

BMJ Open Can electronic monitoring with a digital smart spacer support personalised medication adherence and inhaler technique education in patients with asthma?: Protocol of the randomised controlled OUTERSPACE trial

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ABSTRACT

Introduction Medication adherence and inhaler technique in patients with asthma remain suboptimal. A digital, smart spacer may support personalised adherence and inhaler technique education. The aim of this study is to assess the feasibility of undertaking a definitive randomised controlled trial of personalised, smart spacer data-driven education and explore clinical benefits.

Methods and analysis We present the design of the multicentre, randomised controlled Outcomes following Tailored Education and Retraining: Studying Performance and Adherence feasibility trial of 2 months. Patients will be recruited from four Dutch general practices. At $t=-1$, patients with asthma ≥ 18 years using inhaled corticosteroids \pm long-acting beta-agonists \pm short-acting beta-agonists administered with a pressurised-metered-dose-inhaler and spacer ($n=40$) will use a smart spacer for 1 month. The rechargeable CE-marked smart spacer (Aerochamber Plus with Flow Vu) includes a sensor that monitors adherence and inhalation technique to prescribed dosing regimen of both maintenance and reliever inhalers. After 1 month ($t=0$), patients are 1:1 randomised into two groups: control group (usual care) versus intervention group (personalised education). At $t=-1$, $t=0$ and $t=1$ month, the Asthma Control Questionnaire (ACQ), Work Productivity and Activity Impairment (WPAI) questionnaire and Test of Adherence to Inhalers (TAI) are administered and fractional exhaled nitric oxide (FeNO) is assessed. At $t=0$ and $t=1$, spirometry is performed. At $t=1$, usability and satisfaction will be analysed using the System Usability Scale and interviews with patients and healthcare providers. Primary outcome is the overall feasibility of a definitive trial assessed by patient recruitment speed, participation and drop-out rate. Secondary outcomes are patient and healthcare provider satisfaction and exploratory clinical outcomes are adherence, inhaler technique, TAI score, FeNO, lung function, ACQ and WPAI.

Ethics and dissemination Ethical approval was obtained from the RTP0 in Leeuwarden, Netherlands (number: NL78361.099.21). Patients will provide written informed

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first randomised controlled trial on the usability and potential clinical effects of using a smart spacer for personalised medication adherence and inhalation technique education in patients with asthma.
- ⇒ Inclusion and exclusion criteria are minimal in order to maximise the external validity of the findings.
- ⇒ The findings can be used to inform future larger studies and to further personalise asthma medication management.
- ⇒ An inevitable limitation of this study design is the impossibility to blind clinicians to the group allocation of the patients.

consent. Study findings will be disseminated through conferences and peer-reviewed scientific and professional journals.

Trial registration number NL9637.

BACKGROUND

Asthma is a major cause of disability, health-care services utilisation, work absence and quality of life impairment.¹⁻³ Asthma management aims to achieve good symptom control, minimise exacerbations and reduce side effects.⁴ Although the majority of asthma patients can be effectively controlled, a substantial subset remains uncontrolled despite being offered optimal therapy.⁴

Poor adherence to treatment is one of the most common causes of poor control and is widely reported in patients with all severities of asthma.⁵ Improving adherence can significantly reduce the disease burden. Yet, the biggest challenge facing physicians,

pharmacists and nurses treating patients with asthma is finding a way to ensure good adherence.⁶ While elements of adherence, such as moment of inhalation, have been studied,⁷⁻¹⁰ intervention studies of adherence to treatment between clinic visits, in daily life, including the vital domain of how devices are used are limited.¹¹

Complete adherence for inhaled medications has two components: (1) 'implementation and persistence' and (2) inhaler technique.¹² Implementation and persistence in this context is the extent to which an individual uses the medication at the directed times for a chronic period. This can be measured using self-reported patient diaries, which are prone to reporting bias, or more accurately using electronic inhaler monitors.¹³ Studies with these electronic devices show that persistence with treatment is relatively poor, but this may be improved by educational interventions. A recent UK study showed that average persistence for children with asthma was 49% for those who were monitored but received no reminders, and 70% for those who received reminders to take their treatment.¹⁴ However, while the number of inhalations taken improved, asthma control did not improve, likely due to lack of inhaler technique improvement. While inhaler technique is regularly checked, in mostly primary care clinic visits, this aspect of adherence is much more difficult to monitor remotely.

