Intervention 1 of CIRCUS: The MIME study
Long-term effects on pediatric asthma using video directly observed therapy (vDOT)

SUMMARY
Rationale: Asthma is one of the most common chronic diseases in childhood. One of the problems that can lead to poor symptom control is inadequate inhaler technique. Despite these few studies reporting on the short-term effect of remote observation of therapy, no studies report on the long-term effects of remote inhaler technique training [1,2]. The research gap therefore lies in the follow-up of inhaler technique and asthma outcomes after a remote inhaler technique intervention.
Objective: This study aims to evaluate the long-term effects of video Directly Observed Therapy (vDOT) compared to regular care on asthma control in children with asthma.
Study design: This study is a Randomized Controlled Trial (RCT), designed as the first intervention of the CIRCUS cohort multiple randomized controlled trial (cmRCT). Children in the intervention group started with an observational week of inhalation recording. Thereafter they receive 6 weeks of intervention, followed by 3 months without intervention. Further follow-up will continue within the CIRCUS cohort. The control group consists of other cohort participants and is blinded.
Study population: Children between 4 and 18 years old with asthma from the CIRCUS cohort.
Intervention: The intervention consists of taking a recording of daily inhalation use and receiving four feedback sessions from an asthma nurse based on these home recordings.
Main study parameters: Asthma control. The secondary endpoint is the inhalation technique score within the intervention group.
Nature and extent of the burden and risks associated with participation, benefit, and group relatedness: Asthma is the most common chronic disease in childhood. Within this population incorrect inhalation technique of required maintenance medication (or reliever medication) is of frequent occurrence, causing undertreatment, uncontrolled asthma, and higher risk of exacerbations. Moreover, asthma characteristics in children differ from those in adults. It is therefore important to investigate the inhalation technique, try to improve it, and try to maintain a good inhalation technique throughout childhood. Moreover, individual children may benefit from extra attention and education concerning the inhaler technique. The burden of this study includes the recording of medication intakes for six weeks once daily (10*7=70x +-10seconds ≈ 15minutes), 10 times filling in the (C-)ACT questionnaire (10*3min=30min), and 4 online feedback sessions of 15 minutes (1 hour). These measurements are non-invasive and no risks are associated with participation.

1. INTRODUCTION AND RATIONALE

Asthma is a common chronic pediatric disease that is characterized by episodes of wheezing, cough, shortness of breath, and chest tightness triggered by activity, respiratory infection, and allergy [3–6]. Asthma affected around 7% of the children in The Netherlands in 2021 [7]. Total healthcare costs for pediatric asthma in 2019 in The Netherlands were about 68 million euros of which 40% was spent on medication and inhaler devices. Current asthma medication consists of Long- and short-acting beta-adrenoreceptor antagonists (SABA/LABA), inhaled corticosteroids (ICS), or a combination [8]. Moreover, asthma management focuses on reducing exacerbation risk and achieving symptom control by optimizing inhaler technique, avoidance of environmental triggers, self-management education, and treatment adherence [9]. Despite all precautions and medication, the occurrence of uncontrolled asthma with frequent exacerbations in children ranges from 46% to over 60% [8,10].

One of the problems that can lead to poor symptom control is inadequate medication technique. Earlier studies showed around 50% of children are non-adherent to medication and that the inhaler technique among these children is poor [11,12]. Poor inhaler technique leads to inadequate treatment effects while the amount of drug intake was appropriate [13]. Furthermore, this can result in avoidable healthcare expenditures as effective treatment could mistakenly be seen as ineffective and healthcare utilization (emergency visits/hospital admissions) may be prevented when uncontrolled asthma is effectively treated [14]. Therefore, the inhaler technique requires more focus to improve medication effects and asthma control. Inhalation instruction and education by asthma nurses and pharmacists are supposed to acquire adequate inhaler technique, however, only a small proportion of patients receive this structurally [15]. Moreover, the inhalation

technique demonstrated in front of healthcare professionals overestimates daily techniques at home [16]. Therefore, more comprehensive inhalation instructions are needed to attain a correct inhalation technique [17].

