ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Clinical efficacy and satisfaction of a digital wheeze detector in a multicenter randomised controlled trial – the WheezeScan study

Yen Hoang Do, Wim van Aalderen, Ellen Dellbrügger, Claude Grenzbach, Jonathan Grigg, Ulrike Grittner, Eric Haarman, Camilo José Hernandez Toro, Bulent Karadag, Siri Roßberg, Tina-Maria Weichert, Abigail Whitehouse, Antonio Pizzulli, Paolo Maria Matricardi, Stephanie Dramburg

Please cite this article as: Do YH, van Aalderen W, Dellbrügger E, *et al*. Clinical efficacy and satisfaction of a digital wheeze detector in a multicenter randomised controlled trial – the WheezeScan study. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00518-2023).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©The authors 2024. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Clinical efficacy and satisfaction of a digital wheeze detector in a multicenter randomized controlled trial – the WheezeScan study

Yen Hoang Do[1], Wim van Aalderen[2], Ellen Dellbrügger [3], Claude Grenzbach[3], Jonathan Grigg[4], Ulrike Grittner[5], Eric Haarman[2], Camilo José Hernandez Toro[1,5], Bulent Karadag[6], Siri Roßberg[3], Tina-Maria Weichert[3], Abigail Whitehouse[4], Antonio Pizzulli[3 †], Paolo Maria Matricardi[1], Stephanie Dramburg[1*]

Authors' affiliations:

[1] Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité - Universitätsmedizin Berlin.

[2] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

[3] Pediatric Pulmonologist, Berlin, Germany.

[4] Centre for Genomics and Child Health, Blizard Institute, Queen Mary University of London, London, United Kingdom.

[5] Institute of Biometry and Clinical Epidemiology, Charité - Universitätsmedizin Berlin.

[6] Division of Pediatric Pulmonology, Marmara University, Istanbul, Turkey.

Word count: 3.110

Tables: 4

Figures: 4

[*]**Corresponding author:**

Stephanie Dramburg
Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine
Charité Universitätsmedizin Berlin
Augustenburger Platz 1, 13353 Berlin
Tel.: +49-(0)30-450 559 389
stephanie.dramburg@charite.de

Keywords
pre-school wheezing, digital health, childhood, self-management, wheeze detector

Funding sources
The present study was supported by an unconditional grant from OMRON Healthcare Co., Ltd.

Acknowledgements: We thank all study participants and staff involved in this study.

Authors' contributions:

PMM acted as PI of the study and supervised all the study procedures. PMM, AP and SD were active in designing the study. PMM, SD and UG wrote the study protocol and the statistical analysis plan (SAP). The patient recruitment and monitoring were done by ED, T-M. W, SR, CG, BK, AW in close collaboration with SD and YD. Data analysis was performed by UG, YD and C H-T. The manuscript draft was written by YD. All co–authors contributed to the final version and approved it.

Conflict of interest:

Tina-Maria Weichert, Siri Roßberg, Claude Grenzbach, Ellen Dellbrügger, Bulent Karadag and Abigail Whitehouse have received support for the work on this study via an unrestricted scientific grant. Ulrike Grittner has received support for her work on this study as a biostatistician from OMRON Healthcare Co., Ltd via an unrestricted scientific grant. Stephanie Dramburg and Jonathan Grigg received personal fees from OMRON Healthcare. Paolo Maria Matricardi has received funding and provision of study material from OMRON Health Care for the present study as well as consulting fees from OMRON Healthcare not related to the present study. Camilo Jose Hernandez Toro, Yen Hoang Do, Antonio Pizulli, Wim van Aalderen and Eric Haarman have nothing to disclose.

Support statement:

The study was supported by OMRON Healthcare Co., Ltd. via an unconditional grant.

Ethics approval and consent to participate:

The present study was approved by the ethics committee at Charité Universitätsmedizin Berlin, London and Istanbul, it was registered with the registration number DRKS00026740. All participants provided written informed consent.

Consent for publication:

All co-authors gave their consent for publication. The manuscript has not been submitted or published elsewhere before.

List of Abbreviations

ACT, asthma control test

eDiary, electronic diary

ER, emergency room

IgE, immunoglobulin E

IQR, interquartile range

CI, confidence interval

Q1-Q3, first to third quartile

LRI, lower respiratory tract infection

NPV, negative predictive value

PAMSES, parental asthma management self-efficacy scale

PPV, positive predictive value

RCT, randomized controlled trial

SABA, short-acting beta 2 agonists

SD, standard deviation

SPT, skin prick test

TRACK, test for respiratory and asthma control in kids

URI, upper respiratory tract infection

Abstract

Introduction: Wheezing is common in pre-school children and its clinical assessment often challenging for caretakers. This study aims to evaluate the impact of a novel digital wheeze detector (WheezeScan™, OMRON Healthcare Co. Ltd, Japan) on disease control in a home care setting.

Methods: A multicenter randomized open-labeled controlled trial was conducted in Berlin, Istanbul and London. Participants aged 4-84 months with a doctor's diagnosis of recurrent wheezing in the past 12 months were included. While the control group followed usual care, the intervention group received the WheezeScan™ for at home use for 120 days. Parents completed questionnaires regarding their child's respiratory symptoms, disease-related and parental quality of life, and caretaker self-efficacy at baseline (T0), 90 days (T1), and 4 months (T2).

Results: A total of 167 children, with a mean age of 3.2 years (SD 1.6), were enrolled in the study ($n^{intervention}$=87; $n^{control}$=80). There was no statistically significant difference in wheeze control assessed by TRACK (mean difference 3.8, 95% CI -2.3-9.9; p=0.2) at T1 between treatment groups (primary outcome). Children's and parental quality of life and parental self-efficacy were comparable between both groups at T1. The evaluation of device usability and perception showed that parents found it useful.

Conclusion: In the current study population, the wheeze detector did not show significant impact on the home management of pre-school wheezing. Hence, further research is needed to better understand how the perception and usage behavior may influence the clinical impact of a digital support.

Introduction

Wheezing caused by viral infections is common among pre-school children, with up to 50% experiencing at least one wheezing episode in the first 6 years of their life [1,2]. Studies have shown that children suffering from wheeze, especially persistent phenotypes, have a higher risk of developing asthma later in childhood [3]. The main treatment goals for pre-school wheezing are respiratory symptom control, reduction of exacerbations and increasing quality of life for the child [4]. To achieve these aims, training caregivers to correctly detect airway obstruction and administer pharmacological and supportive treatments is essential. However, when it comes to young children (under the age of 6 years), the correct assessment of wheezing breath sounds is particularly difficult, since the distinction of wheezing sounds from physiological breath sounds may be challenging [5,6]. A misjudgement of respiratory symptoms may consequently result in an under- or overtreatment with reliever medication [7,8]. On the other hand, it has been shown that guided self-management options for respiratory diseases such as wheezing can reduce hospitalizations and visits to the emergency department and improve lung function [9,10]. Therefore, supporting parents in the at home self-management of their child´s respiratory condition is key to obtain and maintain respiratory symptom control and improve patient outcomes.

Over the past years, adoption of digital health technologies has continuously increased, from patient-specific electronic health records over sensor technology and (adherence) monitors to telemedicine options for easier accessibility to health care specialists [11,12]. Digital solutions are often easily available and adaptive into everyday life, due to the increasing access to portable internet and smartphones around the globe [13]. Mobile health also allows an efficient and cost-effective data collection via electronic diaries and is usually well received by both patients and clinicians [11]. Therefore, there is a growing interest in the potential of eHealth solutions to allow tailored self-management options specifically for young children suffering from wheezing disorders as well as their parents.

There are several devices such as portable smart inhalers [14,15], asthma symptom diaries [16,17], wearable trackers [18] and health-education based computer games [19] available for the at home management of wheezing disorders. Despite progress in the development and testing of medication sensors and adherence reminders, only few devices have been built and evaluated to detect pathological airway sounds such as wheezing [20,21]. While most digital support tools are currently being evaluated in feasibility studies and small clinical trials, large randomized controlled trials testing their clinical impact on outcomes such as symptom control and quality of life are scarce. In terms of sound recognition, it is not only important to test the accuracy of devices, but also to evaluate the usability and clinical efficacy. These

aspects are particularly important to determine potential benefits and limitations, ensuring the safe and effective use of digital support for conditions such as pre-school wheezing and pediatric asthma.

The aim of this study was to test the hypothesis that a digital support tool for wheeze recognition improves symptom control in a study population of pre-school children. In addition, the device´s impact on disease-specific and parental quality of life as well as subjective self-efficacy in disease management among parents was evaluated in this randomized controlled trial across culturally diverse pediatric populations. Finally, the usability of and satisfaction with the device were assessed.

