, and BL value) n = 124; MARSA-10 (scored 1 = low, 5 = high) n = 96[28]; severe exacerbations based on prednisone courses n = 131.

period. However, the low daily adherence in nonreminder groups by study end (29%) was consistent with national[33] and international[34] estimates from dispensing data. In accordance with convention, patient adherence was calculated against a benchmark based on their GP's prescription, which assumes appropriate prescribing,[35] but the appropriateness of prescribing could not be assessed. Although adherence declined in all groups, the drop-off was much less than seen after emergency department visits, where the use of controllers decreased to 50% within the first week.[36]

Despite large differences in adherence, no significant difference was seen between groups in asthma control, the primary outcome measure, which was recorded by telephone by blinded study staff. A clinically important improvement in ACT score was seen in all groups over the first 2 months. Baseline fluticasone propionate dose was high at 718 μg/d, consistent with national prescribing patterns,[33] while the maximum efficacy of fluticasone propionate is seen at around 500 μg/d.[37] Overprescribing could have meant that even the modest average adherence of 56% seen in nonreminder groups during the first 2 months (Fig 3, *C*) may have exceeded the threshold for maximal change in asthma control from baseline, with higher adherence rates unable to produce further improvement.

The overall improvement in asthma control from baseline in all groups could also potentially have been due to factors unrelated to randomized study interventions, for example, due to temporal improvements in asthma control. In addition, asthma control may have improved with the UC interventions, that is, brief GP training in written asthma action plans and a single inhaler technique check. In this real-world primary care study, it was important to provide clinically plausible usual care tools to assist blinding and optimize study engagement and patient recruitment by UC GPs. The UC training was brief (10 minutes each for inhaler technique and action plans) and was carefully selected: provision of a written asthma action plan in isolation from comprehensive self-management education is ineffective for improving adherence or clinical outcomes,[38] and the positive clinical effect of inhaler technique education is short-lived if not repeated frequently.[39] However, combination therapy will not necessarily benefit all patients[40]; indeed current guidelines[6,7] recommend referral for specialist advice if asthma symptoms remain uncontrolled despite good adherence, correct inhaler technique, and management of comorbidities and modifiable risk factors. However, access to feasible adherence strategies in primary care could reduce the proportion of patients requiring referral.

Although there was no significant difference between interventions in ACT score, which primarily reflects symptom control, a significant difference in severe exacerbations was seen between patients in reminder and nonreminder groups (11% vs 28%; $P = .013$); this remained close to significant ($P = .06$) after a *post hoc* adjustment for exacerbation history. There is increasing recognition of potential differences between day-to-day symptom control and "future risk" outcomes such as exacerbations.[41] Very low doses of ICS/LABA may be sufficient to maintain reasonable symptom control but may leave the patient vulnerable to exacerbations.[41]

The second intervention, PADs, was rated highly by GPs (as were all the interventions), but appeared ineffective in this study because improvement in outcomes observed in PAD groups was similar to that in those receiving UC alone. The factorial design allowed testing for additive or synergistic effects when the 2 interventions were combined, but the results do not support this having occurred. GPs report barriers to the implementation of interventions at the clinician, patient, and practice level.[42,43] In the present study, PADs were likely more difficult to implement within time-pressured clinical interactions than introducing a reminder device and providing feedback about its output. The

need to practice new communication techniques may have been a barrier to the optimal delivery of the intervention,[44] particularly because GPs were unaware of the nature of study interventions when they enrolled, and some may have lacked interest in learning new communication strategies. Interestingly, IRF + PAD and PAD groups showed a trend of continued improvement in asthma control between 2 and 6 months (Fig 3, *A*) and so a longer study may have been required to determine whether greater gains were achievable with PAD.

