

An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma

Thomas Charles, BSc,^a Dean Quinn, MBChB,^a Mark Weatherall, FRACP,^b
Sarah Aldington, BMBS,^c Richard Beasley, DSc,^c and Shaun Holt, MBChB^a
Wellington, New Zealand

Background: Adherence to medication regimens is poor in the management of chronic diseases, including asthma.

Objective: To determine whether an audiovisual reminder device improves adherence with inhaled corticosteroid (ICS) therapy in adult asthma.

Methods: A randomized open-label parallel group study of 110 adult or adolescent subjects with asthma was undertaken. Subjects were randomized to receive 24 weeks of fluticasone propionate 250 µg, 1 actuation twice daily via a metered dose inhaler (MDI) with or without an audiovisual reminder function (AVRF). All MDIs had electronic covert adherence monitors. The primary outcome variable was adherence, defined as the proportion of medication taken as prescribed over the final 12 weeks of the study. Adherence was also assessed as the proportion of subjects who took >50%, >80%, or >90% of prescribed medication.

Results: The proportion of medication taken in the last 12 weeks was greater in the AVRF group (93%) compared with the control group (74%), with a difference of 18% (95% confidence interval [CI] 10-26%; $P < .0001$). The proportion of subjects taking >50%, >80%, or >90% of their medication was greater in the AVRF group, with a ratio of proportions adherent of 1.33 (95% CI, 1.10-1.61; $P = .003$), 2.27 (95% CI, 1.56-3.3; $P < .0001$), and 3.25 (95% CI, 1.74-6.1%; $P < .0001$), respectively.

Conclusion: An audiovisual reminder function can significantly improve adherence with ICS therapy in adult asthma.

Clinical implications: An audiovisual reminder function has potential to improve adherence with medication regimens across a wide spectrum of diseases, in both research and clinical practice. (*J Allergy Clin Immunol* 2007;119:811-6.)

Key words: Adherence, adults, asthma, compliance, inhaled corticosteroids, reminder function

From ^aP3 Research; ^bthe Wellington School of Medicine & Health Sciences; and ^cthe Medical Research Institute of New Zealand.

Supported by a research grant from GlaxoSmithKline, UK.

Disclosure of potential conflict of interest: R. Beasley has served as a medical advisor for Nexus6 Ltd. The rest of the authors have declared that they have no conflict of interest.

Received for publication October 11, 2006; revised November 5, 2006; accepted for publication November 27, 2006.

Available online March 6, 2007.

Reprint requests: Richard Beasley, DSc, Medical Research Institute of New Zealand, P.O. Box 10055, Wellington 6036, New Zealand. E-mail: Richard.Beasley@mri.nz

0091-6749/\$32.00

© 2007 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2006.11.700

Abbreviations used

ACQ: Asthma control questionnaire
AVRF: Audiovisual reminder function
FP: Fluticasone propionate
ICS: Inhaled corticosteroid
MDI: Metered dose inhaler
PEF: Peak expiratory flow

Adherence to medication regimens is poor in the long-term management of chronic diseases.¹⁻⁴ This result has been shown in both clinical practice and research settings and is associated with worse outcomes. The situation is of particular concern in asthma, in which adherence to inhaled corticosteroid (ICS) therapy is usually less than 50% and is associated with worse outcomes, including an increased risk of mortality.⁵⁻⁸ Numerous strategies have been attempted to improve adherence; however, their effects have been generally disappointing, and it is recognized that innovative strategies are required.

Although the underlying reasons patients do not take their medications as scheduled are multiple and complex, unintentional nonadherence because of poor motivation, limited understanding, or simply forgetting is more common than previously thought.^{5,9} One potential approach to overcome poor adherence is the use of an electronic audio-alarm to remind patients when they should take their medication. Preliminary evidence suggests that this strategy may be effective in the treatment of a range of disorders, including glaucoma, schizophrenia, and vitamin supplementation.¹⁰⁻¹² To extend this approach to the management of asthma, an audiovisual reminder function (AVRF) has been developed for integration in the standard ICS metered dose inhaler (MDI). This device, the Smartinhaler (Nexus6 Ltd, Auckland, New Zealand), has the capability to emit an audible reminder at preset designated times, as well as a visual cue, which shows patients whether they have taken their inhaler during a designated period. The inclusion of an electronic covert adherence log to record MDI use allowed its efficacy to be assessed in this randomized, controlled clinical trial in adult asthma.