Materials and Methods

Study population – The multicenter randomized controlled open-labeled trial consisted of two groups, following usual care with (intervention) and without (control) the use of a digital wheeze detector (WheezeScan™, OMRON Healthcare Co. Ltd, Kyoto, Japan) device, respectively. Patients were recruited between October 2021 and September 2022 in six specialized pediatric pulmonology outpatient departments located in Berlin (ambulatory clinics of Dr. Dellbrügger, Dr. Roßberg, Dr. Weichert, Dr. Grenzbach), London (Blizard Institut at Queen Mary University of London), and Istanbul (ambulatory clinic of Prof. Karadag and Marmara University Istanbul). The inclusion criteria were: (1) age 4 months to 7 years; (2) at least one episode of doctor diagnosed wheezing and/or recurrent cough requiring treatment according to GINA guidelines steps 1 or 2 in the last 12 months [22]; (3) availability of a smartphone. Exclusion criteria were: (1) an anatomic malformation causing chronic nasal and/or bronchial obstruction, (2) presence of another severe chronic disease and (3) wheezing disorders requiring treatment step 3 or 4 according to GINA guidelines. The study was registered in the German Clinical Trials Registry (DRKS00026740) and ethics approval was obtained for at all study sites.

Study design - After randomization, parents were interviewed regarding the personal and family anamnesis of their child including information on allergic diseases and demographic variables. Validated questionnaires regarding diseases severity and disease-specific quality of life were administered. Families of the intervention group were trained to use the digital wheeze detector WheezeScan™ (OMRON Healthcare Co., Ltd) and received their device to take home. A comparison between the device´s measurement and the study physician´s auscultation was recorded. The current treatment scheme was reported for all participants by the study physician. After the recruitment visit (T0) all participating families were asked to fill an electronic daily questionnaire via the mobile application WheezeMonitor® (TPS Production S.rl, Rome, Italy) over a total of 120 observation days. Families of the intervention group were additionally encouraged to use the WheezeScan™ device whenever they felt that their child could be experiencing respiratory distress. An initial follow up visit (T1) was performed after 90 days of the

monitoring period. Parents responded again to questionnaires on disease severity, self-efficacy and quality of life, and the attending physician assessed whether an adaptation of treatment was necessary according to GINA-guidelines. Participants of the intervention group were also asked to fill a usability and satisfaction questionnaire regarding the WheezeScan™ device. After T1, all participants continued the observation period for another 30 days until the final study visit (T2), where any changes in asthma control via the TRACK (Test for Respiratory and Asthma Control in Kids) questionnaire and changes in treatment according to GINA-guidelines were recorded. The aim of the final visit was to evaluate potential clinical improvements after a treatment adaptation. For an overview on the enrolment and randomization please see **[Figure 1]**.

Questionnaires - The primary outcome of symptom control was assessed via the Test for Respiratory and Asthma Control in Kids (TRACK) [23] questionnaire at T1. Secondary outcomes were assessed at T1 via the Parental Asthma Management Self-Efficacy Scale (PAMSES) [24], the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) [25], the TAPQOL on parent´s perception of health-related quality of life in pre-school children [26], and user satisfaction with the device in the intervention group was assessed via a usability and satisfaction questionnaire. An additional secondary outcome was assessed via the TRACK questionnaire at T2. The secondary outcome regarding the frequency of reliever medication use was recorded in the e-diary of the monitoring App during the entire study period.

Digital Wheeze Detector - Families allocated to the intervention group received a digital wheeze detector (WheezeScan™, OMRON Healthcare Co. Ltd, Kyoto, Japan) to be used whenever needed in a home care setting. Performance, safety, and usability of the device had been evaluated in previous studies [27,28]. The WheezeScan™ assesses respiratory symptoms of the child via a sound detector once placed on the chest just below the right collarbone. After approximately 30 seconds of measurement, results are indicated via an integrated display **[Figure e1]**.

Statistics – For information on the sample size calculation, please see the online repository. As descriptive analysis summary measures such as mean and standard deviation (SD), median, first and third quartile (q1-q3), number (n) and percentage (%) depending on the scaling of the variables are reported for the two groups and the total study population. The intervention effect on the primary and secondary outcomes was assessed in the full analysis set using the intention-to-treat principle. All randomized participants were included in the full analysis set.

Primary analysis consisted of a comparison of the TRACK-score at T1 between intervention and control group using ANCOVA with the TRACK score at T1 as dependent variable and treatment group, center, and

TRACK score at T0 as covariates. Mean difference between intervention and control group and 95%CI as well as standardized effect size were estimated. A two-sided significance level of α=0.05 was used for the primary analysis. For information on the secondary and subgroup analyses, please see the online repository. All statistical analysis were performed in R version 4.2.2 (R Foundation for Statistical Computing).

More information on materials and methods can be found in the online repository.

Results

In total, 167 children were enrolled in the study, with 85 (50.9%) of the children being recruited in Berlin, 59 (35.3%) in Istanbul, and 23 (13.8%) in London. Eighty-seven participants were allocated to the intervention group, and 80 to the control group. Of the 167 families, 150 (89.8%) completed the first follow-up assessment and 153 (91.6%) the final study visit. While seven participants were lost to follow-up, another seven actively withdrew their consent due to experiencing technical difficulties with the device and/or monitoring application. On average, participants had a mean age of 3.2 (SD 1.6) years, 116/167 (69.5%) were male and 133/167 (79.6%) had one or more siblings. Relevant differences between the two treatment groups were observed regarding the presence of an allergic disease. While 31% (27/87) of the children in the intervention group suffered from allergy, this was only the case for 17.5% (14/80) of the controls. **[Table 1]**.

Impact of the digital wheeze detector on asthma control (TRACK): Primary Outcome analysis

The intervention group started off with a slightly lower baseline TRACK score (64.5 points, SD 20.9) than the control group (66.3 points, SD 22.8). At T1, the intervention group had an average of 79.1 (SD 17.7) points, while the control group had a mean score of 76.2 (SD 19.8) points **[Table 2]**. Although the absolute increase in the intervention group was higher than in the control group **[Figure 3],** the mean difference (at T1) between the two groups was not statistically significant (3.6, 95% CI -2.3-9.4, p=0.228, primary endpoint). At T2 (120 days after baseline), both groups had a similar mean TRACK score (the intervention group: 78.4 points (SD 18.7), the control group: 78.3 points (SD 19.4)) **[Figure e3 A]**. Regarding a potential impact of treatment changes at T1, no changes in treatment were performed.

When analyzing categorical asthma control ("not well controlled" and "well controlled") between T0 and T1 in each of the treatment groups, the proportion of patients with good control of wheezing increased in both groups with a slightly larger increase among the intervention group (increase in portion of participants with controlled wheezing from T0 to T1 in control group by 15%, in intervention group by 27%) **[Figure 4]**. For subgroup analyses please refer to the online repository.

Disease-specific and parental quality of life and parental self-efficacy in asthma management

The disease-specific quality of life of the participating children improved in both groups between the baseline and follow-up visit. There was no intervention effect at T1, as underlined by the mean difference between groups at T1 of -0.9 (95% CI -4.1-2.3, p=0.6) **[Figure 2 B, F]**. Similar results were observed for parental quality of life (PACQLQ mean difference 0.2, 95% CI -0.1-0.6; p=0.1) **[Figure 2 C, G]** and parental self-efficacy in managing their child´s wheezing condition (PAMSE Score mean difference -0.8, 95% CI -3.6-2.0; p=0.6) **[Figure 2 D, H, Table 2]**. Interestingly, all secondary outcomes improved between study visits with little to no differences between the study groups.

Use of reliever medication and unscheduled healthcare utilization

In case of SABA treatment, no pronounced differences were observed between study arms **[Figure e8]**. Further, the number of unscheduled visits at the pediatrician´s office or emergency department between T0 and T1 (120 days) was slightly higher in the control group than in the intervention group with a mean of 2.16 (SD 3.33) vs. 1.57 (SD 2.45) and 0.81 (SD 1.34) vs. 0.60 (1.73) visits, respectively.

Satisfaction, and usability

Regarding device usability, 80% (60/75) of the intervention group indicated having used the digital wheeze detector without complications and only 14/75 (19%) considered the handling difficult. If parents experienced problems, these were most frequently due to challenges in keeping the child calm enough for the device to function well. Ten families (13%) of the intervention group reported having difficulties in technically operating the device **[Table 4]**. When asked whether they believe their child to have benefitted from the use of the WheezeScan™, the majority answered positively (45/75, 60%). For more information on usability results by study center and age group, please see the online repository.

Discussion

In our multicenter randomized open-labeled controlled trial on the clinical efficacy and usability of a digital wheeze detector for pre-school children we observed: i) no significant difference regarding wheeze control between study groups, ii) no impact on disease-specific or parental quality of life, iii) almost no differences regarding parental self-efficacy in managing the child´s disease, iv) good usability reports by parents, particularly for the older children in our study, vi) positively perceived benefit for the child from device usage, particularly for the very young and older children, and vii) regional differences in device usage and evaluation.

