THERAPEUTIC ADVANCES in
Respiratory Disease

Study Protocol

Cohort multiple randomized controlled trial in pediatric asthma to assess the long- and short-term effects of eHealth interventions: protocol of the CIRCUS study

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Abstract

Background: Asthma is one of childhood's most prevalent chronic conditions significantly impacting the quality of life. Current asthma management lacks real-time, objective, and longitudinal monitoring reflected by a high prevalence of uncontrolled asthma. Long-term home monitoring promises to establish new clinical endpoints for timely anticipation. In addition, integrating eHealth interventions holds promise for timely and appropriate medical anticipation for controlling symptoms and preventing asthma exacerbations.

Objectives: This study aims to provide a pragmatic study design for gaining insight into longitudinal monitoring, assessing, and comparing eHealth interventions' short- and long-term effects on improving pediatric asthma care.

Design: The CIRCUS study design is a cohort multiple randomized controlled trial (cmRCT) with a dynamic cohort of 300 pediatric asthma patients.

Methods: The study gathers observational and patient-reported measurements at set moments including patient characteristics, healthcare utilization, and asthma, clinical, and environmental outcomes. Participants are randomly appointed to the intervention or control group. The effects of the eHealth interventions are assessed and compared to the control group, deploying the CIRCUS outcomes. The participants continue in the CIRCUS cohort after completing the intervention and its follow-up.

Results: This study was ethically approved by the Medical Research Ethics Committee (NL85668.100.23) on February 15th, 2024.

Discussion: The CIRCUS study can provide a rich and unique dataset that can improve insight into risk factors of asthma exacerbations and yield new clinical endpoints. Furthermore, the effects of eHealth interventions can be assessed and compared with each other both short- and long-term. In addition, patient groups within the patient population can be discerned to tailor eHealth interventions to personalized needs on improving asthma management.

Conclusion: In conclusion, CIRCUS can provide valuable clinical data to discern risk factors for asthma exacerbations, identify and compare effective scalable eHealth solutions, and improve pediatric asthma care.

***Trial registration*:** The protocol is registered at ClinicalTrials.gov (NCT06278662).

Plain language summary

A cohort study to assess long- and short-term effects of eHealth tools to help children with asthma: the CIRCUS study plan

Why is this study being done? Asthma is a common condition in children that affects their quality of life throughout childhood and possibly in adulthood as well. Managing asthma

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symptoms is challenging due to a lack of real-time and objective monitoring which may result in many children having uncontrolled asthma. Monitoring asthma at home over long periods of time using eHealth tools can help doctors monitor and anticipate asthma symptoms in order to prevent asthma attacks. This study aims to understand how home monitoring and eHealth tools can improve asthma care for children in the short- and long-term.

What will the researchers do? The CIRCUS study involves 300 children with asthma and is designed as a cohort multiple randomized controlled trial (cmRCT). This means that patients are observed over time and some of these patients are randomly chosen to evaluate eHealth tools. We will collect data from patients at regular intervals, including their health details, their healthcare visits, and questionnaires about their asthma symptoms, self-management level, and quality of life. Moreover, virology data, pollen counts, and environmental data like air quality and weather data will be gathered. Effects on these outcomes will be compared between patients who use the eHealth tools and a control group.

What will the findings mean? The CIRCUS study will provide valuable data on asthma in children, helping to identify risk factors for asthma attacks and establishing new ways to monitor this condition. It will also compare the effectiveness of different eHealth tools in both the short and long term. This can help personalize asthma management and improve care for children with asthma.

Keywords: asthma, clinical trial protocol, cohort studies, internet-based intervention, patient-reported outcome measures, pediatrics, telemedicine

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Background

Pediatric asthma, affecting 7% of Dutch children in 2021, stands as one of the most prevalent chronic diseases.[1] Asthma is characterized by chronic airway inflammation with variable expiratory airflow obstruction.[2] Typical asthma symptoms include wheezing, cough, shortness of breath, chest tightness triggered by physical activity, respiratory infection, and allergies, influencing the patient's quality of life.[2,3] Moreover, pediatric asthma influences the parents' quality of life through caring responsibilities, limitations in workforce participation, and additional health-related costs. Beyond the personal toll, the economic ramifications are considerable, with healthcare costs for pediatric asthma care in the Netherlands reaching 68 million euros in 2019.[4]

Asthma treatment focuses on the management of asthma symptoms thereby minimizing the risk of asthma exacerbations, as highlighted in the Global Initiative for Asthma (GINA) guidelines.[5] Besides adequate controller inhaler therapy, asthma management consists of assessing comorbidities, avoiding personal triggers, and education regarding self-management.[5,6] However, current asthma management lacks tools for healthcare professionals to address these aspects resulting in a prevalence of 46%–60% of uncontrolled asthma in children.[7]