Limitations of the study include the lack of prestudy adherence data (because of the primary care setting) and the short duration of training, particularly for the PAD intervention (2 hours), which required GPs to grasp new communication concepts and practice skills such as goal setting. However, because GPs had difficulty finding time to attend 1 training session, it would not have been feasible to offer more intense training. Top-up training tailored to GP needs was provided by telephone throughout the study. Brief GP training has been successful in other communication training studies,[12] but repeated communication training is reportedly more effective than one-off training.[45] The sample size of 143 (n = 129 for the primary outcome analysis) was lower than planned, even after reduction due to the smaller than anticipated cluster size. The study was clearly sufficiently powered to show differences in adherence between reminder/feedback and nonreminder groups, but given the magnitude of improvement in asthma control in the UC group, and the high prescribed doses of ICS/LABA, it may have been underpowered for the comparison of ACT scores between the interventions and their respective controls.

Strengths of the study include the pragmatic design and real-life primary care setting, the community-based population, the collection of most study data by study staff rather than by GPs, and the recording of adherence using validated electronic devices.[18] These devices provide objective data on the time/date of every actuation made, allowing researchers to report controller use with a level of detail (eg, Fig 3, *C*) not possible using other methods of adherence measurement such as dispensing data. The average adherence of 46% over 6 months in nonreminder groups is consistent with these being community-based patients, with adherence much lower than seen in specialist clinical research settings.[20] Patients were not reimbursed for study participation and were provided with only 1 month's supply of ICS/LABA (to allow initial setup of the SmartTrack). This may have augmented adherence in all groups in the first month, but patients were responsible for obtaining all subsequent medications, and so the cost of purchase could have an impact on adherence, as in normal clinical practice.[46]

In conclusion, this study, which is the first to examine the provision of inhaler reminders and adherence feedback in primary care, suggests that reminders offer a simple, feasible, and highly effective strategy for improving the adherence of general practice patients with asthma. This powerful combination of reminder and feedback allowed patients to receive prompts for missed doses as well as to view their detailed mediation-taking patterns (with their GP, if they wished). A follow-up implementation study is recommended to replicate these results in larger populations, including those with lower prescribed background controller doses. Studies of longer duration may be needed to test the effectiveness of the PADs used in this study. Careful checking of the appropriateness of prescribing and obtaining an assessment of adherence before intervention delivery may help to unpack the relationship between improved adherence, asthma symptom control, and exacerbations in future studies.

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Clinical implications: This primary care study demonstrates that inhaler reminders offer a simple, feasible, and highly effective strategy for improving adherence with controller inhalers in patients with asthma treated in general practice.

REFERENCES

1. Foster JM, Lavoie KL, Boulet L. Treatment adherence and psychosocial factors in severe asthma. In: Chung KF, Bel EH, Wenzel SE, editors. Difficult-to-treat severe asthma. Sheffield, UK: European Respiratory Society Journals Ltd; 2011. pp. 28-49.
2. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114:1288-93.
3. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol 2011;128:1185-91.
4. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332-6.
5. Goeman DP, Hogan CD, Aroni RA, Abramson MJ, Sawyer SM, Stewart K, et al. Barriers to delivering asthma care: a qualitative study of general practitioners. Med J Aust 2005;183:457-60.
6. Global Initiative for Asthma. Global strategy for asthma management and prevention 2014. Available at: www.ginasthma.org. Accessed May 2014.
7. National Asthma Council Australia. Australian asthma handbook. 2014 Version 1.0. Available at: www.asthmahandbook.org.au. Accessed March 2014.
8. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. Cochrane Database Syst Rev 2005;(4): CD000011.
9. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. Health Psychol 2006;25:462-73.
10. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: a comprehensive framework for clinical research and practice? A discussion paper. Int J Nurs Stud 2007;44:1468-77.
11. Reiff-Hekking S, Ockene JK, Hurley TG, Reed GW. Brief physician and nurse practitioner-delivered counseling for high-risk drinking: results at 12-month follow-up. J Gen Intern Med 2005;20:7-13.
12. Butler CC, Rollnick S, Cohen D, Bachmann M, Russell I, Stott N. Motivational consulting versus brief advice for smokers in general practice: a randomized trial. Br J Gen Pract 1999;49:611-6.
13. Marcus BH, Goldstein MG, Jette A, Simkin-Silverman L, Pinto BM, Milan F, et al. Training physicians to conduct physical activity counseling. Prev Med 1997;26: 382-8.
14. DiIorio C, McCarty F, Resnicow K, McDonnell Holstad M, Soet J, Yeager K, et al. Using motivational interviewing to promote adherence to antiretroviral medications: a randomized controlled study. AIDS Care 2008;20:273-83.
15. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. Med Care 2009;47:826-34.

