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Original Article

Long-Term Effectiveness of a Digital Inhaler on Medication Adherence and Clinical Outcomes in Adult Asthma Patients in Primary Care: The Cluster Randomized Controlled ACCEPTANCE Trial

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What is already known about this topic? Digital inhalers can improve medication adherence in the short term, but few studies reported improved asthma control. Long-term effects are unknown.

What does this article add to our knowledge? Use of a digital inhaler in uncontrolled, nonadherent primary care patients with asthma improved medication adherence in the short term but not the long term. However, asthma control was persistently and significantly better over 12 months.

How does this study impact current management guidelines? This study provides real-world evidence for the positive effects of digital inhalers for long-term sustained asthma control in a primary care setting.

BACKGROUND: Digital inhalers can support medication adherence and asthma control in the short-term. Yet, long-term benefits are unknown.
OBJECTIVE: To investigate the clinical effects, usability, and cost-effectiveness of a digital inhaler.
METHODS: This was an open-label cluster randomized controlled trial of 12 months in Dutch primary care. Adults with suboptimal controlled asthma and nonadherence were eligible. General practices were randomly allocated to either intervention or control, stratified by practice size. Intervention and control patients received an electronic monitoring device attached to their budesonide/formoterol SYMBICORT Turbuhaler maintenance inhaler. Intervention patients used a smartphone application for data insights and reminders. Control patients' inhaler use was passively monitored. Primary outcome was 1-year medication adherence. Secondary outcomes included asthma control, quality of life, usability, and cost-effectiveness.
RESULTS: Between June 27, 2019 and September 30, 2022, 136 clusters containing 164 participants were randomized (82 participants across 68 clusters in both groups). Estimated marginal means (EMM) for medication adherence were 71.4% (95% CI, 67.1-75.4) and 59.9% (95% CI, 55.0-64.7) in the

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Conflicts of interest: J.W.H. Kocks reports grants, personal fees, and nonfinancial support from AstraZeneca, Boehringer Ingelheim, and GSK; grants and personal fees from Chiesi and Teva; nonfinancial support from Mundi Pharma; personal fees from MSD, COVIS Pharma, and ALK-Abelló; and grants from Valneva outside the submitted work; and holds fewer than 5% of shares of Lothar Medtec GmbH and 72.5% of shares in the General Practitioners Research Institute. J.F.M. van Boven received grants and/or consultancy fees from ALK-Abelló, AstraZeneca, Chiesi, European Commission COST (COST Action 19132), GSK, Novartis, Pfizer, Teva, Trudell Medical, and Vertex, outside the submitted work and all paid to his institution. B.M.J. Flokstra-de Blok and Y.H. Gerritsma were employed by General Practitioners Research Institute at the time of the study. In past years (2019-2024), General Practitioners Research Institute conducted investigator- and sponsor-initiated research funded by noncommercial organizations, academic institutes, and pharmaceutical companies (including AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, and Teva). The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
ACQ-5- Asthma Control Questionnaire-5
BMQ- Beliefs About Medicines Questionnaire
Brief-IPQ- Brief Illness Perception Questionnaire
eHLQ- eHealth Literacy Questionnaire
EMD- Electronic monitoring device
EMM- Estimated marginal means
GP- General practitioner
HCP- Health care professional
KASE-AQ- Knowledge Attitude Self-Efficacy Asthma Questionnaire
MART- Maintenance and reliever therapy
MCID- Minimal clinically important difference
Mini-AQLQ- Mini Asthma Quality of Life Questionnaire
SABA- Short-acting β-agonist
SUS- System Usability Scale
TAQ- Technology Acceptance Questionnaire

intervention and control groups, respectively. Medication adherence was higher in the intervention group at week 2 (odds ratio [OR] = 2.19; 95% CI, 1.63-2.95). The difference in medication adherence between groups declined over time ($P < .0001$); no significant difference was found at study end (OR = 1.23; 95% CI, 0.91-1.66). Overall, Asthma Control Questionnaire-5 scores were significantly better ($P = .0056$) in the intervention group (EMM, 1.31; 95% CI, 1.18-1.44) compared with control (EMM, 1.56; 95% CI, 1.44-1.68). Quality of life (Mini Asthma Quality of Life Questionnaire scores) did not differ significantly between groups ($P = .0530$). However, the intervention group was almost three times more likely to reach the minimal clinically important difference for asthma-related quality of life (OR = 2.73; 95% CI, 1.02-7.54). Mean system usability score was 80.1 (SD, 13.8). Cost per 0.5-point Asthma Control Questionnaire-5 decrease was €278.

CONCLUSION: Use of this digital inhaler led to significant improvements in medication adherence in the short term and to sustained improved asthma control over 12 months. **© 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).** **(J Allergy Clin Immunol Pract 2025;13:1693-704)**

Key words: *Digital; Digital inhaler; Smart inhaler; Medication adherence; Compliance; Asthma; eHealth; Primary care; General practice*

INTRODUCTION

Although inhaled medication has proven to be effective and widely available, asthma remains uncontrolled in a significant proportion of patients.[1] Arguably the most important yet modifiable factor related to suboptimal asthma control is medication nonadherence.[2,3] Maintenance medication adherence rates in asthma have been reported to range between 13% to 52%.[4] Medication adherence is a complex concept that is influenced by different factors such as inhaler technique, illness perceptions, medication beliefs, forgetfulness, attitude toward the illness, and self-efficacy.[5,6]

Recently developed digital inhalers may be of value in managing poor medication adherence because they capture objective inhaler use data and provide insight into medication adherence to both patients and health care professionals (HCPs). Other features of digital inhalers include sending reminders and motivational messages, tracking symptoms and triggers over time, and predicting future exacerbations.[4,7]

Previous studies found that digital inhalers increase adherence to maintenance medication, yet these were typically short term (12-32 weeks),[8-15] with potential bias owing to seasonal variation in asthma. Although increased adherence has been shown, few studies reported improved asthma control.[9,15] A study in tertiary care patients using digital inhalers found a reduction in high-dose inhaled corticosteroid treatments and a reduction in patients needing add-on biologic therapy compared with control patients.[14] Furthermore, many studies focused on the use of digital inhalers in secondary and tertiary care, whereas the majority of patients with asthma are treated in primary care for most of their lives.[16] Long-term studies of digital inhalers in primary care are absent. Moreover, despite being essential for actual implementation in daily practice, usability and cost-effectiveness data are limited.

Therefore, we performed a cluster randomized controlled trial of 12 months in primary care aiming to (1) evaluate the effectiveness of a digital inhaler for medication adherence and clinical outcomes in adults with uncontrolled asthma, (2) evaluate its usability and acceptability, (3) assess the cost-effectiveness, and (4) investigate which patients benefit most.

