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Original Research

Electronic monitoring with a digital smart spacer to support personalized inhaler use education in patients with asthma: The randomized controlled OUTERSPACE trial

Boudewijn J.H. Dierick [a,b,c], Maria Achterbosch [a,b], Amber A. Eikholt [a], Sandra Been-Buck [d], Titia Klemmeier [d], Susanne J. van de Hei [b,e,i], Paul Hagedoorn [f,g], Huib A.M. Kerstjens [b,h], Janwillem W.H. Kocks [b,g,h,i,j], Job F.M. van Boven [a,b,g,*]

[a] University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy & Pharmacology, Groningen, the Netherlands
[b] University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of General Practice & Elderly Care Medicine, Groningen, the Netherlands
[d] Department of Pulmonary Diseases, Martini Hospital, Groningen, the Netherlands
[e] University of Groningen, University Medical Center Groningen, Department of Health Sciences, Groningen, the Netherlands
[f] University of Groningen, Groningen Research Institute of Pharmacy, Department of Pharmaceutical Technology and Biopharmacy, Groningen, the Netherlands
[g] Medication Adherence Expertise Center of the Northern Netherlands (MAECON), Groningen, the Netherlands
[h] University of Groningen, University Medical Center Groningen, Department of Pulmonology and Tuberculosis, Groningen, the Netherlands
[i] General Practitioners Research Institute, Groningen, the Netherlands
[j] Observational and Pragmatic Research Institute, Singapore

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ABSTRACT

Background: Poor adherence to inhaled medication has been associated with poor outcomes. Smart spacers can monitor inhaler use and technique, yet their feasibility in adults with asthma and their potential benefits are unknown.
Objective: Assessing the feasibility of undertaking a definitive randomized controlled trial (RCT) of smart spacer-based inhaler education and explore potential clinical benefits in adults with asthma.
Methods: Two-month randomized controlled feasibility OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE (OUTERSPACE) trial comparing personalized smart spacer-based inhaler education versus usual care. Patients were recruited in four Dutch primary care centres. Outcomes were feasibility (inclusion speed, patient acceptance), medication adherence, inhaler technique, clinical effects (lung function, ACQ, FeNO) and usability (System Usability Scale [SUS]).
Results: 42 patients were randomized and all completed the study. The feasibility of performing a larger trial focusing on asthma patient education using a smart spacer was demonstrated with all patients included in four months and a participation rate of 86%. In the intervention group, inhalation errors per day decreased by 26.2% while in the usual care group inhalation errors increased by 14.6% ($p = 0.021$). Adherence decreased slightly in the intervention group as opposed to improvement in the control group (difference 12%, $p = 0.028$). No changes in lung function, ACQ or FeNO were observed. Usability was deemed high (SUS patients 71, nurses 89).
Conclusion: This RCT showed that smart spacer-driven education in patients with asthma is feasible and in this short-term study reduced inhaler errors. Longer-term and larger studies are required to assess clinical effects.

1. Introduction

Inhalation of corticosteroids and bronchodilators is the cornerstone of asthma treatment [1]. Inhaler devices used include nebulisers, dry powder inhalers (DPI), soft mist inhalers and pressurised metered dose inhalers (pMDIs). pMDIs are often used in combination with spacers or

* Corresponding author. Department of Clinical Pharmacy & Pharmacology, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, Hanzeplein 1 (AP50), 9700 RB, Groningen, the Netherlands.
E-mail address: j.f.m.van.boven@umcg.nl (J.F.M. van Boven).

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valved holding chambers. A significant proportion of patients remains uncontrolled [1] with insufficient adherence to inhalation therapy as an important contributor [2]. Importantly, poor adherence has been associated with increased mortality, asthma symptoms, direct and indirect costs and reduced quality of life [3,4]. Part of good adherence is an adequate inhalation technique. The majority of patients (over 70%) make mistakes while handling their inhaler device [5]. A Cochrane review concluded that 'guidelines consistently recommend that clinicians regularly check the inhaler technique of their patients (…) whether such interventions have a discernible impact on clinical outcomes, remains unclear' [6].