A Cochrane review of interventions to improve inhaler technique for people with asthma in 2017 concluded that 'Guidelines consistently recommend that clinicians check regularly the inhaler technique of their patients; what is not clear is how clinicians can most effectively intervene if they find a patient's technique to be inadequate, and whether such interventions have a discernible impact on clinical outcomes'.¹⁵

Effective treatment of asthma requires drug delivery to the airways and lungs. The devices which are used to achieve this include nebulisers, dry powder inhalers and pressurised metered dose inhalers (pMDI). The latter are most commonly used in combination with spacers (or valved holding chambers (VHC)) as recommended in many guidelines. There are several reasons behind the preference for pMDI and spacer use including: (1) they are usually the cheapest option and (2) pMDIs are also suitable for people that cannot generate sufficient inspiratory flow. However, also with a pMDI and spacer, many patients persist with critical errors in inhaler technique, leading to poorer disease control and poorer outcomes.¹⁶ Until recently, spacer use has been difficult to measure. This study intends to use a newly developed prototype smart spacer, which simultaneously measures adherence and technique. This will generate significant new data and facilitate appropriate inhaler training by healthcare professionals. Understanding if critical errors in administration of inhaled medications are occurring is vital if healthcare professionals are to be able to effectively educate people with asthma.¹⁷

The aim of this Outcomes following Tailored Education and Retraining: Studying Performance and Adherence

(OUTERSPACE) study is to assess the feasibility of undertaking a definitive randomised controlled trial (RCT) of smart spacer-based inhaler education and explore clinical benefits in adults with asthma.

METHODS

Study design and setting

The design of this feasibility study is a randomised trial of 2 months comparing smart spacer-based inhaler education vs usual care. Recruitment will take place in four primary care centres in the outreach area of the University Medical Center Groningen (UMCG) in the Netherlands. All practices consist of at least one general practitioner (GP), a pharmacy and multiple nurses. All practices have spirometry equipment available and have ample experience with spirometry as part of routine care. Practices will be provided with fractional exhaled nitric oxide (FeNO) devices (Niox Vero with NV TK 60-1 sensors) and trained. The study was reported according to the Standard Protocol Items: Recommendations for Interventional Trials checklist for study protocols of clinical trials¹⁸ (online supplemental appendix A). The study is planned to take place between autumn 2021 and spring 2022.

Participants

Patients need to fulfil the following inclusion criteria: (1) adults ≥ 18 years; (2) physician diagnosed asthma treated in primary care; (3) using inhaled corticosteroids (\pm long-acting beta agonists \pm short-acting beta agonists (SABA)), where at least the controller medication should be administered by pMDI and spacer (AeroChamber or Vortex, given their similar performance¹⁹) and (4) willing to sign written informed consent. The following exclusion criterium will be applied: (1) having had an exacerbation (defined by a short-course prednisone, emergency department [ED] visit or hospital admission due to asthma) in the last 30 days before potential inclusion.

Randomisation and blinding

At $t=0$, participants will be randomised in a 1:1 ratio to either the intervention (personalised smart spacer driven education) or the control group (usual care). All patients will be handed a smart spacer, but the data from the smart spacer will only be available to patients and healthcare professionals in the intervention group.

Smart spacer and inhaler error description

The smart spacer that will be used is based on the AeroChamber Plus with Flow Vu. The smart spacer (figure 1) is a rechargeable device and uses the same components as the existing Conformité Européenne (CE)-marked spacer, except for the adapter at the back of the spacer which has been modified to accommodate the sensing technology. To identify which inhaler a patient uses (eg, controller or reliever inhaler), an identifier is attached to each of the patient's inhalers.

