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IMAGINE I

IMPROVING ADHERENCE BY GUIDING INHALATION VIA ELECTRONIC MONITORING

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PREFACE

I am happy to finally present you my master thesis: “Improving adherence by guiding inhalation via electronic monitoring in children” or IMAGINE I in short. This thesis is written to obtain my Master of Science degree in Health Sciences at the University of Twente and represents the work I have performed in the period between February 2019 and November 2019.

The initial idea for this project had originated before my arrival in the MST. But the idea of providing feedback to improve asthma control and a short protocol was all there was when I started. I was entrusted to transform this conceptual idea to its current state, a project actively working on inclusions and in which first data has been collected. So far, 1 patient has been included in the study with more soon to follow.

My work started off with the preparation of the study in the form of an application for the Medical Ethical Committee Twente. This approval was obtained after some adjustments to the first version. After approval by the Medical Ethical Committee more processes in Medisch Spectrum Twente were initiated and, while this resulted in a long process introducing new spirometers and add-ons to the hospital, I truly learned a lot, more than I could have ever expected beforehand, about the organisations and structures within Medisch Spectrum Twente regarding both scientific research and introduction of medical devices into a hospital. I was able to meet a lot of different persons with their different roles in this process. Finally, I learned a lot about asthma and treatment of asthma. I hope my work can contribute to optimising the asthma care for children in the future and I hope my future work can contribute to improving healthcare as well.

I hope you will enjoy reading this thesis as much as I had during the entire process.

Martijn Oude Wolcherink

ACKNOWLEDGEMENTS

The work in front of you could not have been made without the help of many other people. I would like to express a big 'thank you' to all those specific people and groups.

First of all, to the children who showed interest in participating in the study and visited MST for inclusion. An example many others will hopefully follow soon. Unfortunately, not all of you could be included in the end due to various reasons, but a lack of enthusiasm or willingness to participate was certainly not one of them.

Prof. dr. Job van der Palen, from the start onwards you have been one of the most inspiring persons I ever met. I did not know you at the moment I chose this project for my master thesis, but I am happy that I got to know you during this project. No matter how full your schedule appeared to be, when I needed some advice or counselling, you always found a moment to address my problems and concerns. I really enjoyed your constructive feedback on matters within and without the scope of this project and your immense drive to perform research for novel innovations that could improve healthcare even further. With your help, I got the opportunity to develop new skills in other projects, with new research teams and the possibility to orientate myself in other fields of science within healthcare as well.

Dr. Anke Lenferink, you were the person representing this project during the master thesis market and you managed to motivate me to choose this amazing project. While you were not as directly involved in this project as some others, you were always there to help out from a distance. This also allowed you to have a bit of a different perspective on the project as we had, since we were all fully soaked into all the information of the project and sometimes losing the bigger picture as a result. Your elaborated feedback and clear advice was always much appreciated and I am certain that this improved the quality of the protocol article we wrote a lot!

Drs. Esther Sportel, my project is just a small part of your PhD track, but you always managed to revise all the many documents I had to make to obtain METC approval and we even managed to write a protocol article together. I learned a lot from our conversations and I think by now all other hospital pharmacist know me as well due to the multiple visits I had to make to the hospital pharmacy, because of all the documents that needed to be signed by you. You were always very supportive and you made me always feel that my work was appreciated.

Dr. Marjolein Brusse-Keizer, I have to admit that at the start of this study, I did not know a lot about power analyses and randomization. Luckily for me, you were there to help me out with these measurements and made sure they were performed according to protocol. You also gave me a lot of helpful and constructive feedback on my work, so that I could develop myself even better. Furthermore, I enjoyed your stories about all the new things your children tried out at home and I am definitely going to try creating chocolate bowls by using balloons myself one day!

Dr. Boony Thio, the welcome you gave me during my first day was a typical representation of who you are: enthusiastic, warm and perhaps just very slightly delayed. The door was always open for questions or discussions and you always had some good advice to spare. Your enthusiasm for curing children was only matched by your enthusiasm for football. Although, sometimes you were a bit hard to track, as a colleague of yours described you once and creative searching was now and then required to find you

to discuss new changes to the protocol. However, this was also one of your charms and I really learned a lot from your clinical experience and your insights were of vital importance for this study.

All participants of the scientific meetings of the pulmonology department every Tuesday, during these meetings we always discussed many different projects. Some weeks were more attended than other weeks, but I could always express my problems or share my experiences. I noticed that doing research undeniably means things go wrong. However, it was truly motivating that everybody was thinking along with my struggles helping to find solutions. Besides, I really enjoyed hearing about all those different project within MST and these meetings have always been a source of inspiration.

My research colleagues at the paediatric department in MST, you guys always made sure we had a great working environment. You also always had ideas to solve my problems or gave me some good advice in general. In between long periods of hard work, I always much appreciated the games of table football to blow off some steam. The weekly trips to the market on Tuesday were also a much welcomed change from the walls of our “technical medicine” room.

Laura, I am fully aware that I have not always been the nicest person while being stressed and preoccupied with working on my thesis amongst other things. However, you always unfailingly supported me and kept believing in me no matter what. This surely kept me going and made me performing to the best of my ability. I am sure that all of this would not have been possible without you!

Finally, mom, dad, No matter what I decided to do next, from my bachelor of Technical Medicine to an exchange for 6 months to the northern part of Sweden and from the master of Technical Medicine to Health Sciences, you always kept supporting me unconditionally. I know I am not very good in showing my appreciation for everything you both do for me, but I am really grateful and I hope I will make you both proud when I will be finally graduating!

ABSTRACT

Background

Many asthmatic children suffer from uncontrolled asthma with frequent exacerbations, despite an optimal treatment plan using inhalation medication. Studies have shown that therapy adherence and inhalation technique are suboptimal in asthmatic children, but these have traditionally been hard to measure. A novel device functioning as add-on to the inhaler has been developed to measure both aspects by recording vibration patterns during inhalation. This data on therapy adherence and inhalation technique could be converted to immediate smart feedback on intake of inhalation medication and provided to patients immediately via a mobile application.

The aim of this study is to improve asthma control in children between 6 and 18 years old by providing immediate smart feedback on intake of inhalation medication. Asthma control will be measured by Forced Expiratory Volume in 1 second, (Childhood) Asthma Control Test ((c-)ACT) score, and lung function variability (LFV) and reversibility. The aim of this thesis is to give insight in the design and progress of the IMAGINE I study. This will be done by a thorough description of the study protocol and by a case-report of one patient during the first phase of the study.

Methods

The study will be performed in Medisch Spectrum Twente (Enschede, the Netherlands). The goal is to include 68 asthmatic children between 6 and 18 years old who receive inhalation medication through the Nexthaler®, Ellipta® or Spiromax®. The study consists of *three phases. Phase one is observational and will last 4 weeks to observe baseline adherence and inhalation technique as monitored by the add-on device. A randomised controlled trial lasting 6 weeks will be performed in phase 2. Patients in the intervention group will receive immediate smart feedback about performed inhalations via a mobile application. In the control group, adherence and inhalation technique will be monitored, but patients will not receive feedback. In phase 3, also lasting 6 weeks, the feedback will be ceased for all children and revision of current therapy may occur, depending on findings in phase 2. Asthma control be assessed by means of spirometry (both at home and in the hospital) and (c-)ACT questionnaires. In this thesis, the results of a single subject will be described to obtain better insights in the process of this study.*

Results

Baseline values of subject 1 were determined at the start of and during phase 1. The baseline FEV1 was 2.37 litre, reversibility after intake of inhalation medication was 5.06%, the ACT-score was 15 and the LFV was 8.89%. Therapy adherence was 80% during the first week and remained more or less consistent during the first three weeks. However, it increased to 100% in week 4. No clear trend can be seen with regard to inhalation technique, as the duration of intake of inhalation medication was decreasing slightly over time, while the peak inspiratory flow was increasing slightly over time.

Conclusion

Data on therapy adherence and inhalation technique was adequately collected using an add-on device. Furthermore, data on asthma control was consistently obtained by using a home-based handheld spirometer. Therefore, both devices seem sufficient to monitor all parameters of interest in this subject. The add-on device looks like a helpful tool to provide paediatricians with objective information about hard to measure aspects as therapy adherence based on data of a single patient. However, elaborated upcoming studies with larger patient populations should prove this statement. Providing immediate smart feedback has the potential to improve asthma control by changing patients' behaviour and awareness, but analyses at the end of this study should confirm that statement.