Medical history, self-reported diaries and pharmacy records can give insight into adherence, but are prone to bias and patients often overestimate their adherence to inhalation therapy [7]. Electronic inhaler monitors can measure adherence more accurately [8]. In the past fifteen years, "smart inhalers" have been introduced to monitor adherence objectively and provide patients and caregivers with feedback regarding adherence [8]. Few smart inhalers give the patient feedback on the quality of the inhalation. Although several smart inhalers have been introduced, there is currently no smart solution for assessing inhalation when using a spacer.

The smart spacer used in this study not only monitors the inhaler use, but also gives feedback on the quality of the inhalation (technique). A pre-post pilot study in twelve COPD patients showed that a smart spacer could decrease inhaler errors by about one-third and was well received by patients and healthcare professionals [9]. In asthma, no studies with the smart spacer device have been performed.

The aim of this OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE (OUTERSPACE) study is to assess the feasibility of undertaking a larger randomized controlled trial (RCT) of smart spacer-based inhaler education and explore adherence and inhalation technique benefits and clinical effects in adults with asthma.

2. Material and methods

2.1. Study design & setting

This was a randomized controlled feasibility trial of two months comparing smart spacer-based inhaler education to usual care. Patients were recruited in four primary care centres in the outreach area of the University Medical Centre Groningen (UMCG) in the Netherlands. For more detailed descriptions, we refer to the protocol published previously [10]. This study is registered in the Netherlands Trial Registry (NL9637) and is reported according to the CONSORT checklist for randomized controlled trials (Online repository, Table E1). Ethics approval was obtained from the from the RTPO in Leeuwarden, Netherlands (Number: NL78361.099.21).

2.2. Inclusion and exclusion criteria

Inclusion criteria were: (1) age ≥18 years; (2) physician-diagnosed asthma treated in primary care; (3) using inhaled corticosteroids (±long-acting beta agonists (LABA), ± short-acting beta agonists (SABA), where at least the controller medication should be administered by pMDI and spacer (AeroChamber or Vortex, given their similar performance) [11] and (4) willing to sign written informed consent. Patients who had an exacerbation (defined by a short-course predniso (lo) ne, emergency department [ED] visit or hospital admission due to asthma) in the last 30 days before potential inclusion were excluded.

2.3. Randomization

At t = 0, participants were randomized in a 1:1 ratio to either the intervention (personalized smart spacer driven education) or the control group (usual care) using opaque and sealed envelopes, stratified by primary care centre. All patients were handed a smart spacer, but the data from the smart spacer were only available to healthcare professionals and patients in the intervention group.

2.4. Smart spacer

The smart spacer used is CE-marked for research and is based on the AeroChamber Plus with Flow Vu. The smart spacer is a rechargeable device and uses the same components as the traditional (non-smart) spacer, except for the adapter attached to the back of the spacer which has been modified to accommodate the sensing technology. An identifier was attached to each of the patient's inhalers, to identify which inhaler a patient uses (e.g. controller or reliever inhaler) [10]. Visuals provided data on day-to-day inhaler use (date and time stamped) as well as the errors made. The technique score is based upon an algorithm that combines all inhaler errors into a final score (between 0 and 100, where 100 equates to perfect). The visuals were used for tailored patient education [10].

2.5. Visits

Patients made three study visits to the general practice, including a screening visit (t = 0), a baseline visit (t = 1 month) and a follow-up visit (t = 2 months). At all three visits, the Test of Adherence to Inhalers (TAI) questionnaire [12], the Asthma Control Questionnaire (ACQ-6) [13] and the Work Productivity and Activity Impairment (WPAI) questionnaire [14] were administered and a fractional exhaled nitric oxide (FeNO) test was performed using Niox Vero (Circassia Group plc, United Kingdom) [15]. As the study was conducted during the COVID-19 pandemic, spirometry was only performed during visit t = 1 and t = 2 if COVID-19 measures allowed it. During visit t = 2, the System Usability Scale (SUS) questionnaire [16] was administered to patients and nurses (SUS scores range between 0 and 100, with 100 indicating highest usability).