16. Fenerty SD, West C, Davis SA, Kaplan SG, Feldman SR. The effect of reminder systems on patients' adherence to treatment. Patient Prefer Adher 2012;6:127-35.
17. Mahtani KR, Heneghan CJ, Glasziou PP, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database Syst Rev 2011;(9):CD005025.
18. Foster JM, Smith L, Usherwood T, Sawyer SM, Rand CS, Reddel HK. The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. J Asthma 2012;49: 657-62.
19. Patel M, Pilcher J, Chan A, Perrin K, Black P, Beasley R. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: implications for asthma clinical trial use. J Allergy Clin Immunol 2012;130:1420-2.
20. Charles T, Quinn D, Weatherall M, Aldington S, Beasley R, Holt S. An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. J Allergy Clin Immunol 2007;119:811-6.
21. Australian Bureau of Statistics. Socio-economic indices for areas (technical paper). Canberra: Australian Bureau of Statistics; 2006.
22. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006; 117:549-56.
23. Foster JM, Smith L, Bosnic-Anticevich SZ, Usherwood T, Sawyer SM, Rand CS, et al. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. Intern Med J 2012;42:e136-44.
24. Smith L, Alles C, Lemay K, Reddel H, Saini B, Bosnic-Anticevich S, et al. The contribution of goal specificity to goal achievement in collaborative goal setting for the management of asthma. Res Social Adm Pharm 2013;9: 918-29.
25. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
27. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. J Psychosom Res 2002;52: 69-77.
28. Mora PA, Berkowitz A, Contrada RJ, Wisnivesky J, Horne R, Leventhal H, et al. Factor structure and longitudinal invariance of the Medical Adherence Report Scale-Asthma. Psychol Health 2011;26:713-27.
29. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
30. Campbell MK, Piaggio G, Elbourne DR, Altman DG. CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ 2012;345:e5661.
31. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol 2009;124:719-23.e1.
32. Miller MK, Lee JH, Miller DP, Wenzel SE. TENOR Study Group. Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med 2007;101: 481-9.
33. Australian Centre for Asthma Monitoring. Asthma in Australia 2011. AIHW Asthma Series no. 4. Cat. no. ACM 22. Canberra: Australian Institute of Health and Welfare; 2011.
34. Williams LK, Peterson EL, Wells K, Campbell J, Wang MQ, Chowdhry VK, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. J Allergy Clin Immunol 2010;126: 225-31.
35. Carlton BG, Lucas DO, Ellis EF, Conboy-Ellis K, Shoheiber O, Stempel DA. The status of asthma control and asthma prescribing practices in the United States: results of a large prospective asthma control survey of primary care practices. J Asthma 2005;42:529-35.
36. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. Am J Respir Crit Care Med 2004;170:1281-5.
37. Holt S, Suder A, Weatherall M, Cheng S, Shirtcliffe P, Beasley R. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. BMJ 2001;323:253-6.
38. Toelle BG, Ram FS. Written individualised management plans for asthma in children and adults. Cochrane Database Syst Rev 2004;(2):CD002171.
39. Basheti IA, Reddel HK, Armour CL, Bosnic-Anticevich SZ. Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists. J Allergy Clin Immunol 2007;119:1537-8.
40. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med 2004;170:836-44.
41. FitzGerald JM, Boulet LP, Follows RM. The CONCEPT trial: a 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther 2005;27:393-406.
42. Peto V, Coulter A, Bond A. Factors affecting general practitioners' recruitment of patients into a prospective study. Fam Pract 1993;10:207-11.
43. Mason VL, Shaw A, Wiles NJ, Mulligan J, Peters TJ, Sharp D, et al. GPs' experiences of primary care mental health research: a qualitative study of the barriers to recruitment. Fam Pract 2007;24:518-25.
44. Butler CC, Simpson SA, Hood K, Cohen D, Pickles T, Spanou C, et al. Training practitioners to deliver opportunistic multiple behaviour change counselling in primary care: a cluster randomised trial. BMJ 2013;346.
45. Miller WR, Mount KA. A small study of training in motivational interviewing: does one workshop change clinician and client behavior? Behav Cogn Psychother 2001;29:457-71.
46. Ampon RD, Reddel HK, Correll PK, Poulos LM, Marks GB. Cost is a major barrier to the use of inhaled corticosteroids for obstructive lung disease. Med J Aust 2009;191:319-23.