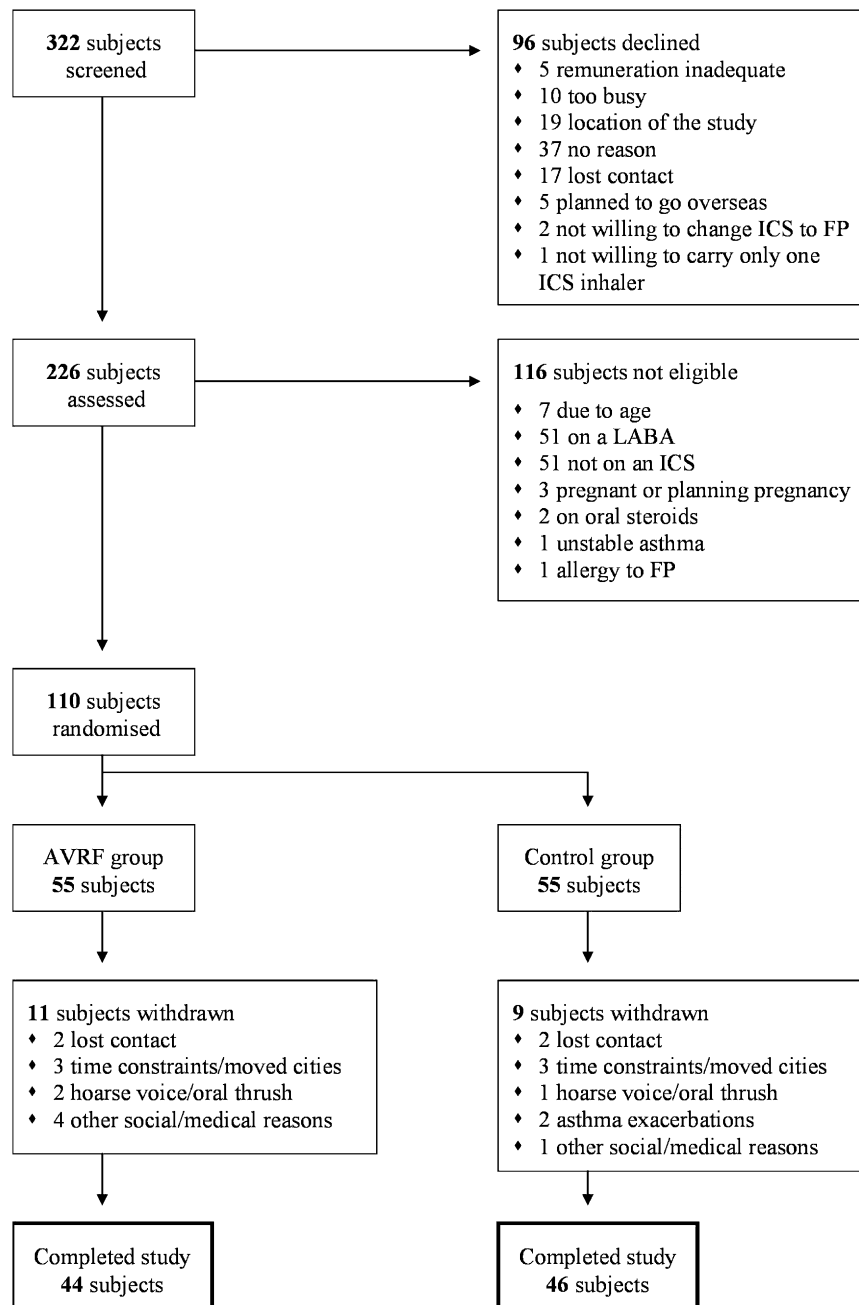


FIG 1. The consort diagram for the inclusion of subjects in the clinical trial. *LABA*, long-acting β -agonist. There were 11 subjects in the AVRF group and 9 subjects in the control group who did not provide data in the final 12-week period of the study. Social/medical reasons included trying to conceive, excessive phlegm, dizziness, chest infection, brain tumor, and heart attack (fatal).