2.6. Intervention group

Those randomized to the intervention group were, in addition to usual care, given personalized inhalation education with detailed information about how and when they used their inhaled medications based on the smart spacer data. The nurse downloaded data from the smart spacer and discussed with the patient. If errors in medication use were identified with data from the smart spacer, protocolled inhaler instructions were provided to help eliminate errors, following standardised Dutch Lung Alliance Netherlands inhaler use protocols. To protocolise potential adherence interventions, the TAI Toolkit was used [17].

2.7. Control group

The control group received usual care according to Dutch primary care asthma guidelines [18].

2.8. Outcomes

As defined in the protocol [10], the primary outcome of this study was the feasibility of performing a definitive randomized controlled trial of a personalized educational approach to assess improvement in disease control in adults with asthma using a smart spacer. Feasibility outcomes included: (i) patient recruitment speed, (ii) participation rate and (iii) drop-out rate.

Secondary outcomes included patient and healthcare provider (nurse) satisfaction with the smart spacer, as assessed by the SUS. Exploratory outcomes included changes in distribution of medication adherence patterns (smart spacer assessed maintenance inhaler usage and inhaler technique as well as self-reported adherence by TAI score) and clinical outcomes (SABA usage, lung function, FeNO, and WPAI and

ACQ) as compared between the intervention and the control group.

2.9. Sample size

Because this was a feasibility study, no formal sample size calculation was performed. Recommended sample sizes for feasibility RCTs vary between 24 and 50. The sample size of this study (n = 40) was chosen based on National Institute for Health and Care Research (NIHR) recommendations [19]. Two additional patients were recruited to allow for potential loss to follow-up.

2.10. Statistical analysis

Adherence was calculated based on the number of controller actuations divided by the prescribed dose. Mean total errors and errors per day were calculated. An inhaler technique score was calculated for each actuation of the controller or rescue inhaler using a weighing for each error made [10]. For statistical comparison of means between intervention- and control group, independent samples T-tests were performed in case of normally distributed data. For comparisons between visit t = 1 and visit t = 2, a paired samples T-test was used.

3. Results

3.1. Study population

In total, 42 patients completed the study. In one patient, after the second visit the smart spacer only recorded data of one day. Following the "intention-to-treat" principle, this patient (in the control group) was not excluded from the analysis. Baseline characteristics are provided in Table 1.

3.2. Feasibility outcomes

3.2.1. Patient recruitment speed

It took each of the four individual primary care centres one to four months to recruit 8 to 14 patients from December 2021 to April 2022. Recruitment speed was mainly driven by time that was allocated to the nurses by the general practice owner to perform recruitment alongside their daily routine.

3.2.2. Participation rate

The nurse pre-selected patients from the healthcare centres' patient database. These patients were known to the nurse and were expected to cooperate well in this study. Subsequently, the local investigator selected eligible patients based on inclusion and exclusion criteria. The nurses thereafter asked the patients to participate. The participation rate was 86%: 42 patients of 49 asked agreed to participate.

3.2.3. Drop-out rate

No drop-outs occurred during follow-up of this study.

Table 1
Baseline characteristics (N = 42).

	Intervention (n = 21)	Control (n = 21)
Sex (% male)	29%	43%
Age, years (mean, SD)	58.8 (18.1)	61.6 (12.3)
BMI (kg/m^2) (mean, SD)	26.8 (6.0)	28.8 (5.1)
Current smoker (N)	3	1
Former smoker (N)	9	9
Never smoker (N)	9	11
FEV_1 (%pred)[a] (mean, SD)	86.2 (19.0)	79.4 (19.5)
FVC (%pred)[a] (mean, SD)	93.0 (19.5)	89.8 (14.4)
PEF (L/min)[a] (mean, SD)	364.9 (117.7)	374.0 (65.4)
FeNO (ppb) (mean, SD)	22.5 (14.7)	34.6 (31.3)
TAI-10 (mean, SD)	47.0 (3.7)	46.1 (6.3)
WPAI-6 (mean, SD)	1.6 (2.1)	1.9 (2.3)
ACQ-6 (mean, SD)	1.9 (0.8)	2.1 (1.0)