Performance of digital interventions for wheezing disorders

Although often limited by small patient numbers and exploratory designs, several studies have reported positive results on the sensitivity and specificity of electronic devices detecting pathological airway sounds such as wheezing or cough [21, 27, 20, 34-35]. For instance, the device used in this study demonstrated high sensitivity (100%) and specificity (95,7%) for wheeze detection when compared to the auscultation of specialized physicians [27]. A study, comparing digital electronic stethoscopes to pediatricians´ auscultation has even suggested that the digital stethoscopes tested were more sensitive to detecting wheeze in children than the clinician when matching both to automated spectrogram analysis [20]. The high sensitivity and improving accuracy of such devices underlines their potential benefit as valuable tools for (remote) diagnosis and monitoring in research settings [36]. However, there is a lack of published randomized controlled trials assessing the clinical efficacy of digital detectors of pathological airway sounds in the hands of patients and/or caretakers. Reviews examining the impact of digital interventions in children with asthma on clinical parameters have also shown inconsistent findings. A systematic review of digital asthma interventions found that half of the studies favored digital interventions [36], while the other half reported no significant difference in asthma control.

Our results suggest that the used wheeze detector has no statistically significant clinical impact among this particular study population. However, trends in the results suggest that the impact of a digital device may be related to a variety of factors such as age, cultural background, disease severity, access to specialized healthcare providers, or usage patterns.

Therefore, the chosen setting and study population might play an important role in studies evaluating clinical efficacy of developed technologies. For example, in a pilot study on the use of WheezeScan™, parents of 20 pre-school children were instructed to use the device once every morning and evening in addition to when they felt it was needed. This led to a more frequent use than in the RCT. Interestingly, the pilot study showed a positive trend in parental self-efficacy (PAMSES), although the absence of a control group and small sample size in the pilot study increases the risk of confounding factors. This observation underlines, that in addition to standardized study protocols, it is essential to consider the characteristics of the target population when interpreting results.

One size/device does not fit all

Potential factors influencing device efficacy have also been identified in the satisfaction and usability evaluation of the present study. The device usability was rated as uncomplicated by most parents and most of them perceived their child to have benefitted from its use. This indicates a high of willingness to use an at-home digital support system among parents of children suffering from recurrent wheeze and is

in line with current research in the field. However, several families reported difficulties, such as result variability and found the device to be too sensitive to background noises. This perception may have impacted the willingness to use the wheeze detector frequently, which in turn may affect the power of outcome analyses. As real-life circumstances may have a significant impact on the use and effectiveness of digital devices, continued efforts to understand usage scenarios are key when evaluating the clinical effectiveness of digital support tools.

In addition, results on the perceived benefit varied not only between age groups, but also according to geographical and cultural background. A more critical evaluation and less frequent use of the device by patients from Berlin compared to Istanbul or London, may imply that in addition to potential differences in the healthcare setting, cultural variations could affect aspects, such as perceived benefit and usage behavior. Therefore, a deep understanding of the perception and usage of a specific digital tool among targeted patient groups is crucial in assessing digital health solutions.

Strengths and Limitations

The study´s strengths include its randomized controlled trial design, enabling a more selective evaluation of the effects of the digital device on the various patient outcomes. A multicenter approach in different geographical and cultural settings, as well as the relatively large sample size compared to previous studies increase the generalizability of results.

However, the study also has important limitations as it focused on mildly to moderately affected children and excluded those with a more severe phenotype. Furthermore, the participants of the study were recruited in slightly different settings according to the study site. While in Berlin and Istanbul children were recruited mainly from pediatric outpatient clinics, the study center in London was a specialized clinic where participants were likely to have their first contact with a specialized pediatric pulmonologist. This may have affected the improvement of wheeze control and quality of life for all participants, independently from the study group. Finally, the recruitment period stretched over several seasons. Although the summer season was avoided by a recruitment break in July and August, the prevalence of wheezing exacerbations was relatively low and may have varied according to the time point of enrolment.

Conclusions and perspectives for future research

The clinical evaluation of digital support tools to be used by patients and/or caretakers is crucial, as their clinical use may differ fundamentally from highly standardized research settings. The present study shows that despite its very good performance in previous validation studies, no significant clinical impact could be observed for the wheeze detector when tested in a multicenter randomized controlled trial. However,

the study underlines the importance of further studies and a deeper understanding of parameters characterizing the target group for digital support tools. Further research is needed to gain better insight into patient perception, usage behavior and barriers to successful implementation.

References

1. Doss AMA, Stokes JR. Viral Infections and Wheezing in Preschool Children. Immunol Allergy Clin North Am. 2022;42(4):727-741.
2. Rajapakse Mudiyanselage SIR, Amarasiri W, Yasaratne B, Warnasekara J, Agampodi S. Epidemiology of wheeze among preschool children: a population-based cross-sectional study from rural Sri Lanka. BMJ Open. 2021;11(7):e046688.
3. Herzog R, Cunningham-Rundles S. Pediatric asthma: natural history, assessment, and treatment. Mt Sinai J Med. 2011;78(5):645-660.
4. Tenero L, Tezza G, Cattazzo E, Piacentini G. Wheezing in preschool children. Early Hum Dev. 2013;89 Suppl 3:S13-17.
5. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008;32(4):1096-1110.
6. Brand PL, Caudri D, Eber E, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. Eur Respir J. 2014;43(4):1172-1177.
7. Vasilopoulou I. Underdiagnosis and undertreatment of asthma in children: a tertiary hospital's experience. Clin Transl Allergy. 2015;5 P19.
8. Lozano P, Finkelstein JA, Hecht J, Shulruff R, Weiss KB. Asthma medication use and disease burden in children in a primary care population. Arch Pediatr Adolesc Med. 2003;157(1):81-88.
9. Morrison D. Digital Asthma Self-Management Interventions: A Systematic Review. J Med Internet Res. 2014;16 (2):e51.
10. Ferrante G, Licari A, Marseglia GL, La Grutta S. Digital health interventions in children with asthma. Clin Exp Allergy. 2021;51(2):212-220.
11. Alvarez-Perea A, Dimov V, Popescu FD, Zubeldia JM. The applications of eHealth technologies in the management of asthma and allergic diseases. Clin Transl Allergy. 2021;11(7):e12061.
12. Ramsey RR, Caromody JK, Voorhees SE, et al. A Systematic Evaluation of Asthma Management Apps Examining Behavior Change Techniques. J Allergy Clin Immunol Pract. 2019;7(8):2583-2591.
13. Report of the International Telecommunication Union (ITU) 2022. https://www.itu.int/itu-d/reports/statistics/2022/11/24/ff22-internet-use/. (last accessed: 19-06-2023)
14. Vasbinder EC, Goossens LM, Rutten-van Mölken MP, et al. e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC): a randomised controlled trial. Eur Respir J. 2016;48(3):758-767.
15. Merchant RK, Inamdar R, Quade RC. Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. J Allergy Clin Immunol Pract. 2016;4(3):455-463.
16. Clark M, Romano C, Olayinka-Amao O, et a. Development and content validation of a self-completed, electronic Pediatric Asthma Symptom Diary. J Patient Rep Outcomes. 2022;6(1):25
17. Mayoral K, Garin O, Caballero MA, et al. Smartphone App for monitoring Asthma in children and adolescents. Qual Life Res. 2021;30(11):3127-3144
18. Hosseini A, Buonocore CM, Hashemzadeh S, et al. Feasibility of a Secure Wireless Sensing Smartwatch Application for the Self-Management of Pediatric Asthma. Sensors (Basel). 2017;17(8).

19. Sarasmita MA, Larasanty LPF, Kuo LN, Cheng KJ, Chen HY. A Computer-Based Interactive Narrative and a Serious Game for Children With Asthma: Development and Content Validity Analysis. J Med Internet Res. 2021;23(9):e28796.

20. Kevat AC, Kalirajah A, Roseby R. Digital stethoscopes compared to standard auscultation for detecting abnormal paediatric breath sounds. Eur J Pediatr. 2017 Jul;176(7):989-992.

21. Urban C, Kiefer A, Conradt R, Kabesch M, Lex C, Zacharasiewicz A, Kerzel S. Validation of the LEOSound® monitor for standardized detection of wheezing and cough in children. Pediatr Pulmonol. 2022 Feb;57(2):551-559.

22. Von Mutius E. Presentation of new GINA guidelines for paediatrics. The Global Initiative on Asthma. Clin Exp Allergy. 2000 Jun;30 Suppl 1:6-10. doi: 10.1046/j.1365-2222.2000.00089.x. PMID: 10849467.

23. Murphy KR ZR, Kosinski M, et al. Test for respiratory and asthma control in kids (TRACK): a caregiver-completed questionnaire for preschool-aged children. J Allergy Clin Immunol. 2009;123(4):833-9.e9. doi:10.1016/j.jaci.2009.01.058.

24. Bursch B, Schwankovsky L, Gilbert J, Zeiger R. Construction and validation of four childhood asthma self-management scales: parent barriers, child and parent self-efficacy, and parent belief in treatment efficacy. J Asthma. 1999;36(1):115-128.

25. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. Qual Life Res. 1996;5(1):27-34.

26. Fekkes Mea. Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1-5-year-old children. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation vol. 9,8 (2000): 961-72.

27. Habukawa C, Ohgami N, Matsumoto N, et al. A wheeze recognition algorithm for practical implementation in children. PLoS One. 2020;15(10):e0240048.

28. Dramburg S, Dellbrügger E, van Aalderen W, Matricardi PM. The impact of a digital wheeze detector on parental disease management of pre-school children suffering from wheezing-a pilot study. Pilot Feasibility Stud. 2021;7(1):185.