At-home evaluation of inhaler technique would provide opportunities to improve inhaler technique. Only a few studies reported monitoring the inhalation technique at home by use of eHealth [18]. In these articles, there were two distinct ways of monitoring the inhalation technique: remote observation of therapy [19–21] and remote electronic measurement of aspects of the inhalation technique [2,22,23]. It was demonstrated that audiovisual support regarding the inhalation technique is feasible [20], can help to improve effective medication use by providing feedback on the inhalation technique [19–21], and can lead to improved asthma control scores [20]. Electronic measurement is feasible for specific inhaler devices and/or specific inhalation errors, but no general sensor has been developed, therefore always still requiring the evaluation of a healthcare professional [23]. Bynum et al. [21] showed that education and feedback for the metered-dose inhaler technique by video consultation were more effective than written instructions.

Despite these few studies reporting on the short-term effect of remote observation of therapy, no studies report on the long-term effects of remote inhaler technique training [1,2]. The research gap therefore lies in the follow-up of inhaler technique and asthma outcomes after a remote inhaler technique intervention. Video Directly Observed Therapy (vDOT), is the most researched low-cost and uncomplicated remote intervention that involves patients themselves taking a video of their medication intake and sending it for review by a healthcare professional [24]. Shields et al. [20] showed that the quality of uploaded videos was good 98.3% of the time for proper evaluation of the inhaler technique. Therefore, this study aims to evaluate the long-term effects on asthma outcomes of the vDOT intervention in children with asthma.

2. OBJECTIVES

The primary objective of this study is to evaluate the long-term effects of video Directly Observed Therapy (vDOT) compared to regular care on asthma control in children with asthma.
The secondary objectives include:

- Evaluate the short and long-term effects of vDOT on the inhaler technique of patients receiving vDOT.
- Evaluate the short and long-term effects of vDOT compared to regular care on the CIRCUS cohort outcomes (Quality of Life, Clinical (asthma) outcomes, quality of care, self-management capacity, healthcare use, and therapy compliance) in pediatric asthma patients.
- Evaluate the usability of vDOT for patients and healthcare professionals.

3. STUDY DESIGN

This study is a Randomized Controlled Trial (RCT) within the CIRCUS cohort multiple Randomized Controlled Trial (cmRCT) of pediatric asthma patients in Medisch Spectrum Twente (MST). This study consists of two groups: 1) the non-blinded intervention group receiving vDOT and 2) the blinded control group. Participants and/or their parents in the intervention group will film the inhalation of the medication. In the observational phase (1 week), participants daily film their inhalation technique. In the interventional phase, children daily film the inhalation technique for six weeks. They receive feedback on the inhalation technique in weeks 1, 2, 4, and 6 via online consultations. After the interventional phase, children will daily film inhalation videos for one week after one month, two months, and three months. Every week of inhalation recording ended with filling in the (C-)ACT questionnaire. Moreover, children continue under follow-up in the CIRCUS cohort. For a study overview, see Figure 1.