Currently, asthma care consists of scheduled consultations for monitoring asthma symptom control.[5,8] However, recall bias of symptoms,[9] a limited perception of asthma symptoms,[10] and seasonal variability of asthma symptoms[11] trouble these scheduled consultations. eHealth technologies, such as communication platforms, remote digital sensors, and home diagnostics, could improve monitoring by allowing real-time, objective, and longitudinal monitoring at home. eHealth monitoring could therefore provide tools to timely anticipate and prevent asthma symptoms.[12–14] However, current studies on eHealth monitoring are heterogeneous in design and endpoints, focus on a single domain or outcome, and

lack multiparameter analysis and interventional design.[15–19] Many studies focus solely on medication monitoring or the digital environment but overlook the combination of multiple domains such as lung function, therapy adherence, and air quality to promote the identification of personal cues of disruption of asthma control.[20] While the combination of multiple domain monitoring may allow for personalized timely anticipation of loss of asthma control and the combination of eHealth interventions in multiple domains may reveal synergistic effects on asthma management these combinations are still underinvestigated.

The randomized controlled trial (RCT) study design is currently widely accepted as the top-level evidence.[21,22] Allocation of patients to either the intervention or control group is randomized to minimize bias.[23] Unfortunately, the RCT design complicates the assessment of multiple reinforcing eHealth interventions in a single RCT. Conducting multiple single RCTs is not preferable due to the time-consuming complexity, comprehensiveness, and associated high costs, as the extensiveness and complexity of the RCT cannot keep up with the fast-changing landscape of eHealth developments.[21] Moreover, from the literature, it becomes clear that the chance to be appointed to the control group following randomization may hinder patients from participating, especially with longer follow-up periods.[22,24] Other disadvantages of the RCT design are the often limited long-term follow-up and low completion rate.[21]

A cohort multiple Randomized Controlled Trial (cmRCT) design, also known as Trials within Cohorts, can be used to overcome the main disadvantages of the classic RCT.[24–26] Participants in this cohort perform measurements at set moments in time, forming the outcome measures of interest, with an emphasis on achieving a minimal study load. The main advantage of this design is its representative pool of eligible participants, facilitating a random selection of participants for interventions from a cohort that accurately reflects the diverse pediatric asthma population.[25] The participants who are not selected serve as a control group and remain in the cohort.[27] Additional informed consent is not required as the design assumes every participant would want the intervention and no additional measurements are needed.[24] These groups therefore allow RCT comparison on the primary outcome measures of the cohort. Moreover, due to the cohort design in the cmRT, regular follow-up measurements of primary outcomes are included and the cmRCT design offers the possibility to re-approach participants for multiple interventions. These multiple eHealth interventions can also be executed in parallel and their outcomes can be compared to each other which may be crucial to compose personalized combinations of interventions to reach the full impact of eHealth.[20] Finally, less drop-out is expected since patients who sign consent for an intervention are always assigned to the intervention group.

This study aims to generate short- and long-term data on clinical and patient-reported outcomes of pediatric asthma patients using a cmRCT design. The two main objectives of the CIRCUS study include (1) the observational assessment of improvements in pediatric asthma care and (2) the assessment of long- and short-term eHealth intervention effects. The first objective includes improving pediatric asthma care quality, comparing the existing eHealth care pathway with regular pediatric asthma care, and predicting asthma control deterioration using Artificial Intelligence (AI). The second objective includes the RCT evaluation of new eHealth innovations and the personalization of pediatric asthma care by matching eHealth interventions to risk groups. The hypothesis is that the CIRCUS study can explore scalable eHealth solutions that improve pediatric asthma care. The resulting dataset could provide insight into asthma control deterioration risk factors.

Methods

The reporting of this study conforms to the SPIRIT statement (see Additional File 1, Supplemental Material)[28,29] and the CIRCUS study is registered at ClinicalTrials.gov (NCT06278662). The hypotheses corresponding to the two main research objectives of the CIRCUS study are shown in Table 1.

Study design and setting

The CIRCUS study employs a cmRCT design and establishes a dynamic cohort of pediatric asthma patients. The participants are selected through random sampling (as part of the cmRCT cohort design) and can be approached for eHealth interventions which are RCT compared to the

Table 1. Hypotheses of the two main research objectives of the CIRCUS study.

Research objective	Hypothesis
Main CIRCUS objective 1: **observational assessment of improvements in pediatric asthma care**	
Improvement of pediatric asthma care quality	The observational analysis results in possible improvements and knowledge gaps which can be used for improvement plans or follow-up research questions
Comparison between eHealth care and regular pediatric asthma care	The eHealth care results in improved care and asthma outcomes as compared to regular pediatric asthma care in similar risk groups
Prediction of asthma control deterioration using AI	Asthma control deterioration can be predicted with sufficient accuracy from the data collected in the CIRCUS study using current AI technologies
Main CIRCUS objective 2: **assessment of long- and short-term eHealth intervention effects**	
RCT evaluation of new eHealth innovations	Depending on the to-be-determined interventions and the superiority or non-inferiority design used, the hypotheses will be tested that these interventions show a positive or equivalent effect compared to the control group (on the outcome measures chosen for this RCT study)
Personalization of pediatric asthma care by matching eHealth interventions to risk groups	The eHealth interventions can be matched to pediatric asthma risk groups using the outcomes and observational assessment, therefore improving healthcare efficiency and patient outcomes

RCT, randomized controlled trial.

control group in the cohort on the outcomes of the cohort study, as shown in Figure 1.

