IMAGINE-I

Improving Adherence by Guiding Inhalation via Electronic Monitoring in Children with Uncontrolled Asthma

A Preliminary Analysis

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Enschede

Medisch Spectrum Twente
een santeon ziekenhuis

UNIVERSITY OF TWENTE.

PREFACE

This thesis is the final product of the research conducted during my internship in the department of paediatrics at the Medisch Spectrum Twente to obtain my Master of Science degree at the University of Twente. This master thesis is called "Improving adherence by guiding inhalation via electronic monitoring in children with uncontrolled asthma", or IMAGINE-I in short. This study was carried out from February 2021 up to July 2021.

The IMAGINE-I study was already in progress when I arrived at the MST. The study is about whether providing feedback to children with uncontrolled asthma will help to improve their asthma control. At the time of my arrival, sixteen children had already finished the entire study period. I focused on the collected data of these sixteen subjects during my graduation project. I was curious to explore whether an early effect of the provided feedback could be discovered. During this period at the MST, I have learned plenty about asthma, inhalation technique, treatment of asthma and different statistical analyses. In the end, it was a very educational period during which I learned to develop myself and my scientific research skills. I hope my work can contribute to optimising asthma care for children in the future.

This thesis could not have been succeeded without the help of my supervisors. I would like to thank my supervisors, Job van der Palen, Marjolein Brusse-Keizer, Kris Movig and Esther Sportel, for their guidance and support during this process. Thank you, Job, for all the elaborated feedback you gave me on my written work and during our regular meetings. I enjoyed your positive guidance, and I experienced pleasant cooperation between us. Marjolein, thank you for repeatedly providing me with sharp and critical feedback. I learned a lot, and it made me look more critically at my work. I think it improved my work significantly. I want to thank Kris for our weekly phone calls. I felt welcome to share my struggles throughout this process with you, and we always thought of a good solution together. In the last few weeks of my research, I met Esther at the hospital for the first time. I was delighted to meet you and discuss my work with you. I want to thank you for the feedback and brainstorm session towards the end of my research period. All of you helped me to grow personally and professionally over the last five months.

I also want to thank my family and friends for their support. All the advice and encouraging words have helped me a lot. Last but not least, I also want to thank Tim. You always motivated and supported me throughout my studies, especially when I was struggling.

I hope you will enjoy reading this thesis!

Amber Eikholt

July 2021

ABSTRACT

BACKGROUND Asthma control is the degree to which manifestations and symptoms of asthma are reduced or removed by therapy. Monitoring asthma control helps to detect whether the current treatment should be maintained or adjusted. Paediatric asthma control failure is commonly due to poor therapy adherence and improper inhalation technique. An add-on to the inhaler has been developed to measure adherence and inhalation technique by recording vibration patterns during inhalation. This data could be converted into personalised smart feedback on inhalation medication and provided immediately to patients via a mobile application.

STUDY OBJECTIVE The aim of this study is to evaluate whether asthma control could be improved in children between 6 and 18 years old by providing immediate smart feedback on the intake of inhalation medication.

METHODS IMAGINE-I is an ongoing randomised controlled interventional trial consisting of three phases. Phase 1 and 3 are observational. Phase 2 is an RCT composed of two randomised groups where one group received immediate smart feedback on their therapy adherence and inhalation technique. The degree of asthma control was measured using four categories: Forced Expiratory Volume in 1 second (FEV_1), (Childhood) Asthma Control Test ((c-)ACT) score, reversibility and lung function variability (LFV). In addition to the categories, seven criteria were conducted to describe paediatric asthma control. If one or more of the seven criteria was completed by a patient, the patient's asthma control is clinically meaningful improved. The performance of the criteria per group was determined. The interaction of the two groups and the mean change over time for the four categories were assessed with mixed model repeated measures analysis with fixed effects. Baseline values were subtracted from the follow-up values to obtain normally distributed values.

RESULTS Data were analysed for sixteen randomised children (control: n = 8; feedback: n = 8). Both groups showed improvement over time between the baseline and the end of phase 2 on all four clinical categories. Still, none of the differences between the groups was statistically significant over time. An increased FEV_1 was seen over time for both groups: the feedback group showed more improvement (median 13.0%, IQR -12.4; 20.9) than the control group (median 9.02%, IQR 4.4; 21.8). The (c-)ACT scores improved slightly more for the control group (median 3.50, IQR 0.8; 5.3) than for the feedback group (median 3.00, IQR -1.0; 8.0). The mean reversibility decreased more within the feedback group (median -67.4 %, IQR -97.8; -23.6) than within the control group (median -24.1%, IQR -81.3; 32.0). The relative difference of the LFV between phase 1 and phase 2 decreased within the feedback group (median -10.0%, IQR -42.0; 150.4), whereas the control group observed an increased LFV (median 5.0%, IQR -22.7; 96.8). Over the entire length of the study, a clinically relevant improvement could be seen in 87.5% of the children regardless of the allocated group (n = 7 in the control group and n = 7 in the feedback group).

CONCLUSION This preliminary analysis showed no significant difference in all outcome measures to prove that providing immediate smart feedback to children improved the degree of their asthma control compared to the control group. However, most of the children showed clinically relevant improvement over the entire study duration despite the allocated group.

NOMENCLATURE

(c-)ACT	(children's) Asthma Control Test
FEV_1	Forced Expiratory Volume in 1 second
IMAGINE	Improving Adherence by Guiding Inhalation via Electronic monitoring
IQR	Interquartile ranges
LFV	Lung Function Variability
MMRMA	Mixed Model Repeated Measures Analysis
PIF	Peak Inspiratory Flow
RCT	Randomised Controlled Trial
SABA	Short-acting beta-adrenoreceptor antagonist
SD	Standard deviation

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1. INTRODUCTION

Paediatric asthma is the most common chronic disease in the Netherlands, with a prevalence of 5-10% in children up to 12.[1] Asthma is a chronic inflammatory disorder of the airways, which causes airflow limitation and is characterised by bronchial hyperresponsiveness to various stimuli.[2,3] This results in respiratory symptoms, such as wheezing, chest tightness, coughing, and shortness of breath, which are often worse at night.[2–4] The level of asthma severity is used to determine the initial therapy.[5,6] Asthma control is the degree to which manifestations and symptoms of asthma are reduced or removed by therapy.[5–8] Uncontrolled asthma is associated with an increased risk of emergency department visits, hospitalisation and absenteeism of school.[9,10] Monitoring asthma control helps detect whether the current therapy should be maintained or adjusted.[5,7,8] International guidelines[5,11] recommend physicians to measure therapy adherence, quality of inhalation technique, environmental factors, and associated comorbidities before determining stepping up paediatric asthma therapy.[7,8,12,13]

However, the two most common factors leading to asthma control failure for children are poor therapy adherence and improper inhalation technique.[12,14] Different trials[15-17] have proven that poor adherence and improper inhalation technique are associated with poor asthma control. Poor adherence to asthma medication occurs in around 50% of all children, resulting in more frequent asthma exacerbations.[18-21] A randomised controlled trial by Morton et al.[22] provided electronic adherence monitoring with daily reminder alarms for asthmatic children, which resulted in significantly better adherence in the intervention group compared to the control group, and the intervention group also used significantly fewer oral steroids and had fewer hospital admissions. Additionally, a high rate of incorrect inhaler handling among asthmatic children has been reported.[23–29] When children fail to use their inhalers correctly, the drug dose is not fully delivered to the lungs, resulting in increased healthcare utilisation and asthma morbidity.[26,30] A better technique is associated with better asthma control and improved quality of life scores.[24,27]A trial by Konevic et al.[24] has proven the effectiveness of education on inhalation technique resulting in significant technique improvement and a higher quality of life for paediatric asthma. Also, Gillette et al.[26] have shown that education and providing continuous feedback on inhalation technique are essential aspects of paediatric asthma to improve inhalator technique.

Therapy adherence and inhalation technique cannot be measured during a single hospital visit. Therefore, monitoring the medication usage and inhalation technique at home with smart inhalers provides the most valuable data.[26,31,32] Recently, AMIKO (London, United Kingdom)[33] has developed the Respiro™ device. This device is an add-on to the patient's inhalator to measure therapy adherence and inhalation technique by recording vibration patterns. The device can evaluate adherence by recording information on the time of use per inhalation, and the device can precisely detect the inspiratory flow of the inhalation, the inhalation duration, and the device's orientation while taking medication. The device is connected to an application for the patient, providing immediate smart feedback on therapy adherence and several aspects of inhalation technique. The Respiro™ add-on has great potential as it is one of the first add-ons that can provide immediate smart feedback to the patient and potentially improve therapy adherence and inhalation technique. The first trial, named Improving Adherence by Guiding Inhalation via Electronic monitoring (IMAGINE) I in children, is set up to evaluate the effect on asthma control by giving immediate smart feedback on therapy adherence and inhalation technique.