ABBREVIATION LIST

(c-)ACT	(Childhood) asthma control test
IMAGINE	Improving adherence by guiding inhalation via electronic monitoring
FEV_1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
IC	Informed consent
IQR	Interquartile range
LABA	Long-acting beta-adrenoreceptor antagonist
LFV	Lung function variability
MMRMA	Mixed model repeated measurements analysis
MST	Medisch Spectrum Twente
NTR	Netherlands trial register
OCON	Orthopedisch centrum Oost-Nederland
PIF	Peak inspiratory flow
RCT	Randomised controlled trial
SABA	Short-acting beta-adrenoreceptor antagonist
SD	Standard deviation
ZGT	Ziekenhuisgroep Twente

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INTRODUCTION

Asthma is a common chronic condition in children, characterised by airflow limitation.[1] Based on Dutch statistics of 2017[2], 641,000 patients were reported with asthma related symptoms by the general practitioner of which 269,700 were children. The total costs for asthma in the Netherlands in 2015 amounted up to 422 million euros.[3] A large percentage (38.1%) of these costs was spent on medication for treatment of asthma, accounting for 160.1 million euros. The medication used to relieve symptoms of asthma consists of short-acting beta-adrenoreceptor antagonist (SABA), long-acting beta-adrenoreceptor antagonist (LABA), inhaled corticosteroids, or a combination between LABAs and inhaled corticosteroids.[4,5] Despite all available (combinations of) medication for treatment, multiple sources claim the percentage of children still suffering from uncontrolled asthma with frequent exacerbations ranges from 46% to over 60%.[6–10]

Recent developments have paved the way for the use of targeted biologics in children suffering from uncontrolled asthma despite optimal treatment.[11] In asthma, the biological drugs suppress the hypersensitive reactions of the body to antibodies, which are generated in response to allergens. Before adding expensive therapy such as targeted biologics,[12] clinicians should always assess therapy adherence and inhalation technique first to distinguish children with poor technique and adherence from children with uncontrolled asthma despite optimal treatment.[10] This assessment is important, as poor therapy adherence and inhalation technique result in high avoidable healthcare expenses, since effective treatment may wrongly be regarded as ineffective and futile use of expensive diagnostics or step-up therapy may be ordered.[9] Poor therapy adherence and inhalation technique of subjects, participating in medicinal studies regarding efficacy of treatment and dose-response relationships, may also cause the study results to underestimate the actual effect of medicinal product. In many prior studies, adherence to inhalers has been reported as suboptimal[13], where on average close to 50% of asthmatic children are considered non-adherent.[14–16] In addition, it has been recognised that inhaler technique is poor among these children, which means a clinical response may not be achieved even though the number of drug intakes were conform prescription and at the appropriate time.[17] A Dutch study[18] emphasises the long-term effect of therapy adherence on asthma control by stating that therapy adherence can be seen as a strong independent predictor for asthma control. Therefore, optimal management of asthma in children requires more focus on monitoring of therapy adherence and inhalation technique and providing stimulation to patients to improve both aspects. The Global Initiative for Asthma (GINA) guidelines[10] also advocate paediatricians to optimise both therapy adherence and inhalation technique before considering step-up therapy in children with uncontrolled asthma.

So far, no reliable real-time techniques for monitoring therapy adherence and inhalation technique have been established.[19] Multiple studies have been performed to provide paediatricians with tools for reliable assessment of these aspects. Techniques most often mentioned in literature to measure therapy adherence include patient self-report and pharmacy refill records.[7,9] However, these techniques are often unreliable, as self-reporting of therapy adherence is subject to both recall and social desirability bias, inaccurate recalling of the actual adherence, and reporting generalised behaviour rather than particular events.[9] Moreover, pharmacy refill records only provide information on the collection of prescriptions and this does not necessarily have to correlate with patients' actual drug use. Therefore, both methods probably overestimate therapy adherence. Assessment of inhalation technique only occurs during outpatient visits by impressions of the paediatrician and no clear insights can be obtained from inhalation technique in the home situation.[20,21] The development of electronic monitors, such as the dose counters (Doser®, Hailee™ or Herotracker®) tracking the time

and date a dose was taken, offers the possibility of measuring therapy adherence objectively in asthmatic patients.[15] However, most electronic monitors only report on adherence and lack assessment of inhalation technique.[15,22] Furthermore, they are prone to dose dumping where patients deliberately spill the inhalation medication in the air to pretend being therapy adherent.[23,24] Finally, they are more expensive than the previously mentioned alternatives, while showing only minor benefits. Only recently, inhalation technique and therapy adherence gained more attention resulting in a study using the Inhaler Compliance Assessment (INCA) device.[25] This was the first study that focussed on collecting data on both therapy adherence and inhalation technique. However, this device was limited to retrospective feedback only, since the data first needed to be processed in the hospital before it could be converted to feedback.

Currently, AMIKO (London, United Kingdom) has developed a new add-on device, Respiro™, which assesses adherence and inhalation technique by recording vibration patterns associated with inhaler use. Analysis of these vibration patterns allows critical technique errors to be identified, in particular failing to reach sufficient inspiratory peak flow and insufficient inhalation duration as well as other non-critical errors. The vibration features can precisely assess the amount of medication that is inhaled by the user. In addition to providing an assessment of the proficiency of use, analysis of the recorded files provides information on the time of use per inhalation and the interval between doses. Through a mobile application called 'Respiro Mobile', immediate smart feedback on inhalation technique and therapy adherence, in detail on orientation of inhaler, time and date of inhalation, peak flow, duration of inhalation, and inhalation volume, could be provided to the user by a mobile application.

The use of such an additional add-on device could greatly contribute to the development of optimal treatment plans for children suffering from uncontrolled asthma. No previous study in children has been performed with the use of immediate smart feedback on intake of inhalation medication with regard to both inhalation technique and therapy adherence, and therefore new insights on this intake could be obtained by providing patients with immediate smart feedback. An earlier performed study in which therapy adherence and inhalation technique was measured has been performed in adults with stage 3 to 5 asthma according to GINA[10] and this showed great improvement in therapy adherence.[25] However, in this study feedback could only be provided in retrospect to participants, since data needed to be processed first in the hospital. Therefore, by providing immediate smart feedback, the Respiro™ add-on has even more potential to increase therapy adherence and inhalation technique. The aim of this study is to improve asthma control in children suffering from uncontrolled asthma by providing immediate smart feedback on intake of inhalation medication.

The aim of this thesis is to give insight in the design and progress of the IMAGINE I study. This will be done by a thorough description of the study protocol and by a case-report of one patient during the first phase of the study. Firstly, the design of the study will be elaborated in the *Method* section and discussed in the *Discussion* section. Thereafter, a case of an individual participant will be described during phase 1 in the *Result* section and a discussion of these results will be given in the *Discussion* section. The *Discussion* will therefore be divided into two subsections: the result subsection and the design subsection.

METHODS

STUDY POPULATION

Children suffering from uncontrolled asthma are being asked to participate in this study and they either performed spirometry at most 6 months prior to the study or they are already scheduled for one. Asthma is considered to be uncontrolled when the (Childhood) Asthma Control Test ((c-)ACT) score is <20 and/or the lung function reversibility in response to a short-acting bronchodilator is ≥12%.

INCLUSION AND EXCLUSION CRITERIA

All subjects are required to be between 6 and 18 years old and they should be all outpatients in either Medisch Spectrum Twente (MST) in Enschede (the Netherlands) or in Ziekenhuisgroep Twente (ZGT) in Hengelo or Almelo (the Netherlands), both large teaching hospitals. Furthermore, they need to suffer from uncontrolled asthma, i.e. they need to have a (c-)ACT score of <20 and/or a lung function reversibility in response to inhalation medication of ≥12%. Children are unable to participate in the study if their inhalation medication cannot be distributed by either the Nexthaler®, Ellipta® or Spiromax®, because the Respiro™ add-on is only compatible with this selection of inhalers thus far. Switching between dose aerosol and dry powder inhaler device is allowed, as the medication remains the same. Patients should use this device at least a month before being included in the study. Moreover, children are excluded, if they, or parents from children below 12 years old, are unable to speak or understand Dutch. Children are also excluded if they suffer from a chronic disease other than asthma, which can potentially affect lung function.

RECRUITMENT

Recruitment started from the first of October 2019 and will continue until the first of September 2021 in both MST and ZGT. However, the study will be entirely performed in MST meaning patients from ZGT need to travel to MST for study-related activities. All subjects and parents of subjects under 16 are informed about the study prior to inclusion via a brochure. Furthermore, a short overview of the study will be given during (regular) appointments by either the paediatrician or a researcher. If patients are interested in participating, a physical appointment will be scheduled for inclusion. During this inclusion visit, the subject will be provided with two devices, a handheld spirometer (Air Next, NuvoAir, Stockholm, Sweden) and an add-on device (Respiro™, AMIKO, London, United Kingdom), and with instructions to use them. Written informed consent (IC) forms will be signed and collected by the researchers before inclusion. If subjects are under 12 years of age, both parents or their guardian(s) need to sign the IC. In case subjects are between 12 and 16 years old, both the children and both parents or guardian(s) need to sign the IC. If children are older than 16, they are allowed to sign themselves. Data of patients will be encoded in order of inclusion. Subjects and/or parents can always withdraw their permission during the study and their data collection will be terminated. Data collected before withdrawal of permission can be used in analyses as stated in the patient information letter.

STUDY DESIGN

To assess the effect of feedback on therapy adherence and inhalation technique on asthma control, a multi-phase study was set up in which phase 1 and 3 are considered observational and phase 2 pertains to a randomised controlled trial (RCT). The randomisation groups of phase 2 will persist in phase 3, but no new randomisation will be performed. The parameters which will be measured during the study include forced expiratory volume in 1 second (FEV1), lung function variability (LFV) and the (c-)ACT score. An overview of the study phases including parameter measurements is shown in Figure 1.