This study takes place in Medisch Spectrum Twente (MST), a large teaching hospital in Enschede, the Netherlands. The pediatric department of MST is a regional expert center for pediatric asthma from which eligible patients are informed of the study.

Participants

Table 2 shows the inclusion, exclusion, drop-out, and stop criteria for the CIRCUS study. We no longer collect data on patients who stopped or dropped out.

The term participants is used for both the children and their parents or carers, as data from parents is also gathered. When needed, a distinction between child and parent is made.

All eligible participants are informed during an outpatient visit. When they are interested, they receive a participant information file and are called to further explain the details of the study, to sign (online) consent, to instruct on the questionnaires, and to fill out the baseline questionnaires.

A sample size of 300 participants was determined for this dynamic cohort. This number approximates 30% of the total pediatric asthma population of the MST hospital and is expected to be representative in size and characteristics, such as age and sex.

The sample size of 300 participants matches three cases of power calculations for future interventions. The first case highlights an intervention with an effect size of 0.33. With an allocation rate of 1:2, sample sizes are 109 and 219 for the intervention and group respectively, a power of 80% can be achieved. The second case highlights an intervention with an effect size of 0.5. With an allocation rate of 1:7, and sample sizes of 36 and 254 for the intervention and control groups, a power of 80% can be achieved. Lastly, the third case highlights an intervention with an effect size of 0.8. With an allocation rate of 1:20, and sample sizes of 13 and 261 for the intervention and control groups, again a power of 80% can be achieved.

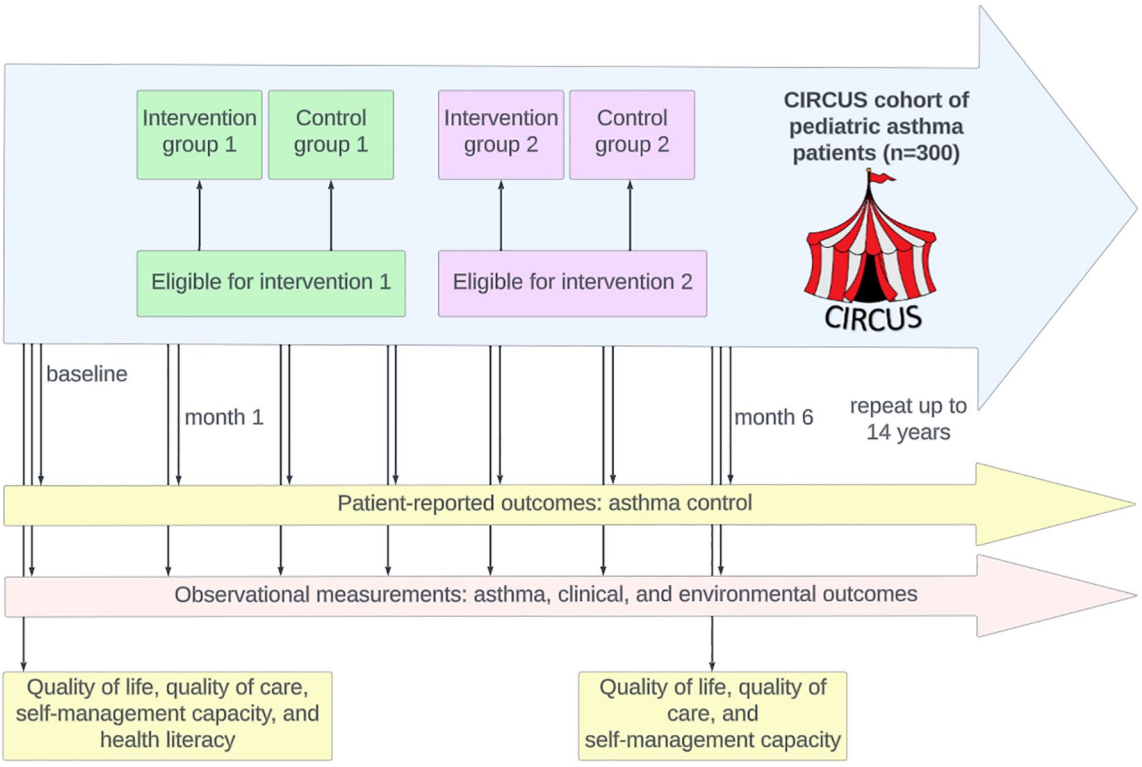

Figure 1. Schematic overview of the CIRCUS design, interventions, control group, and outcome measures.

Patient participation. Patient participation is promoted through monthly newsletters to inform participants of the study news, results, and general updates. Additionally, patient engagement is promoted through brainstorming sessions, polls, questionnaires, and focus groups.