This research aims to clinically improve asthma control in children between the ages of 6 and 18 who have uncontrolled asthma by providing immediate smart feedback on the intake of inhalation medication at home. The leading question of this research is: *Does immediate smart feedback by children between 6 and 18 years old with uncontrolled asthma result in clinically improved asthma control compared to no feedback?*

As a secondary research goal, the therapy adherence and inhalation technique of the patients will be analysed. Therefore, the second question is: *Does immediate smart feedback by children between 6 and 18 years old with uncontrolled asthma result in better therapy adherence and better inhalation technique compared to no feedback?*

2. METHODS

The IMAGINE-I study is an ongoing randomised controlled interventional trial consisting of three phases. Phase 1 covers a four-week observational period to observe the lung function variability (LFV), adherence and inhalation technique used as a baseline reference for comparison over time. Phase 2 consists of two randomised groups, one group receiving feedback and one control group, to study the effect of the feedback and took six weeks. Phase 3 extends another six-week observational follow-up. The three different phases of the study are shown in Figure 1. This multi-phase study was set up to evaluate the degree of clinical improvement of paediatric asthma control over time and between the two groups by providing immediate smart feedback on therapy adherence and inhalation technique.

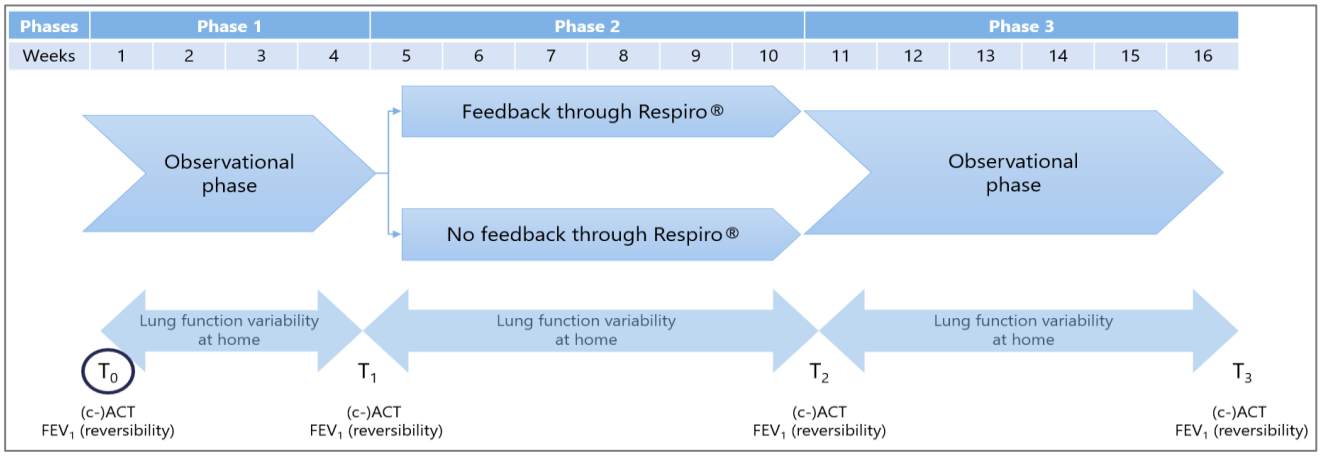

Figure 1: Study design and outcome measurements. The measurements were done at four moments in time: T_0 is the start of the study, T_1 is the start of phase 2, T_2 is the start of phase 3, and T_3 is the end of the study. At T_0, the participants are randomised.

2.1 The Respiro™ add-on device and NuvoAir spirometer

The Respiro™ device is an add-on to the patient's NEXThaler inhalator (Figure 2). This add-on device automatically tracks the generated flows of the user through the inhaler. The device is connected wirelessly to an application on the patient's smartphone, named the Respiro Mobile (Amiko Digital Health), which can be used for synchronising the Respiro™ device. The application can remind the patient when it is time to inhale a dose and thus help the patient improve their therapy adherence. The device can also provide personalised feedback to help the patient to optimise their inhalation technique by detecting the inspiratory flow of the inhalation, the inhalation duration, and the device's orientation while taking medication. These characteristics of an inhalation determine whether the inhalation is taken correctly. Critical inhalation technique errors are failing to reach sufficient inspiratory peak flow or inadequate inhalation duration. A non-critical error occurs when the device's orientation deviates more than 45 degrees from the optimal position. The personalised feedback is provided on the time and date of inhalation, the inhalation peak flow, the duration of inhalation, and the inhaler's orientation. The provider's portal displays a dashboard of all the patients and provides specific insights into the patients' data.

The NuvoAir spirometer (Air Next, NuvoAir, Stockholm, Sweden)[34] can be used to perform spirometry. The Air Next is CE certified as a Class II medical device and FDA cleared. This device needs to be connected by Bluetooth with the Air MD application (NuvoAir) to register the spirometry results such as Forced Expiratory Volume in 1 second (FEV_1).

Figure 2: The AMIKO Respiro™ add-on device connected to the NEXThaler inhalator.

2.2 Study population

Children with uncontrolled asthma aged between 6 and 18 years old at the time of inclusion, despite the use of Foster medication, were qualified for inclusion. The recruitment for inclusion took place between October 2019 and April 2021. Asthma was considered uncontrolled when the child had:

- An Asthma Control Test ((c)-ACT) score lower than 20 and/or
- A difference in FEV_1, five minutes after inhaling 200µg SABA, is equal to or higher than 12%.

The inhalator used to distribute the child's medication needed to be the NEXThaler, with the patient using it for at least one month before joining the study. Patients could not join the study when they, or the guardians of children under 12, could not understand or speak Dutch. In addition, a patient was excluded from the study if they suffered from chronic pulmonary diseases other than asthma. The study received written informed consent from all participants and guardians of children who enrolled in the study.

2.3 Study design

The study consisted of three phases. Phase 1 was an observational phase with a duration of four weeks. During this phase, the patients' inhalation technique and therapy usage were monitored using the Respiro™ add-on device to observe the baseline LFV, therapy adherence and inhalation technique. Phase 2 was the Randomised Controlled Trial (RCT), where the intervention group received immediate smart feedback on the medication usage and inhalation technique using the Respiro™ application for six weeks. The control group received no feedback, but the add-on device still monitored their medication usage and inhalation technique. Finally, phase 3 was an observational follow-up period with a length of six weeks. Within this phase, no subjects received any feedback, yet the patients' inhalations were still monitored.

The patients visited a researcher in the hospital before the study's start and after every phase. During the first appointment, the (children's) Asthma Control Test ((c-)ACT) and FEV_1 reversibility tests were performed to check whether the patients were eligible for the study. After being included, all subjects received a handheld spirometer. The subjects were instructed to perform spirometry twice a week at home for the entire length of the study using the NuvoAir spirometer. Additionally, the Respiro™ add-on device would be attached to the subject's NEXThaler inhalator. Two applications needed to be downloaded during the first appointment: the Respiro Mobile (Amiko Digital Health) for synchronising the Respiro™ device and the Air MD application (NuvoAir) for spirometry at home.

After the first appointment, the subjects were randomly assigned to the intervention or control group. The randomisation was a 1:1 blocked, stratified randomisation performed by an independent person selected by the researcher. In addition, the randomisation was stratified on age (≥ 12 years versus < 12 years) and the use of nasal corticosteroids (usage versus non-usage). Blinding was not possible for either the patients or the staff due to the nature of this study.

2.4 Measurements

The following parameters were measured at fixed time points during the whole study duration. The baseline reversibility and (c-)ACT were measured at the start of phase 1 to determine the current degree of asthma control and at the end of each phase to monitor asthma control over time. Reversibility testing was executed to determine the lungs' response to bronchodilator medication and, if so, by how much. Therefore, spirometry was performed before and after the patient taking a short-acting beta-adrenoreceptor antagonist (SABA), and the reversibility was calculated using equation (1).[8] The (c-)ACT is a self-report, internationally accepted questionnaire consisting of 5 items assessing the patient's perception of asthma complaints and asthma control the previous four weeks.

The ACT was used for children of 12 years and older and consisted of five questions. The children's ACT was used for the children under 12 and consisted of four questions for the child and three additional questions for the parents. With the assistance of the spirometer, the FEV_1 could be measured twice a week at home. After each phase, the lung function variability was determined using the minimum and maximum value of the FEV_1 of a specific patient during a particular phase by using equation (2). The measurement of the parameters is displayed in Figure 1.

$$\text{Reversibility} = \frac{\text{FEV}_1\,(\text{L})\ \text{post SABA} - \text{FEV}_1\ (\text{L})\ \text{pre SABA}}{\text{FEV}_1\ (\text{L})\ \text{pre SABA}} \cdot 100\% \quad (1)$$

$$\text{LFV} = 100\% - \frac{\text{Minimum FEV}_1(\text{L})\text{in phase x}}{\text{Maximum FEV}_1(\text{L})\ \text{in phase x}} * 100\% \quad (2)$$

2.5 Primary outcome

The primary outcome of the IMAGINE-I study[35] was the degree of asthma control, measured at the end of phase 2. In this study, four categories cover clinical asthma control: FEV_1, (c-)ACT, reversibility and LFV. In addition, seven criteria specifically describe paediatric asthma control. An overview of the categories and the corresponding criteria for clinical improvement is displayed in Figure 3. These seven criteria were:

1. A relative FEV_1 increase of ≥ 10% at the end of phase 2, compared to the baseline measured at the start of phase 1;
2. An absolute (c-)ACT-score increase of ≥ 3 points at the end of phase 2, compared to baseline (c-)ACT score measured at the start of phase 1;
3. A (c-)ACT score of ≥ 20 at the end of phase 2;
4. A relative reversibility decrease of ≥ 9% at the end of phase 2, compared to baseline reversibility measured at the start of phase 1;
5. A reversibility of < 12% after administration of salbutamol, at the end of phase 2;
6. A relative LFV decrease of ≥ 10% during phase 2, compared to the LFV of phase 1, and
7. An LFV of ≤ 15% measured during the entire phase 2.