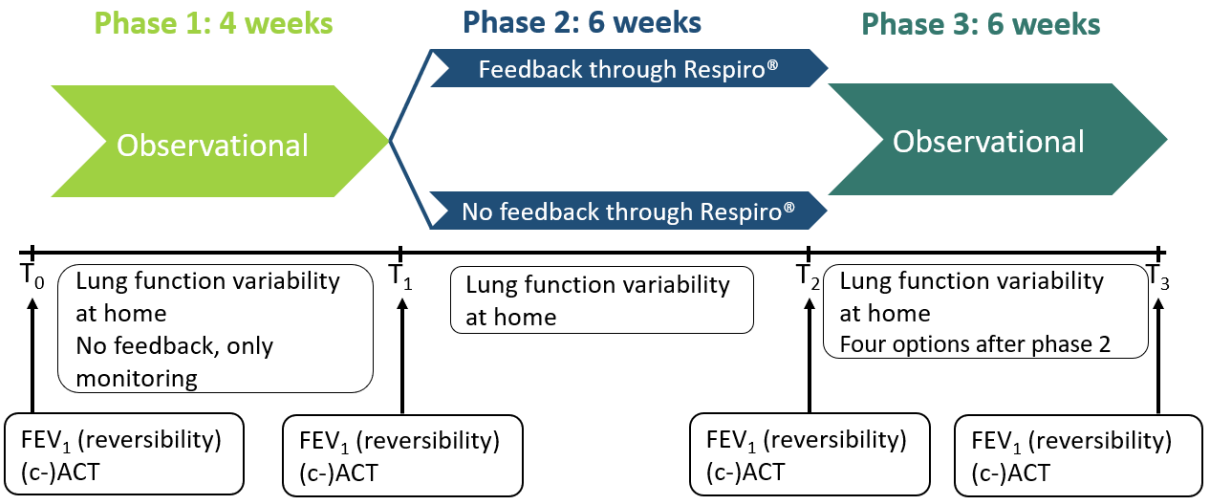

FIGURE 1: OVERVIEW OF THE THREE PHASES INCLUDING THE PARAMETERS WHICH WILL BE ASSESSED AT CERTAIN TIMES OR DURING CERTAIN PERIODS. T0 IS THE START OF PHASE 1, T1 IS THE END OF PHASE 1, T2 IS THE END OF PHASE 2 AND T3 IS THE END OF PHASE 3.

All subjects will receive a handheld spirometer during the first appointment on which subjects will be instructed to perform spirometry at home twice per week at a fixed time during the entire study. Additionally, subjects will receive an add-on device attached to their inhaler. This add-on device will monitor therapy adherence and inhalation technique during all three phases. During the first appointment baseline measurements will also be performed. Subjects are beforehand instructed not to use any long-acting medication (such as Foster) for 24 hours prior to the appointment and no SABA was used up to 12 hours prior to the appointment, since this could (positively) affect those baseline measurements. After the first observational period (phase 1), patients will be randomised into one of two groups at the start of phase 2. In the intervention group, the add-on device will provide the asthmatic child with immediate smart feedback about performed inhalations, while retaining its monitoring function for researcher observations. Immediate smart feedback can be described as feedback which is can provided to patients via a mobile application immediately after intake of inhalation medication and based on whether (critical) errors were made during that particular inhalation. The control group will not receive such feedback and the add-on device will only fulfil a real-time monitoring function. Besides feedback, both groups will receive treatment according to standard care.

After phase 2, an observational follow-up period of 6 weeks (phase 3) will be initiated to determine any differences in therapy adherence and inhalation technique between the intervention and control group. Treatment during phase 3 is depending on previous therapy adherence and asthma control, as shown in Figure 2. None of the subjects will receive feedback anymore during this phase, while the add-on device will retain its real-time monitoring function in all groups. Medication prescription for all subjects will be evaluated depending on asthma control and a combination of therapy adherence and inhalation technique by the paediatrician according to standard care, and in accordance with the GINA recommendations.[10] Subjects with both poor asthma control and poor adherence and inhalation technique will receive another evaluation for medication change, and/or repeated inhalation instructions by the paediatrician, while for others step-up or step-down therapy specifically may be considered.

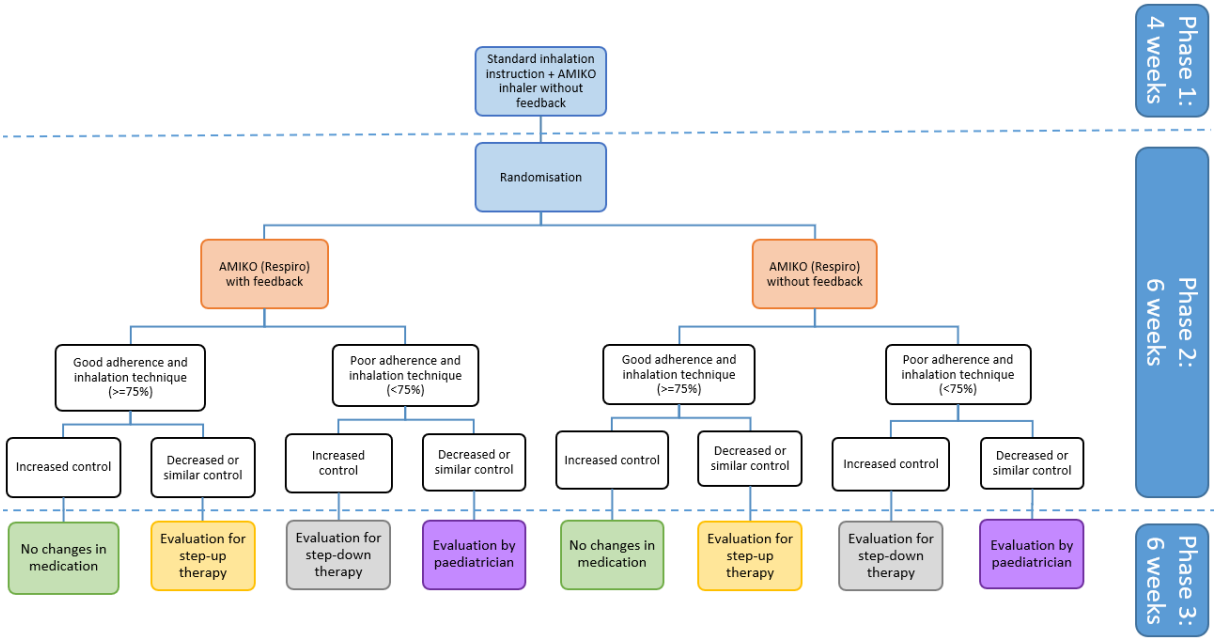

FIGURE 2: OVERVIEW OF DIFFERENT STUDY GROUPS WHICH WILL BE FORMED DURING ALL PHASES. THE DOTTED LINES REPRESENT THE TRANSITION BETWEEN PHASES

When the asthma control of any subject deteriorates rapidly in a short amount of time visualised as a strong decline in FEV1, the paediatrician was contacted by the researchers and the standard protocol of MST will be followed with regard to treatment. Continuing participation in the study will then be evaluated by the paediatrician and discussed with the subject, including his or her parents/guardians in the process.

PRIMARY OUTCOMES

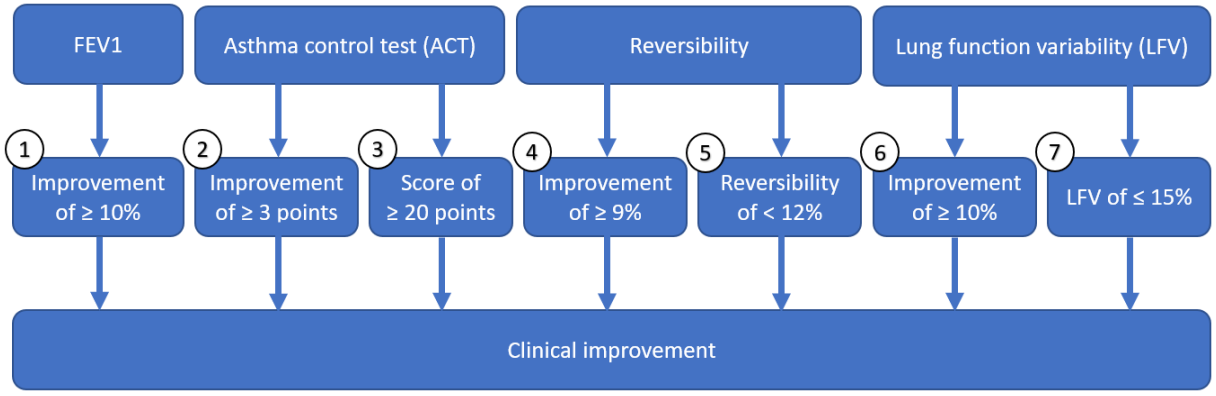

FIGURE 3: OVERVIEW OF THE SUB PARAMETERS THAT DETERMINE IF CLINICAL IMPROVEMENT HAS OCCURRED.