METHODS

Study design

This pragmatic, multicenter, open-label, cluster randomized controlled trial of 12 months was conducted in primary care settings in the Netherlands. The Medical Research Ethics Committee of Assen, the Netherlands, approved this study (NL69909.056.19). The protocol and statistical analysis plan were published elsewhere.[17] In August 2022, after publishing the protocol, one amendment was made. The digital Web portal version used in this study was no longer supported after April 1, 2023. Therefore, new participants could not participate in the study for a full year. We enrolled participants until September 30, 2022, to ensure a minimum participation period of 6 months.

Participants

General practices and pharmacies were recruited via letter, telephone calls, or indirect approaches such as word of mouth. Patients were recruited through electronic medical record screening, or via public channels (eg, social media). Eligibility was confirmed by their general practitioner (GP). Patients who were aged 18 years or older with doctor-diagnosed, suboptimally controlled asthma (Asthma Control Questionnaire-5 [ACQ-5] score of ≥0.75), who had a smartphone, and who were using budesonide/formoterol SYMBICORT Turbuhaler (AstraZeneca, the Hague, the Netherlands) as maintenance therapy for 8 weeks or greater were eligible to enter the 6-week run-in period. Only patients who were nonadherent during week 3 and 4 of this run-in period as measured by electronic monitoring were eligible for inclusion. Being nonadherent was defined as fewer than 80% of adherent days, in which an adherent day was a day on which at least the number of inhalations prescribed was taken. Participants were informed that a final selection would

take place after the run-in period, but they were not informed about what the selection entailed (ie, being nonadherent), to avoid bias.

Exclusion criteria were use of a budesonide/formoterol SYMBICORT Turbuhaler as maintenance and reliever therapy (MART), a change in the prescribed inhaled corticosteroid dose or the use of systemic corticosteroids (including maintenance therapy) in the 4 weeks before the run-in period, the use of asthma biologics, having chronic obstructive pulmonary disease or other significant respiratory conditions, having malignancy with a life expectancy of less than 1 year, being pregnant at inclusion, and an inability to understand Dutch. We obtained digital (using DocuSign) or written informed consent from all participants.

Randomization and masking

To reduce the risk of contamination between the intervention and control groups, cluster-level randomization was applied. Clusters were randomized at a 1:1 ratio to either intervention (digital inhaler program) or control (passive electronic monitoring) using a computer-generated permuted block scheme with random block sizes of 4 and 6, stratified by general practice size ($\leq$2,500 patients or >2,500 patients). Randomization occurred after the first patient of a GP finished the run-in period, after which practice staff were notified of the allocation. Subsequently, no additional patients from the same general practice could start the run-in period, minimizing recruitment bias from allocation awareness. Each patient recruited through public channels or pharmacies was considered a separate cluster and was randomized similarly. Patients were not blinded to allocation owing to the study design. Medication adherence data 1 week before to 1 week after visits was disregarded to minimize the risk of white coat adherence. Outcome assessors were not blinded to allocation, to instruct patients regarding the applications. The data analyst was masked to group allocation.

Procedures

The study flow and data collection overview are presented in Figure E1 and Table E1 (in this article's Online Repository at www.jaci-inpractice.org). We confirmed initial eligibility and collected data on demographics, medical history, and asthma medication use during a remote screening visit (T-1) using video-consulting software. Subsequently, participants completed the 6-week run-in period in which an electronic monitoring device (EMD) (Turbu+ Device, Adherium Ltd, Auckland, New Zealand; CE marked, medical device class I) was attached to the SYMBICORT Turbuhaler inhaler. The EMD logged date and time of inhaler actuations. On final eligibility confirmation, a remote baseline visit (T0) was performed during which participants were informed of the assigned condition and baseline data were collected. Participants were observed for 12 months from baseline, with data collection through remote follow-up visits at 6 (T6) and 12 (T12) months, and through self-administered questionnaires at 3 (T3) and 9 (T9) months. All patients received a new EMD before visit T6, to ensure sufficient battery life throughout the study.

Intervention group participants installed the Turbu+ Insights application on their smartphones at T0. Actuation data logged by the EMD was sent via Bluetooth to the smartphone application throughout the study. The application consisted of several features, including visualization of inhaler use, reminders, missed dose and overuse messages, motivational nudge messages (voice messages based on known drivers and barriers of treatment engagement and treatment perceptions[18]), and the possibility to track symptoms and triggers. If the participant's general practice participated in the study, HCPs could view inhaler data in the online Turbu+ Web portal. To mimic a real-world situation, participants and HCPs were instructed on the application and Web portal concerning the onboarding process, the different functionalities of the app and the portal, and their benefits, but their use was not mandated by the protocol and no specific interaction guidelines (frequency of use or which features) were given.

Control group participants' inhaler use was passively monitored, in which the EMD was connected to the Hailie Lite (Adherium Ltd, Auckland, New Zealand) smartphone application in which actuation data were not visible. The application showed participants only the time of last synchronization between the application and smartphone. Actuation data in the app were automatically uploaded to the Hailie Web portal, accessible only to the research team. The HCPs were instructed to follow usual care guidelines. Use of short-acting β-agonist (SABA) was monitored throughout the study in a subgroup of patients using an EMD-compatible SABA inhaler (Hailie sensor, medical device class I, Adherium (NZ) Ltd; CE marked, compatible with a Bricanyl Turbuhaler (AstraZeneca, the Hague, the Netherlands) containing terbutaline or Ventolin aerosol (GSK, Amersfoort, the Netherlands) containing salbutamol).

Outcomes

The primary outcome was medication adherence, as measured by electronic monitoring. Medication adherence was defined as the percentage of daily inhalations taken as prescribed (the number of recorded inhalations / the number of maintenance inhalations prescribed per day * 100), corrected for dose dumping (ie, six or more actuations within a 5-minute period). Daily adherence was capped at 100%.