METHODS

Subjects

Adolescent and adult subjects aged 12 to 65 years with a diagnosis of asthma were enrolled in this study (Fig 1). Subjects were recruited from research volunteer databases, newspaper advertisements, and informal contacts. Inclusion criteria were the requirement to take regular ICS at a fixed dose, no exacerbation in the previous month or run-in period, not pregnant or lactating, and if of child-bearing potential, using contraception. Exclusion criteria were a diagnosis of chronic

obstructive pulmonary disease, the use of a long-acting β agonist, or a history of other clinically significant disease. The requirement for subjects not to be taking a long-acting β -agonist was to avoid the potential influence of such therapy on adherence to ICS therapy.

Design

The study was undertaken at the P3 Research clinical trials facility in Wellington, New Zealand. Subjects were randomized to receive 1 of 2 fluticasone propionate (FP) treatment regimens:

1. FP 250 μg twice daily via the Smartinhaler MDI with covert adherence monitoring.
2. FP 250 μg twice daily via the Smartinhaler MDI with covert adherence monitoring and AVRF.

The randomization was by reference to a computer-generated random code concealed from the researcher who opened an envelope at the time of randomization. After a 2-week run-in period, subjects were randomized to receive 1 of the 2 FP treatment regimens for a 24-week period. All patients used a salbutamol MDI for relief of symptoms throughout the study. Subjects attended the clinic at weeks 0, 6, 12, 18, and 24. At the clinic visits, subjects completed the asthma control questionnaire (ACQ)¹³ and had 3 measurements of peak expiratory flow (PEF) with the highest value recorded. Subjects were instructed not to take their short-acting β -agonist for 6 hours before the clinic visits. At the end of the study, the subjects completed a written questionnaire, which included a question asking how many doses the subject thought they had missed during the previous 4 weeks.

Blinding

Subjects were informed that the purpose of the study was to determine the outcome when patients with asthma on a wide range of ICS doses and inhaler devices were changed to standard treatment via the novel Smartinhaler MDI device. Subjects were not informed of the electronic adherence monitor placed within their FP MDI. All subjects were instructed to take their FP, 1 actuation twice a day, on the basis that this represented the optimal ICS regimen in asthma. This approach was developed after discussion with the Wellington Ethics Committee, which approved the study. All subjects gave written and informed consent.

Smartinhaler

The Smartinhaler is basically a novel casing in which the standard MDI canister is inserted. Different electronic functions can be contained within the casing. In both groups, the Smartinhaler incorporated a covert electronic monitoring device, which recorded the date and time of actuations of the MDI. This information was uploaded to a computer after the participant's visit to the study center. The incorporation of the monitoring device did not alter the function of the MDI.

In the active group, the Smartinhaler also contained an AVRF. When the alarm was switched on, it generated a single beep, which sounded once every 30 seconds for 60 minutes after the predesignated time, which was programmed into the device. The alarm stopped if the MDI was actuated or after 60 minutes if not taken. The device was programmed to emit the alarm at predetermined times twice a day. The AVRF also had a colored light, which was green before MDI use, changing to red once the MDI was taken. This function served to remind patients whether they had taken the MDI as scheduled. At each clinic visit, the patient was issued with further supplies of FP in the Smartinhaler device.

Statistical methods

The primary outcome variable, adherence defined as the proportion of medication taken as prescribed over the latter half of the trial (expressed as a percentage), was to be compared with a *t* test, and the sample size calculation was performed on this basis. In the event, the adherence data was skewed and a Mann-Whitney test was performed as the primary analysis. To be adherent, subjects had to take 2 separate doses, at least 6 hours apart, every day. Multiple doses taken during any 6-hour period were counted as a single dose. If a subject took a dose after midnight before going to bed, this was considered to represent a dose for the previous day. Thus, for each day, the maximum possible adherence was 100% if subjects took 2 doses, separated by at least 6 hours, with adherence truncated to 100% for doses greater than

this amount. As a secondary analysis adherence was also assessed as the number of subjects who took >50%, >80%, and >90% of the prescribed medication, compared by calculation of the relative risk and its 95% confidence interval (CI), together with a χ^2 test.

Other secondary analyses were the proportion of medication taken as prescribed by time period expressed in 2 ways: first in 2-week periods around the times of clinic assessment, and second in the 4 time periods between clinic assessments. These assessments were analyzed by a Mann-Whitney test at each time period, as normality assumptions were not met as the data were skewed. The relative risk for adherence was also calculated for the number of subjects who took >50%, >80%, and >90% of the prescribed medication. For the secondary outcome variables, the PEF was analyzed by simple *t* tests by visit and by a general linear mixed model. The ACQ scores were analyzed for each clinic visit by a Mann-Whitney test. The difference between estimated and actual inhaler use was tested within subjects by a Wilcoxon signed rank test and between subjects by a Mann-Whitney test.