METHODS

Trial design

In summary, this 6-month pragmatic 2 × 2 factorial cluster parallel-group randomized controlled trial was designed to evaluate the effect of 2 brief adherence interventions on asthma control and morbidity in primary care patients with poorly controlled asthma despite prescription of ICS/LABA. Individual GPs were randomized 1:1 to either the active group or the control group for each intervention, and trained to deliver the relevant intervention(s) with patients recruited from their own practice. The interventions were a brief PAD and an audiovisual IRF. All patients received UC, which included a brief inhaler technique review and provision (where necessary) of a customized written asthma action plan. There were thus 4 study groups: group 1: UC; group 2: UC + PAD; group 3, UC + IRF; group 4: UC + PAD + IRF.

To maximize the relevance of the findings to normal clinical practice, no run-in period was required, only 2 study visits were requested, and most outcome data were collected by telephone by study personnel. At the first visit, the patient was screened, provided consent, and was enrolled, and then the GP decided on an appropriate dose of controller treatment and delivered the initial intervention (details below). At the second visit, suggested for 4 weeks later, the GP was asked to reassess asthma control and review discussion points from the first visit. Apart from this, the patient's asthma management and the frequency of visits were completely according to the GP's clinical judgment.

Approval for the study was obtained from the Human Research Ethics Committee of the University of Sydney. Written informed consent was obtained from all GPs and patients before their participation.

Electronic inhaler monitoring

To obtain objective adherence data, all patients were provided with an electronic device (SmartTrack, Nexus, Auckland, NZ; see Fig 1 in main paper) that clipped around an ICS/LABA inhaler without interfering with its functions. Device reliability and accuracy have been reported.[E1] The device recorded the date/time (to the second) of all actuations for assessment of adherence, recorded removal and insertion of pressurized metered dose inhalers (pMDIs), and battery voltage level. Data were stored in nonvolatile memory. A battery charger was provided to each patient. For IRF groups, patients were shown how to program the device to provide audiovisual reminders for missed doses, customized to their preferred times. The device contained a phone chip and an external aerial, and it automatically uploaded data to a secure Web site each month. This minimized loss of study data if devices were lost, avoided the need for patients to be seen by study staff, and, in the IRF groups, allowed adherence feedback to be regularly reviewed by patients and their GPs.

With approval of the institutional review board, only GPs and patients in the 2 IRF groups were made aware of the recording capabilities of the device. As a distractor for the non-IRF groups, the SmartTrack screen prompted all patients to answer 3 questions about their asthma control at monthly intervals. For non-IRF groups, the device was described as "helping to keep track of patients' asthma control." These strategies have been used successfully in other adherence studies by the research team.[E2] For study purposes, the device was called "Asthmatrack" rather than its commercial name of "SmartTrack" to support the concealment of the study aim.

Participants

GP recruitment and eligibility. GPs from across the greater urban area of Sydney, Australia, were recruited by letter of invitation from general practice administrative divisions, followed up with personal contact by research staff. GP recruitment included areas of low to high socioeconomic disadvantage, based on national data.[E3]

GP inclusion criteria were access to a computer and e-mail (applicable to >90% of Australian GPs), and not currently participating in another adherence-promoting study. The latter was elicited with a general question about asthma or chronic obstructive pulmonary disease studies to avoid revealing the study focus on adherence. Only 1 GP was recruited per practice to reduce the risk of contamination between active and control interventions.