Secondary outcomes included (1) the proportion of patients who shifted from being nonadherent to being adherent at the study end, in which being adherent is defined as 80% adherence or greater; (2) the number of zero adherent days (ie, days on which patients had taken no inhalations); (3) underuse days (ie, days on which patients had taken fewer inhalations than prescribed; (4) a change in asthma control as measured by ACQ-5; (5) asthma-related quality of life according to the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ); (6) the number of exacerbations during the study (self-reported and retrieved from the general practices' electronic health records system at the study end); (7) cost-effectiveness alongside the trial (based on health use data; self-reported and retrieved from the patient's general practice electronic health record system at the study end); (8) usability as measured by the System Usability Scale (SUS), a generic instrument to measure the usability of a technology or service containing 10 items adapted to the specific technology or service and rated on a 5-point Likert scale from 1 indicating strongly disagree to 5 indicating strongly agree, with scores ranging from 0 to 100 (>68 is considered above average usability, 50-68 marginal usability, and <50 poor usability)[19] and acceptability as measured by the Technology Acceptance Questionnaire (TAQ), based on the technology acceptance model and the unified theory of acceptance and use of technology, which addresses intended use and different factors determining the behavioral intention to use a digital inhaler program, consisting of 22 items scored on a 5-point Likert scale) of the digital inhaler program from the perspective of patients and HCPs in the intervention group; (9) absenteeism, presenteeism, work productivity loss, and activity impairment as measured by Work Productivity and Activity Impairment questionnaire; and (10) use of SABA retrieved from the patient's pharmacy at the study end and measured via electronic monitoring in a subgroup of patients.

To be able to perform a subgroup analysis regarding which patients would benefit most from the intervention, these questionnaires were administered: (1) the Knowledge Attitude Self-Efficacy Asthma Questionnaire (KASE-AQ) (knowledge part omitted), (2) the Beliefs About Medicines Questionnaire (BMQ)-specific, (3) the Brief Illness Perception Questionnaire (Brief-IPQ), and (4) the eHealth Literacy Questionnaire (eHLQ). The KASE-AQ measures various aspects of attitude and self-efficacy regarding controlling asthma symptoms and disease, with each domain consisting of 20 questions. Higher scores on the self-efficacy scale indicate more confidence in managing and controlling asthma, and higher scores on the attitude scale indicate a more positive attitude toward asthma.[20] The BMQ-specific measures beliefs about asthma medication and consists of 10 items about the necessity and concerns of a patient's prescribed medication. The items are rated on a 5-point Likert scale from 1 indicating strongly disagree to 5 indicating strongly agree.[21] The Brief-IPQ assesses the emotional and cognitive representation of illness and consists of nine items rated on a 11-point scale.[22] The eHLQ is based on the eHealth Literacy Framework and consists of seven domains that include individual factors that are necessary to use eHealth, system factors (eg, access to digital services that work), and user−system interaction factors (eg, motivation to engage with digital services). The questionnaire consists of 35 items rated on a 5-point Likert scale from 1 indicating strongly disagree to 5 indicating strongly agree.[23,24] At each follow-up visit, participants were asked about any health change suggestive of an adverse event (ie, any undesirable experience occurring to a subject during the study, considered to be related to asthma, SYMBICORT Turbuhaler, or the EMD).

Statistical analysis

A sample size of 242 patients (121/arm) across approximately 30 clusters was estimated to have a power of 90% at the 5% significance level, with an absolute difference of 15% in mean medication adherence and a 0.30 SD.[8] In this calculation, a design effect of 1.075 (based on an intra-cluster correlation coefficient of 0.025 and a cluster size of 4), and an expected dropout rate of 25% were taken into account.[25] The expected 15% difference in adherence was based on an expected adherence rate of 65% in the control group and 80% in the intervention group. The impact on recruitment pace and strain on health care owing to the COVID pandemic made it difficult to predict recruitment and dropout rates.[17] Different scenarios were explored, indicating that 81 patients/arm would be sufficient to have a power of 80% with 16% dropout.[26]

We analyzed the primary outcome in the intention-to-treat population (ie, included all available data from clusters that were randomized). Additionally, a per-protocol analysis was performed for the primary outcome, excluding all data of patients with a gap in medication adherence data of more than 1 month and patients who withdrew after randomization or were lost to follow-up. We carried out statistical analyses using R (version 4.2.1,[27] Vienna, Austria; R Studio IDE, version 2023.06.1+524[28]). A multilevel linear mixed-model analysis was used to assess the effect of the intervention on medication adherence and on changes in medication adherence over time (lme4 v1.1.31 and lmerTest v3.1.3 packages). We did not impute missing data for participants with incomplete follow-up or gaps because we could not reasonably assume that the data were missing at random (ie, a day with no recorded inhaler use still constitutes valid data). To account for differences in follow-up duration, we modeled time as a continuous variable (ie, number of weeks). Furthermore, in our model, we applied a weighting factor based on the number of days per week with available data. This approach avoided the need to introduce assumptions about the missing data mechanism and ensured that the observed data contributed appropriately without distorting the results through potentially incorrect assumptions. Estimated marginal means (EMM) for both groups are presented, which are model-based group means adjusted for covariates, allowing improved comparisons. Statistical analyses are further detailed in Supplemental Material E1 (in this article's Online Repository at www.jaci-inpractice.org). *P* less than .05 was considered statistically significant. The study was registered with the Netherlands Trial Register (NL7854) and was reported in accordance with the Consolidated Standards of Reporting Trials statement for the reporting of cluster randomized trials.[29]

RESULTS

Between June 27, 2019 and July 15, 2022, 6,656 patients were invited, 889 of whom were interested in participating (Figure 1). An additional 237 patients expressed interest in participation via social media recruitment. Between September 30, 2019 and September 30, 2022, 983 patients were assessed for eligibility, 281 started the run-in period, and 164 were enrolled. In total, 136 clusters were randomized (82 participants across 68 clusters to the control group and 82 participants across 68 clusters to the intervention group). Eleven participants withdrew and eight participants were lost to follow-up. Moreover, 62 participants were included after April 1, 2022 and therefore participated for less than 12 months (see Figure E2 and Table E2 in this article's Online Repository at www.jaci-inpractice.org for participation period per participant and visit attendance).

Baseline characteristics were well balanced between study groups (Table I); overall 58.5% were female, mean age 45.7 years (SD, 15.3 years), mean ACQ-5 score 1.7 (SD, 0.8), and mean medication adherence during weeks 3 and 4 of the run-in period, 64.0% (SD, 24.8). Characteristics of participating general practices and clusters are presented in Table E3 and E4 (in this article's Online Repository at www.jaci-inpractice.org).

Medication adherence at week 2 was higher in the intervention group versus controls (odds ratio [OR] = 2.19; 95% CI, 1.63-2.95). The between-group difference in medication adherence declined over time ($P < .0001$), and we found no significant difference at the study end (OR = 1.23; 95% CI, 0.91-1.66) (Figure 2). A *post hoc* analysis showed a persistent difference between groups of at least 6 months (week 26 intervention vs control group OR = 1.64; 95% CI, 1.23-2.17). Estimated marginal means for the primary outcome were 71.4% (95% CI, 67.1-75.4) in the intervention group and 59.9% (95% CI, 55.0-64.7) in the control group (intention-to-treat; n = 163, 136 clusters). The per-protocol analysis showed a significant difference in medication adherence in favor of the intervention group at week 50 (ie, study end) (n = 113; OR = 1.41; 95% CI, 1.08-1.85) (see Table E5 in this article's Online Repository at www.jaci-inpractice.org) and confirmed the other results found for the primary outcome.