The primary outcome of this study, measured at the end of phase 2, is asthma control. If one or more of the following seven criteria are fulfilled, the patient will be deemed to have clinically improved in asthma control. An overview can be seen in Figure 3. The seven criteria are: (1) relative improvement of FEV_1 of ≥10%, compared to baseline measured at the start of phase 1[26], (2) absolute increase in (c-)ACT score of ≥3 points compared to baseline (c-)ACT score measured at the start of phase 1[27], (3) absolute (c-)ACT score of ≥20, (4) relative decrease in reversibility of ≥9% compared to baseline reversibility measured at the start of phase 1, (5) absolute reversibility of <12% after administration of salbutamol[10], (6) a decrease in lung function variability (LFV) of ≥10% compared to the LFV of phase 1, (7) absolute LFV of ≤15% measured during the entire phase 2.

SECONDARY OUTCOMES

Secondary outcomes include therapy adherence and inhalation technique. Subjects are considered to be adherent if they take as many inhalations during the day as prescribed, i.e. once or twice daily. The exact time of the inhalation does not matter for calculation of therapy adherence. Therefore, adherence can be calculated by actual medication intake divided by the prescribed intake per day. The sum of all percentages will be taken and divided by the number of days adherence is assessed. Besides the often used cut-off of 75% for good adherence, therapy adherence will also be studied in more detail. Next to the dichotomous way of measuring adherence, patients will also be classified as underusers (<50%), suboptimal users (50-<75%), optimal users (75-125%), and overusers (>125%) based on adherence rates.[28] Furthermore, inhalation technique is assessed through two critical errors: peak inspiratory flow (PIF) lower than 30 L/min[29], and inhalations of less than 1 second.[30] For the transition between phase 2 and 3, the cut-off range for adherence and inhalation technique is set at 75%, i.e. 75% of all inhalations should be at the appropriate date without critical errors to be considered acceptable. Non-critical parameters as orientation, opening and loading of the inhaler will also be assessed, where orientation is regarded as poor if the device deviates more than 45 degrees from the optimal position (90 degrees is optimal, so between 45 and 135 degrees is considered acceptable).

MEASUREMENTS OF PARAMETERS

At the start of phase 1, demographics and use of nasal corticosteroids will be retrieved from the electronic health record or they will be asked during the first meeting. Moreover, reversibility in response to inhalation medication will be determined by spirometry. In case reversibility was already determined in the 6 months prior to the start, no new measurement has to be performed and the earlier measured value will be used as baseline. Moreover, the (c-)ACT score will be determined for each subject at the start of phase 1. Both reversibility and (c-)ACT score are regarded as baseline measurements to determine asthma control at the start.

After the initial measurements of the first visit, participants will be provided with the Respiro™ add-on device and the Air Next spirometer. The Respiro™ add-on will be attached to the inhaler of the subject until the end of the study and will measure the PIF, duration of the inhalation, orientation, 'opening and loading of the inhaler', and the date and time of the inhalation. Participants are instructed to perform spirometry at home twice a week at a fixed time. The spirometry data including the FEV_1 will be assessed during the entire study and the LFV will be determined according to equation 1. The LFV of phase 1 will be regarded as baseline LFV.

$$LFV = 100\% - \frac{MIN(FEV1\ in\ phase\ x)}{MAX(FEV1\ in\ phase\ x)} \times 100\% \quad \textbf{(1)}$$

At the end of each phase, spirometry will be performed in the hospital to assess FEV_1 and this value will be compared to baseline. After initial measurement salbutamol is administered and after waiting for 5 minutes another spirometry will be performed to determine the reversibility. Participants, and parent(s) or guardian(s) of participants between 6-11 years old, will also be asked to complete the (c-)ACT questionnaire to determine their ACT score. Finally, data collected by the add-on will be used to determine therapy adherence and inhalation technique over an entire phase.

An overview of the moments of measurement for all parameters is presented in table 1. Data to calculate the LFV will be collected during phases 1, 2 and 3, but final values will be determined at the end of every phase.

TABLE 1: AN OVERVIEW OF ALL PARAMETERS INCLUDING THE MOMENT OF MEASUREMENT AND THE REPORTER OF INFORMATION

	Start phase 1	*End phase 1*	*End phase 2*	*End Phase 3*	*Reported by*
Demographics	X				Researcher
Nasal corticosteroids	X				Researcher
FEV_1[a]	X	X	X	X	Researcher
FEV_1 reversibility	X	X	X	X	Researcher
(c-)ACT[b]	X	X	X	X	Patient
LFV[c]	→	X	X	X	Patient
Therapy adherence		X	X	X	Researcher
Inhalation technique		X	X	X	Researcher

[a] *FEV_1 = forced expiratory volume in 1 second*
[b] *(c-)ACT = (childhood) asthma control test*
[c] *LFV = lung function variability*

RANDOMISATION

Before phase 2, a 1:1 blocked, stratified randomisation[31] will be performed by an independent person selected by the researcher. The program Block Stratified Randomization by Piantadosi[32] was used to create a randomisation list and a block size of 4 was used. Randomisation will be stratified on age (≥12 years of age vs. <12) and use of nasal corticosteroids (usage vs non-usage). Stratification for nasal corticosteroids will be done, as this medication could affect asthma control.[33] One group will receive immediate smart feedback during phase 2 via a mobile application connected to the Respiro™ device, while the other group will only be real-time monitored by the device.

BLINDING

Because of the nature of the intervention blinding of patients and staff to classification of groups was not be possible.

SAMPLE SIZE CALCULATION

The number of subjects required for this study was determined by performing a two independent proportions power calculation and the two sided Z-test was used as test statistic. The proportion of patients with improvement of asthma control was expected to be 10% in the control group and 40% in the intervention group. Since these proportions were just rough estimates, due to missing literature on the effect of feedback on asthma control to base these estimates on, an interim analysis according to the O'brien-Fleming approach[34] will be performed (target alpha at the final analysis equals 0.0492) when half of the desired number of participants of this study has completed the second phase. If the effect of immediate smart feedback turns out to be 10% or less compared to the control group, the trial should be stopped for futility and if the effect exceeds the expectation (significant difference with $p<0.0054$ according to O'brien and Fleming), inclusion should be stopped. Patients who are already included in the study will continue the study until they went through all phases. Furthermore, the power is set to 80%. This sample size analysis was performed with PASS (PASS 11, NCSS Statistical Software) and showed the requirement of a minimum of 62 subjects to obtain significant results. To compensate for potential drop-outs, a small buffer of 10% was created and therefore the aim is to recruit 68 patients for this study. The buffer is relative low based on historical dropout rates.

STATISTICAL ANALYSIS

Baseline characteristics will be displayed as means with standard deviations (SD) or medians with interquartile range (IQR) for continuous variables depending on the distribution of the variable; categorical variables will be displayed as counts with corresponding percentages. Differences in baseline characteristics between the two groups in terms of continuous variables will be tested by the independent T-test or the Wilcoxon rank sum test, depending on the distribution of the variable. Differences in categorical variables will be tested by the Chi-square test or the Fisher exact test.

For the between-group comparison of the number of patients who clinically improved in asthma control, the Chi-square test will be used.[35] Continuous variables over time, such as FEV_1 and (c-)ACT-scores changing over the 3 phases, will be analysed via a mixed model repeated measurements analysis (MMRMA). The advantage of this method is that incidental missing data can be estimated by patterns of other participants.[32] Moreover, the data in this study will be collected in multiple phases leading to more than two measurements per patient. MMRMA is well-suited to analyse multiple measurements at once and determining trends in these measurements.[36,37] Data will be analysed with SPSS (IBM SPSS statistics 25, Armonk, New York, United States of America). P-values of ≤ 0.0492 are deemed statistically significant for the primary outcome. P-values of ≤ 0.05 are deemed statistically significant for secondary outcomes.

One interim analysis will be performed after half of the required patients finished phase 2. The power in the power analysis was adjusted for this single interim analysis. The interim analysis will be performed to assess the effect of feedback on inhalation of medication in an early stage. This is desired, since the effect is estimated in the two-sided Z-test and an interim analysis allows the opportunity to perform slight modifications to population size or design, or termination due to effectiveness or futility, if the effect does not correlate with original estimations.[38]

RESULTS

PRIMARY OUTCOMES

In this section primary and secondary outcomes of a single subject (subject 1) during phase 1 will be shown for a period of 26 days in order to increase comprehension of the IMAGINE I study. Subject 1 was screened during a visit to orthopedisch centrum Oost-Nederland (OCON) in Hengelo at the 22nd of September with a decrease in FEV1 of 25% during an exercise challenge test being fully reversible after salbutamol. During his control appointment at the 25th, subject 1 was informed about the IMAGINE I study and a patient information brochure was provided. After a week, contact with the parents of subject 1 was initiated by the researchers via the telephone to find out if they were willing to participate in the study. They gave their approval and the first meeting was scheduled at 8 October 2019. During this appointment informed consent, signed by both parents and subject 1, was collected before further actions were initiated.

Subject 1 is 12 years old, Caucasian and male. At time of the first appointment he was 1.50 m tall and weighed 32 kg. Furthermore, he was prescribed Foster medication twice daily via a Nexthaler®. During this first appointment, subject 1 reported that his asthma control was moderately controlled. The ACT-score obtained during this appointment was 15, which was considerably lower than the threshold for uncontrolled asthma (being 20). The parts of the ACT that scored particularly low were 'ability to do what you want' and 'number of times shortness of breath occurred'. After filling in the ACT, a lung function test was performed with the handheld spirometer. The best result out of a series of three consecutive measurements included an FEV1 of 2.37 litre, which was 95% of predicted with regard to his demographics. After the spirometry 200 µg of salbutamol was administered in two doses of 100 µg and after waiting for 5 minutes, another lung function test was performed. This time the best out of three performances valued 2.49 litre, considered 100% of predicted. This resulted in a reversibility after intake of inhalation medication of 5.06% and thus did not exceed the threshold of 12%. However, subject 1 could be included in this study due to his ACT-score. An overview of the demographics and data required for inclusion is given in Table 2.