For this CIRCUS study, we further promote patient participation by assembling a panel that convenes semi-annually for collaborative discussions. This patient panel consists of 10–15 participants. This panel actively collaborates in all stages of collaboration, for example, participant, advisor, consultor, co-designer, knowledge translator, and co-researcher (following the review of Bird et al).[30] This includes advising on suitable interventions; carefully weighing the study burden, and continuously evaluating the study design.

Outcomes

The CIRCUS study gathers participant characteristics as baseline characteristics. Clinical (asthma) outcomes, healthcare utilization, and environmental outcomes are the outcomes of interest. All outcomes are gathered observationally and additionally, specific clinical (asthma) outcomes are patient-reported. Furthermore, additional outcomes could be gathered in both intervention and control groups depending on the specific eHealth intervention.

Baseline characteristics. The child's characteristics include age, sex, weight, height, Body Mass Index, comorbidities, ethnicity, medication usage, allergies, inhalation allergies, school level, and asthma-related history such as sports, symptoms, family history, prematurity, and smoking. These child characteristics are retrieved from the electronic health record and updated for each outpatient visit. Furthermore, the parent characteristics include education level, age, and family situation. The parents' characteristics are inquired from the parents during inclusion and updated when changes are noticed during outpatient visits.

Clinical (asthma) outcomes. All medical patient data is collected observationally. This includes laboratory results, allergy tests, lung functions, X-rays, CT scans, and all physician's notes in the patient's electronic health record. In MST, we also perform annual exercise challenge tests in

Table 2. Overview of inclusion, exclusion, drop-out, and stop criteria.

Inclusion criteria
Age 4–18 years
Under treatment in MST for pediatric asthma
Pediatrician-diagnosed asthma conform GINA guidelines[5]: • Medical history fitting asthma; asthma symptoms, atopy, family history AND • Spirometry expiratory airflow limitation measured by at least one of the criteria: ◦ FEV_1 reduction compared to the lower limit of normal (Z-score $\leqslant -1.64$) ◦ FVC reduction compared to the lower limit of normal (Z-score $\leqslant -1.64$) ◦ Positive bronchodilator responsiveness (increase of $FEV_1 > 12\%$) ◦ Positive exercise challenge test (decrease of $FEV_1 \geqslant 13\%$) ◦ Excessive variation in lung function between spirometry tests in the past (variation of $FEV_1 > 12\%$ from predicted)
Exclusion criteria
Inadequate proficiency in the Dutch language for either participant or parents
Drop-out criteria
Three consecutive monitoring questionnaires not filled out by participants or parents.
Participants and/or parents want to stop
Stop criteria
Participant turns 18
The participant is referred to a general practitioner or another hospital
Follow-up of participated interventions is no longer relevant
Participant no longer has asthma: • No longer having asthma medication • No longer fitting asthma diagnostic criteria

which patients perform lung function before and after exercise.[31] From these tests, we observationally collect the lung function, the physician's notes, and the validated Visual Analog Scale for dyspnea.[32] Moreover, in MST a specific group of uncontrolled and severe pediatric asthma patients is included in eHealth care through the Puffer app.[8] This app allows for a chat function with a healthcare professional and the ability to fill in questionnaires and to couple measurement devices such as spirometry and pulse oximetry. We observationally collect this data from the app. A schematic overview of the gathered clinical outcomes is shown in Figure 2. Therapy compliance is measured through the hospital pharmacy by gathering the name of the medicine, date of issue, dose, expected period of use, and quantity provided.

Asthma exacerbations are defined as episodes characterized by a progressive increase in symptoms, requiring corticosteroids, hospital admission, or a combination of both.[5,33] These outcomes are collected through the electronic patient dossier and procedural codes of the pediatric department of MST.

Patient-reported outcomes are questionnaires regarding asthma control, quality of life, quality of care, and self-management capacity. Asthma control is measured using the validated (Child-) Asthma Control test (C-ACT or ACT).[34] Quality of life is measured using the validated Pediatric Asthma Quality of Life Questionnaire (PAQLQ)[35,36] and the adult-validated Health Literacy Questionnaire (HLS).[37] Quality of care is assessed using the adult-validated Client