The proportion of patients who shifted from being non-adherent to adherent after 12 months was 32.0% in the intervention group versus 6.7% in controls (n = 55; OR = 6.58; 95% CI, 1.25-34.74) (Table II; see Table E6 in this article's Online Repository at www.jaci-inpractice.org). The proportion

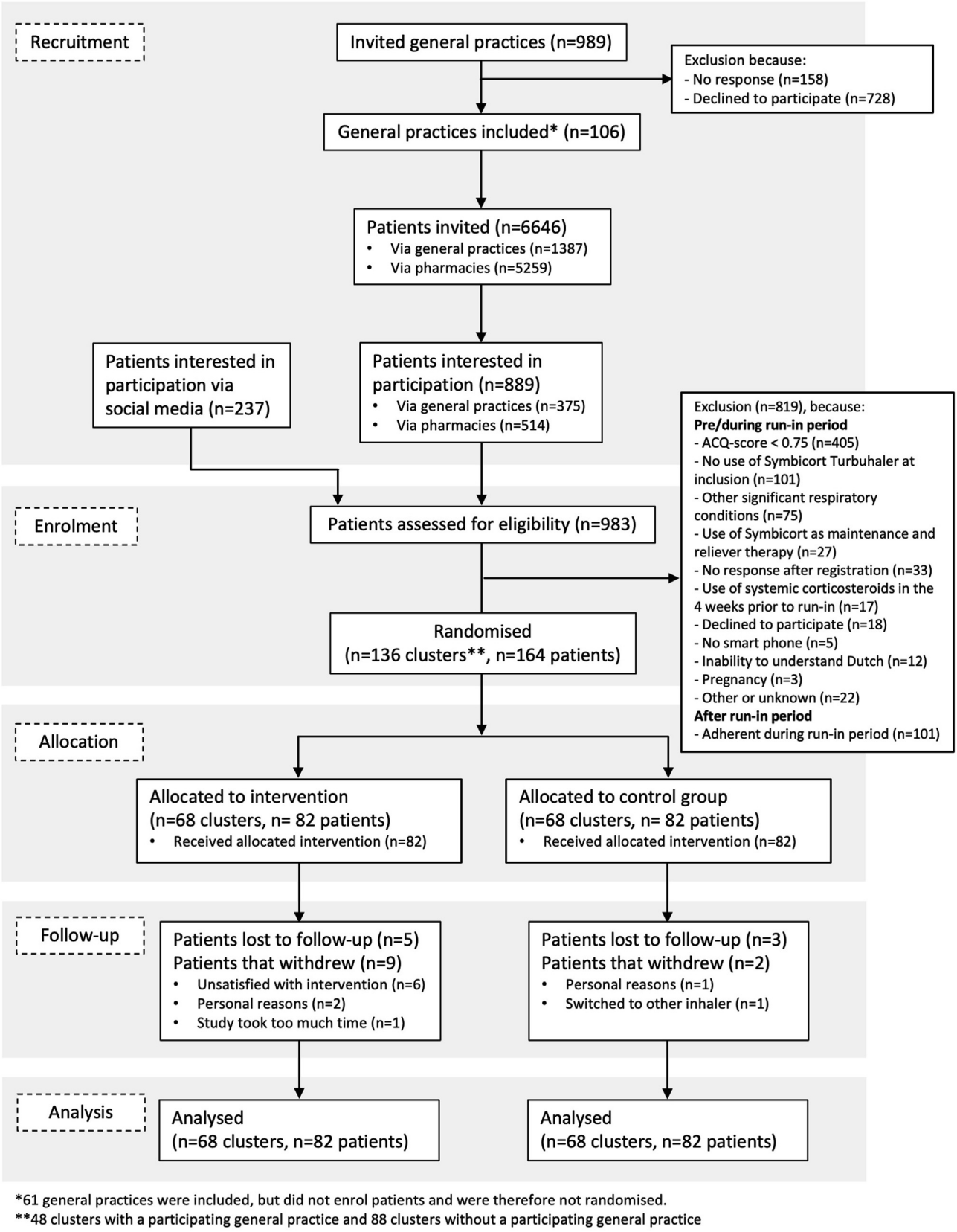


FIGURE 1. Flow of clusters and participants through the study (Consolidated Standards of Reporting Trials diagram). *ACQ*, Asthma Control Questionnaire.

TABLE I. Baseline characteristics of ACCEPTANCE trial participants (n = 164)