TABLE 2: OVERVIEW OF DEMOGRAPHICS AND DATA REQUIRED FOR INCLUSION OF SUBJECT 1

Parameters	*Values Subject 1*
Age	12 years
Race	Caucasian
Sex	Male
Length	1.50 meters
Weight	32 kilograms
Outpatient in MST or ZGT?	Yes
ACT-score	15
Reversibility after SABA	5.06%
Inhalation device	Nexthaler®
Able to understand Dutch?	Yes
Other chronic disease?	No

After the baseline measurements during the first appointment, the add-on device was attached to the Nexthaler® of subject 1, where it could monitor both therapy adherence and inhalation technique. Subject 1 was also provided with a handheld spirometer to measure his lung function during the study. Data of the spirometry was sent by subject 1 via email to the researcher every Tuesday and Friday evening. This data included the FEV1 of each measurement and this data was used to determine the LFV over phase 1. The FEV1 values of all spirometry tests during phase 1 are shown in Figure 4. The highest value of the dataset was 2.45 litres at 25 October and the lowest value of the dataset was 2.25 litres at 22 October. Therefore, the LFV amounted to 8.2%.

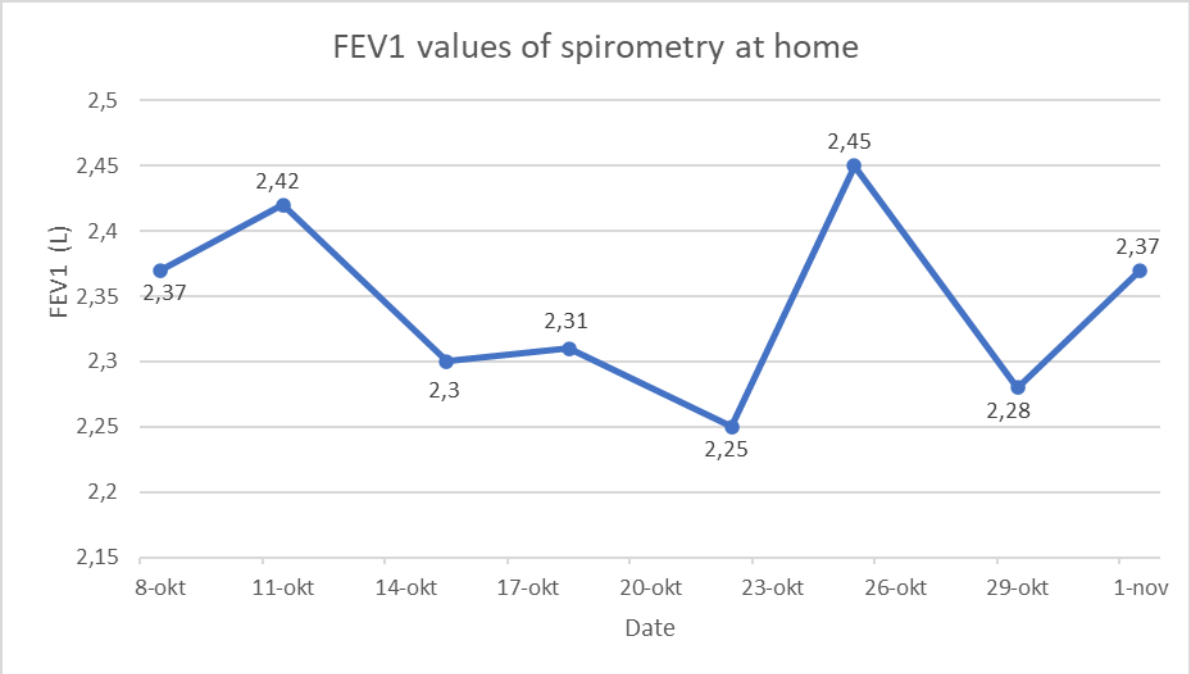

FIGURE 4: THE VALUES OF THE FORCED EXPIRATORY VOLUME IN 1 SECOND OF SPIROMETRY AT HOME DURING THE 4 WEEKS OF PHASE 1

SECONDARY OUTCOMES

The data with regard to therapy adherence and inhalation technique collected by the add-on device was provided as a .csv file by AMIKO on Monday 4 November and was analysed in Excel (Office 365, Microsoft, Redmond, Washington, United States). The dataset included data ranging from 8 October 2019 until 3 November 2019. First, an analysis was made with regard to therapy adherence and an overview per week is shown in Figure 5. During the first week, subject 1 was therapy adherent during 80% of the days. Therapy adherence was lowest during week 2 and 3 with appropriate intake of inhalation medication during 71% of the days. Therapy adherence was the highest in week 4 with appropriate intake of inhalation medication in 100% of the days.

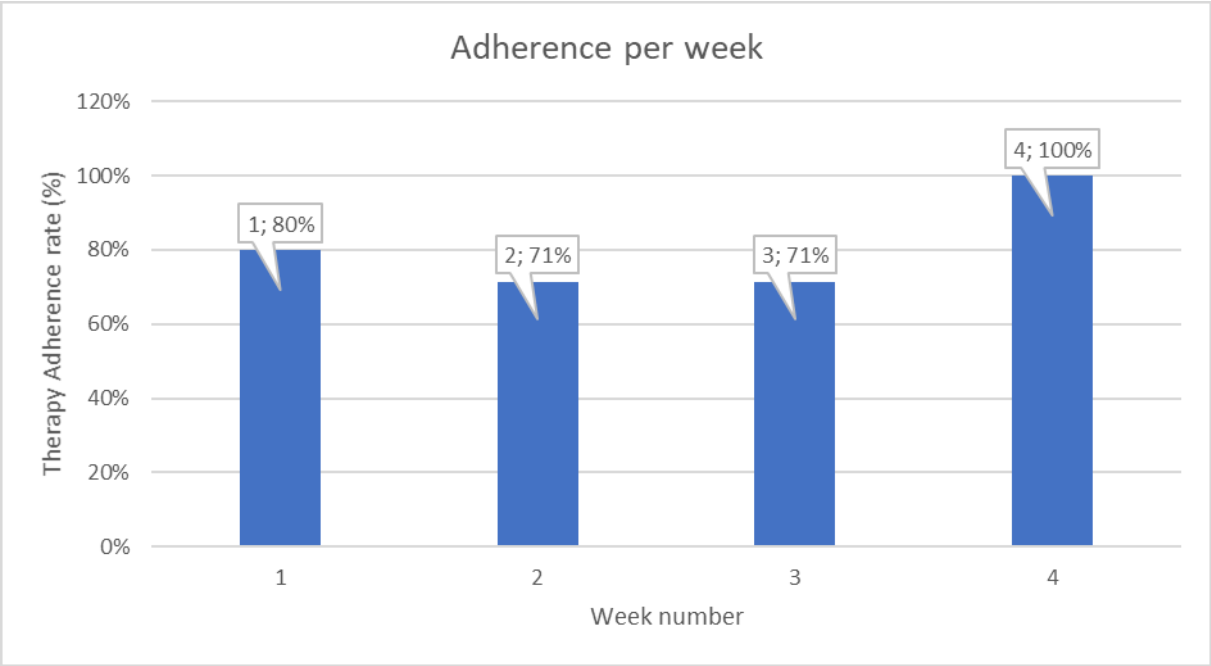

FIGURE 5: THERAPY ADHERENCE SHOWN PER WEEK IN PERCENTAGES

Besides analysis of therapy adherence per week, the data was also analysed per day of the week. An overview of these results is shown in Figure 6. Therapy adherence was highest on Mondays, Wednesdays and Fridays with appropriate intake of inhalation medication 100% of the times. The adherence rate scored a bit lower on Thursday and Saturday with both 75%. Tuesday scored 67% and the lowest adherence rate was measured on Sundays with 33%.