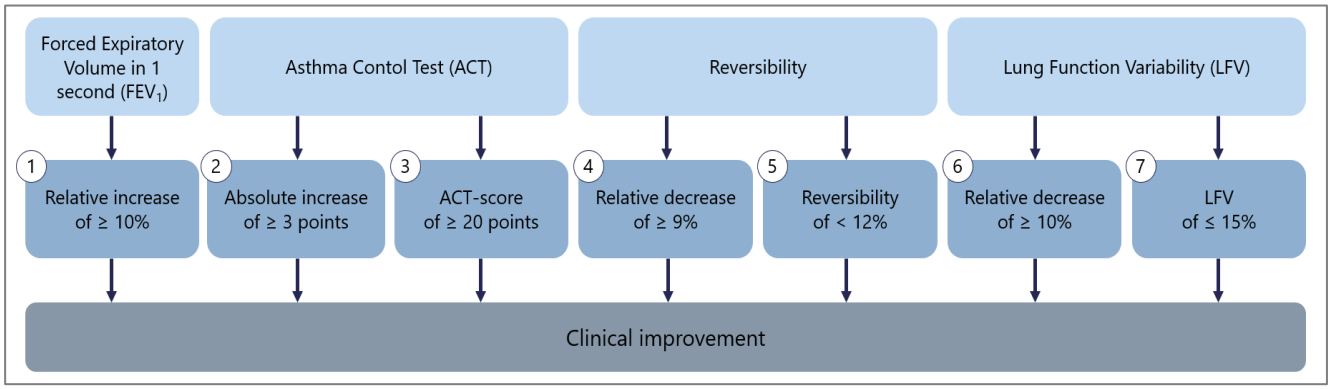

Figure 3: Four categories divided into seven clinical criteria for paediatric asthma control.

The original criterion in the study protocol stated that if one or more of the seven criteria was completed by a patient, the patient's asthma control is clinically meaningful improved. However, two inclusion criteria correlate to two clinical improvement criteria: the ACT score must be < 20, or the reversibility must be ≥ 12%. These inclusion criteria are respectively criteria three and five. When one of these two inclusion criteria was already satisfied at baseline, that specific patient was not included in the analysis for that particular criterion.

2.6 Secondary outcomes

Therapy adherence and inhalation technique were considered secondary outcome measures. Therapy adherence was calculated using equation 3. The percentage of adherence can be qualified dichotomously as insufficient or good. The used cut-off for good therapy adherence is ≥ 75%.

The quality of the inhalation technique was assessed regarding two critical errors. An inhalation contained a critical error if the Peak Inspiratory Flow (PIF) was slower than 30L/min[36] or the inhalation duration was less than one second[37]. An inhalation was classified as incorrect when one of these two critical errors occurred. When ≥ 75% of inhalations contained no critical error, the inhalation technique can be qualified as good. The percentage of good inhalations was calculated using equation 4. This percentage is based on the number of completed inhalations.

$$\text{Therapy adherence } (\%) = \frac{\text{actual number of medication intake}_{\text{ in phase x}}}{\text{prescribed number of medication intake}_{\text{ in phase x}}} \cdot 100\% \qquad (3)$$

$$Good\ inhalation\ (\%) = \frac{number\ of\ inhalations\ without\ critical\ errors_{\ in\ phase\ x}}{completed\ number\ of\ inhalations_{\ in\ phase\ x}} \cdot 100\% \qquad (4)$$

Additionally, a non-critical error could be measured: the device's orientation. The orientation was qualified as poor if the device deviated more than 45 degrees from the optimal position. The optimal position of the NEXThaler was set at 90 degrees. The percentage of inhalations containing a non-critical error during a specific phase was assessed similarly for each patient.

The mean percentage of therapy adherence and mean percentage of good inhalations containing no critical errors for each patient were calculated per phase and are used to analyse the secondary outcomes. A combination of good adherence together with good inhalation technique was also evaluated.

2.7 Statistical analysis

The between-group comparison consisted of three analyses. At first, the performance per criterion was tested to see the clinical difference between the two groups. These variables were tested with the Wilcoxon rank-sum test, as a normal distribution seemed unlikely. The second between-group analysis assessed the seven criteria on completion of the thresholds and compared the two groups on completing each criterion with a Fisher exact test. Thirdly, the mean change over time for the continuous variables (the FEV_1, (c-)ACT scores, reversibility and LFV) were assessed with mixed model repeated measures analysis (MMRMA) with fixed effects. A mixed model was made for each of these variables using the optimal covariance type. For each analysis, the FEV_1, (c-)ACT scores, reversibility or LFV was qualified as the dependent variable. Baseline values were subtracted from the follow-up values to obtain normally distributed values. The interaction of the two groups by time was tested within this MMRMA. All patients enrolled at baseline were included in the analyses.

Additionally, the percentages of therapy adherence and inhalation without critical errors were also assessed with an MMRMA with the interaction of the two groups by time. The percentages of adherence and good inhalations during phase 1 were subtracted from the values of the following phases to obtain normally distributed values. Also, a between-group comparison on achievement for good therapy adherence and good inhalation technique was performed using the Fisher exact test.

All these analyses were done according to the intention-to-treat reporting analysis. The data was analysed using SPSS (IBM SPSS statistics 27, Armonk, New York, United States of America). P-values of < 0.05 were considered to be statistically significant.

3. RESULTS

Between October 2019 and April 2021, 40 children were approached to participate in the study, of which 22 did not meet the inclusion criteria, and two declined to participate. In total, 16 children with severe uncontrolled asthma were included and randomised (Figure 4). At baseline, the patients had a mean age of 10.8 (± 3.0) years, 12 patients (75%) were male, the predicted percentage of FEV_1 was 85.2% (± 21.9%), and the mean (c-)ACT score was 15.4 (± 6.3). All demographic and baseline characteristics are displayed in Table 1, and these characteristics did not differ significantly between the control and feedback groups. In Table 2, the characteristics of phase 1 are presented.

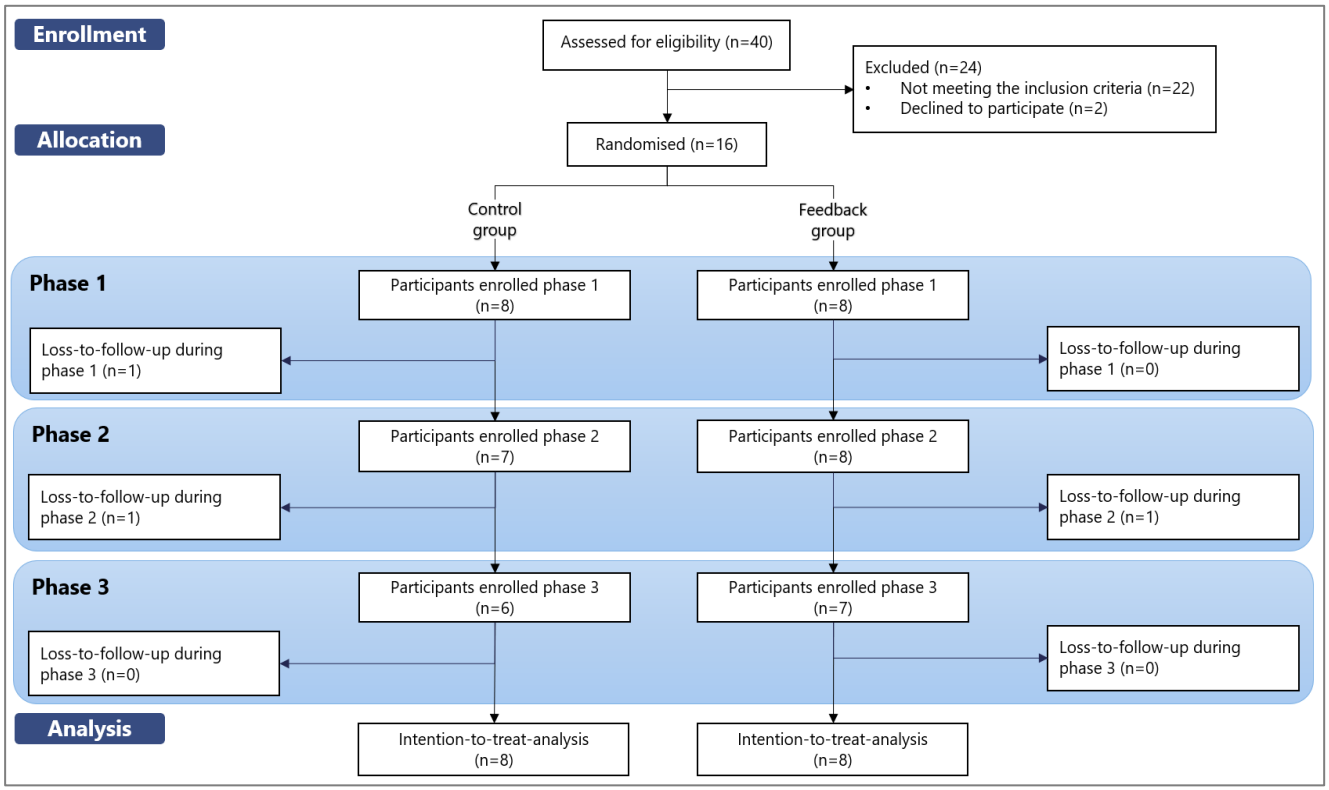

Figure 4: Patient flow graph. A total of 40 children were approached to participate in the study, two patients declined to participate, and 22 patients did not meet the inclusion criteria. Therefore, in total, 16 children are included and randomised.