For the general linear mixed model for PEF, the visit 1 measurement was treated as a baseline covariate and an unstructured variance-covariance matrix was specified for the correlation structure for the repeated measurements. A treatment by visit interaction was tested for statistical significance, and if this was not significant ($P > .05$), then treatment main effect and visit main effect were also tested for significance. Although a conventional level of significance, $P = .05$, was used for individual statistical tests and associated 95% CIs, caution should be used in interpreting the secondary analyses because of the multiple statistical tests carried out.

"Dose dumping" was identified if ≥ 10 actuations occurred within a 3-hour period. Poisson regression was used to estimate the ratio of the count of dumping episodes to the number of periods of observation for each treatment group and the difference between the 2 groups. As Poisson regression operates on a logarithmic scale, the result was expressed as a ratio of rates of dumping.

SAS version 9.1 (SAS Institute, Inc., Cary, NC) and Minitab version 14 (Minitab, Inc., State College, Pa) were used.

Power calculation

Power calculations were based on an estimated mean adherence of about 70%, with an SD of 18, in a group without a reminder function. To detect an absolute difference of adherence of 10% at the 5% level of significance and with 80% power, 50 participants are needed in each arm of a 2-arm trial and 100 in total. Therefore, allowing for a dropout rate of around 10%, 110 subjects were recruited in the study.

Role of sponsor

The sponsor had no involvement in the study design; collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit for publication.

RESULTS

There were 110 subjects with asthma (50 men) randomized in the study. These subjects were aged between 13 and 65 years and on entry were taking a median (range) daily dose of BDP or equivalent of 500 μg (100-4000 μg per day). There were no differences in baseline characteristics between the 2 groups (Table I). By the completion of the study, 11 and 9 subjects in the AVRF and control groups, respectively, did not provide data in the final 12-week period of the study (Fig 1).

TABLE I. Characteristics of subjects with asthma

	AVRF (n = 55)	Control (n = 55)
Age (y): median (range)	39 (13-65)	35 (15-64)
Baseline ICS dose: median (range)*	500 (100-2000)	500 (100-4000)
PEF: mean (SD)†	434 (99)	444 (128)
Male	28	22
Withdrawals‡	11	9

*ICS dose: $\mu\text{g/day}$ beclomethasone dipropionate or equivalent.

†PEF: L/min.

‡See Fig 1.

Primary outcomes

The mean (SD) of the percentage of medication taken in the last 12 weeks of the trial was 88% (16) and 66% (27) in the AVRF and control groups, respectively. The median (interquartile range) was 93% (88% to 97%) and 74% (49% to 88%), respectively. The absolute difference in median percentage between the 2 groups was 18% (95% CI, 10% to 26%), $P < .0001$ by the Mann-Whitney test.

Secondary outcomes

The proportion of subjects taking $>50\%$ of their medication was 95.5% (42/44) in the AVRF group compared with 71.7% (33/46) in the control group. The ratio of proportions adherent with $>50\%$ of their medication associated with the AVRF was 1.33 (95% CI, 1.10-1.61; $P = .003$).

The proportion of subjects taking $>80\%$ of their medication was 88.6% (39/44) in the AVRF group compared with 39.1% (18/46) in the control group. The ratio of proportions adherent with $>80\%$ of their medication associated with the AVRF was 2.27 (95% CI, 1.56% to 3.30; $P < .0001$).

The proportion of subjects taking $>90\%$ of their medication was 63.6% (28/44) in the AVRF group compared with 19.6% (9/46) in the control group. The ratio of proportions adherent with $>90\%$ of their medication associated with the AVRF was 3.25 (95% CI, 1.74% to 6.10; $P < .0001$).

In both treatment groups, adherence fell during the first 12 weeks of the trial but then remained relatively stable for the remaining 12 weeks of the trial. At all time points, the adherence with medication was higher in the AVRF group (difference in median adherence by visit was 7% to 21%; all $P < .0001$) (Table II and Fig 2).