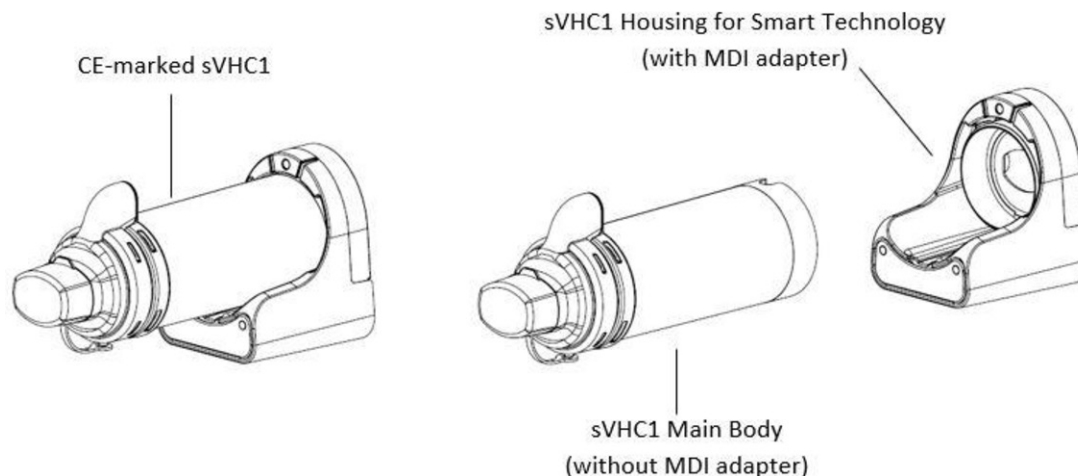


Figure 1 Smart spacer. CE, Conformité Européenne; MDI, metered dose inhaler; sVHC, smart valved holding chamber.

Performance of the smart spacer

Design verification testing was performed by the manufacturer of the device (Trudell Medical International) in order to support the CE mark declaration of the prototype smart spacer in Europe. The design process was compliant to ISO13485 and included the verification that the adherence and technique measurements were accurately and reproducibly transferred into data outputs. Note that this prototype device is being used for evaluating the clinical value of capturing this type of inhaler and spacer usage data. Usability (including industrial design), data visualisation and connectivity will all need to follow and be optimised within a commercial device. Our own testing (table 1) confirmed that the smart spacer meets flow performance specifications and aerosol drug output specifications, compared with the original spacer. The department Pharmaceutical Technology and Biopharmacy of the University of Groningen has performed calibrations to verify the effect of the Smart Technology Housing in comparison with the original AeroChamber Plus Flow Vu. A flow-pressure drop test was performed which demonstrated that the Smart Technology Housing has no effect on the internal resistance of the original AeroChamber in combination with the maintenance and reliever inhalers. These tests were performed with differential pressure gauges from Hottinger Baldwin Messtechnik, type PD1, Darmstadt, Germany and a calibrated mass flow metre from Brooks Instrument, type 5863S, Veenendaal, the Netherlands.

Definitions of adherence and inhaler errors

The prototype smart spacer monitors inhaler use in terms of adherence to prescribed dosing regimen and inhalation technique.

The adherence to dosing can range from 0% to 100% and is calculated based on the number of controller (ie, long-acting medication) doses taken divided by the prescribed dose (eg, two puffs twice daily). To achieve a 100% score, discrete doses must be at least 8 hours apart.

The score for inhalation technique, ranging from 0% (poor) to 100% (good), is calculated for each actuation of the controller or rescue inhaler. To define inhalation technique, five different errors are defined based on previous research and recommendations¹⁶ (table 2). Each error is initialised to 100% for each actuation and adjusted after the inhalation. Scores take into account the type of pMDI connected to the smart spacer.

Data output smart spacer

Figure 2 shows an example of the output of the smart spacer data visualisation. To assess this output, the memory card from the smart spacer needs to be manually removed and the data file should be transferred to a computer to be analysed using a Microsoft Excel file. Together with the patient, the adherence report is then analysed by the nurse. Using this output, tailor made inhalation education can be given. As such, patients will be asked to bring their smart spacer to the study visits.

Table 1 Flow-pressure differential relationship of the smart spacer in relation to the standard Aerochamber

Flowrate (L/min)	Pressure drop in Pa (mean of 2)			
	Smart+reliever pMDI	Standard+reliever pMDI	Smart+controller pMDI	Standard+controller pMDI
30	82	82	100	100
60	160	160	220	216
90	320	320	438	438

pMDI, pressurised metered dose inhaler.



Table 2 Technique error summary, as measured by the smart spacer

Technique error #	Technique error name	Description	Possible values
1	Multiple actuations	Multiple actuations before a full breath has occurred	*0%, 100%
2	No inhalation	No inhalation within 30s of an actuation	*0%, 100%
3	Delayed inhalation	Based on time between the actuation and start of inhalation	0%, 25%, 50%, 75%, 100%
4	Excessive flow	Inhalation flow >120 L/min, >80 L/min or <80 L/min	50%, 75%, 100%
5	Low volume	Based on volume (in mL) within 15s of an actuation	0%, 25%, 50%, 75%, 100%

*If technique error 1 or 2=0%, technique score for the entire actuation is 0%.