29. van Buuren S, Groothuis-Oudshoorn K (2011). “mice: Multivariate Imputation by Chained Equations in R.” *Journal of Statistical Software*, 45(3), 1-67. doi:10.18637/jss.v045.i03.

30. Bates D, Mächler M, Bolker B, Walker S (2015). “Fitting Linear Mixed-Effects Models Using lme4.” *Journal of Statistical Software*, 67(1), 1–48. doi:10.18637/jss.v067.i01.

31. Russel V. Lenth. R package emmeans: Estimated marginal means. https://github.com/rvlenth/emmeans. Date last updated: July 13 2023. Date last accessed: July 13 2023.

32. Wickham H (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. ISBN 978-3-319-24277-4, https://ggplot2.tidyverse.org.

33. Lüdecke D (2018). “ggeffects: Tidy Data Frames of Marginal Effects from Regression Models.” *Journal of Open Source Software*, 3(26), 772. doi:10.21105/joss.00772.

34. Lee SH, Kim YS, Yeo MK, et al. Fully portable continuous real-time auscultation with a soft wearable stethoscope designed for automated disease diagnosis. Sci Adv. 2022;8(21):eabo5867.

35. Birring SS, Fleming T, Matos S, Raj AA, Evans DH, Pavord ID. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-1018.

36. Morrison D, Wyke S, Agur K, et al. Digital asthma self-management interventions: a systematic review. J Med Internet Res. 2014;16(2):e51.

37. Merchant RK, Inamdar R, Quade RC. Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. J Allergy Clin Immunol Pract. 2016;4(3):455-463.

Table 1 Baseline characteristics

	Overall (n= 167)		**Intervention** (n= 87)		**Control** (n=80)	
	n	**%**	**n**	**%**	**n**	**%**
Sex (male)	116	*69.5*	65	*74.4*	51	*63.7*
Age in years, mean (*SD*)	3.2 *(1.6)*		3.1 (1.6)		3.5 *(1.6)*	
Patient distribution by center						
Berlin	85	*50.9*	44	*50.6*	41	*51.2*
Istanbul	59	*35.3*	31	*35.6*	28	*35.0*
London	23	*13.8*	12	*13.8*	11	*13.8*
Number of siblings						
0	34	*20.4*	15	*17.2*	19	*23.8*
1	78	*46.7*	47	*54.0*	31	*38.8*
2	40	*24.0*	17	*19.5*	23	*28.7*
3	12	*7.2*	7	*8.0*	5	*6.2*
4	1	*0.6*	1	*1.1*	0	*0.0*
5	2	*1.2*	0	*0.0*	2	*2.5*
Week of pregnancy at birth, mean (*SD*)	38.6 (2.5)		38.5 (2.9)		38.7 (2.1)	
Body weight at birth in gr, mean (*SD*)	3 400 (640)		3 450 (677)		3 355 (596)	
Body height at birth in cm, mean (*SD*)	50.8 (3.8)		50.8 (4.2)		50.9 (3.3)	
Allergic comorbidities						
Any allergy	41	*24.6*	27	*31*	14	*17.5*
Allergic rhinoconjunctivitis	9	*5.4*	5	*5.7*	4	*5.0*
Atopic dermatitis	8	*4.8*	6	*6.9*	2	*2.5*
Food allergy	8	*4.8*	4	*4.6*	4	*5.0*
Other allergy	8	*4.8*	7	*8.0*	1	*1.3*
Allergy Diagnostics						
Positive SPT* and/or serum IgE test	47	*28.1*	32	*36.8*	15	*18.8*
Family history of allergies						
Father allergic	53	*31.7*	34	*39.1*	19	*23.8*
Mother allergic	38	*22.8*	25	*28.7*	13	*16.2*
Allergic sibling	23	*13.8*	16	*18.4*	7	*8.8*

* skin prick test

Table 2 Primary and secondary outcomes by study group and time point (T1 = 90 days)

Scale	Total Participants		Intervention group		Control group		Difference Intervention vs Control group (95% CI)
	T0 n=167	**T1** n=150	**T0** n=87	**T1** n=78	**T0** n=80	**T1** n=72	
TRACK mean (SD)*	65.4 (21.8)	77.7 (18.7)	64.5 (20.9)	79.1 (17.7)	66.3 (22.8)	76.2 (19.8)	3.59 (-2.26-9.44); p=0.23
PAMSE mean (SD)	49.9 (8.8)	51.0 (9.4)	50.5 (8.6)	51.1 (8.9)	49.1 (9.0)	51.0 (10.0)	-0.80(3.64-2.04); p=0.58
PACQLQ mean (SD)	5.5 (1.3)	6.3 (1.0)	5.6 (1.3)	6.4 (1.0)	5.5 (1.4)	6.1 (1.0)	0.24 (-0.07-0.55); p=0.12
TAPQOL mean (SD)	62.9 (11.0)	68.1 (11.2)	62.6 (12.0)	67.2 (12.8)	63.1 (9.9)	69.1 (9.1)	-0.91 (-4.12-2.31); p=0.58

*Primary endpoint. Calculation of all intervention effects were based on multiple imputation estimates and ANCOVA

Table 3 No. of days with wheezing episodes and unscheduled healthcare utilization between T0 and T1 (120 days) per study group

	Intervention (n=87)	**Control (n=80)**
Days with little wheezing, mean (SD)	7.9 (10.3)	7.8 (11.9)
Days with strong wheezing, mean (SD)	0.9 (2.5)	1.4 (4.9)
Unscheduled doctor´s visit, mean (SD)	1.6 (2.5)	2.2 (3.3)
Visit of an emergency department, mean (SD)	0.6 (1.7)	0.8 (1.3)

Table 4 Satisfaction and device usability among different age groups of the intervention group at T1

	4-12 months (n=17)		**13-48 months** (n=43)		**> 48 months** (n=15)	
How was the handling of the WheezeScan at home?	**n**	**%**	**n**	**%**	**n**	**%**
without complications	13	*76*	32	*74*	15	*100*
difficult	3	*18*	11	*26*	0	*0*
impossible	1	*6*	0	*0*	0	*0*
If there were problems in use, what were they most likely to be?						
difficulties in operating the device	2	*12*	5	*12*	3	*20*
child didn´t tolerate the measurements	4	*24*	11	*26*	4	*27*
no problems occured	9	*53*	24	*56*	8	*53*
no answer possible	2	*12*	3	*7*	0	*0*
Do you think your child benefitted from using the device?						
yes	6	*35*	15	*35*	10	*67*
rather yes	5	*29*	8	*19*	1	*7*
rather no	2	*12*	9	*21*	3	*20*
no	4	*24*	11	*26*	1	*7*
Would you recommend the device to other parents?						
yes	10	*67*	17	*40*	9	53
rather yes	2	*13*	8	*19*	2	12
rather no	0	*0*	10	*23*	2	12
no	3	*20*	8	*19*	4	24
Are you interested in continuing to use the device?						
yes	10	*59*	16	*37*	8	53
rather yes	0	*0*	8	*19*	3	20
rather no	1	*6*	6	*14*	0	0
no	6	*35*	13	*30*	4	27

Legend to figures

Figure 1 – Consort chart with inclusion criteria, recruitment, study design and timeline.

Figure 2 –Wheeze control (TRACK), disease-specific quality of life (TAPQOL), parental quality of life (PACQLQ) and parental asthma management self-efficacy (PAMSES) by study groups (control group n=80, intervention group n=87) and time points (T0: baseline and T1: 90 days) depicted as box plots /rain cloud plots (A-D). Additionally, estimated marginal means using linear regression models are shown by group at T1 (90 days) with 95%CI (E-H).

Figure 3 – Individual measures of wheeze control (TRACK) at baseline (T0: baseline) and follow-up (T1: 90 days) for the intervention (n = 78) and control group (n=72)

Figure 4 – Proportion of well-controlled (TRACK ≥80 points) and not well-controlled (TRACK <80) by study group (control group n=80, intervention group n=87) and time point. Total number of participants in each TRACK group per treatment group per time point are shown at the top of each section of the bar plot.