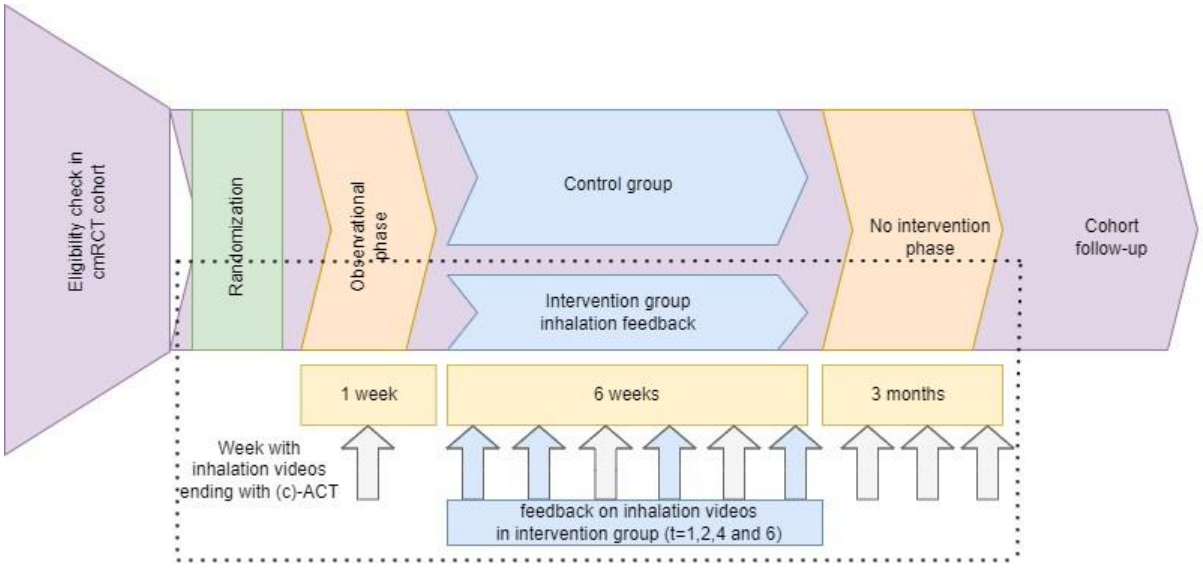

Figure 1: Study design. Within the dotted line is the MIME intervention visualized (the blue arrows indicate weeks with inhalation videos and feedback, and the white arrows weeks with only inhalation videos). After the intervention, both the control and intervention groups will be followed up in the CIRCUS cohort.

4. STUDY POPULATION

The study population consists of pediatric asthma patients between 4 and 18 years old from the CIRCUS cohort. Furter inclusion criteria:

- Participating in CIRCUS cohort & consented willingness to participate in interventions.
- (C-)ACT < 20
- Using controller inhalation therapy through one of the most common inhaler device types for children (aerosols with spacer, breath-actuated aerosol (Redihaler or Autohaler), dry powder inhalator (Nexthaler, Diskus or Ellipta) for asthma at least once daily.

Exclusion criteria:

- An appointment with the asthma nurse for inhalation instruction has already been scheduled.

4.1 Sample size calculation

To investigate whether the intervention effect remains in follow-up, we should at least replicate the intervention effect. The results of Shields et al. [20] showed an intervention effect from a (C-)ACT score of 13.1±5.7 at baseline to 17.8±4.3 after vDOT in uncontrolled (difficult-to-treat) asthmatic children. Calculating the effect size using these data, provides an effect size of 0.93.

Although the decay of the inhaler technique after vDOT has never been explicitly investigated in asthmatic children, it is known that general inhalation technique decay is significant [25,26]. This loss of technique may interfere with the sustained intervention effects on the ACT score. Therefore, we estimated a 30% lower effect size (Effect size D = 0.93-(0.93*0.30) = 0.65). Using a two-sided t-test sample size calculation (Gpower version 3.1.9.7), an allocation ratio of 3 (by using the CIRCUS cohort as the control group), a power of 0.8 and the type 1 error (α) of 0.05, the sample size calculation resulted in the sample size of 26 for the intervention group and 76 for the control group. Taking into account potential dropouts and the intention to treat method a sample size of 30 is expected to provide sufficient power.

5. TREATMENT OF SUBJECTS

Participants (and parents) in the intervention group are instructed to record the inhalations with their own (or their parents) smartphones, with the following requirements:

- Shoot the recording “in profile”, with the head, upper chest, and the inhaler in the shot.
- Record from the first moment of grabbing to stowing away the inhaler.
- Take the environment into account. For example, ensure a quiet and low-noise environment. Also, make sure that there is enough light to see the child and inhaler clearly in the recording.
- Take privacy aspects into account. For example, ensure no other persons other than the participant are in the video, no traceable information is in the video (e.g. names), and limit the amount of visible environment to reduce the risk of sharing privacy sensitive information.

During the intervention period, four feedback sessions of approximately 15 minutes will be given by the asthma nurse who has access to the inhalation videos and the error scoring. The treatment consists of those four feedback sessions, aiming to educate and imprint participants on a proper inhalation technique and therefore aim to improve medication effectiveness. These sessions will take about 15 minutes, will take place with the participant, and are structured in the following order:

- Discuss the experience of the participant. (How did the inhalations of last week?)
- Going through the inhalation videos of last week and discuss the inhalations and notable errors and provide practical tips for the child/parents to apply.
- Watch the inhaler instruction video of (inhalatorgebruik.nl) together with the asthma nurse.
- Room to ask for additional questions regarding inhaler technique.