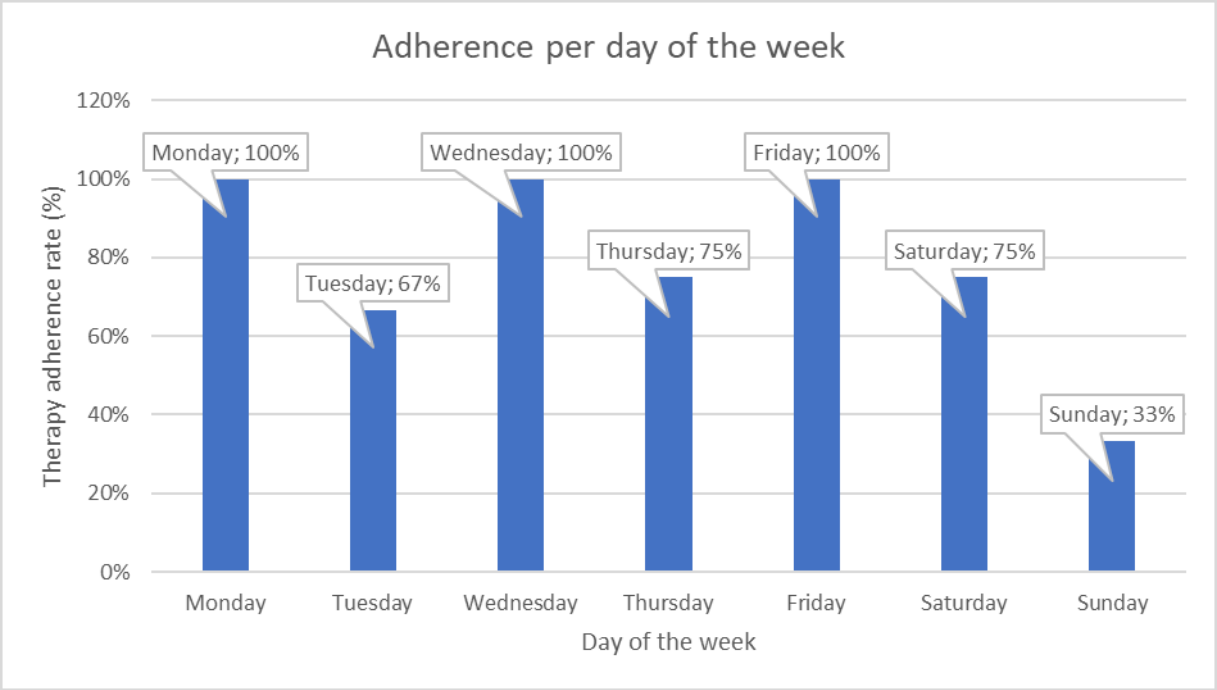

FIGURE 6: THERAPY ADHERENCE PER DAY OF THE WEEK

Next to therapy adherence, the inhalation technique was also assessed by means of critical and non-critical errors. To be able to refer to specific intakes of inhalation medication, all intakes in the dataset were numbered in chronological order. In 95.7% of all inhalations during these 4 weeks no critical errors were found. In total, two critical errors were found in the dataset. The first critical error consisted of failure to reach the duration threshold (intake 14), while the second critical error consisted of failure to reach the PIF threshold (intake 38).

The average duration of all inhalation manoeuvres was 1.68 seconds. An overview of the durations of all inhalation manoeuvres of inhalation medication is given in Figure 7. The average duration of intake of inhalation medication is represented in the figure as a single line. Furthermore, the average PIF of all inhalation manoeuvres was 63 litres per second. The duration of inhalation manoeuvres of inhalation medication seems to decrease slightly over time. The average of the first half of phase 1 amounts to 1.71 seconds, while the average of the second half amounts to 1.65 seconds

An overview of the PIFS of all intakes of inhalation medication is given in Figure 8. The average PIF is represented as a single line. The first half of all inhalation manoeuvres of inhalation medication had an average of 63.1, while the second half of all inhalation manoeuvres had an average of 63.8. The final 7 inhalation manoeuvres of medication had PIFs with an average of 68.7. It should be noted that the critical error with regard to PIF (very low PIF) was located in the second half of the intakes.

Finally, no errors with regard to orientation were found, since all orientation errors were smaller than 45 degrees. In comparison to duration, PIF did not decrease and seemed to increase slightly over time based on the averages.