Figure 1

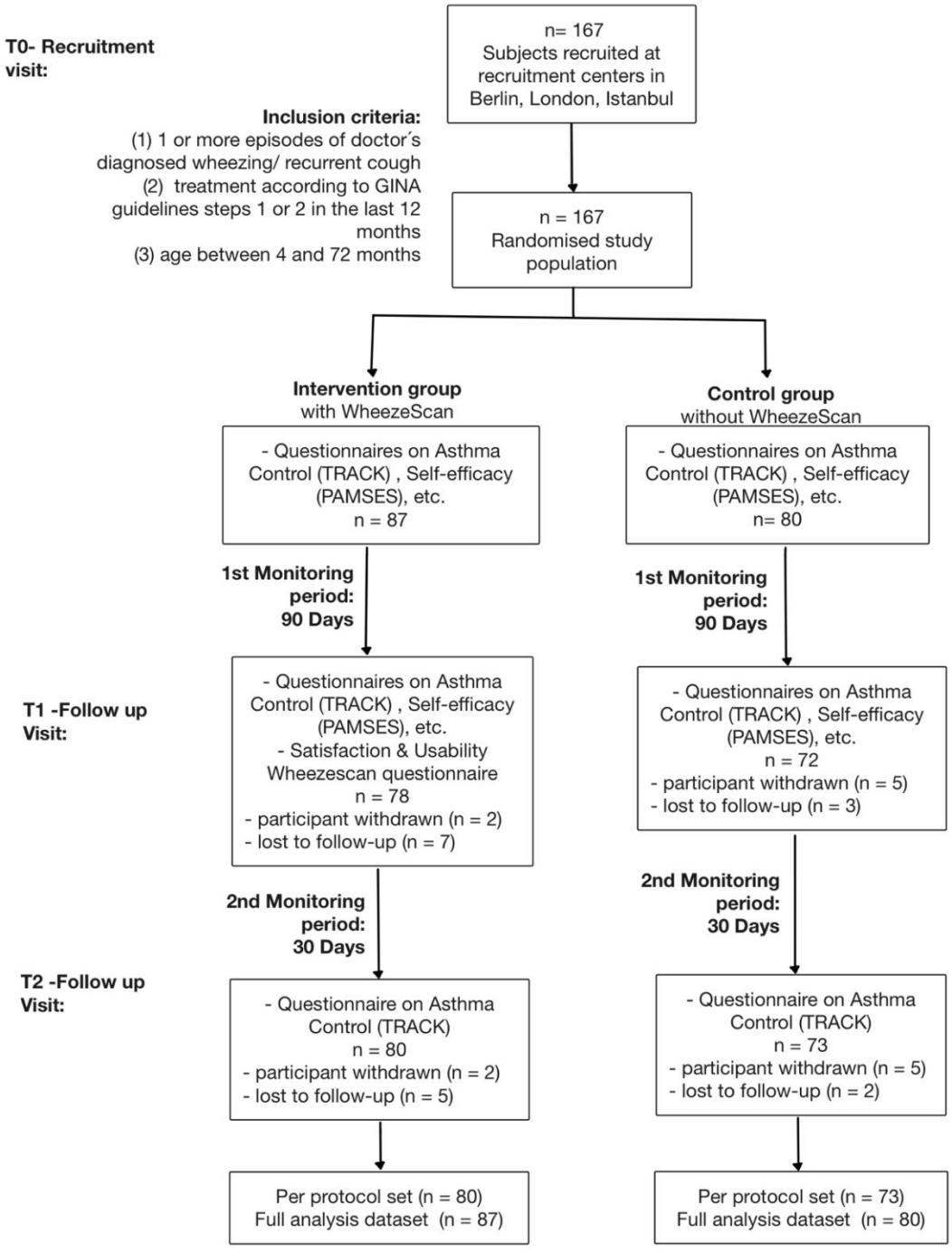

T0- Recruitment visit:
n= 167
Subjects recruited at recruitment centers in Berlin, London, Istanbul
Inclusion criteria:
(1) 1 or more episodes of doctor´s diagnosed wheezing/ recurrent cough
(2) treatment according to GINA guidelines steps 1 or 2 in the last 12 months
(3) age between 4 and 72 months
n = 167
Randomised study population
Intervention group
with WheezeScan
Control group
without WheezeScan
- Questionnaires on Asthma Control (TRACK) , Self-efficacy (PAMSES), etc.
n = 87
- Questionnaires on Asthma Control (TRACK) , Self-efficacy (PAMSES), etc.
n= 80
1st Monitoring period: 90 Days
1st Monitoring period: 90 Days
T1 -Follow up Visit:
- Questionnaires on Asthma Control (TRACK) , Self-efficacy (PAMSES), etc.
- Satisfaction & Usability Wheezescan questionnaire
n = 78
- participant withdrawn (n = 2)
- lost to follow-up (n = 7)
- Questionnaires on Asthma Control (TRACK) , Self-efficacy (PAMSES), etc.
n = 72
- participant withdrawn (n = 5)
- lost to follow-up (n = 3)
2nd Monitoring period: 30 Days
2nd Monitoring period: 30 Days
T2 -Follow up Visit:
- Questionnaire on Asthma Control (TRACK)
n = 80
- participant withdrawn (n = 2)
- lost to follow-up (n = 5)
- Questionnaire on Asthma Control (TRACK)
n = 73
- participant withdrawn (n = 5)
- lost to follow-up (n = 2)
Per protocol set (n = 80)
Full analysis dataset (n = 87)
Per protocol set (n = 73)
Full analysis dataset (n = 80)

Figure 2

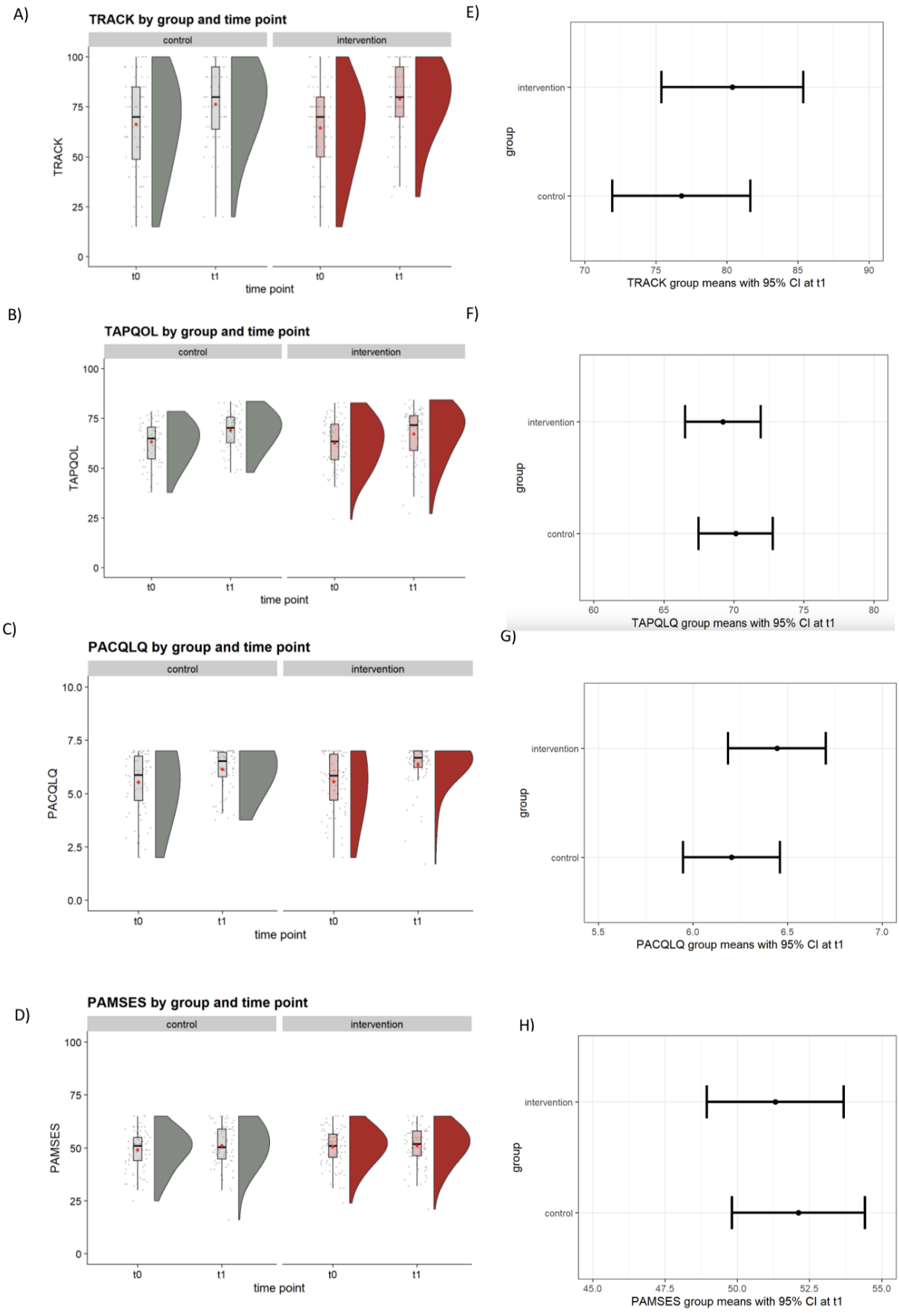

A)
TRACK by group and time point
control
intervention
TRACK
time point
t0
t1
E)
group
intervention
control
TRACK group means with 95% CI at t1
B)
TAPQOL by group and time point
TAPQOL
F)
TAPQLQ group means with 95% CI at t1
C)
PACQLQ by group and time point
PACQLQ
G)
PACQLQ group means with 95% CI at t1
D)
PAMSES by group and time point
PAMSES
H)
PAMSES group means with 95% CI at t1