Participants	Overall (n = 164)	Control (n = 82)	Intervention (n = 82)
Age, y (mean [SD])	47.5 (15.3)	47.0 (15.6)	48.1 (15.0)
Male sex, n (%)	68 (41.5)	36 (43.9)	32 (39.0)
Body mass index, kg/m^2 (mean [SD])	28.0 (5.4)	28.0 (5.1)	27.9 (5.7)
Education level, n (%)			
Low education (ISCED 0-2)	30 (18.3)	13 (15.9)	17 (20.7)
Medium education (ISCED 3-4)	61 (37.2)	36 (43.9)	25 (30.5)
High education (ISCED 5-8)	73 (44.5)	33 (40.2)	40 (48.8)
Smoking status, n (%)			
Current smoker	13 (7.9)	7 (8.5)	6 (7.3)
Stopped <1 y ago	27 (16.5)	13 (15.9)	14 (17.1)
Stopped ≥1 y ago	37 (22.6)	16 (19.5)	21 (25.6)
Never smoker	87 (53.0)	46 (56.1)	41 (50.0)
Pack-years (n = 75) (median [IQR])	8.0 (2.0-14.4)	3.0 (1.1-16.3)	10.0 (5.6-12.7)
Age at asthma onset, y (n = 163) (median [IQR])	20.0 (7.5-40.0)	22.0 (6.0-40.0)	20.0 (11.0-40.0)
Exacerbations in year before study participation, n (%)			
0	140 (85.4)	69 (84.1)	71 (86.6)
1	20 (12.2)	13 (15.9)	7 (8.5)
2	2 (1.2)	0 (0.0)	2 (2.4)
≥3	2 (1.2)	0 (0.0)	2 (2.4)
Comorbidities, n (%)			
Eczema	53 (32.3)	21 (25.6)	32 (39.0)
Hay fever	99 (60.4)	44 (53.7)	55 (67.1)
Allergies	91 (55.5)	43 (52.4)	48 (58.5)
Bronchitis	32 (19.5)	15 (18.3)	17 (20.7)
Other	7 (4.3)	3 (3.7)	4 (4.9)
Symbicort dose, n (%)			
100/6	7 (4.3)	2 (2.4)	5 (6.1)
200/6	94 (57.3)	47 (57.3)	47 (57.3)
400/6	63 (38.4)	33 (40.2)	30 (36.6)
Symbicort regimen, n (%)			
Once daily 1 inhalation	8 (4.9)	4 (4.9)	4 (4.9)
Once daily 2 inhalations	1 (0.6)	0 (0.0)	1 (1.2)
Twice daily 1 inhalation	108 (65.9)	51 (62.2)	57 (69.5)
Twice daily 2 inhalations	46 (28.0)	26 (31.7)	20 (24.4)
Twice daily 3 inhalations	1 (0.6)	1 (1.2)	0
Short-acting β-agonist prescription, n (%)	74 (45.1)	43 (52.4)	31 (37.8)
Asthma Control Questionnaire-5 score (n = 153) (mean [SD])	1.7 (0.8)	1.7 (0.8)	1.6 (0.7)
Asthma control level based on Asthma Control Questionnaire-5 score (n = 153), n (%)			
≤0.75	13 (7.9)	9 (11.0)	4 (4.9)
0.75-1.5	58 (35.4)	26 (31.7)	32 (39.0)
≥1.5	82 (50.0)	45 (54.9)	37 (45.1)
Mini Asthma Quality of Life Questionnaire score (n = 148) (mean [SD])			
Total	5.4 (0.8)	5.3 (0.9)	5.5 (0.7)
Symptoms	5.2 (0.9)	5.1 (1.0)	5.3 (0.8)
Environment	5.2 (1.2)	5.1 (1.2)	5.4 (1.1)
Emotions	6.0 (0.9)	5.9 (0.9)	6.1 (0.8)
Activities	5.4 (1.0)	5.3 (1.1)	5.5 (0.9)
Medication adherence during wk 3 and 4 of run-in period (%) (median [IQR])*	42.9 (14.3-71.4)	50.0 (21.4-71.4)	42.9 (14.3-64.3)
Medication adherence during wk 3 and 4 of run-in period, in-study definition (%) (mean [SD])†	64.0 (24.8)	65.4 (25.0)	62.6 (24.8)

IQR, interquartile range; *ISCED*, International Standard Classification of Education.
*Adherent days per total number of days (ie, when taking not all prescribed inhalations on a day, this counted as a nonadherent day).
†Daily inhalations taken per daily inhalations prescribed.

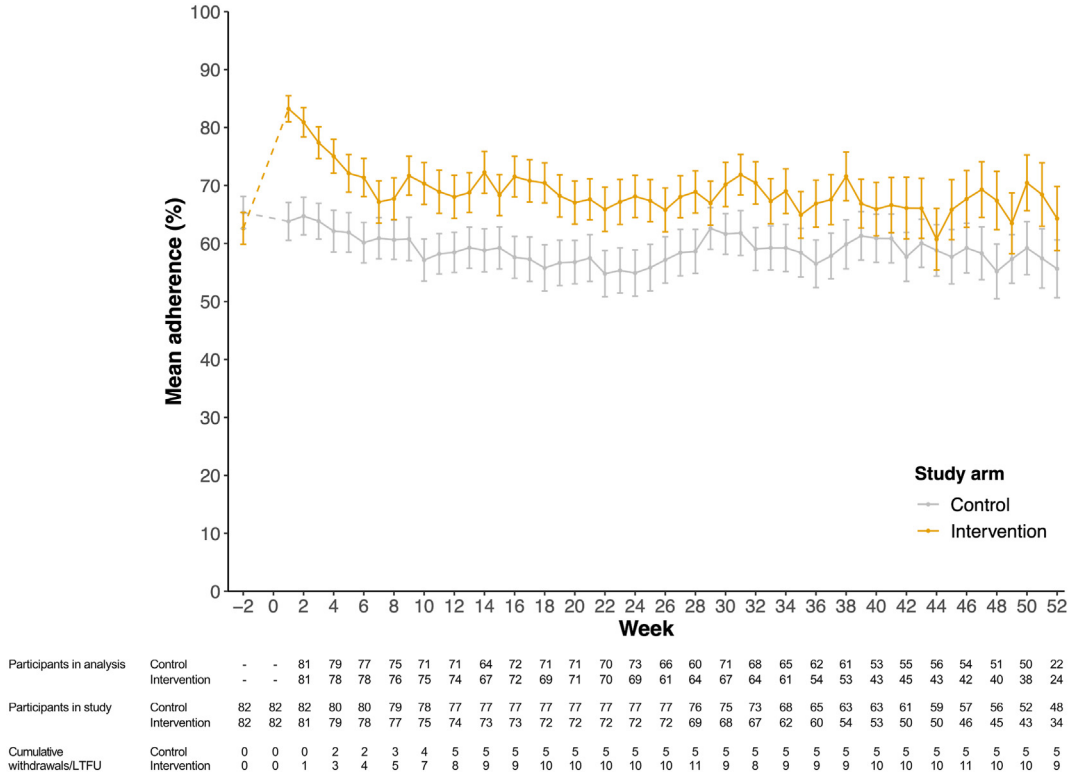


FIGURE 2. Mean medication adherence by study group and week. *LTFU*, Lost to follow-up.