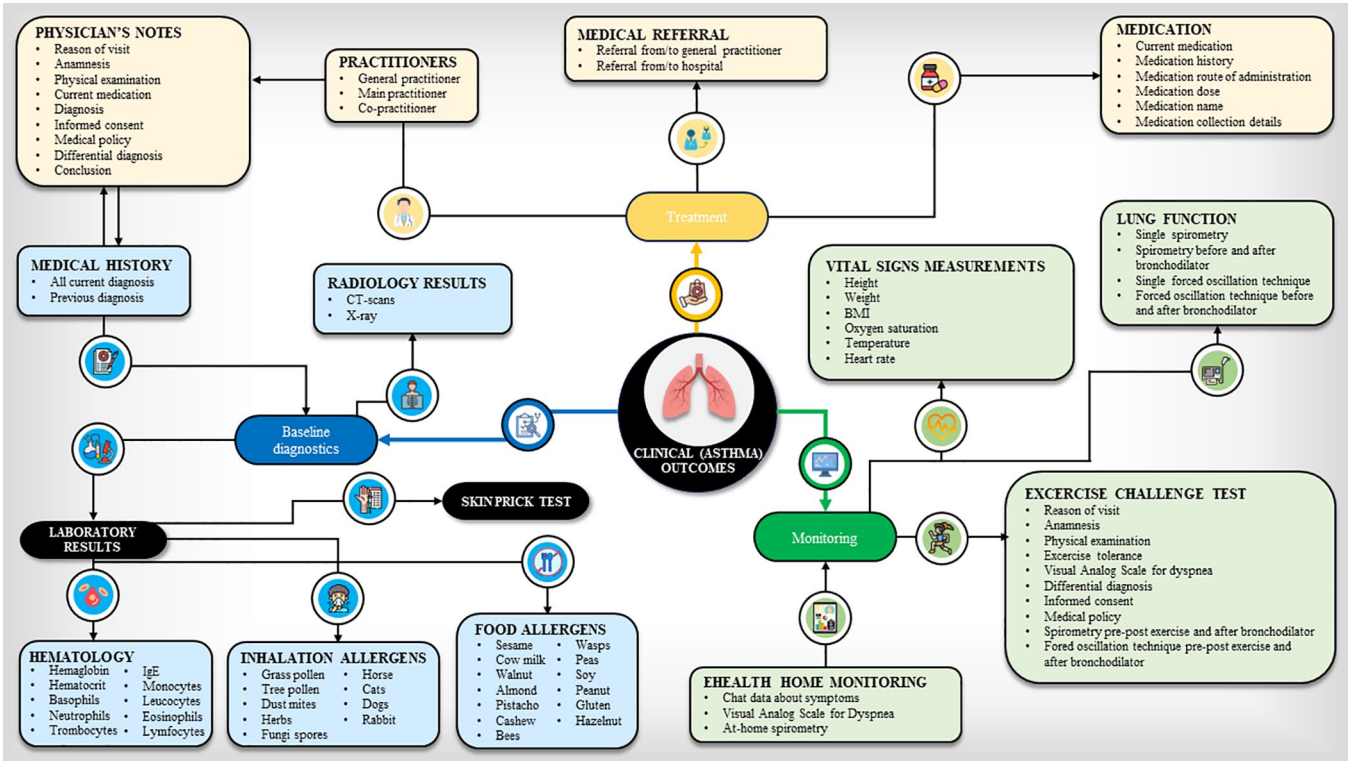

Figure 2. Schematic overview of the gathered clinical outcomes of the CIRCUS study. Blue text fields indicate baseline diagnostics, yellow text fields indicate treatment and green text fields indicate monitoring.

Satisfaction Questionnaire (CSQ-4).[38] The self-management capacity is assessed through the validated Dutch Patient Activation Measurement (PAM-13).[39] The Dutch and English questionnaires of the ACT and C-ACT can be found in Additional File 2 (Supplemental Material), the other questionnaires are copyright protected and can be found via the corresponding sources. As shown in Figure 3, participants fill out all questionnaires during the baseline visit. Subsequently, monthly (C-)ACT submissions are made. PAQLQ is submitted every 6 months, and participants aged 12 and above additionally respond to CSQ-4 and PAM-13. The HLS is filled out every 4 years. The participants' parents fill out the PAQLQ, (C-)ACT, CSQ-4, and PAM-13 every 6 months and the HLS every 4 years. Additionally, if participants fail to complete questionnaires, an automated reminder is sent after 1 week. After 2 weeks, personalized reminders via email or phone calls are initiated for participants who have not yet completed the questionnaires.

Healthcare utilization. Healthcare utilization is measured through the number and types of hospital admissions, outpatient visits, diagnostic tests, telephonic consultations, total healthcare costs, hospital costs regarding asthma care, medication costs, and patient additional costs such as travel costs. These outcomes are collected through procedural codes of the pediatric department of MST.

Environmental outcomes. The environmental outcomes measured in the CIRCUS study are weather data, air quality, and pollen counts. Weather data is measured daily by the Dutch National Meteorological Institute and includes temperature, wind speed, duration of sunshine, duration of cloud cover, amount of rain, atmospheric pressure, and humidity.[40] A more comprehensive list is shown in Table 1 in Additional File 3 (Supplemental Material). Air quality is measured daily by the Dutch National Meteorological Institute, list of particles in Table 2 in Additional File 3 (Supplemental Material).[41] Furthermore, average daily pollen data is taken into account, measured by Elkerliek Hospital and Leiden University Medical Center.[42,43] Measured pollen includes the most common grass, tree, and