[a] Only available in 22 patients (11, intervention, 11 control); ACQ: Asthma Control Questionnaire, BMI: Body Mass Index, FeNO: Fractional exhaled Nitric Oxide, FEV1: Forced Exhaled Volume in 1 s, FVC: Forced Vital Capacity, L: liters, PEF: Peak Expiratory Flow, ppb: parts per billion, SD: standard deviation, TAI: Test of Adherence to Inhalers, WPAI: Work Productivity and Activity Impairment questionnaire.

4. Satisfaction and usability outcomes

All patients and all nurses completed the SUS questionnaire. Patients scored on average 70.8 (SD 11.1). The four nurses who coached all the patients using the smart spacer scored an average of 88.8 (SD 3.5).

5. Medication adherence outcomes

Medication adherence and clinical outcomes are provided in Table 2.

In one patient, the data from the smart spacer turned out to be incorrect. The smart spacer manufacturer's technical team has made an analysis of the data. First, the connector (identifier) of the reliever was found to have been swapped in error with that of the controller. Secondly, there appeared to be an error in one sensor of the smart spacer, potentially due to dropping the device, so that at a high inhalation flow an extra actuation was registered by the smart spacer. These errors could be fixed and the recovered data for that patient are included here.

In the intervention group, inhalation errors per day decreased by 26.2%, while in the usual care group inhalation errors increased by 14.6% (p = 0.021). In the intervention group, the technique score increased from 70.2 to 80.1, while in the usual care group the technique score remained almost the same (64.2–64.7). Of note, adherence improved significantly in the usual care group while it declined in the intervention group (p = 0.028). Self-reported adherence, as measured by the TAI scores (lower scores indicate lower adherence), did not differ significantly. Fig. 1 shows the total different inhalation errors in the usual care group and in the intervention group. The term "session" refers to the moment the patient takes his/her medication. The term "actuation" refers to the actual firing of the pMDI. The main inhalation error was "inhaling with a too high flow".

5.1. Clinical outcomes

At visit t = 2, in 22 of 42 patients (52%) lung function data were available. Both in the intervention and in the usual care group, FEV_1% predicted improved minimally (0.7 and 1.6). There was no difference between the groups (p = 0.676). No significant changes in FeNO were observed either (p = 0.340). Also, the ACQ and WPAI scores did not differ significantly between the intervention and the usual care group. Reliever use declined minimally in both the intervention and usual care group, but differences were not significant (0.1–0.2 actuations per day, p = 0.785).

6. Discussion

6.1. Main findings

In this study, we have demonstrated the feasibility of performing a trial focusing on asthma patient education using a smart spacer. The design of this study was such that it should be possible to include larger groups of asthma patients in primary care in a potential follow-up trial. Both nurses and patients were highly satisfied with the smart spacer. Exploratory clinical outcomes indicated that inhaler technique improved significantly by approximately 30%.

6.2. Interpretation

The recruitment speed as well as participation rates were acceptable

Table 2
Outcomes of intervention group vs control group (N = 42).