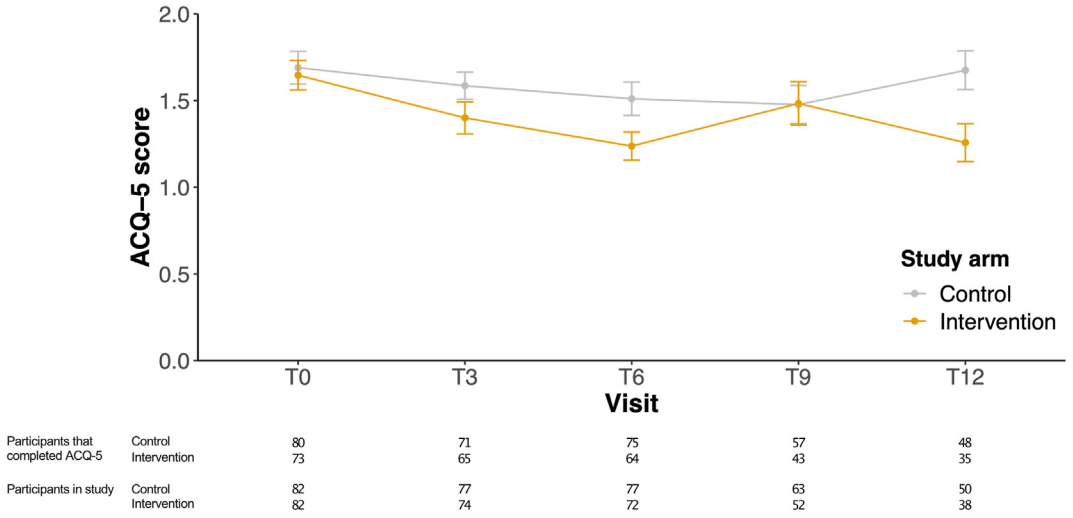
TABLE II. Secondary outcomes

Participants	n	Control (n = 82)	n	Intervention (n = 82)	Odds ratio intervention vs control (95% CI)
Change of −0.5 or less in Asthma Control Questionnaire-5 from baseline to T12 (n = 80), n (%)	45	9 (20.0)	35	15 (42.9)	3.000 (1.133-8.345)
Change of 0.5 or greater in Mini Asthma Quality of Life Questionnaire from baseline to T12 (n = 77), n (%)	48	11 (22.9)	29	13 (44.8)	2.733 (1.018-7.540)
Shift in Asthma Control Questionnaire-5 category (≥0.75 to <0.75) from baseline to T12 (n = 74), n (%)	41	2 (4.9)	33	5 (15.2)	3.482 (0.630-19.257)
Shift from nonadherent to adherent from baseline to T12 (n = 55), n (%)*	30	2 (6.7)	25	8 (32.0)	6.588 (1.249-34.739)
Patients reporting exacerbations from baseline to T12 (n = 77), n (%)	42	8 (19.0)	35	7 (20.0)	—
Total self-reported exacerbations from baseline to T12 (n = 77), n	42	12	35	12	$P = .8448$
Patients with exacerbations as retrieved from GP EHRs from baseline to T12 (n = 73), n (%)	41	5 (12.2)	32	2 (6.3)	—
Total exacerbations as retrieved from GP EHRs from baseline to T12 (n = 73), n	41	6	32	6	$P = .8682$
Proportion zero adherent days (% [95% CI])	82	23.7 (23.1-24.2)	82	17.2 (16.7-17.8)	—
Proportion underuse days (% [95% CI])	82	58.5 (57.8-59.1)	82	44.4 (43.8-45.1)	—

EHR, electronic health record; *GP*, general practitioner; *T12*: time point 12 mo.
*Medication adherence of ≥80% in past 28 d of participation. Only patients who were nonadherent at baseline using the definition of daily inhalations used/daily inhalations prescribed and who participated for 12 mo were included.

of zero adherent days and underuse days differed slightly between groups (Table II).

We found an overall significant difference in asthma control (ACQ-5 score) between groups, with lower (ie, better) scores in the intervention group (n = 142; $P = .0056$; EMM intervention group 1.31, 95% CI, 1.18-1.44 vs control group 1.56, 95% CI, 1.44-1.68) (Figure 3). No interaction between treatment group and time was found for the ACQ-5 score ($P = .2510$). At T12, 42.9% of the intervention group and 20.0% of the control group participants had an improvement in ACQ-5 that exceeded the minimal clinically important difference (MCID) (n = 80; OR = 3.00; 95% CI, 1.13-8.35) (Table II and Figure 4).[30] In addition, 15.2% and 4.9% of the intervention and control group participants, respectively, shifted from being uncontrolled (ACQ-5 ≥



		T0	T3	T6	T9	T12
Participants that completed ACQ-5	Control	80	71	75	57	48
	Intervention	73	65	64	43	35
Participants in study	Control	82	77	77	63	50
	Intervention	82	74	72	52	38

FIGURE 3. Mean Asthma Control Questionnaire-5 (ACQ-5) score by study group and time point.

0.75) to controlled (ACQ-5 < 0.75) (n = 74; OR = 3.48; 95% CI, 0.63-19.26). The waterfall plot in Figure E3 (in this article's Online Repository at www.jaci-inpractice.org) shows the individual changes in asthma control according to the ACQ-5.

Quality of life (Mini-AQLQ scores) differed, but not significantly, between groups (n = 142; $P = .0530$; EMM intervention group 5.69, 95% CI, 5.55-5.82 vs control group 5.51, 95% CI, 5.39-5.63) (Figure 5). However, 44.8% of the intervention group and 22.9% of the control group participants achieved an improvement in Mini-AQLQ exceeding the MCID at T12 (n = 77; OR = 2.73; 95% CI, 1.02-7.54).[31] No significant difference was found between groups in the number of self-reported exacerbations ($P = .8448$) (Table II). The waterfall plot in Figure E4 (in this article's Online Repository at www.jaci-inpractice.org) shows the individual changes in quality of life according to the Mini-AQLQ.

Annual costs per patient were €284 in the control group and €528 in the intervention group. With a delta ACQ-5 score from baseline to T12 of −0.027 in the control group and −0.465 in the intervention group, the calculated cost per 0.5-point decrease in ACQ-5 score, which is the MCID for the ACQ-5, was €278 (see Tables E7 and E8 in this article's Online Repository at www.jaci-inpractice.org). We found no significant differences in work productivity indicators (see Table E9 in this article's Online Repository at www.jaci-inpractice.org).

Mean SUS score of participants was 80.1 (SD, 13.8) at T12.[19] Scores of HCPs were lower, with a mean SUS of 63.0 (SD, 12.5). Mean acceptability scores (TAQ) of participants was 3.7 (SD, 0.7) at T12 (Likert scale, 1 indicating least acceptable and 5 indicating most acceptable), and mean TAQ score of HCPs was 3.1 (SD, 0.4) at T12 (see Table E10 and Supplemental Material E2 and E3 in this article's Online Repository at www.jaci-inpractice.org). The subgroup analyses showed that the intervention effect on medication adherence and asthma control was not significantly modified by attitude, self-efficacy, and medication beliefs (see Figures E5-E8 in this article's Online Repository at www.jaci-inpractice.org). Mean BMQ, Brief-IPQ, eHLQ, and KASE-AQ scores can be found in Table E11 (in this article's Online Repository at www.jaci-inpractice.org). No significant differences over time were found in attitude, self-efficacy, and medication beliefs scores (*post hoc* analyses using linear mixed models; $P = .761$, $P = .480$, and $P = .795$, respectively); also, no differences were found between groups (P interaction term time × study arm: $P = .659$, $P = .278$, and $P = .486$, respectively). We did not perform significance testing for illness perception and eHealth literacy because our intervention was not expected to change these outcomes, and to avoid multiple testing. No serious adverse events were reported (see Supplemental Material E4 in this article's Online Repository at www.jaci-inpractice.org). Sensitivity analyses confirmed the main results (Table E5). Other outcomes are shown in the Online Repository (see Tables E12-E15, Figures E9-E13, and Supplemental Material E5-E9 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This 1-year cluster randomized controlled trial in primary care showed that the use of a digital inhaler led to higher short-term medication adherence and better long-term asthma control. Patients who used the digital inhaler were almost three times more likely to reach the MCID for asthma-related quality of life. We did not find significant effects on exacerbations and work absence.