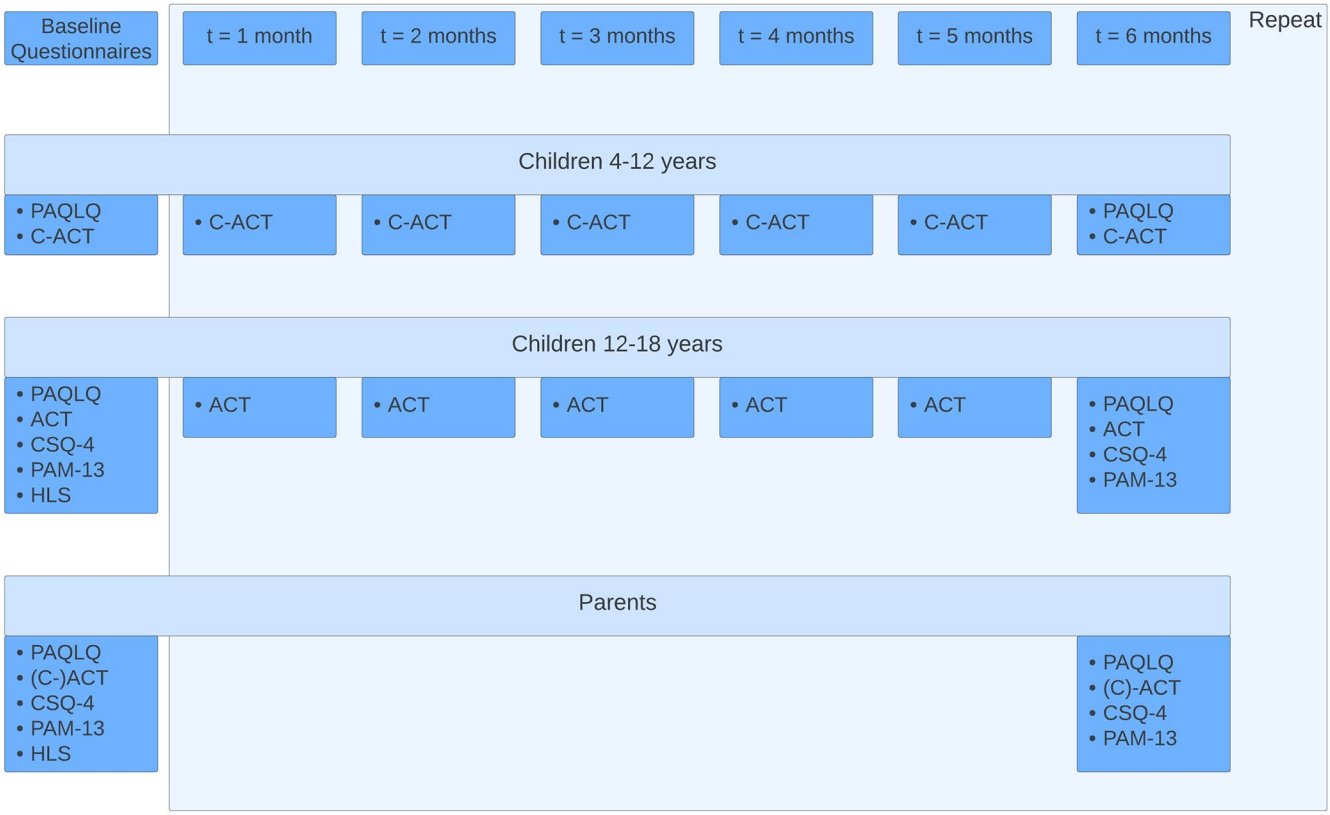

Figure 3. Schematic view of the timing of questionnaires.

plant pollen in the Netherlands, the comprehensive list is seen in Table 3 in Additional File 3 (Supplemental Material). Virological data is measured weekly by the Dutch Working Group on Clinical Virology from the Dutch Society for Clinical Microbiology and includes the number of positive virological tests in the Netherlands.[44,45] The measured virological data includes exposure to viruses such as SARS-COV19, Influenza, rhinovirus, and RS-virus. A more comprehensive list is shown in Table 4 in Additional File 3 (Supplemental Material). The weather data, air quality data, pollen counts, and virological data will be downloaded monthly and stored using MATLAB (MATLAB 2023b, The MathWorks Inc, Massachusetts, United States of America).

Interventions

Within the cohort, eHealth interventions can be RCT compared to each other and the control group. Together with the patient panel, researchers select eHealth interventions that show potential for improving different aspects of pediatric asthma care. Each eHealth intervention undergoes a careful assessment to determine if additional outcomes beyond the general CIRCUS outcomes mentioned above are necessary. Each of the proposed interventions undergoes ethical consideration by the Medical Research Ethics Committee.

All participants in the cohort will be checked for eligibility for each proposed intervention, schematically shown in Figure 1. The sample size calculation will be performed for every intervention separately. Minimization randomly allocates eligible participants to the intervention and control group.[46] Participants in the intervention group are asked for informed consent. Participants in the control group are not asked for informed consent as the cohort outcomes are used for comparison. The criteria for discontinuing interventions and strategies for improving adherence are determined for each intervention separately. The protocol of the first intervention can be seen in Additional File 4 (Supplemental Material).