In the final 4 weeks of the trial, the AVRF group underestimated missed doses by a mean (SD) of 3 (10.8) doses and the placebo group by a mean (SD) of 12.2 (13.1) doses. This underestimation was considerably greater in the placebo group compared with the AVRF group, with an estimated median difference of 8 (95% CI, 3-15; $P = .001$). The median number of missed doses not self-reported by the patients was 2.0 and 11.5 in the AVRF and control groups, respectively.

There were 53 occasions on which subjects self-administered ≥ 10 actuations within 3 hours, 12 (23%)

TABLE II. Difference in median adherence by visit (Mann-Whitney test)

Visit	AVRF minus control		P value*
	%	(95% CI)	
1	7	(4-14)	<.0001
2	14	(10-22)	<.0001
3	21	(11-29)	<.0001
4	18	(10-29)	<.0001
5	18	(10-29)	<.0001

*Mann-Whitney test.

occurring on the day of the scheduled visit (Fig 3). There were 10 occasions on which dose dumping occurred in the AVRF group and 43 occasions in the control group. The difference in the rates of dose dumping was 0.25 (95% CI, 0.09-0.7; $P = .008$).

No significant differences occurred in clinical outcomes between the 2 groups. At the last clinic visit, the mean (SD) PEF was 456 (113) L/min and 454 (129) L/min in the AVRF and control groups, respectively (difference 2 L/min; $P = .95$). At the last clinic visit, the median (interquartile range) ACQ score was 0.5 (0-1.0) and 0.5 (0.2-1.2) in the AVRF and control groups, respectively (difference 0; $P = .33$).

DISCUSSION

This study has demonstrated that an AVRF can significantly improve adherence with ICS therapy in adult asthma. The absolute difference in adherence was large, at around 18%, and the proportion of subjects who achieved more than 80% and 90% adherence was between 2- and 3-fold higher in the subjects who had the AVRF.

Methodologic issues

Several methodological issues were considered in the study design that are relevant to the interpretation of the study findings. The study was of 6-month duration to ensure sufficient time to allow the subjects to revert to normal practice during the study, with adherence likely to be higher initially because of participation in the research project. This pattern was observed in our study in which adherence fell during the initial 12-week period of the study and then remained relatively stable.

Subjects were informed that the purpose of the study was to assess the efficacy of a standard dose of ICS from a new asthma inhaler in a large group of patients, with asthma previously taking different ICS doses from different devices. Subjects were not told that the assessment of adherence was the primary outcome of the study as this had the potential to change patient behavior.^{5,9,14-16} Ethical approval for this approach was obtained on the basis that there was no other way to collect this information, no harm was anticipated, and the subjects were likely to benefit from participating in this clinical trial.

For the subjects in the AVRF group, the device was programmed to emit an audible reminder at the

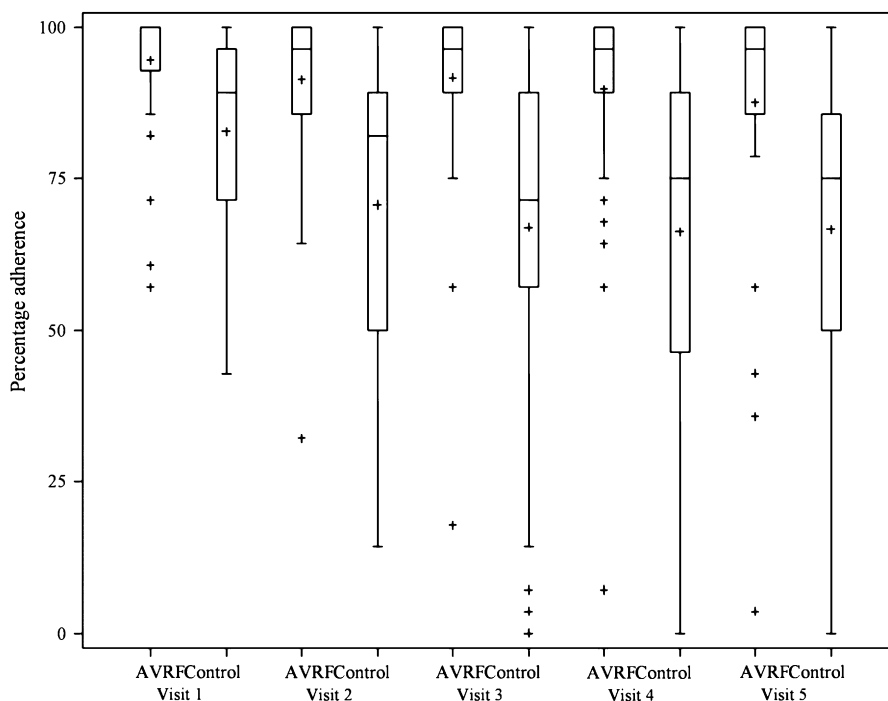


FIG 2. Box plot of adherence versus visit and treatment.