We found enhanced medication adherence shortly after initiating the digital inhaler intervention. The same effect was shown previously, although the increase in our study was of greater size.[10] This could be because the patients in the current study were not aware of being monitored during the run-in period. Also, we did not provide training during the screening visit, whereas Moore et al[10] provided training on correct inhaler technique, making patients more aware of their inhalation behavior.

However, the increase in adherence faded over time, with a persistent difference between groups of at least 6 months, as shown in the *post hoc* analysis. This effect is similar to the effect found in previous studies in adults (all of which monitored patients for no more than 7 months, and all of which found an

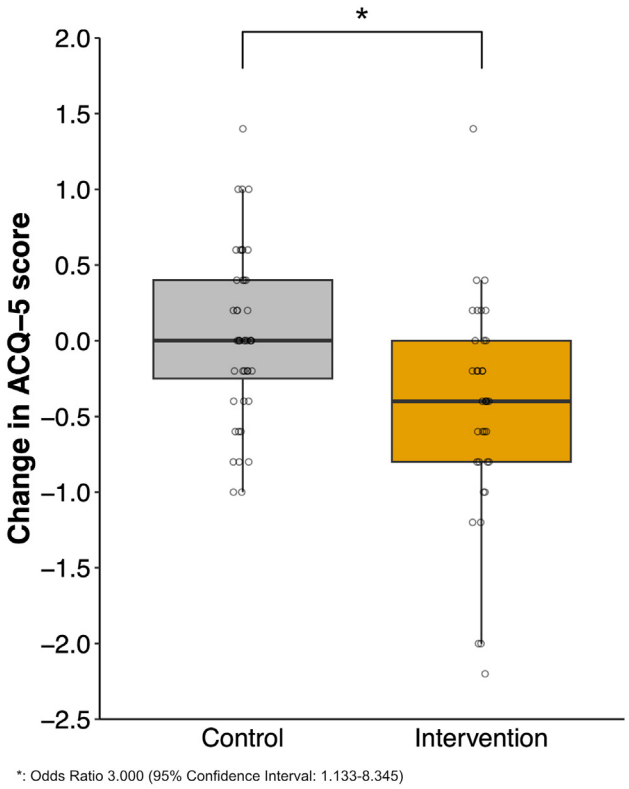


FIGURE 4. Change in Asthma Control Questionnaire-5 (ACQ-5) score from baseline to T12 by study group.

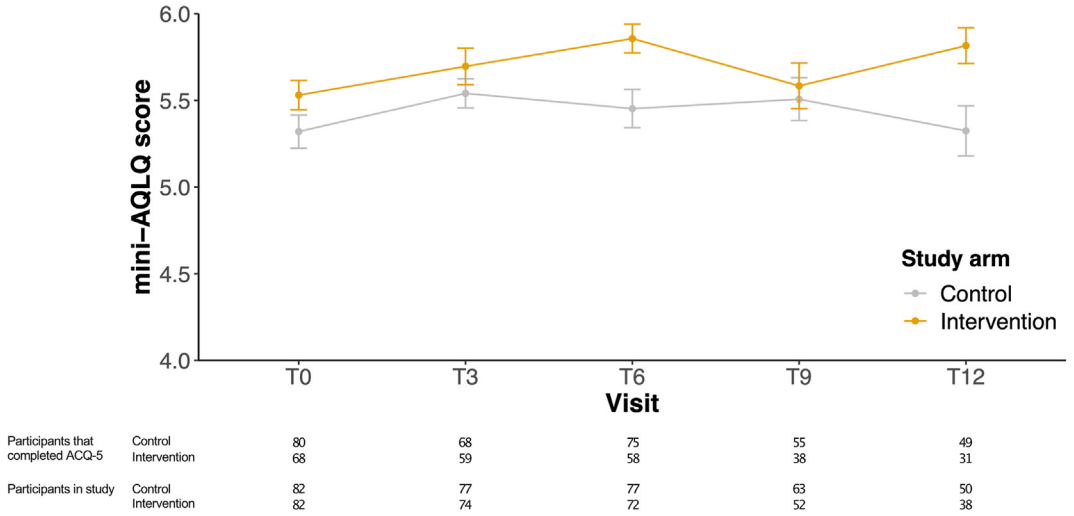
increase in adherence among digital inhaler users).[8,10,11,13,14] To our knowledge, this is the first study to evaluate the effect of digital inhaler use on controller adherence for longer than 7 months. Importantly, given the seasonal variation of asthma symptoms, a 1-year follow-up seems relevant.[32,33]

This study showed that using a digital inhaler led to improvements in long-term asthma control, which has not been found in previous digital inhaler studies focusing on controller medication in adults.[8,10-14] This could be due to the selection of nonadherent patients and the pragmatic setup of this study (ie, primary care setting, few and minimal intervening remote visits). The decrease in medication adherence over time but sustained improvement in asthma control is noteworthy. This is remarkable because higher medication adherence is typically associated with better asthma control.[2] Although our study was not designed to test the correlation between changes in ACQ-5 scores and recent adherence, given the 3-month interval used for ACQ reporting, such an analysis could provide valuable insights. However, adherence is not the only factor associated with asthma control. For example, comorbidities, inhaler technique, illness perception, and self-efficacy could have roles.[34-37] We did not find significant differences in self-efficacy, attitude, and medication beliefs. Illness perception scores between groups were not statistically tested. Another possible contribution to the decrease in adherence with sustained improved asthma control could be the timing of medication use. Patients who time the use of the inhaler based on symptoms or triggers could experience better asthma control, as has been shown in MART and anti-inflammatory reliever strategies.[38] While MART was an exclusion criterion, our self-management based smartphone app may have enhanced adherence during (expected) periods of worsening asthma. Unfortunately, we do not have high granularity data on asthma control to assess this possibility in our dataset.