Figure 3

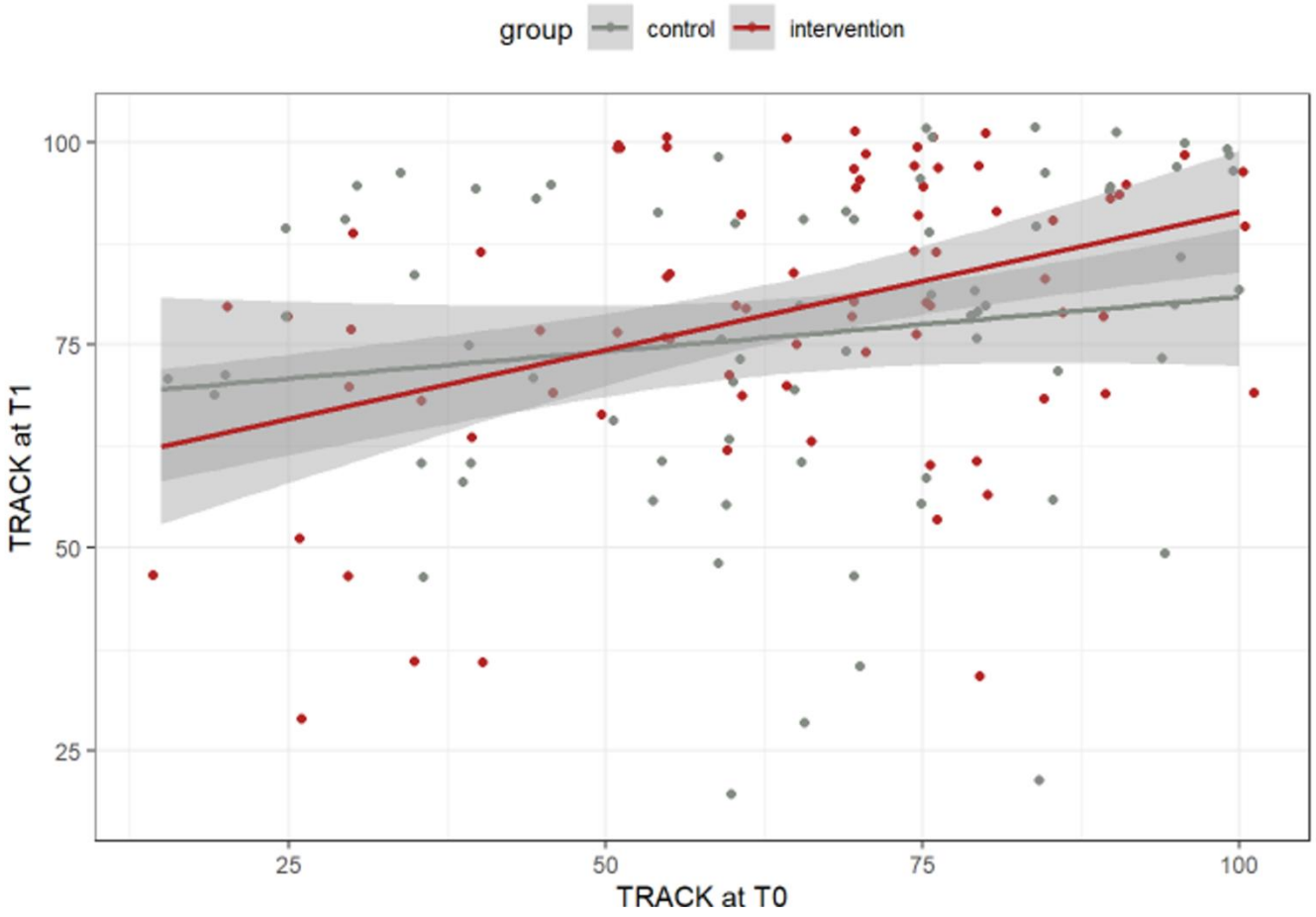
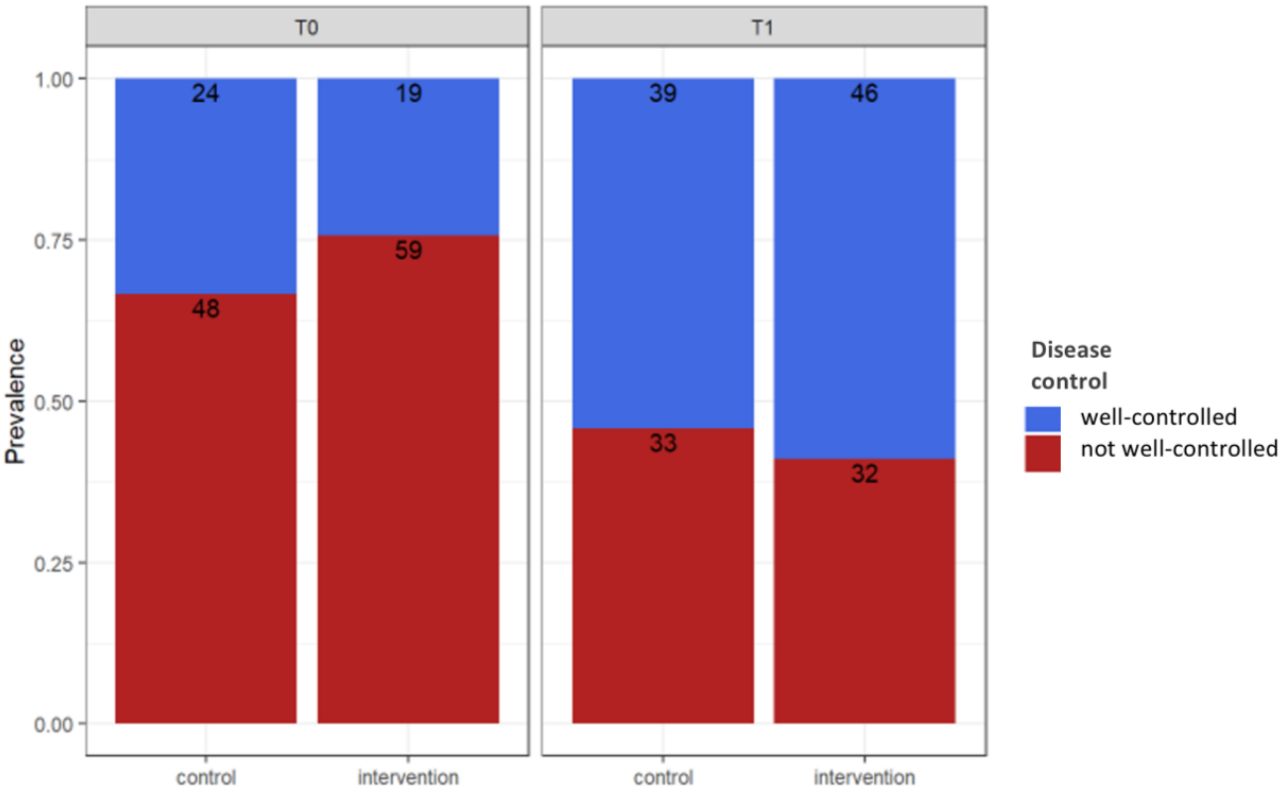

group
control
intervention
100
75
50
25
TRACK at T1
25
50
75
100
TRACK at T0

Figure 4


T0
T1
1.00
0.75
0.50
0.25
0.00
Prevalence
24
19
48
59
39
46
33
32
control
intervention
control
intervention
Disease control
well-controlled
not well-controlled

Clinical efficacy and satisfaction of a digital wheeze detector in a multicenter randomized controlled trial – the WheezeScan study

- Electronic Repository –

Yen Hoang Do [1], Wim van Aalderen [2], Ellen Dellbrügger [3], Claude Grenzbach[3], Jonathan Grigg [4], Ulrike Grittner[5], Eric Haarman [2], Camilo José Hernandez Toro[1,5], Bulent Karadag[6], Siri Roßberg [3], Tina-Maria Weichert [3], Abigail Whitehouse [4], Antonio Pizzulli[1†], Paolo Maria Matricardi [1], Stephanie Dramburg [1*]

Authors' affiliations:

[1] Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité - Universitätsmedizin Berlin.

[2] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

[3] Pediatric Pulmonologist, Berlin, Germany.

[4] Centre for Genomics and Child Health, Blizard Institute, Queen Mary University of London, London, United Kingdom.

[5] Institute of Biometry and Clinical Epidemiology, Charité - Universitätsmedizin Berlin.

[6] Division of Pediatric Pulmonology, Marmara University, Istanbul, Turkey.

Word count: 1.630
Figures: 9

[*]**Corresponding author:**
Stephanie Dramburg
Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine
Charité Universitätsmedizin Berlin
Augustenburger Platz 1, 13353 Berlin
Tel.: +49-(0)30-450 559 389
stephanie.dramburg@charite.de

Methods

Study population - The parents and/or guardians of all participating children gave written informed consent regarding the child's participation in the study. In comparison to the study protocol, the age eligibility criteria for recruitment were adjusted by 12 months to include the full range of children in the pre-school age group.

Questionnaires - The safety outcomes regarding the emergency visits or hospital stays, and the unscheduled physician visits were recorded in the e-diary of the study app.

Digital Wheeze Detector - Parents were instructed to remove nasal mucous before the measurement and to create a calm environment to avoid confounding environmental sounds. In case of interference, e.g. by ambient sounds, the detector gives a visual error signal, and parents were instructed to repeat the measurement.