Feedback is given using the sandwich-feedback method (i.e. you executed the preparation steps perfectly. However, try to fully blow out before starting the inhalation as this way the medication can be inhaled more effectively. I'm proud of what you learned so far in getting the right technique.)

6. METHODS

The main study parameter is the asthma control score assessed with the (C-)ACT questionnaire.
The secondary study parameter is the inhalation technique score, described elsewhere [28,29] and shown in Table 1. Total score = correct steps / total step (%), Score per series (check, preparation, inhalation) = correct steps per series/steps per series (%). As an outcome, the score will be averaged per week.

Table 1: Scoring of inhalation videos

	Aerosol + spacer		*Breath actuated aerosol*	*Dry powder inhaler*
Check	1. Expiration date 2. Remaining usages (if counted on device or count-air add-on or self-registered) 3. Spacer clean		1. Expiration date 2. Remaining usages (if counted on the device or self-registered)	1. Expiration date 2. Remaining usages (if counted on the device or self-registered)
Preparation	1. Shaking 2. Cap removed 3. Correctly attached to spacer		1. Shaking 2. Cap removed/opened	1. Cap removed/opened
Inhalation	*1.* Upright posture, chin 90° *2.* Full exhalation 3. Lips sealed around the mouthpiece 4. Slow breaths *5.* At least 5 OR 10 times *(depending on age)*	1. Upright posture, chin 90° 2. Full exhalation 3. Lips sealed around the mouthpiece 4. Deep full slow inhalation 5. Breath-hold ≥ 10sec	1. Upright posture, chin 90° 2. Full exhalation (not in the device!) 3. Lips sealed around the mouthpiece 4. Deep full inhalation (click-sound with autohaler) 5. Breath-hold ≥ 10sec	1. Upright posture, chin 90° 2. Full exhalation (not in the device!) 3. Lips sealed around the mouthpiece 4. Deep full & strong inhalation (click-sound (>35L/min) on Nexthaler) 5. Breath-hold ≥ 10sec
Aftercare + check	1. Cap attached 2. Stored properly		1. Cap attached 2. Stored properly	1. Cap attached 2. Stored properly

Further outcomes include the general CIRCUS outcomes (e.g. clinical (asthma) outcomes, self-management, quality of life, quality of care, healthcare utilization, and environmental outcomes. Moreover, the usability is an outcome of the percentage of correct videos and results from semi-structured interview data with patients and input from an open interview with the pediatric asthma nurse. The semi-structured interview focuses on

research burden, privacy, usability, and frequency of the intervention. Moreover, a focus is put on the feedback sessions with the asthma nurses regarding content, burden, frequency, and helpfulness.

6.1 Minimisation of intervention

Minimization will be used to aim for an equal distribution of patients and their prognostic factors among the study arms. Minimization will take place using the Minimpy software (biased-coin probability method, base probability 0.75) using the following factors:

- Asthma control: (C-)ACT score < 15 OR (C-)ACT score ≥ 15. (Weight = 3)
- Inhaler type: aerosol with aerochamber OR breath-actuated aerosol OR dry-powder inhaler. (Weight = 1)
- Age: < 12years OR ≥ 12years. (Weight = 1)
- eHealth care: yes OR no. (Weight = 1)

For the intervention group, no blinding will be used, as the intervention (recording inhalations and receiving feedback) cannot be blinded. The control group is blinded and data is gathered within the CIRCUS cohort.

6.2 Process of Intervention

Recruitment: Every month the cohort will be screened for eligibility (according to in and exclusion criteria mentioned in 4.2 and 4.3). This frequency was chosen as the (C-)ACT frequency in the CIRCUS cohort is monthly. CIRCUS participants who are found eligible for the mime study will be run through the minimization algorithm (Minimpy). Participants who are selected for the intervention group will be contacted and informed. The participants that are selected for the control group will automatically form the control group. This process is repeated every month.