Table 1: Demographic characteristics and baseline measurements of the 16 study participants. Data are presented as mean ± standard deviation (SD) unless otherwise stated. IQR = Interquartile Range, kg = kilograms, and cm = centimeters.

Demographic characteristics and baseline measures	**Control group (n=8)**	**Feedback group (n=8)**
Age (years)	10.6 (± 3.3)	10.9 (± 2.8)
Height (cm)	142.8 (± 12.5)	146.1 (± 16.2)
Weight (kg)	38.3 (± 12.0)	48.0 (± 14.3)
Gender (% male)	87.5	62.5
Race (% Caucasian)	62.5	50.0
Nasal corticosteroids (% users)	62.5	75.0
(c-)ACT score	17.5 (± 4.3)	13.4 (± 7.5)
(c-)ACT ≥ 20 (% yes)	12.5	25.0
Predicted FEV_1 pre SABA (% predicted)	86.6 (± 15.5)	83.8 (± 27.9)
FEV_1 reversibility (%), median (IQR)	18.1 (9.1; 23.8)	18.7 (13.8; 39.0)
FEV_1 reversibility < 12% (% yes)	37.5	12.5

Table 2: Characteristics during phase 1.

Parameters measured in phase 1	Control group (n=8)	Feedback group (n=8)
LFV (%), median (IQR)	14.1 (8.2; 32.2)	30.7 (11.0; 40.2)
Therapy adherence		
Therapy adherence (%), mean (SD)	69.2 (± 32.5)	66.4 (± 36.2)
Good therapy adherence (% yes)	62.5	62.5
Inhalation technique		
Inhalations without critical errors (%), mean (SD)	50.2 (± 30.0)	62.4 (± 36.9)
Inhalations without errors (%), mean (SD)	43.7 (± 29.6)	46.2 (± 38.0)
Good inhalation technique (% yes)	12.5	50.0
Good therapy adherence and good inhalation technique (% yes)	12.5	25.0

3.1 Clinical improvement of asthma control

The performances on the seven clinical criteria during the first two study phases and at the end of phase 2 were evaluated between both groups, and the same seven criteria were assessed for a clinically relevant improvement as defined with the thresholds (Figure 3). In Table 3, the performance and completion of the seven clinical criteria are displayed. No statistically significant differences were observed between the performances and percentage of completion per criterion between the control and feedback groups. The time-by-group-interactions of the four clinical categories (FEV_1, (c-)ACT, reversibility and LFV) are visually displayed in Figure 5. The changes over time were normalised to the baseline measure or phase 1 as a reference phase. The estimated means and standard errors demonstrated similar trends over time for both groups. Again, no statistical differences were found between the two groups. However, differences over time were observed. The numerical differences between the control and feedback group in performance and completion of the seven clinical criteria and time-by-group interaction on the four categories are evaluated in the following paragraphs.

Forced Expiratory Volume in 1 second

The baseline predicted FEV_1 before SABA were comparable for the two groups (Table 1). Criterion 1, the change in FEV_1 between the baseline and the end of phase 2, showed that the median change was slightly higher for the feedback group (median 13.0%, IQR -12.4; 20.9) than for the control group (median 9.02%, IQR 4.4; 21.8). The percentage of completion for this criterion was roughly the same for both groups (control: 50.0%, feedback: 57.1%). The time-by-group interaction (Figure 5A) showed that during phase 2, where feedback was provided, the FEV_1 of the control group increased, whereas the FEV_1 of the feedback group decreased. At the end of phase 3, the feedback group had a higher mean FEV_1 difference than the control group, and therefore, the feedback group had the most remarkable improvement compared to the baseline measure.

Asthma Control Test

The baseline (c-)ACT score differed slightly between the two groups. Whereas the mean (c-)ACT score of the control was four points higher, the feedback group contained more patients with a (c-)ACT score of 20 points or more (Table 1). The improvement of the (c-)ACT score (criterion 2) for the control group (median 3.50, IQR 0.8; 5.3) was greater than the improvement within the feedback group (median 3.00, IQR -1.0; 8.0). Also, the percentage of completion for this criterion was slightly higher for the control group (66.7%) than the feedback group (57.1%). Next to the improvement, the absolute scores of the (c-)ACT measured at the end of phase 2 (criterion 3) were higher within the control group than the feedback group (control: median 19.0 IQR 16.8; 21.3, feedback: median 18.0 IQR 10.8; 21.3). More patients completed criterion 3 within the feedback groups (50.0%) than the control group (33.3%). The time-by-group interaction, presented in Figure 5B, showed an improvement of the (c-)ACT score of the feedback group during phase 2; no further improvement was seen. The control group showed more improvement during phase 2 than the feedback group, and the increment continued during phase 3.

Reversibility

In Table 1 can be seen that the median baseline reversibility was similar between both groups; however, the percentage of patients with a reversibility < 12% at baseline was higher for the control group (control: 37.5%, feedback: 12.5%). A difference in the relative improvement in reversibility (criterion 4) between the two groups was seen. The reversibility decrease from the baseline to the end of phase 2 was more prominent for the feedback group (median -67.4%, IQR -97.8; -23.6) than for the control group (median -24.1%, IQR -81.3; 32.0). More patients achieved a relative improvement of ≥ 9% within the feedback group (85.7%) than the control group (66.7%). The reversibility at the end of phase 2 (criterion 5) was lower for the control group (median 3.85%) than for the feedback group (median 9.54%). The completion for criterion 5 was for both groups 66.7%. Figure 5C shows that the mean reversibility decreased more within the feedback group than within the control group. During phase 2, the reversibility of the control group decreased, whereas the mean reversibility of the feedback group increased. The most considerable reversibility difference from baseline to the end of the study was demonstrated within the feedback group.

Lung Function Variability

The LFV baseline was measured during phase 1 (Table 2). The median LFV of the feedback group (median 30.7%, IQR 11.0; 40.2) was larger than the LFV of the control group (median 14.1%, IQR 8.2;32.2). Table 3 shows that the performance on criterion 6, which is the relative difference of the LFV between phase 1 and phase 2, decreased within the feedback group (median -10.0%, IQR -42.0; 150.4), whereas in the control group, an increased LFV is observed (median 5.0%, IQR -22.7; 96.8). Criterion 6 was completed by 50.0% of the patients in the feedback group, compared to 28.6% completion within the control group. Additionally, the LFV during phase 2 (criterion 7) showed an almost statistically significant difference between the control and feedback group (p = 0.064), where the control group obtained lower variabilities in lung function than the feedback group (control: median 16.1%, IQR 14.5; 22.4, feedback: median 19.8%, IQR 17.1; 50.1). The analysis of the time-by-group interaction is corrected for this baseline difference, and Figure 5D visualises a similar trend over time for the LFV for both groups.