Study app - The mobile application WheezeMonitor® (TPS Software Production S.r.l, Rome, Italy) was used for recording respiratory symptoms, medication intake, and unscheduled visits to the doctor's office or emergency department as well as the results of the WheezeScan™ device via a daily electronic questionnaire. Automated daily reminders to fill the questionnaire were activated on the caretaker´s phone. After three consecutive days of missed reporting, parents were contacted by the study team via e-mail or phone call to check whether technical or other support was necessary.

Monitoring period - After the recruitment visit (T0) all participating families filled a daily questionnaire in the WheezeMonitor® app over 120 observation days. Questions addressed the child´s respiratory symptoms, medication intake, absence from day-care, missed workdays, and visits to the doctor´s office or emergency department. Families of the intervention group were additionally encouraged to use the digital wheeze detector whenever they felt that their child could be experiencing respiratory distress. The results of the device were also recorded via the study app.

Randomization - Randomization was performed by the study statistician Ulrike Grittner. The random assignment of the study participants into the two treatment groups (allocation ratio 1:1) was performed by blocked randomization with varying block size (block sizes: 2, 4, and 6) stratified by study center.

Sample size calculation - Based on the results of the pilot study [28] a sample size of 164 patients was calculated. In the pilot study the mean Asthma Control Test (ACT) score at baseline was 18.3 points (SD: 3.9), and 21.3 (SD: 4.4) after intervention. This variance measures corresponds to a pooled standard deviation of 4.2. We expected a higher variance of 6 in this study, which is comparing two groups (intervention and control). The sample size was estimated assuming that the intervention group would

have an improvement of the ACT score 3 points higher than the expected improvement with conventional treatment. A mean difference between intervention and control groups in ACT score of 3 points and a common standard deviation of 6 points corresponds to an effect size (Cohen's d) of 0.5. Although the outcome in the pilot study was not the TRACK score but the ACT, we assume similar effect sizes for the TRACK Score. Based on that assumption it was estimated that the enrolment of 164 children would provide 80% power with a two-sided 5% significance level allowing for a 22% dropout rate.

Missing data - Missing values in the data were assumed to be missing at random or completely at random. Thus, all missing values in the full analysis set were imputed using multiple imputation by chained equations with 30 imputed datasets and predictive mean matching to estimate values in a realistic range.

Multiple imputation methods - Multiple imputation by chained equations was performed with the mice package [29]. Estimated adjusted mean differences for the primary and secondary analysis were performed with lme4 [30] and emmeans [31] packages. All figures were produced using the ggplot2 [32] and ggeffects [33] packages.

Statistical analysis of secondary outcomes and subgroup results - Secondary analyses consisted of a comparison of the specific scores at the follow-up between intervention and control group using ANCOVA with the score as dependent variable and treatment group, center, and the respective score at T0 as covariates. Secondary analyses were done in an exploratory manner with no adjustment for multiple testing. For all secondary analyses, effect estimates, and corresponding 95%CI were estimated. Additionally, sensitivity analysis of the primary and secondary outcomes and safety analysis were conducted using the per-protocol data set (all participants, who recorded the study diary for at least 30% of the observation days between the study visits and attended T0, T1 and T2 visits within the scheduled timeframe +/- 3 days) **[Figure e1].**

Pre-specified subgroup analyses were performed using the full analysis set to identify probable differential treatment effects. Subgroups were defined by age at baseline (children of 4 to 12 months, 13 to 48 months, above 48 months of age at baseline), by severity of disease at baseline (children with controlled, TRACK at T0 >= 80 points, or uncontrolled, TRACK at T0 < 80 points, symptoms, and by study country were performed by testing an interaction term of subgroup by intervention in the specific regression models and marginal treatment effects and 95%CI per subgroup were estimated.

Safety rules

If a patient in the intervention group visited the emergency department or hospital two or more times during the study period, the intervention for that patient would have been stopped and the therapy

regimen reevaluated. Additionally, if there was a misbalance of safety events that could be related to the intervention, the study would have been halted immediately for further investigation.

Results

Adverse events

No severe adverse events were reported, and all but one device functioned well. The malfunctioning device was replaced by a new one at the study center in Berlin.

Baseline differences between intervention and control group

While 31% (27/87) of the children in the intervention group suffered from allergy, this was only the case for 17.5% (14/80) of the controls. This difference was also reflected in a higher prevalence of positive skin prick test and/or serum IgE results and a more frequently indicated allergy among parents of the intervention group.

Subgroup analyses of the impact on wheezing control (TRACK)

When looking at TRACK scores at T1 by study country **[Figures e3 B, e4]**, differences become apparent with a larger intervention effect between treatment groups in Berlin and less or no differences in Istanbul or London. The subgroup analysis by asthma control (well controlled: TRACK at T0 ≥ 80 points; not well controlled: TRACK at T0 <80 points) showed a slight difference between treatment groups in the "not well controlled" subgroup, but no difference was seen in the "well controlled" subgroup **[Figure e2].**

A subgroup analysis by age groups (>48 months, 13-48 months, 4-12 months) revealed similar slight differences between treatment groups for children aged 13 months or older, while for younger infants, no differences between treatment groups could be observed (TRACK mean difference a) Age between 4 an 12 months: -5.71 (-26.05-14.63), Age between 13 and 48 months: 5.00 (-2.59-12.59), Age above 48 months (2.62, -8.44-13.67) **[Figure e3 C].**

Adherence to recording

During the complete monitoring period of 120 days, the median proportion of recorded days was 77% (Q1-Q3: 58%-94%) in the intervention and 80% (Q1-Q3: 68%-93%) in the control group. For more detailed information on the individual recording behavior, please see **[Figure e5]**.

The use of short-acting beta 2 agonists (SABA) was asked in the daily questionnaire and the participants required no SABA use during most days.

Device use

The frequency of device use was very heterogeneous, ranging between 1 and 255 times as recorded by the patients in the WheezeMonitor® app (median number of device usage 41, IQR 73). Differences in the usage behavior could be observed between study sites. For example, participants in Istanbul used the WheezeScan™ more frequently (individual patients up to 200 times, in the median participants used the device 78 times, IQR 94) while most patients from Berlin used it less than 50 times (median 28, IQR 74) **[Figure e6]**. The measurement results reflected a broad clinical heterogeneity ranging from 1-100% of positive ("wheeze") results per patient (median number of „wheeze" results 11, IQR 27.5) **[Figure e9B]**. However, high proportions of positive results were mainly observed among patients with low numbers of device use. No specific pattern could be observed for the occurrence of error signals regarding frequency of usage **[Figure e9A]**.

Device usability evaluation by study center

Notably, the proportion of participants without complications while using the device varied among the different trial sites. Specifically, in Berlin, only 66% of participants had no complications, while in Istanbul, 97% used the device without complications, and none of the participants in London had any complications with device usage. This also reflects in the satisfaction of the device at the different study centres. Only 24% (10/41) of the participants in Berlin think their child has benefitted from the device, much less than the participants in Istanbul (69%). In line with the information on challenges in device usage, the age group with the largest proportion of parents who perceived a benefit from using the WheezeScan™ was that with the oldest (>48 months) children **[Figure e7]**. Notably, more than 60% (45/75) of parents would continue to use the wheeze detecting device in the future and 64% (48/75) would recommend it to other parents whose children experience wheezing. When asked in an open question about their evaluation of the device, the high noise sensitivity of the device was mentioned repeatedly.

Discussion

Clinical efficacy of other types of digtal health interventions - Studies testing other types of digital health interventions in self-management or at home care settings have shown conflicting results regarding usability and clinical efficacy. For example, a study on a smart inhaler with remote monitoring and feedback features found no significant increase in asthma control [37], while another study using a similar device with adherence reminders via SMS demonstrated improvement [14].

Legends to the Figures

Figure e1 – Functional description of the digital wheeze detector

Figure e2 – Interventions effects for primary and main secondary endpoints for the per-protocol dataset at T1 (sensitivity analysis). A) **TRACK** mean difference (intervention vs. control ANCOVA): (2.6, 95%CI:-4.08-9.29, p=0.442); B) **PAMSES** mean difference (intervention vs. control ANCOVA): (-2.17, 95%CI:-4.95-0.61, p=0.125); C) **PACQLQ** mean difference (intervention vs. control ANCOVA): (0.18, 95%CI:-0.15-0.52, p=0.277); D) **TAPQLQ** mean difference (intervention vs. control ANCOVA): (-3.17, 95%CI:-6.66-0.31, p=0.074).