Parameter	Intervention			Control			p value
	Visit t = 1	Visit t = 2	Difference	Visit t = 1	Visit t = 2	Difference	Difference
Errors/day (mean, SD)	2.8 (1.9)	2.1 (1.1)	−0.7 (1.8)	3.5 (1.8)	4.1 (2.5)	0.6 (1.8)	0.021
Adherence (mean, SD)	50.2 (21.3)	45.1 (21.5)	−5.1 (15.9)	47.2 (25.7)	54.1 (24.0)	6.9 (18.2)	0.028
Technique (mean, SD)	70.2 (22.5)	80.1 (14.2)	9.9 (22.6)	64.2 (17.8)	64.7 (17.3)	−0.5 (17.6)	0.141
Reliever use/day (mean, SD)	0.2 (0.5)	0.1 (0.2)	−0.1 (0.5)	0.4 (0.8)	0.2 (0.4)	−0.2 (0.7)	0.785
FEV_1 (%pred, mean, SD)	89.0 (16.6)[1]	89.7 (17.3)[2]	0.7 (3.7)	78.6 (18.5)[3]	79.5 (18.3)[4]	1.6 (6.6)	0.676
FeNO (ppb, mean, SD)	20.6 (14.6)	22.2 (16.2)	1.6 (11.3)	27.0 (16.9)	25.3 (14.5)	−1.7 (10.4)	0.340
TAI (mean, SD)	47.5 (4.0)	48.3 (2.5)	0.8 (3.0)	47.5 (3.9)	47.4 (6.7)	−0.1 (7.6)	0.595
WPAI (mean, SD)	1.9 (2.1)	1.4 (2.0)	−0.5 (1.6)	2.6 (2.9)	2.3 (3.0)	−0.3 (2.1)	0.743
ACQ (mean, SD)	1.9 (0.9)	1.8 (0.7)	−0.0 (0.5)	2.1 (1.0)	2.0 (1.0)	−0.1 (0.5)	0.793
SUS (mean, SD)		69.4 (12.6)			72.3 (9.6)		0.412

ACQ: Asthma Control Questionnaire, BMI: Body Mass Index, FeNO: Fractional exhaled Nitric Oxide, FEV1: Forced Exhaled Volume in 1 s, FVC: Forced Vital Capacity, ppb: parts per billion, SD: standard deviation, SUS: System Usability Scale, TAI: Test of Adherence to Inhalers, WPAI: Work Productivity and Activity Impairment questionnaire. [1] N = 14, [2] N = 14, [3] N = 12, [4] N = 10.