Patient recruitment and eligibility. Patients whose asthma was not well controlled were identified from the ACT, a validated 5-item tool that takes less than 2 minutes to complete.[E4,E5] In accordance with CONSORT guidelines for cluster randomized trials,[E6] GPs were asked, where possible, to have an independent person, such as the practice receptionist, identify suitable patients so that potential selection bias by participating GPs would be minimized.[E7] Patients whose asthma was not well controlled (ACT score ≤19) were provided with information about the study. The GP then checked other eligibility criteria and obtain written informed consent.

Patient inclusion criteria were age 14 to 65 years, asthma not well controlled (ACT score ≤19), and prescription for ICS/LABA twice daily for at least 1 month. Exclusion criteria were asthma exacerbation (defined by oral corticosteroid use, emergency department visit, or hospitalization) in the last month, other major respiratory disease, for example, chronic obstructive pulmonary disease, or serious uncontrolled medical condition, use of single inhaler budesonide/formoterol maintenance and reliever therapy, shift work with a variable roster, pregnancy or lactation, clinically important visual or auditory impairment, and currently participating in another asthma study.

Interventions

UC (all GPs). GPs were asked at the first visit to review the patient's asthma control, prescribe a clinically appropriate dose of fluticasone propionate/salmeterol, review and correct the pMDI technique, and provide and review a written asthma action plan if the patient did not already have one. To allow electronic inhaler monitoring, patients using budesonide/formoterol (Turbuhaler) or fluticasone propionate/salmeterol (Diskus) were, with the patients' agreement, switched to fluticasone propionate/salmeterol pMDI for the duration of the study. The GP gave each enrolled patient a bag containing 1 salbutamol inhaler, 1 month's supply of fluticasone propionate/salmeterol at the dose prescribed by the GP that day, the SmartTrack device, a baseline questionnaire, a portable electronic peak flow meter (miniWright Digital, Clement Clarke, Harlow, United Kingdom), a booklet including instructions of use for the SmartTrack and miniWright Digital, and, if appropriate, a large-volume holding chamber. Apart from reliever and controller inhalers for the first month of treatment, no medications were provided to patients, to avoid interfering with normal cost pressures on adherence. As soon as contact details for enrolled patients were forwarded by the GP, the patient was contacted by study staff to arrange a telephone call to collect initial data and activate the SmartTrack device; the target was for this to occur within 7 days of enrollment. During this call, patients were trained by telephone in the use of the SmartTrack including how to replace an empty pMDI, how to complete the monthly asthma questions, and, for IRF group patients, how to set up and change reminder ringtones and ring times. The telephone training was piloted with community patients before study start. Additional telephone support was available to patients during the study if needed.

Follow-up care. At the follow-up visit, preferably after 4 weeks, the GP was asked to assess the patient's asthma control, review the asthma action plan, and follow up on any discussions from the first visit. At the follow-up visit, and throughout the study, any change in medications or doses, and scheduling of other visits, was according to clinical need and the GP's judgment, that is, usual care. All changes in medications or doses were recorded for subsequent adherence calculations.

PAD (groups 2 and 4). GPs were trained in empathic communication skills and goal-setting strategies, focusing on known barriers and facilitators for intentional poor adherence. At the first visit with the GP, the patient completed an evidence-based questionnaire on his or her attitudes and beliefs about asthma and medications, developed by the researchers to identify barriers to asthma adherence.[E2] From this, the GP used a preprinted plastic template laid over the patient's completed questionnaire to quickly identify the patient's strongest responses, indicating likely adherence barriers, and used these to start a brief conversation about medication-taking attitudes and behaviors; the GP then assisted the patient in setting 1 to 2 asthma management goals and strategies with which to achieve these goals.[E8] GPs were provided with suggestions for nonconfrontational/empathic open-ended questions, customized color-coded discussion sheets relevant to each barrier identified by the questionnaire, and goal-setting cards. These resources were

developed by the researchers in collaboration with a Community Advisory Committee including asthma patients and GPs, checked for readability and comprehension with patients and piloted with patients with asthma, and approved by the ethics committee. The discussion sheets were printed on color-coded 3-copy no carbon required copy paper, and the GP recorded with checkboxes which topic(s) was addressed. The patient was given 1 copy of the discussion sheet and the goals and strategies card at the end of the visit and mailed a second copy the following day, and the GP kept the third copy in the patient's file. The GPs were prompted to use their practice software or post-it notes to facilitate following up at any subsequent visits on issues identified during these discussions.