When participants are selected for the intervention group they will be contacted (phoned) by the researcher. After a verbal explanation of the study by phone participants and their parents will be provided with written study information. A week later participants will be contacted by the researcher by phone to review if there are any questions left and whether they would like to participate. After the verbal agreement of the participants and the parents, an inclusion session is planned that suits the participants and their parents.

Inclusion session (30min): At the start of the inclusion session, there is room to discuss any questions from the participants and informed consent is obtained, at which the healthcare professional does pay specific attention to the opinion of the participant. The protocol is walked through carefully in understandable language and informed consent is retrieved. Thereafter, the session will be used to explain the procedure of the study and instruct the participant and their parents on the requirements of recording the inhalation videos and using the Zivver app.

Observational phase (5-10 minutes): In the observational phase, participants will record daily inhalations (at least 1 per day). These measurements and the (C-)ACT at the end of the week will be used to assess the baseline inhalation technique and asthma control. The 7 video recordings and filling in the short (C-)ACT questionnaire will take about 5-10 minutes throughout the week. Each video will be downloaded within one week from the mail by the researcher and stored in the research database. Moreover, all these videos will be judged according to the inhalation scores by 2 researchers with asthma care experience.

Intervention phase (1-1.5 hours): In the intervention phase (6 weeks), participants will record daily inhalations (at least 1 per day) and fill in a (C-)ACT at the end of each week. In weeks 1,2, 4, and 6 an online feedback session is planned. In the last feedback session, a semi-structured interview is included to evaluate the usability of the inhalation videos and feedback session. This interview is performed by the coordinating researcher.

No intervention phase (15-20 minutes): In the no-intervention phase of 3 months, participants will record daily inhalations (at least 1 per day) during the last week of every month (3 weeks in total). Each of these 3 weeks ends with filling in a (C-)ACT questionnaire. These measurements are observational and not used for intervention. After the no-intervention phase, children continue in the CIRCUS cohort follow-up.

7. STATISTICAL ANALYSIS

For these research questions within the CIRCUS cmRCT the Intention-To-Treat (ITT) principle is primarily taken into account in the statistical analysis (as representing real-life effect). We supplement the ITT analysis (both

before and after informed consent) with a Per Protocol (PP) analysis to additionally estimate the sole effect of the intervention.

(C-)ACT score data from the intervention group is compared to (C-)ACT score data from the control group before the observational phase, the week after finishing the intervention phase, and the week after finishing the follow-up phase. This is analyzed in SPSS and visually inspected for normal distribution. Results are expressed as mean +/- standard deviation (SD) or with median +/-interquartile range (IQR), as appropriate. Levene's Test is used to check for equality of variances. A two-sample t-test or a Mann-Whitney-U test is used, as appropriate. Moreover, the data over time will be analyzed with Mixed Model Repeated Measurement.

The other CIRCUS outcome variables are similarly analyzed as the (C-)ACT score between the intervention and control group. Furthermore, all (C-)ACT scores of the intervention group are analyzed over time. For the inhalation technique score in the intervention group, a pre-post analysis is appropriate with a paired t-test or Wilcoxon signed rank test, as appropriate. From the interview, an overview of the issues was made by grouping similar issues and those were converted into categorical codes (0=negative, 1=positive) to allow for statistical analyses. Moreover, the issues were categorized as minor, serious, or critical based on the frequency and consequences as described by Duh et al. [30]. Interim analysis will take place for futility after half of the participants (n=15) finished the intervention period. If vDOT shows a significant negative effect on the (C-)ACT score compared to the control group, no positive effect is expected and therefore the study will be stopped for futility.

8. Data Management

Handling of personal data will comply with the *EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (AVG).* Patients will receive an investigational code based on the inclusion number. The investigational code is composed as follows: MIME_XXX, with XXX corresponding to the number of inclusion, e.g. MIME_014. All data (except the inhalation videos) will be stored and coded in Castor. The key to the code will be stored digitally in MST, safeguarded by a password. The investigators will have access to this key. The personal inhalation videos cannot be coded, so after analysis, they will be stored password-protected for later monitoring purposes, the inhaler technique scores from the videos are stored in Castor. Data will be stored for a minimum of 15 years. This study will be monitored by the study monitor of MST.

9. REFERENCES

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