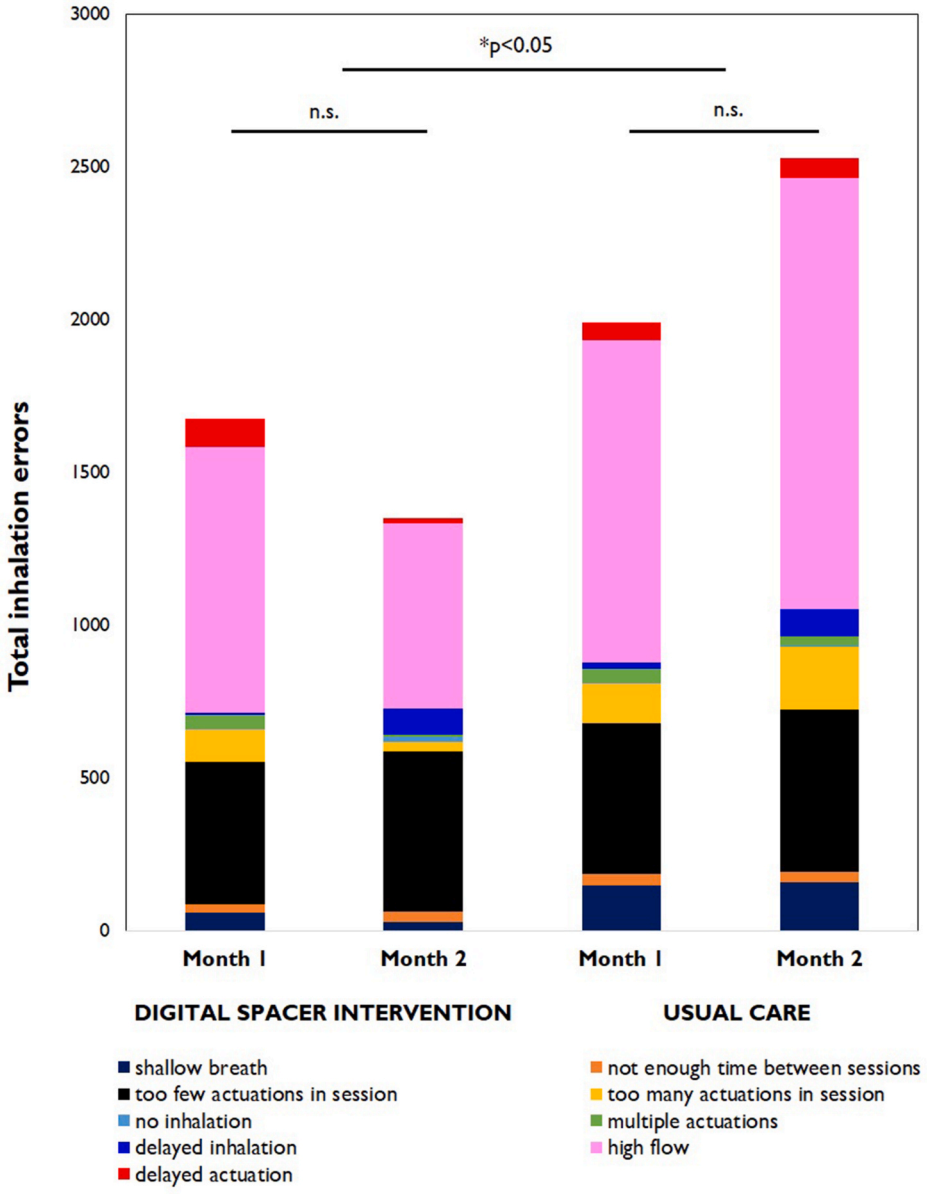

Fig. 1. Inhalation errors in usual care group and intervention group pre (t = 1) and post (t-2) intervention (N = 42).

with zero drop-outs. Recruitment speed was mainly limited by the nurse's lack of practical space and scarce time. The study was deliberately designed "lean" with a minimum burden on the patient, whereby we aimed to connect as much as possible to the routine care check-up schedule of the nurses. As a result, it was not difficult to find sufficient patients consenting to participate. Additionally, the smart spacer was found to be user-friendly by both patients and nurses. Patients scored an average of 71 on the SUS and the nurses scored an average of 89. According to Bangor et al. SUS scores above 68 are considered good and scores above 80 as excellent [20]. In a previous study with a registered digital inhaler, patients scored a mean of 79.8 on the SUS and study sites scored 74.6 [21]. The fact that patients in our study scored lower may be related to the fact that they used a prototype (to be further optimized for commercial use), had no direct access to the dashboard data and were only able to see their own data during the clinic visit.

While the number of inhalation errors per day decreased by around one third in the intervention group, mean adherence also decreased. By contrast, in the usual care group, the number of errors per day increased considerably, yet adherence increased. This is a phenomenon that has been observed in previous studies as well [22,23]. It is likely that in patients who improve their inhaler technique, the effect of their inhalation improves, and therefore the need for taking more medication decreases. In patients whose inhalation technique does not improve, the need for medication remains similar or even increases due to clinical deterioration. This group is therefore more likely to retain or develop an inclination to take their medication on time. A previous large database study noticed a similar effect in patients with moderate to severe asthma. Their assumption was referred to as reverse causality: more severely affected patients may have more symptoms and therefore maximize their inhaled preventer use [24]. In our study, we hypothesize that one of the reasons that no enhanced adherence was seen in the intervention group is that the smart spacer did not provide reminders. Previously, reminders have been particularly effective in enhancing adherence in asthma [25,26].

Our study design corresponds well with a previous trial combining adherence and technique feedback using a digital device [27]. O'Dwyer et al. studied adherence and technique with the INCA™ device in 152 patients with asthma and COPD. In this 6-month community-pharmacy based study, the intervention group (feedback with INCA™ device and subsequent training) was compared with a comparator group (patient demonstrated their inhalation technique to the pharmacist and were then instructed) and with a control group (patients were dispensed inhalers as normal) resulting in 2-month attempted adherence rates of 76.4, 66.5, and 54.9 respectively. Technique error rates did not differ significantly at 2 months, but did differ at 6 months, indicating the need for repeated education. Our adherence rates were slightly lower (around 50%, similar to other real-world asthma studies [28,29]), yet inhaler technique errors decreased significantly after one month, probably reflecting the focus of the dashboard and educational interventions provided.