At the follow-up visit, the GP was asked to review the patient's goals and strategies. The GP and the patient could also choose to continue the previous discussion topic, or to discuss a different adherence barrier.

IRF (groups 3 and 4). At the first visit, the GP explained to the patient that the SmartTrack would record the date and time of each ICS/LABA actuation and would play audiovisual reminders if scheduled doses were missed. Patients received feedback about their daily inhaler usage whenever they made an actuation or switched on the device. When a reminder sounded, it recurred at increasing frequency for a maximum of 24 minutes, ceasing if actuation occurred. With advice from the GP and/or telephone assistance from study staff, patients set their own reminder times for morning and evening, weekdays and weekends (this took <1 min). During the study, patients were able to choose a different ringtone (from 14 options), change reminder times, choose a "flight" option if traveling, cancel a reminder that was ringing, or switch reminders off, mimicking the way the device would likely be used in clinical practice; any such changes were recorded automatically by the device. Each month, the GP and the patient received an e-mail prompt (including Web link) to view a graph of each of their patients'/their own daily adherence over the previous 4 weeks. GPs were encouraged to review adherence data with the patient at the follow-up visit and any subsequent consultations. Patients could access their own adherence data at any time on a password-protected secure Web site. It was expected that the delivery of the interventions would add 10 to 20 minutes to the length of a consultation, depending on the randomization group.

Randomization of GPs

Each GP's patients represented 1 cluster. GPs were randomized separately 1:1 to active and control groups for the 2 interventions, using a 2×2 factorial design, allowing the effect of the 2 interventions (given in addition to UC) to be tested separately and together, in comparison with UC alone. Randomization of GPs was by a computer-generated program prepared by an independent statistician before study start, with an automated minimization algorithm to ensure a balance of randomization across 3 stratification factors: practice location by socioeconomic area, GP speaking a second language at home (as a surrogate for the likely ethnic balance of their patients), and GP participation in asthma/chronic obstructive pulmonary disease clinical management training in the past 12 months.

Blinding and allocation concealment

As with any behavioral strategy, blinding of GPs and patients to their own randomized intervention(s) was not possible. To avoid selection bias, no information about the study hypotheses or interventions was provided to GPs during recruitment, in accordance with published guidelines about blinding of nonpharmacological interventions and ethics for adherence studies.[E9] Instead, for promotion to GPs and patients, the study was described as testing different strategies to improve asthma control in primary care, using practical tools customized to patient needs. Blinding was facilitated by the provision of training in asthma action plan writing and inhaler technique review for all groups; for the UC group, this was the only intervention. Allocation concealment for GPs was maintained before study start, and revealed to each GP only during the training workshop.

Patients were aware of the intervention that they received from their own GP but not of the nature of other study interventions. With the approval of the institutional review board, separate participant information statements and consent forms were provided for each group. After each patient completed the study, those in non-IRF groups received a verbal debrief explaining the SmartTrack functions, and were offered a confidential record of their medication use. After data collection was completed, all patients and GPs were informed in writing about the concealed study aims, interventions, and study results. The research assistant collecting the primary outcome measure (ACT score) was blinded to randomization groups.

GP training

GP training workshops (1-2 hours) were provided at convenient times and locations. Participating GPs received Continuing Professional Development points for attending training and for study participation. They receive a per-patient reimbursement of AU $100, based on standard Australian primary care rates, to cover workshop attendance, additional consultation time required for study purposes, and retrieval of data from practice records.

Training for UC (all GPs). GPs in all groups were trained in brief inhaler technique review and education, using methods developed for and implemented in brief pharmacy interventions.[E10,E11] They were also provided with brief training in practical GP-focused strategies for discussing, writing, and reviewing individualized written asthma action plans.[E12] All GPs were shown the basic SmartTrack functions, including the questionnaire menu and how to replace a pMDI when empty.