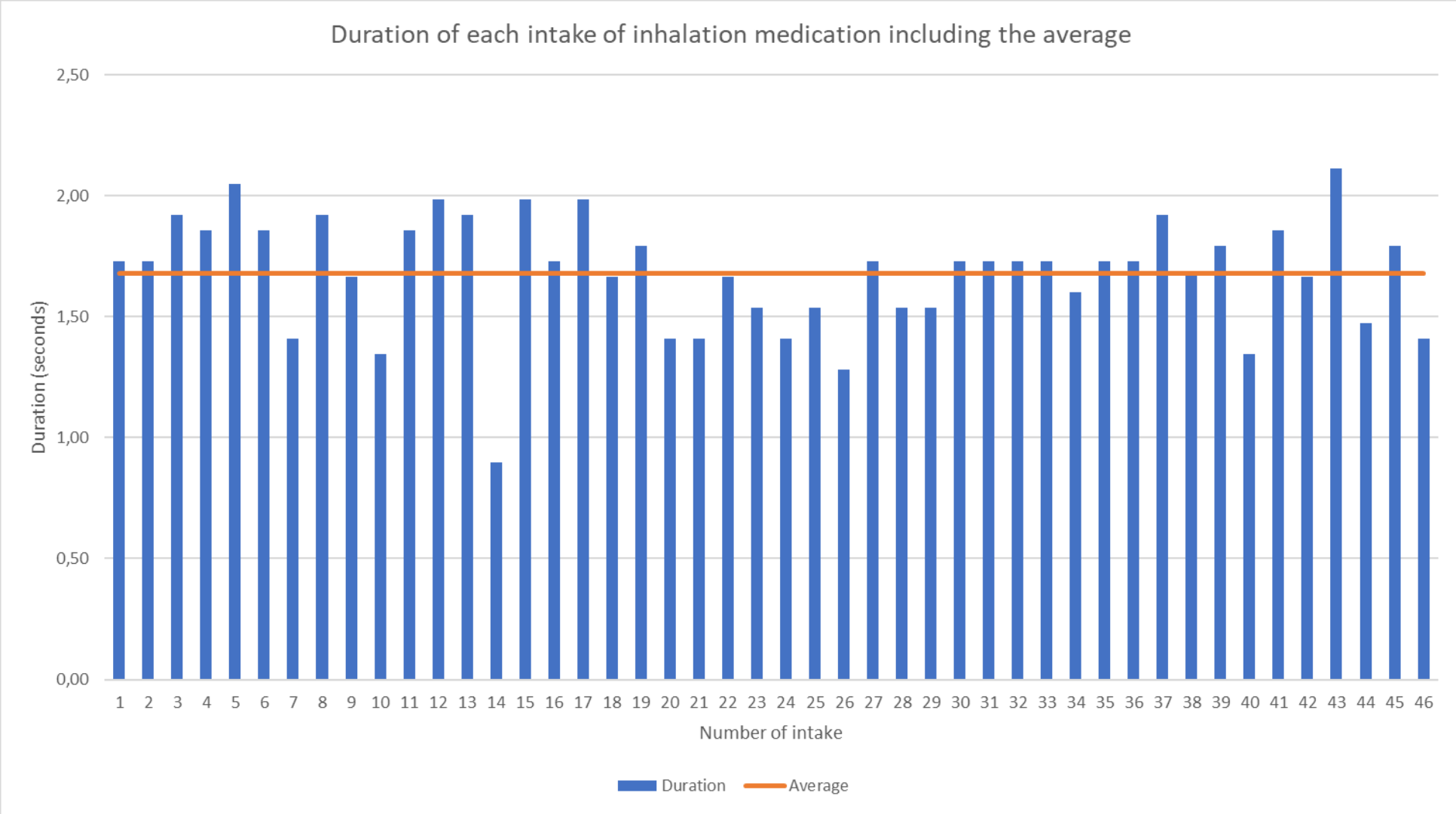

FIGURE 7: DURATION OF EACH INTAKE OF INHALATION MEDICATION INCLUDING A LINE REPRESENTING THE AVERAGE

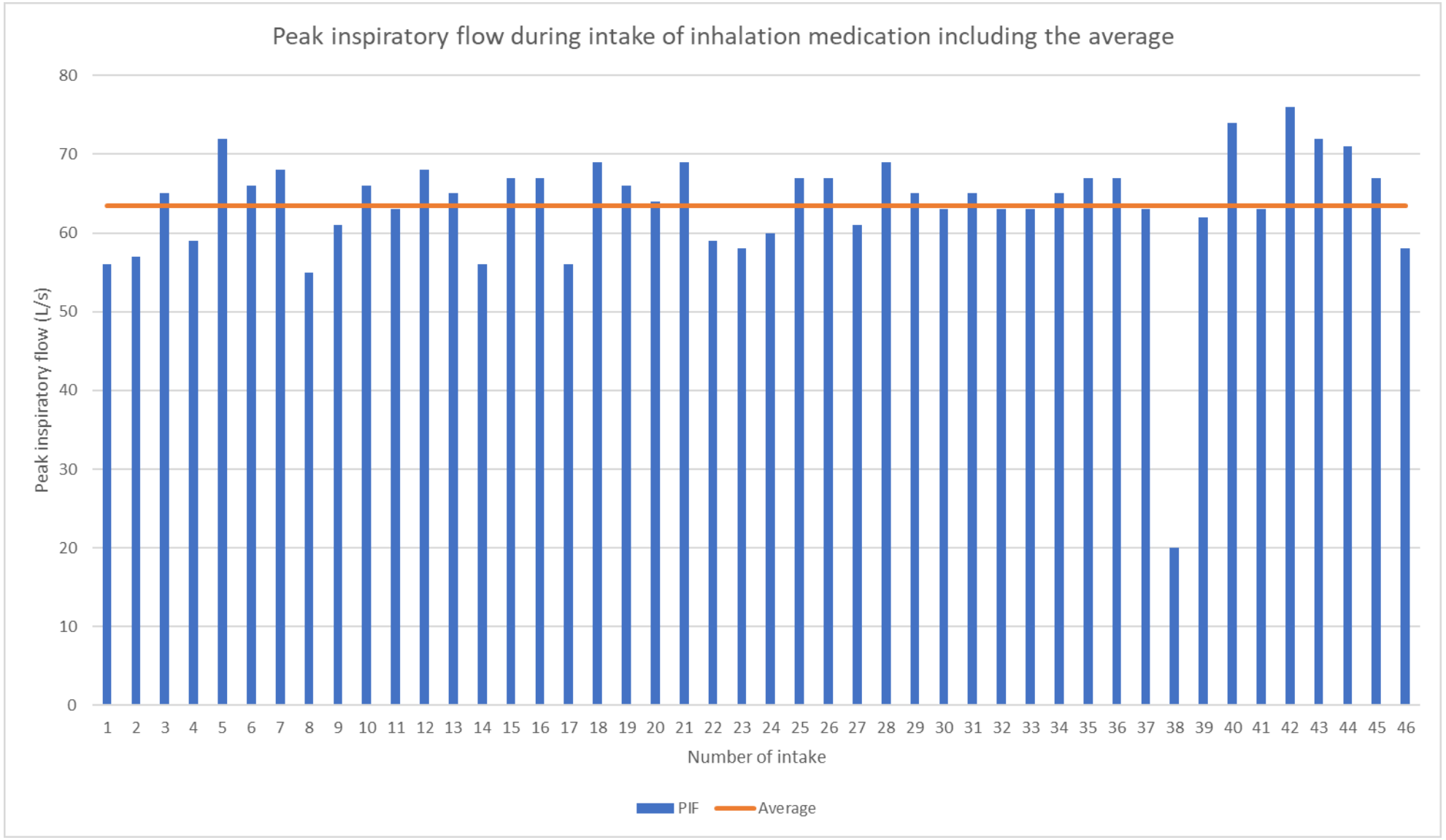

FIGURE 8:PEAK INSPIRATORY FLOW OF EACH INTAKE OF INHALATION MEDICATION DURING THE FIRST 30 INHALATIONS INCLUDING A LINE REPRESENTING THE AVERAGE

DISCUSSION

RESULTS

Subject 1 was able to participate without any problems in phase 1 and according to study protocol. No (serious) adverse events occurred and the lung function of the patient remained more or less consistent during those 4 weeks. The AMIKO portal showed real-time data about trends of therapy adherence and inhalation technique. Near the end of phase 1, more detailed data was provided by AMIKO on request. The patient did not experience technical issues with the add-on device. It was noted before the start of the study that the automatic synchronisation of the add-on did not work properly and feedback was given to the manufacturer about this issue. For this study, subject 1 was instructed to manually synchronise the device after intake of inhalation medication and thus deviating slightly from the protocol. Furthermore, the data from performing spirometry at home was collected properly, based on the flow-volume graphs and consistently sent to the researchers every Tuesday and Friday via email. Home-based handheld spirometry is a relatively novel way of measuring lung function. It has already been shown that home-based handheld spirometry is just as reliable as in-clinic spirometry.[39]

Inclusion in the study is based on (c-)ACT score and reversibility after intake of inhalation medication. For inclusion of subject 1, both parameters varied greatly. While reversibility (5.06%) was well within acceptable range (12%), the ACT-score of subject 1 (15) was much lower than the 20 that signifies well controlled asthma. This may be explained by airway remodelling. If patients have suffered from severe asthma for a longer period of time, more airway remodelling tends to occur resulting in thicker reticular basement membrane and airway smooth muscle.[13] Whenever remodelling has occurred, it is harder to reverse the symptoms of asthma. This means that asthma symptoms in children may fluctuate a lot more. Periods of less symptoms are followed by periods of more symptoms in a relatively short time span. The ACT-score respresents asthma control over a longer period and may therefore differ from reversibility, which is just a snapshot.

The original data set contained some measurements that included some unlikely values for duration and PIF. These odd measurements all had the same three properties: they were performed at the same time as either the previous or the following measurement, had a (very low) PIF of exactly 20 and a duration of exactly 0.5 seconds. These measurements also lacked information on orientation, while they all contained very high errors for orientation. Since these measurements were unlikely to be actual measurements of intakes of inhalation medication, they were removed before analysis. Also, the first and last day were excluded from analysis, because both days included only one moment of measuring. Therapy adherence was determined per day and based on the number of inhalations prescribed per day. In this case, subject 1 was prescribed intake of inhalation medication twice daily. Therefore, no reliable assessment of adherence could be performed for the first and last day, since they only had the possibility to take medication once.

The first four weeks of phase 1 from subject 1 were assessed for the case description of this study. Therapy adherence was determined at 81% during this period and therefore subject 1 is considered to be an optimal user (between 75%-125%). Therapy adherence was the lowest in week 2 and 3 (both 71%). The lower adherence during week 3 could possibly be explained by the autumn holidays occurring in the Netherlands during that period. It has been previously described that therapy adherence is lower during weekends and holidays[40], but no actual drop in therapy adherence during week 3 occurred compared to week 2. However, therapy adherence was lowest in both week 2 and 3. Furthermore, therapy adherence was lowest on Sundays with 33% and this is conform the previous statement on therapy adherence. The perfect adherence (100%) in the final week could possibly be

explained by the Sunday which is excluded from actual analysis, as Sunday turns out to be the day with the poorest adherence.

In general, therapy adherence and inhalation technique have the tendency to decline over time.[41] Therefore, it was surprising to see that therapy adherence increased to 100% in the fourth week, since no immediate smart feedback was provided during the first phase and no new information was given to the patient during phase 1. Conversation with subject 1 may give insights to these finding during appointment 2.It was found that duration of intake of inhalation medication decreased over time from an average of 1.71 seconds in the first half of the measurements to 1.65 seconds in the second half of the measurements. On the other hand, PIF increased during phase 1 from 63.1 to 63.8 litres per second. Especially the last seven intakes had relatively high PIFs with an average of 68.7. Therefore, no clear conclusions can be made with regard to inhalation technique. While one of the critical parameters seems to decrease over time, the other critical parameter is increasing.

The results of this case report show that the add-on is a valuable device for obtaining objective real-time data on therapy adherence and inhalation technique for intake of inhalation medication. This information is very helpful for paediatricians in their choice for the course of treatment plan, since therapy adherence and inhalation technique are both included in the GINA guidelines.[10] Due to this information, paediatricians can better locate problems if children persist to suffer from uncontrolled asthma, locating the cause to poor therapy adherence and/or inhalation technique, insufficient medication prescription or a combination.

Finally, it should be noted that all results shown above are acquired from only a single subject. This does not mean that the data is representative for asthmatic children, since multiple factors are influencing the parameters measured. For viable data more subjects need to be included according to protocol before actual reliable results can be determined. However, this first overview may give some insights in therapy adherence and inhalation technique over time of a subject participating in phase 1 of this study and did not give grounds for reconsidering study protocol so far.

DESIGN

With regard to the design of the study, the option to provide immediate smart feedback to patients about inhalation technique and therapy adherence could be a great addition to the current asthma care in children, since inhalation technique and therapy adherence both appear to be poor in the current asthmatic children.[14–17] Immediate smart feedback on intake of inhalation medication could have a positive influence on asthma control and thus on the quality of life of asthmatic children. Improved asthma control with fewer exacerbations allows children to experience less limitations in daily life, better participation in society, and better development in school. In practice, children often tend to accommodate their activities and behaviour to their (chronic) limitations.[42] This can be illustrated by a child who favours gaming over playing outdoors, as the child does not experience the same limitations caused by asthma while gaming. The true impact of asthma on daily life is, therefore, less obvious. Use of add-ons to stimulate optimal intake of inhalation medication could just be the final step for children to achieve optimal asthma control without any symptoms. No additional efforts need to be performed either, since the add-on is attached to the inhaler once and can remain in place until the inhaler is empty. Synchronisation of the mobile device and the Respiro™ add-on should soon occur automatically when the two devices are near each other. Hence, the device is capable of detecting periods of poor adherence or technique, and can increase awareness of these aspects in asthmatic children or their parents respectively, while providing the paediatrician with highly desirable information on therapy adherence and inhalation technique.

Besides, the GINA guidelines[10] emphasise the need to optimise both therapy adherence and inhalation technique before considering a step-up in therapy. The patients who will be included in this study all suffer from uncontrolled asthma and receive a combination of a corticosteroid and a LABA. Step-up in therapy would often involve targeted biologics and, while the effectiveness of targeted biologics has been proven[11], this form of treatment is very expensive. Therefore, the Respiro™ add-on, which provides feedback on the inhalation of medication to the user, could be an innovative tool to prevent unnecessary step-up therapy in children with poor asthma control as result of poor therapy adherence and/or inhalation technique. Furthermore, by improving asthma control, it is expected that fewer asthma situations escalate to hospital admissions. Self-evidently, fewer hospital admissions will also lead to fewer costs. Finally, by monitoring patients in the home situations, it seems likely that less consultations with paediatricians are necessary. Altogether, this tool may be able to keep asthma care affordable without conceding quality.