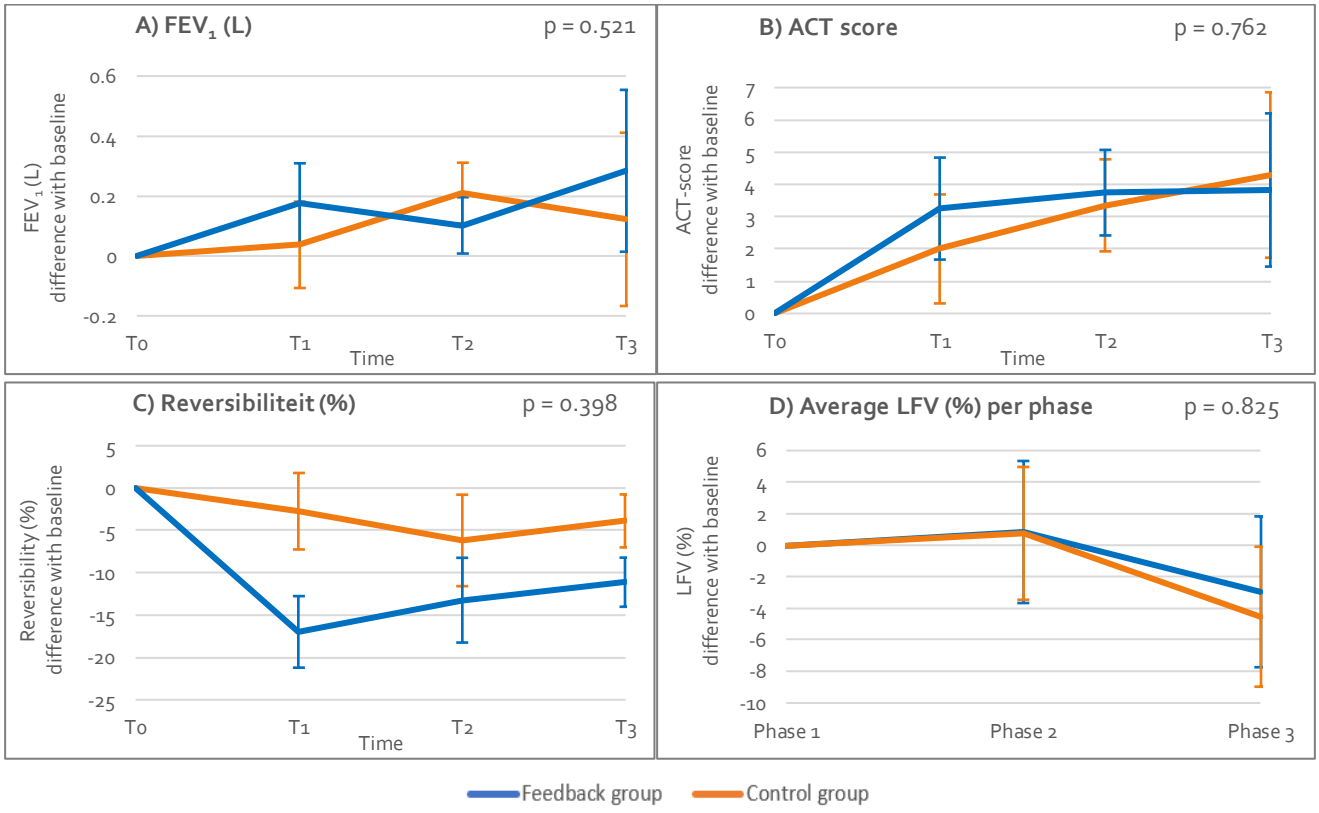

Figure 5: The time-by-group-interaction of the mean change with reference to the baseline measure: the FEV_1 (A), ACT scores (B), reversibility (C), and LFV (D). The estimated marginal means of the mixed model with repeated measures are presented for each time measure per group: T_0 is the start of the study, T_1 is the start of phase 2, T_2 is the start of phase 3, and T_3 is the end of the study.

Table 3: Performance and completion per criteria.

Criteria			Control group	Feedback group	Between-group analysis p-value
1	A relative FEV_1 increase of ≥ 10% at the end of phase 2, compared to baseline.	Performance Completion (%)	9.02 (4.4; 21.8) 50.0	13.0 (-12.4; 20.9) 57.1	0.668 1.000
2	An absolute (c-)ACT score increase of ≥ 3 points at the end of phase 2, compared to baseline.	Performance Completion (%)	3.50 (0.8; 5.3) 66.7	3.00 (-1.0; 8.0) 57.1	0.886 1.000
3	A (c-)ACT score of ≥ 20 at the end of phase 2.	Performance Completion (%)	19.0 (16.8; 21.3) 33.3	18.0 (10.8; 21.3) 50.0	0.572 1.000
4	A relative reversibility decrease of ≥ 9% at the end of phase 2, compared to baseline.	Performance Completion (%)	- 24.1 (- 81.3; 32.0) 66.7	- 67.4 (- 97.8; - 23.6) 85.7	0.283 0.559
5	A reversibility of < 12% after administration of salbutamol at the end of phase 2.	Performance Completion (%)	3.85 (0.0; -) 66.7	9.54 (0.29; 20.3) 66.7	0.697 1.000
6	A relative LFV decrease of ≥ 10% during phase 2, compared to the LFV of phase 1.	Performance Completion (%)	5.00 (- 22.7; 96.8) 28.6	- 10.0 (- 42.0; 150.4) 50.0	0.643 0.608
7	An LFV of ≤ 15% measured during the entire phase 2.	Performance Completion (%)	16.1 (14.5; 22.4) 28.6	19.8 (17.1; 50.1) 0.00	0.064 0.200

The performance on the seven criteria for both groups is displayed as median and interquartile ranges unless otherwise stated. The completion of the criteria is displayed with a percentage of patients who completed each criterion. The between-group analysis for the performance is executed with a Wilcoxon rank-sum test. For the between-group comparison of the completion per criterion, the Fisher exact test is used.

3.2 Clinical improvement

The original criterion in the study protocol stated that if one or more of the seven criteria (that was not fulfilled at baseline) were completed by a patient, the patient's asthma control was clinically meaningful improved. Table 4 presents the number of completed criteria and the corresponding percentage of completion per patient. In Appendix A.1, the extensive table for completion of each specific criterion per patient is shown. At this moment, this criterion would imply that in fourteen patients (87.5%), n = 7 in the control group and n = 7 in the feedback group, the asthma control has been clinically meaningful improved. Only two patients have not met the threshold: one of these patients stopped during phase 1 of the study and the other patient stopped during phase 2 of the study.

However, working with the number of completed criteria was not comparable due to patients who already fulfilled one of the criteria at the baseline. Therefore, the percentage of completed criteria was used. These percentages were corrected by the number of criteria to be evaluated per patient. Both groups improved approximately the same percentage of criteria (control: mean 34.2% ± 25.8, feedback: mean 35.1% ± 10.2); however, the variation is larger in the control group.

Table 4: The completion of the seven clinical criteria for asthma control improvement presented per subject.

Patient ID	RCT group	Number (n) of completed criteria per patient:	Percentage (%) completion per patient:
Subject01*	Control	1	16.7
Subject02*	Feedback	4	66.7
Subject03	Feedback	5	71.4
Subject04*	Feedback	0	0.00
Subject05	Control	3	42.9
Subject07	Control	2	28.6
Subject08	Control	5	71.4
Subject09*	Control	1	16.7
Subject10	Control	2	28.6
Subject11	Feedback	5	71.4
Subject12	Feedback	5	71.4
Subject13*	Feedback	2	33.3
Subject14*	Control	5	83.3
Subject15	Feedback	1	14.3
Subject16*	Control	0	0.00
Subject17	Feedback	3	42.9

The number of completed criteria displayed per subject and the corresponding percentage of completion, corrected (*) for the completed criteria at inclusion.

3.3 Therapy adherence and inhalation technique

The therapy adherence and inhalation technique were assessed for both groups per phase. The time-by-group interaction of the secondary research question is graphically displayed in Figure 6. No statistically significant differences were observed for the therapy adherence and critical errors for the time-by-group-interaction. Appendix A.2 (Table 7) contains all secondary outcome measures separately for each patient during each phase.

In Table 2 can be observed that the adherence during phase 1 was almost equal for both groups (control: mean 69.2% ± 32.5, feedback: mean 66.4% ± 36.2). Figure 6A shows that the feedback group had a lower average therapy adherence during phase 2 than the reference value of phase 1. However, during phase 3, the highest mean percentage of adherence was reached for the feedback group. The control group showed no difference in adherence over phase 2 compared to phase 1, and during phase 3, the adherence decreased.

The percentage of inhalations without critical errors, qualified as good, was slightly higher for the feedback group (mean 62.4% ± 36.2) than for the control group during phase 1 (mean 50.2% ± 30.0) (Table 2). In Figure 6B can be observed that the percentage of inhalations without critical errors was similar during phase 2 compared to phase 1 for both groups. However, in phase 3, the percentage of inhalations without critical errors decreased more for the control group than for the feedback group. The outcomes of the mixed model analyses for the different inhalation technique criteria (PIF errors, duration errors, and orientation errors) were also analysed separately and are further elaborated in Appendix A.3.

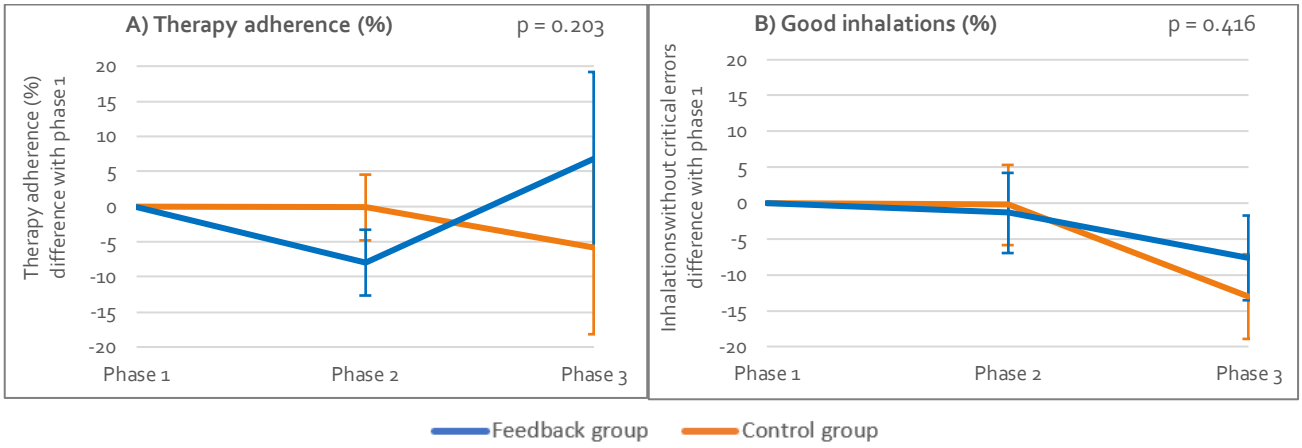

Figure 6: The time-by-group-interaction of the mean change with reference to phase 1: the therapy adherence (A) and the percentage of good inhalations (B) displayed per group over the time.