Study visits

An overview of the study visits is provided in [figure 3](#).

Training of study sites

To learn how to handle the smart spacer, interpret its data and standardise the education, the nurses received a protocolled 2-hour training from a specialised respiratory nurse who had experience with the smart spacer.

The study has three visits, further detailed below.

First visit (t=-1 month)

At baseline during the first visit, all participants' demographics and medical history are recorded (age, sex, weight, height, smoking status, comorbidity, date of

last exacerbation, prescribed medication), a FeNO test is performed, and the Asthma Control Questionnaire (ACQ),²⁰ Work Productivity and Activity Impairment (WPAI)²¹ questionnaire and Test of Adherence to Inhalers (TAI)²² are administered. Pharmacy dispense records from the previous year will be extracted to assess 1-year history of medication use, including oral steroid and antibiotics short-courses. Patients receive the smart spacer with user instruction.

Second visit (T=0)

One month after the first visit, the second visit takes place where a lung function test is performed (forced

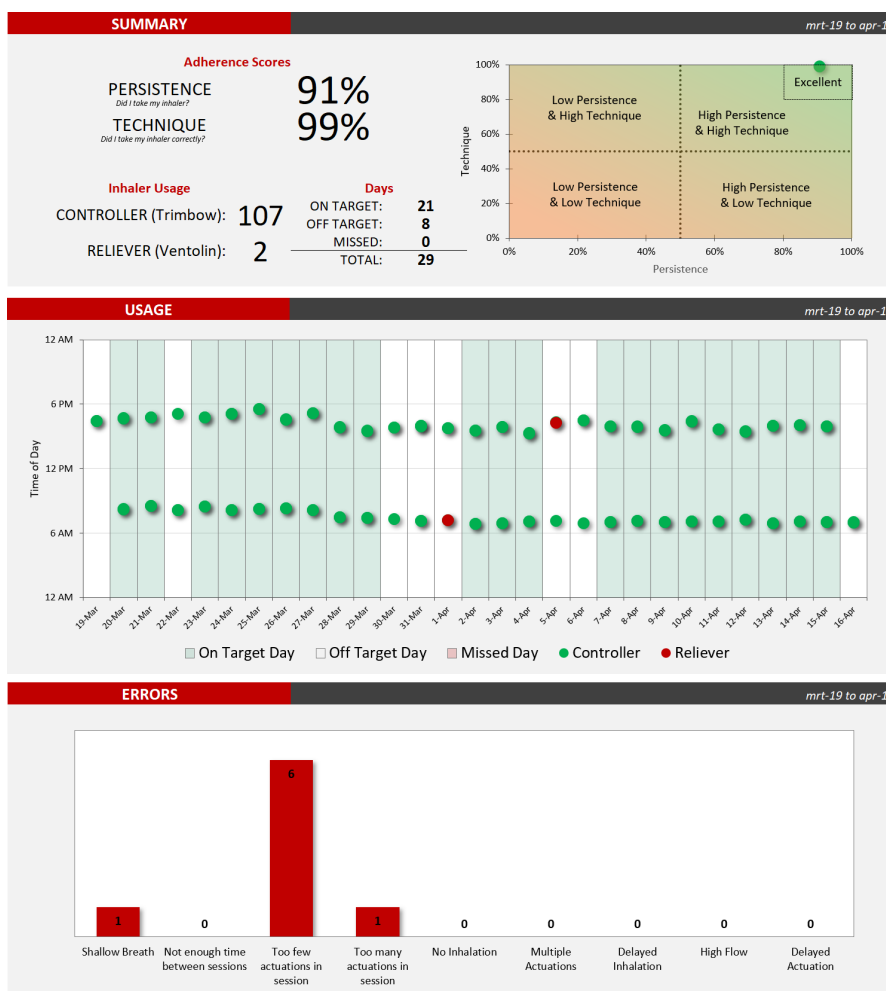


Figure 2 Example data output smart spacer.