While the aim of this study should be clear, several decisions made in this research protocol deserve further elaboration. To start off, the intervention time is only 6 weeks. As mentioned previously, therapy adherence has the tendency to decline. This would hypothetically mean that longer intervention periods may improve the effect of the Respiro™ add-on, since feedback on inhalation keeps stimulating the users to improve both aspects. However, a longer intervention period also increases the burden for participants in this study, since they need to perform additional spirometry twice a week. Since the general effect of immediate smart feedback on inhalation technique and therapy adherence is yet unknown, this study focusses on short term effects to verify effectiveness and minimise the burden for participants. Besides, the airway remodelling has not affected children as much as adults suffering from asthma for a long time. This justifies the relatively short time span, as children tend to show improvements more rapidly than adults do.

Based on both the combination of therapy adherence and inhalation technique, and asthma control at the end of phase 2, the feedback will cease for all children and revision of medication may occur. When the combination of therapy adherence and inhalation technique (critical errors) results in less than 75% of the medication being properly inhaled and asthma control is not improving, this will be a cue to schedule another consult with the paediatrician. However, in daily practice, inhalation medication can also be overused by patients (more than twice a day) and overuse is considered a form of suboptimal use of medication as well. For the transition between phase 2 and 3, they will, however, be considered as therapy adherent. This can be explained as overusers are likely to be in need of more relief of symptoms. Treatment evaluation for step-up therapy should therefore be considered in these patients as asthma control is still lacking despite prescribed intake of medication. Nonetheless, the percentage of overusers in both randomisation groups will be determined to assess whether feedback on inhalation technique and therapy adherence will either encourage or discourage overuse. Another point of debate are the two critical errors regarding inhalation technique defined in this study, because no general consensus is reached on what errors are considered critical.[43,44] In practice a critical error is defined as an error that limits the effectiveness of drugs.[44,45] In this study, both peak flow and inhalation duration are considered to be critical errors as they have the highest impact on drug delivery and directly impact the quantity of medication reaching the lungs of the patients. Ideally, the time the patients hold their breath after inhalation is also included as critical error.[44] However, the Respiro™ add-on is not capable of recording this (similar to all other current devices measuring therapy adherence and inhalation technique) and therefore holding breath too short after inhalation is not included as critical error in this study.

An interim analysis will be performed after half of the subjects finished phase 2. As mentioned previously, the true (short-term) effectiveness of feedback on inhalation technique and therapy

adherence is yet unknown. This interim analysis gives more insight into the effect of feedback and small adjustments to the study design or population could be made if necessary. If the effect turns out to differ greatly from the expected effect, the study can be terminated for futility or inclusions can be stopped for effectiveness, to prevent unnecessary burdens to future participants.

The (c-)ACT questionnaire is the current validated gold standard in modern Dutch healthcare to assess the severity of asthma in children. However, this questionnaire is a subjective measure which needs to be filled in by the patients (and parents/guardian) resulting in a score that determines asthma severity. Therefore, the (c-)ACT comes with a number of drawbacks.[46] Asthma control in children is fluctuating greatly and the (c-)ACT questionnaire fails to regard this variability. Furthermore, exacerbations occur in both children with good and poor short-term asthma control and they are an important indicator for asthma control. However, they are not included as such in the (c-)ACT questionnaire.[47] Unfortunately, agreement between asthma control as determined by the (c-)ACT questionnaire and the GINA guidelines is lacking. (c-)ACT scores tend to underestimate the asthma control, as defined by GINA.[10] Despite the drawbacks of this questionnaire, the (c-)ACT score is included as parameter to this study to respect the Dutch guidelines for asthma treatment (and assessment).[5] However, to compensate for the drawbacks of the (c-)ACT questionnaire other objective parameters, such as FEV_1, lung function reversibility after intake of medication, and LFV, are included.

RCTs characteristically have high internal validity, but low external validity.[48] This means that patients who are participating in this study are likely to be more concerned with their treatment and thus could be better motivated to improve therapy adherence and inhalation technique than the average young asthma patient in the Netherlands. Therefore, this may not reflect the effect on the entire population. An advantage of the design of an RCT is nullification of the Hawthorne effect[49]. According to this effect, patients are more therapy adherent and pay more attention to inhalation technique when they know they are observed. In this study, both groups, the feedback group and the non-feedback group, know they are being observed to avoid this bias.

Previous research[50] has shown that the circadian rhythm influences the severity of asthma symptoms. Symptoms tend to be worst around 4:00 am and gradually improve during the day. To avoid any bias due to the circadian rhythm during this study, spirometry at home needs to be performed twice per week at fixed times. This time should be approximately equal for all participating subjects and therefore they are instructed to perform spirometry measurements prior to dinner.

Finally, this study is specifically focussed on improving asthma control in children, because children tend to react differently to behavioural interventions than adults would.[51] Therefore, it is import for further decisions regarding asthma treatment that research focussed on children is performed.

CONCLUSION

Based on data of subject 1, technical performance of the protocol is feasible. Data on both therapy adherence and inhalation technique was collected consistently using the Respiro® add-on device. Both aspects have been proven to be essential parameters for further treatment decisions by paediatricians, but are traditionally hard to measure objectively. Furthermore, data on asthma control was obtained by using home-based handheld spirometers. Therefore, both devices seem sufficient to monitor all parameters of interest in asthmatic children. Subject 1 did not encounter any technical issues during phase 1 and no deviations of the protocol did occurred so far. The FEV1 of subject 1 remained more or less consistent during the observational period with a LFV of 8.2% and without any (major) events. The add-on device seems like a helpful tool to provide paediatricians with objective information about hard to measure aspects as therapy adherence based on data of a single patient. However, elaborated upcoming studies with larger patient populations should prove this statement. Providing immediate smart feedback has the potential to improve asthma control, but analyses at the end of this study should confirm that statement.

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APPENDIX A:

DATASET REGARDING DURATION AND PIF

Date	Inhalation	Time		WeekDay	Duration	Average Duration	PIF	Average PIF
9-10-2019	1	07:25		Wed	1,73	1,68	56	63
9-10-2019	2	20:19		Wed	1,73	1,68	57	63
10-10-2019	3	08:41		Thu	1,92	1,68	65	63
10-10-2019	4	20:36		Thu	1,86	1,68	59	63
11-10-2019	5	07:24		Fri	2,05	1,68	72	63
11-10-2019	6	20:31		Fri	1,86	1,68	66	63
12-10-2019	7	07:34		Sat	1,41	1,68	68	63
12-10-2019	8	21:31		Sat	1,92	1,68	55	63
13-10-2019	9	20:26		Sun	1,66	1,68	61	63
14-10-2019	10	07:57		Mon	1,34	1,68	66	63
14-10-2019	11	20:35		Mon	1,86	1,68	63	63
15-10-2019	12	07:57		Tue	1,98	1,68	68	63
15-10-2019	13	20:27		Tue	1,92	1,68	65	63
16-10-2019	14	07:27		Wed	0,90	1,68	56	63
16-10-2019	15	20:59		Wed	1,98	1,68	67	63
17-10-2019	16	07:25		Thu	1,73	1,68	67	63
17-10-2019	17	21:18		Thu	1,98	1,68	56	63
18-10-2019	18	08:09		Fri	1,66	1,68	69	63
18-10-2019	19	21:02		Fri	1,79	1,68	66	63
19-10-2019	20	22:30		Sat	1,41	1,68	64	63
20-10-2019	21	20:24		Sun	1,41	1,68	69	63
21-10-2019	22	11:08		Mon	1,66	1,68	59	63
21-10-2019	23	20:50		Mon	1,54	1,68	58	63
22-10-2019	24	22:21		Tue	1,41	1,68	60	63
23-10-2019	25	09:30		Wed	1,54	1,68	67	63
23-10-2019	26	20:57		Wed	1,28	1,68	67	63
24-10-2019	27	20:18		Thu	1,73	1,68	61	63
25-10-2019	28	09:36		Fri	1,54	1,68	69	63
25-10-2019	29	20:43		Fri	1,54	1,68	65	63
26-10-2019	30	10:34		Sat	1,73	1,68	63	63
26-10-2019	31	21:19		Sat	1,73	1,68	65	63
27-10-2019	32	11:59		Sun	1,73	1,68	63	63
27-10-2019	33	21:22		Sun	1,73	1,68	63	63
28-10-2019	34	07:21		Mon	1,60	1,68	65	63
28-10-2019	35	20:32		Mon	1,73	1,68	67	63
29-10-2019	36	07:26		Tue	1,73	1,68	67	63
29-10-2019	37	20:47		Tue	1,92	1,68	63	63
30-10-2019	38	07:22		Wed	1,69	1,68	20	63
30-10-2019	39	20:44		Wed	1,79	1,68	62	63

31-10-2019	40	07:27		Thu	1,34	1,68	74	63
31-10-2019	41	21:30		Thu	1,86	1,68	63	63
1-11-2019	42	07:26		Fri	1,66	1,68	76	63
1-11-2019	43	20:53		Fri	2,11	1,68	72	63
2-11-2019	44	07:56		Sat	1,47	1,68	71	63
2-11-2019	45	21:23		Sat	1,79	1,68	67	63
3-11-2019	46	20:31		Sun	1,41	1,68	58	63