6.2.1. Strengths and limitations

This is the first clinical study examining the use of a smart spacer in adult patients with asthma. The study was performed in a primary care setting, largely reflecting real-world practice. In the Netherlands, most patients with asthma are treated by a general practitioner (GP). The design of the study is such that it can be performed within the usual care setting of a GP practice, enabling relatively easy scale-up.

Being a feasibility study, the number of participating patients was limited. Furthermore, patients were nominated by the nurse based on the nurse's expectations about the patients' willingness to cooperate which could have positively affected both the participation and dropout rate. Given that this selection bias will have influenced both study groups, the differences are not expected to be affected. It may however be that overall adherence was relatively higher in both groups as a result of this pre-selection. Of note, the smart spacer used was a prototype. Some features which could positively influence the results, such as improvements in design, were not yet implemented.

According to the nurses and the patients, a number of issues could be optimized for the smart spacer to be implemented in real-world practice: although being rechargeable, battery life could be extended (from the current one month) and a Bluetooth/Near Field Communication connection with a smartphone could be added. Sending automated reminders would also be a good addition to further improve interactivity and support adherence in patients with forgetfulness.

6.3. Recommendations for future studies

In future studies, using smart spacers or other smart inhalers could be of importance as it provides granular and objective information on patients' adherence patterns and inhalation technique in their daily life. Digital adherence monitoring has been found cost-effective in difficult-to-treat asthma patients considered for step-up to biologics [30,31]. Additionally, even in patients already on biologics, it is important that patients continue to use their inhaled medication properly. Of note, a study using pharmacy dispensing records as a proxy for adherence to ICS showed that higher refill rates were associated with better effects of mepolizumab in terms of OCS and exacerbation reductions [32]. Whether this effect was driven by inhaler technique or daily adherence, and whether effect differences between individual biologics exist is yet to be uncovered and smart inhalers and spacers could help finding out.

We can imagine that in the future, if a patient does not respond well to inhalation therapy, caregivers will not immediately opt for a step-up of therapy (e.g. to higher ICS dose, OCS or biologics), but instead choose to observe for a certain period of time how a patient uses his or her inhalation medication using a smart device. Only if a patient is adherent and still does not respond well enough to an inhalation medicine, it would be necessary to adjust the dose or type of medication. While cost of many digital devices are still unknown due to their pre-market phase, if sufficiently cost-effective, we expect that they could significantly contribute to reducing the escalation of therapy in patients with asthma and simultaneously help improving efficiency and reducing costs of asthma care [30,31].

7. Conclusions

In this small and short-term study, positive and significant effects on inhalation errors were found. The smart spacer was deemed an easy-to-use device that can however be further improved. A larger RCT exploring clinical benefits of the smart spacer in adults with asthma is feasible and recommended.

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CRediT authorship contribution statement

Boudewijn J.H. Dierick: Conceptualization, Methodology, Formal analysis, Software, Data curation, Investigation, Project administration, Writing – original draft. **Maria Achterbosch:** Methodology, Writing – review & editing. **Amber A. Eikholt:** Methodology, Writing – review & editing. **Sandra Been-Buck:** Investigation, Writing – review & editing. **Titia Klemmeier:** Investigation, Methodology, Writing – review & editing. **Susanne J. van de Hei:** Methodology, Writing – review & editing. **Paul Hagedoorn:** Methodology, Validation, Writing – review & editing. **Huib A.M. Kerstjens:** Conceptualization, Methodology. **Janwillem W.H. Kocks:** Conceptualization, Writing – review & editing. **Job F.M. van Boven:** Funding acquisition, Conceptualization, Methodology, Supervision, Resources, Validation, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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