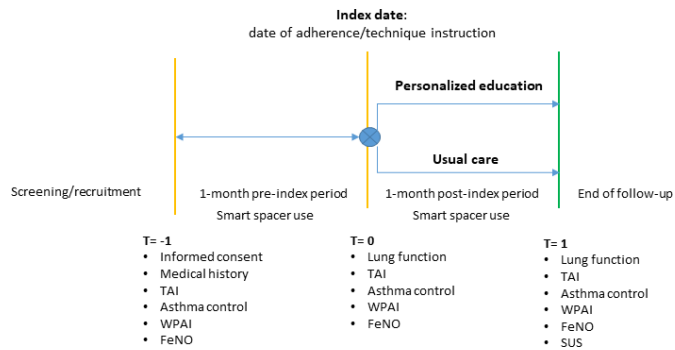


Figure 3 Study design and visits of the OUTERSPACE study. FeNO, fractional exhaled nitric oxide; OUTERSPACE, OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE; SUS, System Usability Scale; TAI, Test of Adherence to Inhalers; WPAI, Work Productivity and Activity Impairment.

expiratory volume in 1 second [FEV1], peak expiratory flow [PEF]), FeNO will be reassessed and the ACQ, WPAI and TAI will be readministered.

Intervention group

Those randomised to the intervention group will, in addition to usual care, be given personalised inhalation education with detailed information about how and when they used their inhaled medications based on smart spacer data. Data from the smart spacer will be downloaded by the nurse and discussed with the patient. If errors in medication use are identified with data from the smart spacer, protocolled inhaler instructions will be provided to help eliminate errors, following standardised Dutch Lung Alliance Netherlands inhaler use protocols. To protocolise the adherence interventions, the TAI Toolkit²³ will be used.

Control group

The control group receives usual care, that is, a regular review of their asthma according to Dutch primary care asthma guidelines.

All participants will be given a fully charged smart spacer to use for the remainder of the study period (a further month).

Third visit (t=1 month)

After another month, at the third visit, all patients will complete a second lung function test (FEV1, PEF), FeNO test, ACQ, TAI and WPAI and return the smart spacers. Patients and study nurses will complete the System Usability Scale (SUS),²⁴ will be asked to report any difficulties encountered with the devices to the study team, and views will be specifically sought about how the device and training could be improved.

Outcomes

This primary outcome of this study is the feasibility of performing a definitive study of a personalised educational approach to improve disease control in adults with asthma using a smart spacer. Feasibility outcomes include

(1) patient recruitment speed, (2) participation rate and (3) sample size calculation for a definitive trial.

Secondary outcomes include patient and healthcare provider satisfaction with the smart spacer (assessed by the SUS and interview) and feasibility of study procedures in the general practice as well as time investment (assessed by end-of-study interviews with nurses). Furthermore, exploratory outcomes include the changes in distribution of medication adherence patterns (total number of inhaler errors, overall inhaler technique score, individual error distribution and adherence (number of controller actuations divided by the prescribed dose)) and clinical outcomes (lung function, ACQ, WPAI, TAI, SABA use, oral steroid bursts) as compared between the intervention and the control group.

Treatment fidelity

To ensure GPs and nurses fidelity to study protocol, the nurses will be trained and supported directly by the project leader and by a specialised pulmonary nurse from the Martini hospital in Groningen who has experience with the smart spacer (OUTERSPACE-chronic obstructive pulmonary disease [COPD] study).²⁵

Sample size calculation

This is a feasibility trial to inform a larger definitive RCT. We lack the data for a formal power calculation to determine study size. Recommended sample sizes for feasibility RCTs vary between 24 and 50. The recruitment target of 40 has been pragmatically chosen based on National Institute for Health and Care Research recommendations.²⁶ It should provide us with sufficient information to determine SD to inform a formal sample size for a larger definitive outcome RCT.

Planned statistical analysis

Continuous variables (eg, age, adherence, inhaler errors, ACQ, WPAI, TAI, FEV1, FeNO, SUS) will be descriptively summarised as number of observed values, number of missing values, mean and SD, or median and IQR and minimum and maximum, where appropriate. Categorical data (eg, gender, comorbidity) will be summarised as number of observed values, number of missing values, number and percentage in each category.

For statistical comparison between study groups: when continuous data are normally distributed, the student T-test will be used. For non-normally distributed data, the Mann-Whitney U test will be used. Categorical data will be compared using χ^2 or Fisher exact test, where appropriate.

Data management

In this study, the data will be collected, processed and archived in accordance with the General Data Protection Regulation and the Findable, Accessible, Interoperable, Reusable principles under the responsibility of the principal investigator. A research data management plan has been drawn up to describe the further operational details and procedures.

All study data will be with a patient pseudonymised number, safely and structurally captured using a study folder and stored electronically in the UMCG REDCap system. Individual study maps will be stored in a locked cabinet.