Data collection, management, and analysis

The data is electronically collected and code-based stored in numerical order of inclusion in Castor (Castor v2023.4.4.0, Castor, Amsterdam, the Netherlands), offering an audit trail. The data is stored online on the MST server for a minimum of 15 years after completing the CIRCUS cohort. The data management adheres to the Dutch Act of Implementation of the General Data Protection Regulation and the EU General Data Protection Regulation. Only investigators involved in designing and deploying the CIRCUS protocol can access the collected data.

The observational data analysis consists of assessing the risk factors for loss of asthma control and asthma exacerbations, and to discern patient groups within the cohort population. The interventional data analysis consists of assessing the long- and short-term effects of multiple eHealth interventions tailored to the specific patient groups and further modified to the patient's personalized needs. The intervention research questions are analyzed using the intention-to-treat principle to assess the real-life effect, which is further divided into intention-to-treat before and after consent. Furthermore, a per-protocol analysis is performed to estimate the sole effect of the intervention. The patients being offered an intervention are a random sample of the 300 participants of the CIRCUS study. Therefore, as in true randomization, the potential confounding variables should be equally distributed among both groups. However, if relevant, we could correct for these potential confounding variables retrospectively in the analyses as information on these variables is collected.

Data is analyzed using SPSS (IBM SPSS Statistics 29, IBM, New York, NY, USA). Data is visually inspected for normal distribution and results are presented as mean ± standard deviation or as median ± interquartile range as appropriate. For all analyses, significance is set at $p < 0.05$. Analyses of specific interventions will be described for each intervention separately. For two-group comparisons, a two-sample *t*-test or Mann–Whitney *U* test is deployed, as appropriate. Pre-post differences between the two groups are assessed using a paired t-test or Wilcoxon signed rank test, as appropriate. Coherence between continuous variables is examined with the Pearson correlation or the Spearman Rank Correlation. When comparing more than two groups, Analysis of Variance is used to assess normally distributed variables, with Tukey HSD for post-hoc analysis. Non-normally distributed variables are tested using the Kruskal–Wallis tests, followed by Mann–Whitney *U* tests with Holm-Bonferroni correction for post-hoc analysis. Repeated measurements within or between groups over time are assessed using the Mixed Model Repeated Measurement or generalized estimating equations (GEE). Multivariate linear regression is used to assess relationships between continuous variables considering potential confounders. Logistic regression is executed for binary outcome variables. Variables with multi-collinearity > 0.8 are not used simultaneously.

The researchers distinguish between data missing at random and missing not at random. Missing at-random data is less likely to significantly influence findings, depending on its extent, whereas missing nonrandom data may introduce bias. To address this, baseline characteristics of drop-outs and current participants are compared. For analyses involving repeated measures, such as GEE, missing data is inherently managed, and imputation is unnecessary. For other analyses, missing data is handled through listwise or pairwise deletion depending on the data type and extent of missingness, or by applying multiple imputation regression methods. When appropriate, single or Bayesian imputation approaches are also considered to account for missing data.

Monitoring

No data monitoring committee is composed as this study does not pose a risk for the participants.

An interim analysis is performed every 2 years from the start of the CIRCUS cohort. The interim analysis is conducted by the principal investigator, the coordinating investigator, a pediatrician, an epidemiologist, and the patient panel. Analyses will include patient perspectives on study burden and study relevance, outcomes of interventions assessed within the CIRCUS cohort, the amount of study drop-out, and whether future research is relevant for both patients and researchers.

The study can be halted anytime in the process if it hurts the participant's health or safety. The medical research ethics committee is notified and decides on study continuation. Since participation in this observation cohort does not result in extra risks for participants, (serious) adverse advents are not reported.

An independent study monitor will check the eligibility of participants, informed consent, protocol compliance, and overall integrality of gathered data.

Discussion

This research can provide insight into the effects of multiple (eHealth) interventions on pediatric asthma patients' short- and long-term clinical and patient-reported outcomes. Furthermore, it can improve knowledge of the risk factors for asthma exacerbations. This research produces an extensive database and therefore provides an opportunity to discern risk factors for predicting the loss of asthma control. In future studies, this database further provides opportunities to develop AI models for pattern analysis, enabling the prediction of asthma symptoms.[47] Moreover, this research can iteratively contribute to the improvement of current asthma care and allow for better asthma management.