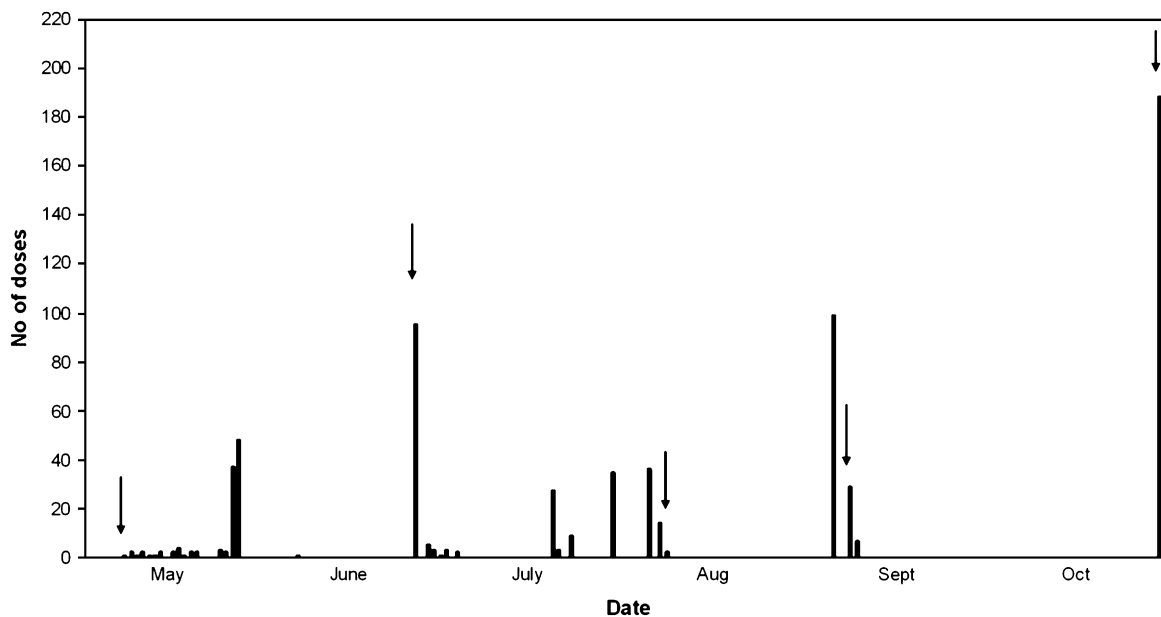


FIG 3. Medication use in control subject with the worst adherence. Note proximity of dose dumping to clinic visits (↓).

predetermined times designated by the participant. The alarm would sound (regular beeps) at this time and stop once the subject had used the MDI or alternatively after 60 minutes if the MDI was not actuated. As a result, the MDI would not be used only if the subjects deliberately chose not to do so or if they were not within an audible distance of the device. In addition, the visual display would change

from green to red once the dose had been taken to remind subjects that they had done so.

FP was prescribed at 500 µg per day to ensure that most subjects received the maximum possible benefit from their ICS therapy. We have previously shown that, for all clinical outcome measures including exacerbations, 80% to 90% of the maximum obtainable benefit of FP is

achieved at a daily dose of 200 µg per day and that on average the maximum benefit is achieved at 500 µg per day.^{17,18} As a result, this regimen ensured that, even if subjects had 50% adherence, they would gain most of the maximum obtainable benefit of FP, which is likely to explain the lack of difference in lung function or quality of life between the 2 groups.

Main findings

In this study, the AVRF improved adherence from a median of 74% to 93%, with a 2- to 3-fold greater number of subjects achieving 80% and 90% adherence with the AVRF, respectively. Perhaps more importantly, around 1 in 4 subjects had <50% adherence in the control group, compared with around 1 in 20 with the AVRF. Improving adherence to >50% is likely to have major clinical benefit in the long-term management of asthma.