- ▶ Tooling (eg, software and procedures) used for collecting, processing, analysing and storing data will be compliant with the UMCG policy and Standard Operating Procedures in the UMCG Research Toolbox.²⁷
- ▶ Data will be pseudonymised by use of a code list during data collection.
- ▶ Indirect and direct identifiable information collected will be minimised and only collected for the purpose of this study.
- ▶ Direct identifiable information (eg, contact details, code list/encryption key/subject identification log) will be stored separately from pseudonymised data.
- ▶ Direct identifiable information can only be accessed by the principal investigator and study delegates after authorisation by the principal investigator.
- ▶ Pseudonymised/anonymised data can only be accessed by the Principal Investigator and study delegates after authorisation by the principal investigator.
- ▶ Data roles, responsibilities, access and authorisation—during the study and after study completion—will be managed and documented.
- ▶ Digital data will be archived on the UMCG network complying with strict UMCG security and back-up policy.
- ▶ Paper source data and study files will be archived within the UMCG facilities.
- ▶ Source data, study files and digital data will be stored 15 years after the study is completed.

Patient and public involvement

Before this study, a pilot study (N=12) applying the same concept of smart spacer-data driven education was carried out in patients with COPD.²⁵ Feedback from these patients was used to inform the current trial protocol. After the study, a qualitative evaluation will take place with patients participating in this study. Results from this study will actively be communicated to patients involved in the study and beyond.

Ethics and dissemination

Ethical approval was obtained from the RTPO MCL in Leeuwarden, The Netherlands (Number: NL78361.099.21). All patients will provide written informed consent before participation in this study. Findings of this study will be disseminated through national and international conferences and peer-reviewed scientific and professional journals.

DISCUSSION

Proper adherence to inhalation medicines is a topic of major concern in patients with asthma. Numerous studies

have been performed trying to find means to improve adherence to inhalation medicines. These studies can roughly be divided into two groups: studies that aimed to improve adherence and studies that aimed to improve inhaler technique.²⁸ Most studies are however confronted with the same problem: how to gain insight into the continuous daily use of the inhalation medicines.

To assess adherence, patients are often asked if they used their medicine often enough at the correct time of the day. Yet, overestimation and socially desirable answers are common. Indeed, Bourdin *et al*²⁹ state in their review: ‘Most of the severe asthma patients overestimate their level of observance because of memory recall, defence or desire to please their health care provider. As a result, most of the physicians tend to overestimate their severe asthma patients’ adherence too’.

To assess inhaler technique, patients are usually asked by their caregiver to show how they use their inhalation device. This only provides insight into how patients use their device in a clinical setting knowing that they are being observed. These studies do, however, not give an understanding of the actual inhalation technique at home.³⁰

Data from the OUTERSPACE programme (that also includes smart spacer studies in patients with COPD and paediatric asthma) can bring us to the next level: not only can we objectively monitor intake of inhalation medicines, we also obtain continuous data on inhaler technique at of multiple inhalers in the home setting. With this data, the caregiver can interact with the patient and personalise their education. The caregiver can give the patient an insight into his or her ‘inhalation behaviour’ during their usage at home. For these data to be optimally used for educational purposes, further real-world validation of the smart spacer data is required. Although design verification was performed by the manufacturer, including the verification that the adherence and technique measurements were accurately and reproducibly transferred into data outputs, the clinical validation to drive clinical decisions should be further tested.

With the data of this smart spacer study, we not only hope to improve adherence to inhalation medicines and outcomes, we also hope that this data will help to improve the ‘ownership’ of patients to their own adherence and to their own responsibility of achieving an optimal asthma control.

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Competing interests HAMK reports a fee for a one time consultancy outside the realm of this study, and grants and fees for consultancy or advisory board participation from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Novartis all outside of the submitted work. All were paid to his institution. JK reports grants, personal fees and non-financial support from AstraZeneca, grants, personal fees and non-financial support from Boehringer Ingelheim, grants and personal fees from Chiesi Pharmaceuticals, grants, personal fees and non-financial support from GSK, grants from Mundi Pharma, grants and personal fees from TEVA, personal fees from MSD, personal fees from COVIS Pharma, outside the submitted work; and Janwillem Kocks holds 72.5% of shares in the General Practitioners Research Institute. JFMvB received grants and/or consultancy fees from AstraZeneca, Chiesi, European Commission COST (COST Action 19132), GSK, Lung Alliance Netherlands, Novartis, Teva, and Trudell Medical, outside the submitted work and all paid to his institution. Other authors declare no relevant conflicts of interest.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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