Also, a between-group analysis on the threshold for good therapy adherence and good inhalation technique was performed, and no statistically significant differences were found. The number of subjects with good therapy adherence or good inhalation technique over the different phases was nearly the same for both groups during all phases (Table 5). The percentage of good therapy adherence during phase 1 is identical for both groups. During phase 2 the lowest adherence over time for both groups was observed. In phase 3, both groups performed the best and the feedback group received the highest adherence percentage.

The inhalation technique was qualified as good for 12.5% of the patients in the control group compared to 50.0% within the feedback group during phase 1. During phases 2 and 3, the percentages were the same for both groups. Due to the lower percentage of good inhalation technique for the control group at the baseline, an incline in patients with good inhalation technique could be seen, whereas in the feedback group, a decline was observed.

Table 5: Good therapy adherence and proper inhalation technique.
Data are presented in percentages unless otherwise stated.

	Control group	**Feedback group**
Good therapy adherence		
Phase 1	62.5	62.5
Phase 2	42.9	42.9
Phase 3	66.7	83.3
Good inhalation technique		
Phase 1	12.5	50.0
Phase 2	42.9	42.9
Phase 3	33.3	33.3

Appendix A.2 displays the complete performance table (Table 8) regarding therapy adherence and inhalation technique specifically per patient. This table shows that good therapy adherence together with good inhalation technique was seen for only three or four patients during the entire study length. These patients were equally distributed between the control and feedback group.

4. DISCUSSION

This study aimed to determine whether immediate smart feedback by children with uncontrolled asthma would result in clinically meaningful improved asthma control compared to the control group receiving no feedback.

4.1 Interpretation of the results

The results show no significant difference in performance or completion of the seven clinical criteria to prove that providing immediate smart feedback to children improved the degree of their asthma control compared to no feedback. Also, the four clinical categories (FEV_1, (c-)ACT, reversibility and LFV) were assessed for a difference in time-by-group interaction. Again, no statistical differences between the two groups over time were found. Nonetheless, some asthma improvements can be seen. The clinically relevant differences between the two groups are discussed below to demonstrate the current state of affairs for the IMAGINE-I study.

The results of criterion 1 showed that the feedback group contained more patients with a higher percentage of improvement of their FEV_1 values between the baseline and the end of phase 2. The overall higher FEV_1 of the feedback group is the preferable outcome for clinical improvement. Within both groups, improvement can be seen compared to the baseline FEV_1. Interestingly, the improvement of the feedback group was not during phase 2, where feedback was provided, but during the observational phases 1 and 3.

Criterion 2 was the (c-)ACT improvement between baseline and the end of phase 2, and criterion 3 was the overall (c-)ACT score. The desired effect was a more considerable (c-)ACT improvement from the baseline to the end of phase 2 and a higher overall score at the end of phase 2. The (c-)ACT improved in both groups. Nevertheless, the control group performed a little better than the feedback group. This difference is even more remarkable because the control group already had higher baseline (c-)ACT scores than the feedback group, and therefore less improvement was expected.

Criteria 4 and 5 were about reversibility and demonstrated a very high percentage of completion of the clinical criteria for both groups. Clinical improvement of the reversibility was defined as a decrease in reversibility and thus overall lower reversibility. Both groups showed clinical improvement over time. Compared to the baseline, the reversibility of the feedback group showed overall more improvement during the entire study than the control. However, fewer patients started with a baseline reversibility of < 12% within the feedback group compared to the control group, so more improvement for criterion four was possible within the feedback group. When only considering phase 2, where the feedback was provided, the control group performed better than the feedback group, which is unexpected. For criterion 5, which stated a reversibility < 12%, the patients who already achieved the criterion at the baseline were not included in the analysis for criterion 5 (n = 4). Unfortunately, three out of four of these patients were in the control group, so only three patients were left within the control group for the analysis.

The last two criteria showed clinical improvement when the LFV decreased over time and displayed a lower percentage variability. At the end of the study, both groups showed an improvement of LFV compared to the baseline. The between-group analysis about the LFV during phase 2 showed an almost statistically significant difference ($p = 0.064$), where the LFV for the control group was lower than the variability within the feedback group. Nonetheless, the mixed model showed no difference between the two groups based on the trend seen with the time-by-group-interaction analysis. Therefore, at the end of the study, the control group had a lower LFV than the feedback group.

Clinical improvement

Over the entire length of the study, clinically relevant improvement based on the seven criteria could be seen in 87.5% of the children regardless of the allocated group. This overall improvement could signal a placebo effect, also known as the Hawthorne effect.[38] Monitoring medication intake precisely and frequently measuring clinical parameters would encourage patients to perform better over time. The results of this preliminary analysis are in

contrast with some literature. Morton et al.[22] and Dardouri et al.[39] proved in comparative studies significant improvement in clinical health outcomes for children due to digital interventions and education programs compared to a control group. However, the study size was significantly larger for these trials (n = 90, and n = 82). No other trials were found to evaluate a similar number of clinical parameters.

The original criterion for clinical improvement stated that if one or more of the seven criteria were completed by a patient, the patient's asthma control was considered clinically meaningful improved. The results of this preliminary analysis show that maintaining this criterion will not distinguish an accidental improvement over time from a genuine improvement or a clinically relevant improved patient provided with feedback from a patient in the control group. A consideration may be to specify the threshold per category. For example, one out of the four categories was a subjective measure and based on an asthma control questionnaire about the perception of the patient's asthma. The other three categories were based on objective lung function values, with one of these long function values based on spirometry outcomes measured at home and the other two categories measured in the hospital. For the evaluation of asthma control, both subjective, as well as objective assessments were essential.[7] One could consider defining a clinical improvement based on completing one subjective category and one objective category. Thus far, the data collected would give the following results: Within the feedback group, 62.5% will achieve this new threshold, and for the control group, the percentage would be 37.5% (Fisher's exact test, $p = 0.315$). This threshold seems to distinguish the two groups more considerably than the original criterion (87.5% clinical improvement for both groups).

However, some patients already fulfilled one of the criteria at baseline and correction was needed. To distinguish patients who already completed one of the criteria at baseline (either an ACT score ≥ 20 or reversibility < 12%), another recommendation would be to use a percentage of completion as the threshold of clinical improvement. Patients who achieved only one of these criteria may experience fewer asthma complaints than patients who score below the threshold for both criteria. The total number of assessed criteria will differ between these two types of patients. For example, a percentage of completing at least three criteria will include patients who fulfilled three out of six assessed criteria (50.0%) and three out of seven assessed criteria (42.9%). The outcome for this data-set will be that three patients (37.5%) completed this new threshold within the control group, whereas, within the feedback group, six patients (62.5%) completed this threshold. Again, more distinction is visible between the two groups.

Therapy adherence and inhalation technique

The secondary goal of this study was to analyse the therapy adherence and inhalation technique of these children and evaluate whether immediate smart feedback resulted in an improved inhalation technique and better therapy adherence compared to the group who received no feedback. Over time no significant difference was observed in therapy adherence and inhalation technique between the two groups. Additionally, no Hawthorne effect was observed for both groups. According to this effect, patients would also be more therapy adherent and pay more attention to the inhalation technique when they know they are observed. Therefore, some progress in adherence and a better technique was expected in both groups.

Over the entire length of the study, the adherence improved slightly for the feedback group, which is the desired effect. Whereas the adherence of the control group was stable during phases 1 and 2, and during phase 3, it decreased. This trend is also seen in Mosnaim et al.[40], an RCT with severely uncontrolled asthmatic adults, where the feedback group received electronic medication monitoring to track real-time usage. In this trial, the adherence showed no improvement compared to the baseline in the feedback group, but a decrease was seen in the control group.

The desirable outcome for the critical errors is to diminish the occurrence. Unfortunately, both groups showed an increase in critical errors, whereas the feedback group had a smaller incline than the control group. In contrast to these results, corresponding literature showed several trials that prove the effectiveness of providing education and feedback on correct inhaler usage to improve the children's inhalation technique.[16,28,29,39]

4.2 Implications of this study

Many children have uncontrolled asthma, which is frequently due to poor adherence or a lack of knowledge on inhalation techniques. In daily practice, the need for a solution is considerable since many paediatricians and nurses struggle with what to do with these uncontrolled asthmatic children. Research and development for e-health technologies are growing, and plenty of devices are already available. Nevertheless, literature is not consolidated around the most effective solution for children. This research contributes to this search to see whether this immediate smart feedback provided by this Respiro™ add-on device will affect paediatric asthma control. At this moment, these results show no signs of the effect of the provided feedback compared to no feedback. However, many children did improve clinically throughout the study regardless of the allocated group.

Education, training and feedback will always be essential steps for asthma control improvement. Nonetheless, actively including the guardians is equally essential.[18] A low level of knowledge about asthma and medication among the caregivers was three times more likely to result in low adherence than caregivers with the highest level of knowledge.[18] Unfortunately, paediatric asthma patients and their guardians tend to overestimate the level of asthma control, either by underestimating asthma severity or assuming that better control is impossible. The knowledge of parents concerning asthma management and asthma medication was linked to poor adherence.[19] Therefore, education for children and their guardians is highly essential in daily practice.

For implementation in daily practice, this generation of electronic monitoring devices offers significant advantages: the feedback provided in real-time, measured at home, gives more opportunity to influence behaviour. The Respiro™ device can provide clinicians and nurses with in-depth insights into their patient's records of adherence and inhalation technique. Therefore, it can be of great value when medication revision is necessary and unnecessary therapy set-ups could be prevented. Additionally, patients could gain more insight into their asthma management and medication intake. Because of the advantages for clinicians and the patients, this generation of e-health devices is favourable for patient engagement, asthma management, asthma education and shared decision making between the patients and the clinicians.