Training for PAD. GP training for groups 2 and 4 included an established educational module for teaching communication skills and goal-setting strategies,[E8,E13] including a video, created for this study, showing good and bad communication techniques, and role-playing of communication skills in GP pairs with feedback from a trainer experienced in motivational interviewing. The GPs were also given brief written resources, including suggested language for eliciting and addressing relevant attitudes and beliefs, and examples of relevant goals and strategies. GPs were specifically trained in how to use the patients' questionnaire responses and customized topic-specific information sheets (driven by patients' individual responses to a questionnaire on attitudes and beliefs about asthma and medication)[E2] to discuss patients' concerns about asthma or medications and to set asthma management goals and strategies using empathic communication skills based on motivational interviewing.

Training for IRF. GPs in groups 3 and 4 were trained in reminder functions of the SmartTrack so that they could assist patients if required. GPs were shown how to access the password-protected secure Web site each month to obtain graphed feedback of their patients' adherence.

Outcome and process measures

Data collection. GPs recorded basic demographic characteristics and ACT score at the initial visit; other baseline characteristics including exacerbation history, smoking status, and medications were collected at either the initial telephone call by study staff (T0), aimed for within 7 days after enrollment, or by baseline postal questionnaire. The primary outcome measure (ACT score) and other patient-reported outcome measures, adverse events and health care utilization, were collected by telephone at 2, 4, and 6 months after enrollment. Patients recorded FEV_1 and peak expiratory flow on the MiniWright Digital device every 2 months; this was done during a telephone call with direct coaching by study staff and feedback to ensure maximal effort and reproducible results. These methods were piloted with community patients with asthma before study commencement, and compared with results from conventionally supervised maneuvers on the same day. A copy of the FEV_1 results was provided to the patient's GP. Patient attitudes (for non-PAD groups) and patient and GP satisfaction data were collected by post.

The aim of these data collection strategies was to minimize contact between study staff and patients, and to minimize the workload for GPs, so that outcomes would represent real-life clinical practice. Data for health care utilization and prescribing were provided by patients at each telephone call or obtained from GP records at study end.

Primary outcome measure. The ACT is a validated 5-item questionnaire (scored 5 = poor, 25 = good) for assessing asthma control in clinical practice.[E4,E5] An ACT score of 19 or less has 71% sensitivity and 71% specificity for uncontrolled asthma by physician assessment. Improvement in physician assessment by 1 level corresponds to an increase in of 1.88 ± 3.1

ACT score,[E5] and the published minimum important difference in ACT score is 3.[E14] It has been estimated that 50% of the patients in primary care will have an asthma score of 19 or less.[E8] For the primary outcome analysis, ACT score was recorded by telephone at T0, aimed to be within 1 week of enrollment, and at 2, 4, and 6 months, by a researcher blinded to the randomization group.

Secondary outcome measures. Secondary outcome and explanatory variables included electronically recorded adherence with controller medication; a perceived adherence behavior questionnaire (the Medication Adherence Rating Scale for Asthma [scored 1 = low, 5 = high])[E16]; patient attitudes to asthma medications (scored 4 = strongly agree [low adherence barriers]; 0 = strongly disagree [high adherence barriers])[E2]; the Hospital Anxiety and Depression Scale (scored 0 = low, 21 = high [scores ≥11 indicate probable mood disorder])[E17]; asthma-related quality of life (Mini Asthma Quality of Life Questionnaire; scored 1 = poor, 7 = good)[E18]; scheduled doctor visits; exacerbations as indicated by asthma-related urgent doctor visits, emergency department visits, or courses of oral corticosteroids; FEV_1 (as an independent predictor of risk of exacerbations); and adverse events.

GP satisfaction. After the workshop, GPs completed brief questionnaires about their satisfaction with the training. They rated their satisfaction with and use of the interventions and study tools after initial training, and at 3-monthly intervals and the end of the study. The use of the study tools was also assessed from GP patient records at the end of the study.