There was a noteworthy increase in ACQ-5 score in the intervention group at T9, followed by a decrease at T12. This difference remained evident when considering only participants who participated in the study for 12 months (see Figure E14 in this article's Online Repository at www.jaci-inpractice.org). We initially assumed a seasonal effect, but this was not observed (see Table E16 and Figure E15 in this article's Online Repository at www.jaci-inpractice.org). The theory that it could be a self-learning effect (ie, medication adherence dropped after improved asthma control was achieved) could not be confirmed (see Figure E16 in this article's Online Repository at www.jaci-inpractice.org). Other explanations could be the impact of social distancing measures and lockdowns during the COVID pandemic and the variability of asthma within patients.

A strength of this study includes the follow-up of 12 months. Additionally, this effectiveness study was performed in a real-world setting in primary care where most patients with asthma are treated.[16] Patients' eligibility was based on established suboptimal adherence and control, so all participants had room for improvement. This resembles real-world practice, because HCPs would provide patients with a digital inhaler only if they could benefit from it and if it would reduce health care costs. Also, we chose to have a minimum number of remote visits, thus affecting as little as possible patients' medication adherence behavior.

Owing to recruitment delay and the HCP Web portal becoming unavailable, part of the participant sample had a reduced follow-up time (ie, between 6 and 12 months).



		T0	T3	T6	T9	T12
Participants that completed ACQ-5	Control	80	68	75	55	49
	Intervention	68	59	58	38	31
Participants in study	Control	82	77	77	63	50
	Intervention	82	74	72	52	38

FIGURE 5. Mean Mini Asthma Quality of Life Questionnaire (AQLQ) score by study group and time point. *ACQ-5*, Asthma Control Questionnaire-5.

Although the sample size was sufficient at randomization, this affected the study power in relation to the evaluation of long-term effects. However, sensitivity analyses taking into account the duration of participation confirmed results for the main outcome. Next, the lack of objective clinical outcome measures, such as lung function or FeNO, could be interpreted as a limitation. Moreover, because of the moderate involvement of HCPs (ie, GPs and practice nurses did not receive specific instructions on the interaction with the Web portal and on the use of patient data generated by the digital inhaler), it is unclear what impact HCPs could have when they would actively interact with the digital inhaler Web portal and use the data in consultations with the patient. This likely reflects barriers to implementing digital inhalers, such as the lack of compatibility between digital inhaler platforms and electronic health record systems.[39] Finally, most clusters consisted of one participant. Although larger clusters were expected, cluster randomization still prevented contamination between groups.

Poor medication adherence is a common reason for suboptimal asthma control that, according to international guidelines, should be regularly assessed.[38] Use of digital inhalers in daily clinical practice could help HCPs identify nonadherent patients and give insight into their adherence behavior. Furthermore, inhaler use data that are available to HCPs in a Web portal may provide information regarding which patients require more intensive treatment (eg, more frequent consultations, step-up treatment), and patients for whom face-to-face monitoring visits could be minimized. This study showed that the use of digital inhalers can improve medication adherence and asthma control when used in a group of suboptimal controlled, nonadherent patients managed in primary care. Factors such as attitude, self-efficacy, and medication beliefs, were not found to modify the effect of the intervention on adherence and asthma control. Perhaps other factors, such as inhalation technique, side effects, and comorbidities have a role. Many patients with asthma have poor inhalation technique, which is associated with uncontrolled asthma.[40] Some digital inhalers measure inhaler technique; one study showed that patients who received biofeedback on inhalation technique had improved inhalation technique after 6 months.[41] Additionally, patients using digital inhalers that provide feedback on inhaler technique can have greater odds of achieving clinically meaningful improvement in asthma control.[15] Future research might focus on incorporating inhalation technique and other possible modifying factors to find which subgroup of patients would derive the greatest benefit from digital inhalers. In addition, future research may identify the optimal number of face-to-face visits and education alongside the digital inhaler for patient subgroups.

It is still up for debate when patients might benefit from using a digital inhaler.[42] Many studies focus on using digital inhalers before stepping up to biologics (Global Initiative for Asthma step 5). Because this group represents only 5% to 10% of the population with asthma, and the largest burden on society from asthma is caused by patients with mild asthma, this study was greatly needed.

For digital inhalers to be implemented in the health care system, some barriers need to be overcome.[43] Two key barriers found in a previous study were the lack of evidence about clinical effectiveness and the lack of reimbursement agreements.[39] This study provides the needed evidence by showing improvement in asthma control in digital inhaler users. Furthermore, we evaluated cost-effectiveness alongside the trial, providing input to policymakers regarding reimbursement decisions. The improvement in asthma control we found would probably pay off after a longer period. This could be analyzed in a cost-effectiveness model, as was done for difficult-to-treat asthma.[44]

The use of digital inhalers in a suboptimally controlled, nonadherent population with asthma in primary care led to better medication adherence and persistently improved asthma control. Close collaboration among the various stakeholders remains important for further development and to overcome remaining implementation barriers.

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S.J. van de Hei, C.C. Poot, E. Meijer, B.M.J. Flokstra-de Blok, J.F.M. van Boven, N.H. Chavannes, and J.W.H. Kocks

conceptualized the study and contributed to the methodology. J.F.M. van Boven, M.J. Postma, N.H. Chavannes, and J.W.H. Kocks contributed to funding acquisition and resources and validation. S.J. van de Hei, C.C. Poot, and L.N. van den Berg were responsible for the data curation and project administration and verified the underlying data for analysis. S.J. van de Hei and Y.H. Gerritsma were responsible for the formal analysis, software, and visualization. S.J. van de Hei wrote the original draft and subsequent versions of the manuscript. S.J. van de Hei, C.C. Poot, L.N. van den Berg, Y.H. Gerritsma, E. Meijer, J.F.M. van Boven, B.M.J. Flokstra-de Blok, M.J. Postma, N.H. Chavannes, and J.W.H. Kocks reviewed the manuscript and gave final approval for submission. Deidentified data including the data dictionary are available on reasonable request from the authors. We thank the members of the patient advisory panel, J. Donkers, B. Frankemölle, J. Groenendijk, and S. Sturkenboom, for their valuable input in the setup and execution of this study. We also thank N. van Geloven for statistical advice. Also, we thank Prof Dr H. Pinnock, Dr S. Bosnic-Anticevich, and Emeritus Prof Dr T. van der Molen for their valuable input on the interpretation of the study data. Moreover, we thank Chantal Arling, Hilda Egberts, Riny van Melzen, and Margot Leeuwenburgh for their efforts in the operational work that made this study possible.

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