An essential strength of this study is the study design: the combination of the immediate smart feedback device on therapy adherence and inhalation technique and the measurement of clinical health outcomes to evaluate the degree of asthma control. Not much literature can be found using this combination; especially the multiple clinical improvement criteria are unique. All the clinical outcomes were measured several times or continuously, which provided a clear overview of the possible clinical improvement of the patients over time. More trials can be found concerning the adherence and inhalation technique among children, however not always combined with clinical improvement. Additionally, multiple trials with adults can be found to evaluate these aspects in a randomised controlled trial. However, more research on children was highly recommended in literature, and the IMAGINE-I study is a promising start. Another strength of the study design is the existence of multiple phases. This design started with a baseline period that could be used as a reference, followed by an RCT and subsequently a follow-up period. Observations and measurements in the baseline have high added value to monitor the current situation and provide insight. The randomised control trial can provide an understanding of the between-group effect. The follow-up period will show the lasting effect of the provided feedback in the RCT.

4.3 Limitations

The main limitation of this preliminary analysis was the small sample size, which impacted the reliability of these results. At this point, no statistical differences were found between the two groups over time. This outcome may be fair. However, due to the sample size calculation and the power of the study, more patients need to be included in the study to prove the potential added value of immediate smart feedback compared to a control group. The study's minimum required number of subjects to obtain significant results was calculated to be 62 patients. This calculation was based on an estimation of 10% asthma control improvement within the control group compared to 40% improvement within the feedback group. In this preliminary analysis, the percentage of clinical improvement within the control group was higher than 10% and closer to the effect seen in the feedback group.

Secondly, the Respiro™ devices and application had several limitations: the batteries were often empty, the provided feedback was limited, the application did not work correctly, and the application is only available for Android software. Most of these limitations were not noticed by the patients but could be optimised before usage in daily practice. The most considerable impediment for patients was to access the feedback portal frequently on a computer. Also, very young children do not have their own phones or computer. Therefore, the feedback through the application had to be watched together with an adult.

Thirdly, the lung function measurements at home had to be performed three times per session and two sessions a week. The best lung function out of the three attempts was reported. Practice showed that patients seem very ignorant towards this request. The lung function variability had to be based on the minimum and maximum lung function during a specific period, and the guides of the study's protocol stated that each patient had to have 32 values during the entire study. However, the average amount was 18 lung function tests per patient. This limitation of data occurred in more trials, whereas Morton et al.[22] suggested that a high rate of not fulfilling the protocol's rules can reflect the attitude of many patients and their families who did not necessarily consider asthma a significant condition. This suggestion is also acknowledged by Desager et al.[19], who stated that asthma control is often overestimated by underestimating asthma severity or by assuming that better control is not possible.

4.4 Recommendations

Based on the main findings and comparison with the literature, some recommendations can be made. The first recommendation concerns the inclusion rate. Thus far, a slow inclusion rate could be seen. Fewer inclusions may partly be due to the COVID-19 pandemic, which resulted in fewer physical activities and fewer patients' visits to the hospital. Another constraint of the low inclusion rate might be the inclusion criteria: Children aged between 6 and 18 years old who have uncontrolled asthma, despite Foster medication. Uncontrolled asthma is defined as (c)-ACT score lower than 20 and/ or reversibility equal to or higher than 12%. However, in Figure 3 can be seen that 22 out of 40 patients (55%) were excluded based on these inclusion criteria. This percentage was probably underestimated because of a lack of administration when patients were evaluated during multidisciplinary discussions. The asthma of 45% of these patients was not considered uncontrolled. In daily practice, when asthma is considered uncontrolled despite the use of Foster, the medication is often immediately altered or adjusted. When the patient's asthma was considered uncontrolled during multidisciplinary discussions by the physicians, assistants, and nurses, the medication was altered. However, after the medication switch, the ACT and reversibility did not show uncontrolled asthma anymore. The IMAGINE-I study aims to prevent early therapy step-ups; however, daily practice routines cannot be interrupted or changed easily. The inclusion of uncontrolled asthmatic children is problematic because of the patients' undesirable condition, and future studies should take this into account. Conversations with paediatricians and nurses are recommended to create awareness for this problem and continue the inclusions for the IMAGINE study faster.

Secondly, further research with more patients is needed to determine the actual effects of the provided feedback. An official interim analysis is needed after the inclusion of half of the desired number of participants to see whether the results will be similar between the groups as well. Additionally, evaluations of different clinical improvement thresholds could be explored when more data is available.

The last recommendation is about this assessment of clinically meaningful improvement. Clinical criteria seem to be used more often in literature. However, the current threshold of completion of only one out of seven criteria is too sensitive for natural fluctuations of lung function. Two alternative options were explained in section 4.1, which concerned completing specific categories or a percentage related to completing a specific number of criteria. Further research is needed to clarify what is expected by clinical improvement of asthma control by clinicians and nurses. In addition, evaluating the patient's perspective on their asthma improvement may also be valuable to include for this consideration.

5. CONCLUSION

This preliminary analysis demonstrated no significant difference in all outcome measures that were analysed to prove that providing immediate smart feedback to children improved the degree of their asthma control compared to the control group. However, most of the children showed clinically relevant improvement over the entire study duration despite the allocated group. The therapy adherence and inhalation technique showed no statistical difference between the groups as well, and only a minimal improvement towards better adherence and inhalation technique was seen in the feedback group compared to the control group.

This research clearly illustrated that some asthma control improved over time, but it also raised the question of the underlying reason for this improvement. Several recommendations can be evaluated for the continuation of the IMAGINE-I study. This research must be continued to increase the number of inclusions for more reliable results and perform a complete interim analysis. The analysis conducted for this preliminary study is helpful and accurate and is suitable for repetition. Additionally, the assessment of clinically meaningful improvement must be reconsidered regarding the distinction between the two groups and the expected effect size in combination with the expected participants that are needed.

Overall, these findings demonstrate the importance of research in the field of uncontrolled asthmatic children. Poor inhaler technique is common among children, and the effects of poor technique are broad. E-health feedback interventions have shown to be promising to improve clinical outcomes, adherence and inhalation technique. Such solutions can potentially improve the quality of life of children and eventually decrease morbidity and healthcare costs.

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APPENDIX

A.1 Clinical improvement

Table 6 shows the completion of the seven criteria for each patient separately. When the criterion was already fulfilled at the baseline (criteria 3 or 5), a NA is presented. When a patient has stopped during the study, a (-) is presented.

The two most completed criteria are criteria two and four, respectively an increased (c-)ACT score and a decreased reversibility. The majority of the children (n=10) improved equal to or larger than 9% on their reversibility and 50% improved at least 3 points on their (c-)ACT scores, both measured between the baseline and at the end of phase 2. Furthermore, in the last column of Table 6 can be seen that only two patients did not improve one of the seven criteria (completion of 0%). One of these patients stopped during phase 1 of the study and the other stopped during phase 2 of the study.

Table 6: An overview of the completion per criterion per subject.

Patient ID	RCT group	Age	Criterion 1 FEV_1 ≥ 10%	Criterion 2 (c-)ACT increase ≥ 3 points	Criterion 3 ACT ≥ 20 points	Criterion 4 Reversibility decrease ≥ 9%	Criterion 5 Reversibility < 12%	Criterion 6 LFV decrease ≥ 10%	Criterion 7 LFV ≤ 15%	Total completion per patient: n (%)
Subject01	Control	12		✓			NA			**1 (16.7)**
Subject02	Feedback	10		✓	✓	✓	NA	✓		**4 (66.7)**
Subject03	Feedback	6	✓	✓	✓	✓		✓		**5 (71.4)**
Subject04	Feedback	12	-	-	NA (-)	-	-			**0 (0.00)**
Subject05	Control	12	✓	✓					✓	**3 (42.9)**
Subject07	Control	8				✓	✓			**2 (28.6)**
Subject08	Control	12	✓	✓	✓	✓	✓			**5 (71.4)**
Subject09	Control	17				✓	NA			**1 (16.7)**
Subject10	Control	9	-	-	-	-	-	✓	✓	**2 (28.6)**
Subject11	Feedback	12	✓	✓		✓	✓	✓		**5 (71.4)**
Subject12	Feedback	10	✓		✓	✓	✓	✓		**5 (71.4)**
Subject13	Feedback	11			NA	✓	✓			**2 (33.3)**
Subject14	Control	8	✓	✓	✓	✓	NA	✓		**5 (83.3)**
Subject15	Feedback	10	✓							**1 (14.3)**
Subject16	Control	7	-	-	NA (-)	-	-	-	-	**0 (0.00)**
Subject17	Feedback	16		✓		✓	✓			**3 (42.9)**
Total completion per criterion:			**7**	**8**	**5**	**10**	**6**	**6**	**2**	

The criterion is fulfilled (✓), the criterion was already completed at the baseline measure (NA), or the patient could not fulfil the criteria because of loss to follow-up (-).

A.2 Therapy adherence and inhalation technique

Table 7 shows the percentages of therapy adherence per subject displayed per phase. Also, the percentages of inhalation technique errors are displayed per subject and per phase. The percentages of critical errors were used in the mixed model with repeated measures and included the PIF errors and duration errors. The non-critical error that was measured was the orientation errors.