In the literature, cmRCTs are employed in multiple applications; interventions for breast cancer,[48] clinical effects and cost-effectiveness of podiatry interventions,[49] risk factors and impacts of COVID-19,[50] factors influencing care and outcomes in diabetes mellitus type 2,[51] early life interventions,[52] and interventions for small renal masses.[53] The CIRCUS study's aims align with most of the literature's application by evaluating (eHealth) interventions, assessing risk factors for asthma exacerbations, and evaluating factors influencing pediatric asthma (care). The number of included participants in cmRCT varies heavily from 50000 in the BIBBS study[52] to 200 in the NEST study[53] with the number of participants in the CIRCUS study on the lower end of the range. However, the number of participants equals 30% of the pediatric asthma population, therefore considered sufficient. All cmRCT studies in the literature use patient-reported outcomes.[48–53] The ABCD cmRCT additionally gathers healthcare utilization[51] and the UMBRELLA cmRCT gathers clinical outcomes.[48] The CIRCUS study is unique in its multi-extensive outcome lists combining patient-reported outcomes with healthcare utilization data, environmental outcomes, and clinical outcomes from the medical patient file. Notably, this study fills a significant research gap by providing a comprehensive perspective on outcomes, which is essential for a thorough understanding of the interventions' effectiveness. The follow-up periods vary greatly, from 1 year in the REFORM study[49] to 11 years in the BIBBS study.[52] The CIRCUS study is similar to the BIBBS study with a maximum follow-up period of 14 years as they both have a specific focus on the pediatric age range. Patient participation was promoted using informing patients about study results,[48] establishing an advisory group made up of community representatives that aids in study design, and recruitment, and providing feedback,[52] and monthly webinars.[50] Similarly, the CIRCUS study aims to minimize drop-out rates, which are greater in cohort studies, through the use of newsletters, keeping the study burden at a minimum, and establishing the patient panel. These attempts to minimize the drop-out rate can be seen in the results of the UMBRELLA study which reported a 67% questionnaire participation rate[48] and in the COVIDENCE study with 8% for study withdrawal.[50]

This research's strengths include its extensive cohort of pediatric asthma patients, which provides a robust dataset for a comprehensive analysis of asthma risk factors over both short- and long-term periods and throughout multiple stages of development and puberty. Notably, this study uniquely combines the assessment of intervention effects, healthcare utilization, and asthma outcomes. This approach opposes a tendency in existing research to focus on only one domain of eHealth interventions, as highlighted in the scoping review by Van der Kamp et al.[20] Furthermore, this cmRCT design not only ensures a thorough examination of multiple interventions but also enables meaningful comparisons between interventions and with a control group. The cmRCT design assumes that all participants would want to participate in the intervention. This limitation of the design is addressed by estimating the intervention perception by evaluating proposed interventions with the patient panel. A strength of this study is the intention-to-treat analysis that assesses the real-life effect of the interventions, which is common in cmRCT studies, as highlighted in the review by Narzari et al.[27] This real-life effect could be influenced by a high percentage of participants not wanting to join the intervention. This influence can be seen in the difference between the intention to treat analysis and the per-protocol analysis. However, this influence is constrained by a minimum intervention participation rate of 70%. The intervention will only proceed if the minimum participation rate is achieved. Furthermore, this protocol is now

employed in a mono-center study, but its design allows for a future expansion to a multicenter study. The HLS and CSQ-4 questionnaires are not yet validated for children. To address this limitation, we counteract it by having the parents complete the questionnaires, for whom the questionnaires have been validated.

The patient's interests are aligned with this research, as active involvement is emphasized through the patient panel. Close engagement in research can enhance the patient's knowledge, confidence, and personal support in navigating the challenges of their illness.[30] Moreover, patient participation can improve further trust in future care, gain knowledge about research processes, and establish a social network.[30,54] Increased involvement in research is viewed as a valuable incentive to participate more regularly in treatments, which, in turn, can enhance asthma patients' overall health.[30]

Conclusion

The outcomes of the CIRCUS study could contribute significantly to the future landscape of pediatric asthma healthcare. Researchers, clinicians, and the technology industry could gain valuable insight into identifying effective eHealth solutions. Furthermore, the unique design of this cmRCT study allows a high impact on future asthma care as the effectiveness of interventions can be related to health care use, general asthma outcomes, quality of life, and quality of care.

In conclusion, this research will gather observational, clinical, and patient-reported data to provide insight into risk factors in asthma management and into eHealth interventions' short- and long-term effects to ultimately improve pediatric asthma care.

Authors' note

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Declarations

Ethics approval and consent to participate

This study was ethically approved by the Medical Research Ethics Committee (NL85668.100.23) on February 15th, 2024 for CIRCUS protocol 3.0 of February 2nd, 2024. Informed signed consent statements will be obtained from all participants before inclusion by the principal or coordinating investigator. Both parents also sign informed consent statements depending on the participant's age. When adjusting the protocol of the CIRCUS cohort in any way, an amendment will be submitted to the medical research ethics committee for approval. All participants will be notified of changes to the protocol. Furthermore, proposed interventions performed within the CIRCUS cohort will be submitted separately to the medical research ethics committee for ethical approval before implementation through amendment protocols. Informed signed consent will be obtained for all participants approached for interventions within the CIRCUS cohort.

Consent for publication

Not applicable.

Author contributions

Tamara Ruuls: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Romi Sprengers: Conceptualization; Methodology; Writing – review & editing.

Vera Hengeveld: Conceptualization; Methodology; Writing – review & editing.

Boony Thio: Conceptualization; Methodology; Writing – review & editing.

Monique Tabak: Writing – review & editing.

Deborah Zagers: Methodology; Writing – review & editing.

Job van der Palen: Conceptualization; Methodology; Writing – review & editing.

Mattiènne van der Kamp: Conceptualization; Methodology; Supervision; Writing – review & editing.

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The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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