In normal clinical practice, adherence is less than in the research setting. The magnitude is illustrated by the study from the United States in which electronically measured adherence to both oral and ICS dropped to around 50% within 7 days of discharge from hospital after a severe exacerbation⁸ compared with around 70% in our control group after 6 months. Whether the impact of the AVRF on adherence is relatively greater in clinical practice, rather than in the research setting, will require further study.

Clinical implications

The findings have major implications beyond those of asthma in which poor adherence can be considered to be a major determinant of outcome.^{7,19} This strategy could be adapted for use with other non-inhaled forms of medication in chronic diseases (for example, HIV, mental health disorders, and diabetes), patient groups (for example, elderly and adolescent), or other specific conditions (for example, *Helicobacter pylori* eradication) in which adherence may be poor or outcomes may be strongly associated with adherence.

The findings also have major implications regarding the design and conduct of clinical research studies. Poor adherence to medication regimens can markedly reduce the ability of a clinical trial to determine efficacy or, for that matter, adverse effects. For example, it has been estimated that, when study participants have an average adherence rate of 50% of the therapeutic dose, it can take 4 times as many participants to detect an effect of a given size than if the adherence rate was 100%.²⁰ Consideration needs to be given to using a simple electronic alarm device in clinical trials of therapeutic agents.

In summary, this study has shown that the AVRF can significantly improve adherence with ICS therapy in adult asthma. The AVRF has major potential to improve adherence with medication regimens across the spectrum of chronic diseases, both in research and in clinical practice.*

REFERENCES

- McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA* 2002; 288:2868-79.
- Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;27:1218-24.
- Zygmunt A, Olfon M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. *Am J Psychiatry* 2002;159: 1653-64.
- Solomon DH, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM, et al. Compliance with osteoporosis medications. *Arch Int Med* 2005; 165:2414-9.
- Cochrane GM. Therapeutic compliance in asthma: its magnitude and implications. *Eur Respir J* 1992;5:122-4.
- Bauman LJ, Wright E, Leickly FE, Crain E, Kruszon-Moran D, Wade SL, et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. *Pediatrics* 2002;110(1 Pt 1):e6.
- 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.
- Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adult with asthma. *Am J Respir Crit Care Med* 2004;170:1281-5.
- Spector SL, Kinsman RA, Maulinney M, Siegel SC, Rachelefsky GS, Katz RM, et al. Compliance of patients with asthma with an experimental aerosolized medication: implications for controlled clinical trials. *J Allergy Clin Immunol* 1986;77:65-70.
- Laster SF, Martin JL, Fleming JB. The effect of a medication alarm device for medical adherence research. *J Am Optom Assoc* 1996;67: 654-8.
- Frick PA, Lavreys L, Mandaliya K, Kreiss JK. Impact of an alarm device on medication compliance in women in Mombassa, Kenya. *Int J STD Aids* 2001;12:329-33.
- Ruskin PE, Van Der Wende J, Clark CR, Fenton J, Deveau J, Thapar R, et al. Feasibility of using the Med-eMonitor system in the treatment of schizophrenia: a pilot study. *Drug Inform J* 2003;37:283-91.
- Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and evaluation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
- Yeung M, O'Connor SA, Parry DT, Cochrane GM. Compliance with prescribed drug therapy in asthma. *Respir Med* 1994;88:31-5.
- Mawhinney H, Spector SL, Kinsman RA, Siegel SC, Rachelefsky GS, Katz RM, et al. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. *Ann Allergy* 1991;66:294-9.
- Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. *Am Rev Respir Dis* 1992;146:1559-64.
- Holt S, Suder A, Weatherall M, Cheng S, Beasley R. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001;323:253-6.
- Masoli M, Weatherall M, Holt S, Beasley R. Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax* 2004;59:16-20.
- 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.
- Goldsmith CH. The effect of compliance distributions on therapeutic trials. In: Haynes RB, Taylor DW, Sackett DL, eds. *Compliance in Health Care*. Baltimore, MD: Johns Hopkins University Press; 1979. p. 297-308.
- Tilson HH. Adherence or compliance? Changes in terminology. *Ann Pharmacother* 2004;38:161-2.
- Lask B. Compliance, adherence, concordance. *Br J Psychiatry* 1998;173: 271-2.

*In this manuscript, the term *adherence* has been used instead of the term *compliance* because of the willing partnership between the clinician and patient in the setting of the research study.^{21,22}