Data analysis

The primary analysis was by intention to treat. The effect on the ACT score of the 2 interventions separately, and of their interaction, was tested with a mixed-model analysis. Outcomes measured at baseline (T0) and prestudy ICS dose were included as covariates in the above mixed model, with GP clusters and patients assigned as random effects to incorporate clustering by GP and all available observations per patient over the 6-month study. A similar approach was taken for secondary outcomes. The binary variable "proportion of patients experiencing ≥1 severe exacerbation" was analyzed using a generalized estimating equation model, with adjustment for exacerbation history (prednisone courses in past 12 months at baseline) and clustering by GP. Analyses were conducted using SAS statistical software (SAS Institute, Inc, Cary, NC).

Protocol violations

Given the pragmatic design of the study, and the desire to include a real-life asthma population,[E19] it was decided that if, after enrollment, a patient was identified from the records submitted by the GP or from information divulged by the patient during the T0 telephone call to have been ineligible, he or she would not be removed from the study except if his or her participation would have put him or her at risk. Of the 143 patients enrolled in the study, 8 failed 1 or more inclusion criteria (5 had received oral corticosteroids within the previous 30 days, and 3 were not taking ICS/LABA before the enrollment visit, but were commenced on it by the GP at that visit). Of these, 1 patient was excluded from the intention-to-treat analysis because of newly diagnosed asthma and no prescription for ICS/LABA therapy at enrollment.

REFERENCES

E1. Foster JM, Smith L, Usherwood T, Sawyer SM, Rand CS, Reddel HK. The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. J Asthma 2012;49:657-62.

E2. Foster JM, Smith L, Bosnic-Anticevich SZ, Usherwood T, Sawyer SM, Rand CS, et al. Identifying patient specific beliefs and behaviours for conversations about adherence in asthma. Intern Med J 2012;42:e136-44.

E3. Australian Centre for Asthma Monitoring. Asthma in Australia 2011. AIHW Asthma Series no. 4. Cat. no. ACM 22. Canberra: Australian Institute of Health and Welfare; 2011.

E4. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the Asthma Control Test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59-65.

E5. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117:549-56.

E6. Campbell MK, Elbourne DR, Altman DG. CONSORT Group. CONSORT statement: extension to cluster randomised trials. BMJ 2004;328:702-8.

E7. Hahn S, Puffer S, Torgerson DJ, Watson J. Methodological bias in cluster randomised trials. BMC Med Res Methodol 2005;5:10.

E8. Smith L, Alles C, Lemay K, Reddel H, Saini B, Bosnic-Anticevich S, et al. The contribution of goal specificity to goal achievement in collaborative goal setting for the management of asthma. Res Social Adm Pharm 2013;9:918-29.

E9. Boutron I, Guittet L, Estellat C, Moher D, Hrobjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. PLoS Med 2007;4:61.

E10. Bosnic-Anticevich SZ, Sinha H, So S, Reddel HK. Metered dose inhaler technique: the effect of two educational interventions delivered in community pharmacy over time. J Asthma 2010;47:251-6.

E11. Basheti IA, Reddel HK, Armour CL, Bosnic-Anticevich SZ. Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists. J Allergy Clin Immunol 2007;119:1537-8.

E12. Reddel HK. Rational prescribing for asthma in adults – written asthma action plans. Aust Prescr 2012;35:78-81.

E13. O'Connor J, Seeto C, Saini B, Bosnic-Anticevich S, Krass I, Armour C, et al. Healthcare professional versus patient goal setting in intermittent allergic rhinitis. Patient Educ Couns 2008;70:111-7.

E14. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol 2009;124:719-23.e1.

E15. Schatz M, Zeiger RS, Drane A, Harden K, Cibildak A, Oosterman JE, et al. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. J Allergy Clin Immunol 2007;119:336-43.

E16. Mora PA, Berkowitz A, Contrada RJ, Wisnivesky J, Horne R, Leventhal H, et al. Factor structure and longitudinal invariance of the Medical Adherence Report Scale-Asthma. Psychol Health 2011;26:713-27.

E17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

E18. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.

E19. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, et al. Integrating real-life studies in the global therapeutic research framework. Lancet Respir Med 2013;1:e29-30.