Table 7: The percentage of therapy adherence and critical errors per patient and per phase.

Phase	RCT group	Age	Therapy adherence (%)			Inhalations with a critical error (%)			Inhalations with PIF errors (%)			Inhalations with duration errors (%)			Inhalations with orientation errors (%)		
			1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Subject01	Control	12	101.7	86.8	90.0	13.1	12.1	23.6	11.5	3.0	11.1	11.5	12.1	18.1	1.6	3.0	2.8
Subject02	Feedback	10	103.7	81.8	91.3	3.6	2.8	4.8	3.6	1.4	2.4	1.8	1.4	3.6	5.4	1.4	0.0
Subject03	Feedback	6	96.3	96.3	100.0	94.2	93.7	89.7	78.8	58.2	46.6	94.2	92.4	89.7	5.8	16.5	0.0
Subject04	Feedback	12	24.1	-	-	11.1	-	-	11.1	-	-	11.1	-	-	3.7	-	-
Subject05	Control	12	89.7	74.4	86.5	30.8	14.8	31.3	21.2	6.6	9.6	13.5	8.2	25.3	17.3	13.1	16.9
Subject07	Control	8	60.6	68.3	52.4	87.5	89.0	97.7	50.0	53.7	83.7	87.5	89.0	95.3	60.0	14.6	25.6
Subject08	Control	12	88.9	94.0	82.6	31.2	24.1	21.1	10.4	7.6	3.9	29.2	19.0	19.7	0.0	8.9	0.0
Subject09	Control	17	26.9	28.5	5.3	41.4	43.9	71.4	6.9	0.0	0.0	37.9	43.9	71.4	48.3	36.6	57.1
Subject10	Control	9	15.0	10.7	-	58.3	66.7	-	25.0	66.7	-	58.3	22.2	-	41.7	66.7	-
Subject11	Feedback	12	83.7	74.4	76.8	36.8	58.0	76.7	8.0	19.3	20.2	35.6	55.5	76.7	5.7	7.6	9.3
Subject12	Feedback	10	78.8	73.8	-	95.1	71.0	-	63.4	54.8	-	95.1	67.7	-	0.0	0.0	-
Subject13	Feedback	11	96.2	95.8	82.4	8.0	6.5	17.9	0.0	4.3	0.0	8.0	2.2	17.9	96.0	97.8	60.7
Subject14	Control	8	95.7	114.6	117.3	36.4	50.0	69.0	5.7	14.9	12.4	35.2	37.2	67.4	2.3	0.0	0.0
Subject15	Feedback	10	13.2	20.7	104.2	22.2	47.1	26.0	22.2	29.4	10.0	22.2	47.1	20.0	11.1	58.8	48.0
Subject16	Control	7	75.0	-	-	100.0	-	-	66.7	-	-	100.0	-	-	66.7	-	-
Subject17	Feedback	16	35.4	8.5	10.7	29.4	21.4	27.8	13.7	0.0	22.2	25.5	21.4	27.8	27.5	7.1	16.7

The completion of the threshold for good therapy adherence and good inhalation technique is displayed in Table 8. This table shows that good therapy adherence together with good inhalation technique was seen for only three or four patients: subjects 1, 2 and 13 during the entire study, and subject 8 only during phases 2 and 3. These patients were equally distributed between the control and feedback groups.

Table 8: Completion of good therapy adherence and limited critical errors during each phase for each patient.

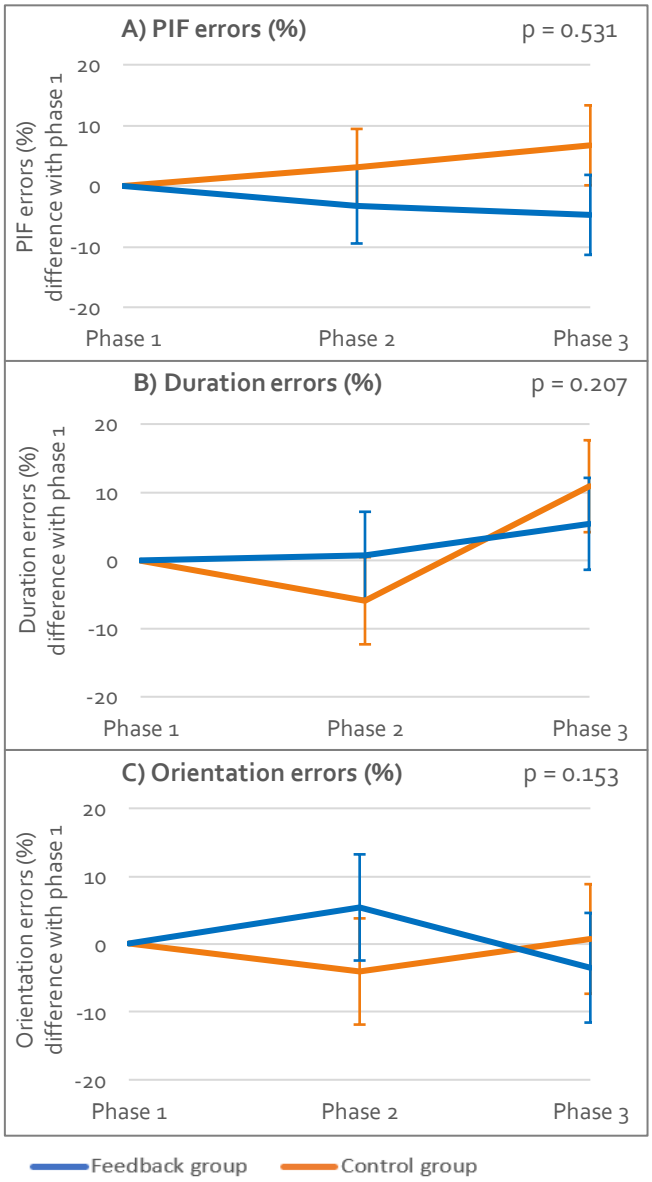
Patient ID	**RCT group**	**Therapy adherence ≥ 75%**			**Critical errors < 25%**		
		Phase 1	**Phase 2**	**Phase 3**	**Phase 1**	**Phase 2**	**Phase 3**
Subject01	Control	✓	✓	✓	✓	✓	✓
Subject02	Feedback	✓	✓	✓	✓	✓	✓
Subject03	Feedback	✓	✓	✓	x	x	x
Subject04	Feedback	x	-	-	✓	-	-
Subject05	Control	✓	x	✓	x	✓	x
Subject07	Control	x	x	x	x	x	x
Subject08	Control	✓	✓	✓	x	✓	✓
Subject09	Control	x	x	x	x	x	x
Subject10	Control	x	x	-	x	x	-
Subject11	Feedback	✓	x	✓	x	x	x
Subject12	Feedback	✓	x	-	x	x	-
Subject13	Feedback	✓	✓	✓	✓	✓	✓
Subject14	Control	✓	✓	✓	x	x	x
Subject15	Feedback	x	x	✓	✓	x	x
Subject16	Control	✓	-	-	x	-	-
Subject17	Feedback	x	x	x	x	✓	x
Number of patients with completion of the criteria n (%)		10 (62.5)	6 (42.9)	9 (75.0)	5 (31.3)	6 (42.9)	4 (33.3)

A.3 In-depth analysis of inhalation errors

A mixed model analyses with repeated measures is performed for the percentage of PIF errors, duration errors, and orientation errors. Baseline values measured during phase 1 are presented in Table 9, and these values were subtracted from the follow-up values to obtain normally distributed values. Results are displayed, and interpretations are discussed in this Appendix.

Table 9: Characteristics of phase 1 for inhalation technique parameters. Data are presented as mean ± standard deviation (SD) unless otherwise stated.

Percentage (%) of inhalations with errors during phase 1	**Control group (n=8)**	**Feedback group (n=8)**
PIF errors	24.6 (± 7.87)	25.1 (± 10.4)
Duration errors	46.6 (± 11.6)	36.7 (± 13.2)
Orientation errors	29.7 (± 9.77)	19.4 (± 11.3)



In Figure 7, three graphs are shown. The mean percentage of PIF errors was similar for both groups in phase 1 (Table 9). The percentage of PIF errors decreased during phases 2 and 3 for the feedback group and increased during these phases for the control group (Figure 7A). Fewer PIF errors are seen over time for the feedback group compared to the control group.

The mean percentage of duration errors was slightly higher for the control group than the feedback group in phase 1 (Table 9). In Figure 7B, an increase in the percentage of duration errors is seen in phase 3 for both groups. The percentage of duration errors started higher for the control group at the baseline and decreased during phase 2, whereas a large increase is seen during phase 3. In the end, the feedback group had the slightest incline in duration errors.

In addition, the non-critical error occurrence, the inhalator's orientation errors (%), was evaluated. The percentage of orientation errors in the control group is higher than the feedback group at baseline (Table 9). In the end, the feedback group showed a small decrease in orientation errors, and the control group stayed constant, as can be seen in Figure 7C. However, these effects differ too little in percentages to conclude something at this point.

Figure 7: The time-by-group-interaction of the mean change with reference to phase 1: the percentage of PIF errors (A), duration errors (B) and orientation errors (C) displayed per group over the time.