Figure e3 – TRACK mean difference (intervention vs. control, based on multiple imputation estimates and ANCOVA) by study group at T2 (A) and by B) study centres (Berlin (BER) $n^{control}$= 40 , $n^{intervention}$=42; Istanbul (IST) $n^{control}$=24 , $n^{intervention}$=31; London (LON) $n^{control}$=8 , $n^{intervention}$=5); C) age group (>48 months: $n^{control}$= 18 , $n^{intervention}$=15; 13-48 months $n^{control}$=44 , $n^{intervention}$=45; 4-12 months $n^{control}$=10 , $n^{intervention}$=18); and D) wheeze severity at T0 (mild = TRACK 80+; $n^{control}$= 24, $n^{intervention}$=19; severe = TRACK <80: $n^{control}$= 48 , $n^{intervention}$=59)

Figure e4 – Wheeze control (TRACK) at baseline (T0: baseline) and follow-up (T1: 90 days) by study centre (Berlin n=82, Istanbul n=55, London n=13)

Figure e5 – Individual adherence to e-diary reporting in the WheezeMonitor® app by study centre (Patients with App records and without problematic e-diary entries: Berlin n=81, Istanbul n=57, London n=20). Red line: end of first monitoring period (90 days), green line: end of complete monitoring period (120 days)

Figure e6 – Distribution of device use by study centre (Berlin n=85, Istanbul n=59, London n=23) as recorded via the study app

Figure e7 – Perceived benefit of device use as reported by parents after 90 days of usage

Figure e8 – Daily use of short-acting beta 2 agonists (SABA) as reported in the study app by study group (control group n=77, intervention group n=81).

Figure e9 – A) Total number and results of measurements with the WheezeScan™ device as reported in the study app (intervention group with valid WheezeScan™ measurements recorded in WheezeMonitor® n=81) during the whole monitoring period (until T2). **B)** Proportion of measurement results per participant of the intervention group (intervention group with valid WheezeScan™ measurements recorded in WheezeMonitor® n=81) during the whole monitoring period (until T2).

Figure e1

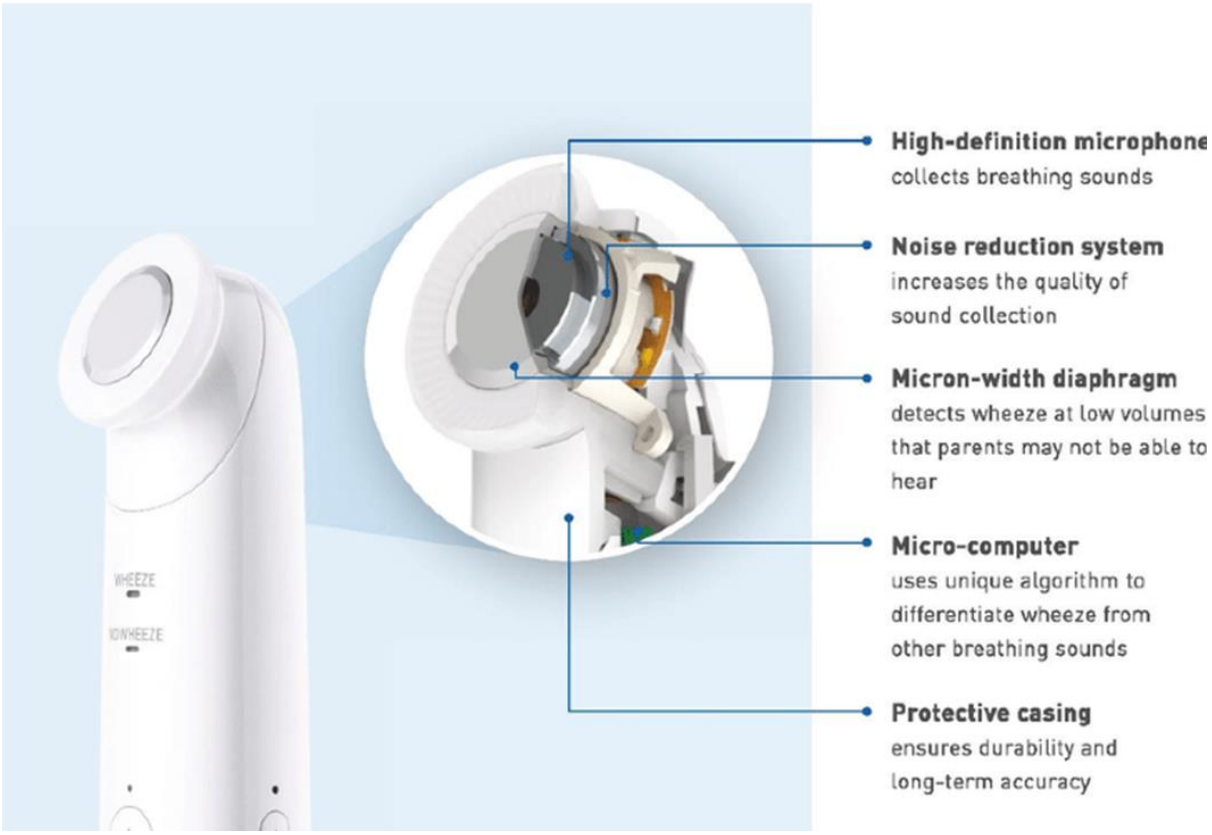

WHEEZE
NONWHEEZE
High-definition microphone
collects breathing sounds
Noise reduction system
increases the quality of
sound collection
Micron-width diaphragm
detects wheeze at low volumes
that parents may not be able to
hear
Micro-computer
uses unique algorithm to
differentiate wheeze from
other breathing sounds
Protective casing
ensures durability and
long-term accuracy

Figure e2

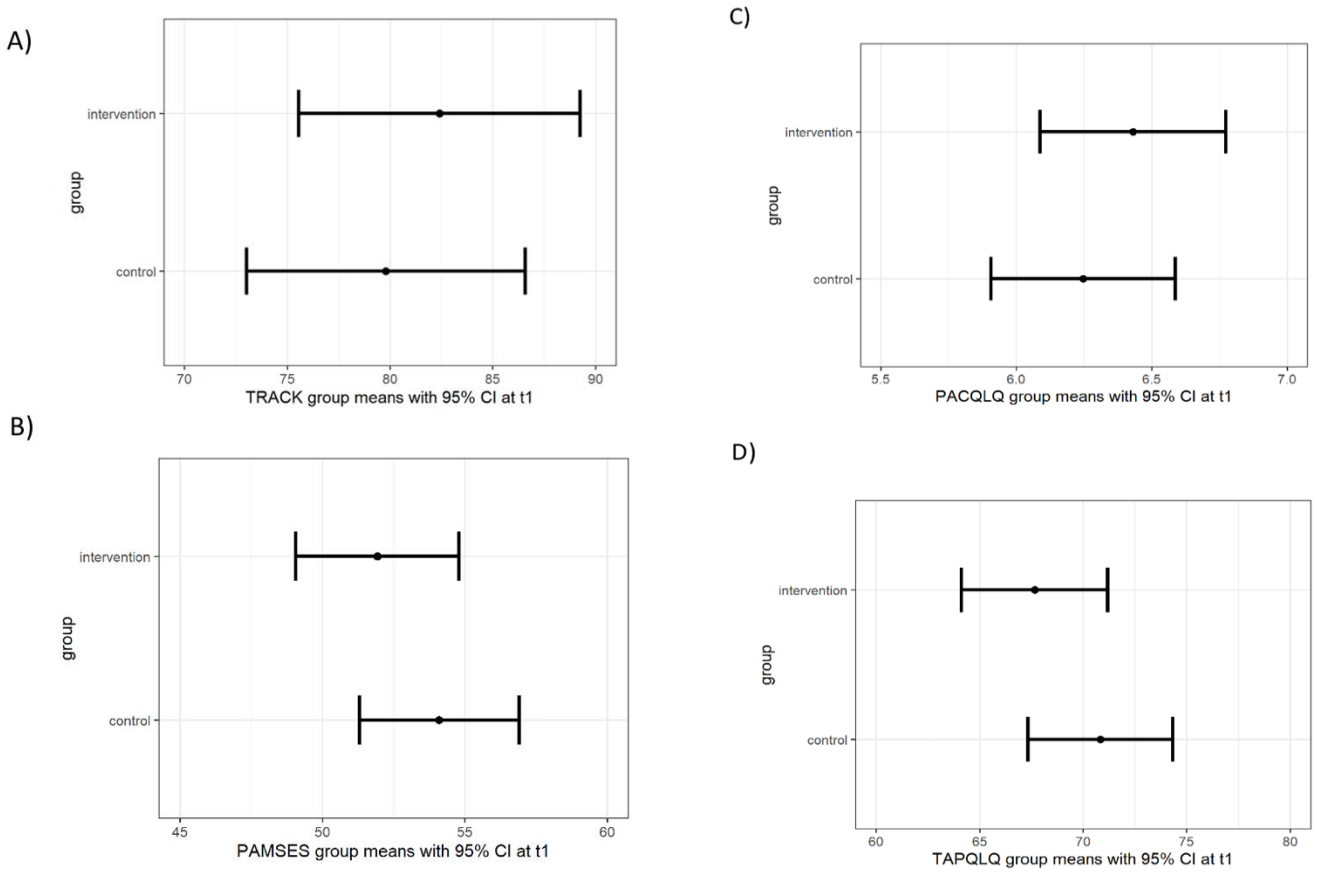

A)
intervention
control
group
70
75
80
85
90
TRACK group means with 95% CI at t1
B)
intervention
control
group
45
50
55
60
PAMSES group means with 95% CI at t1
C)
intervention
control
group
5.5
6.0
6.5
7.0
PACQLQ group means with 95% CI at t1
D)
intervention
control
group
60
65
70
75
80
TAPQLQ group means with 95% CI at t1

Figure e3

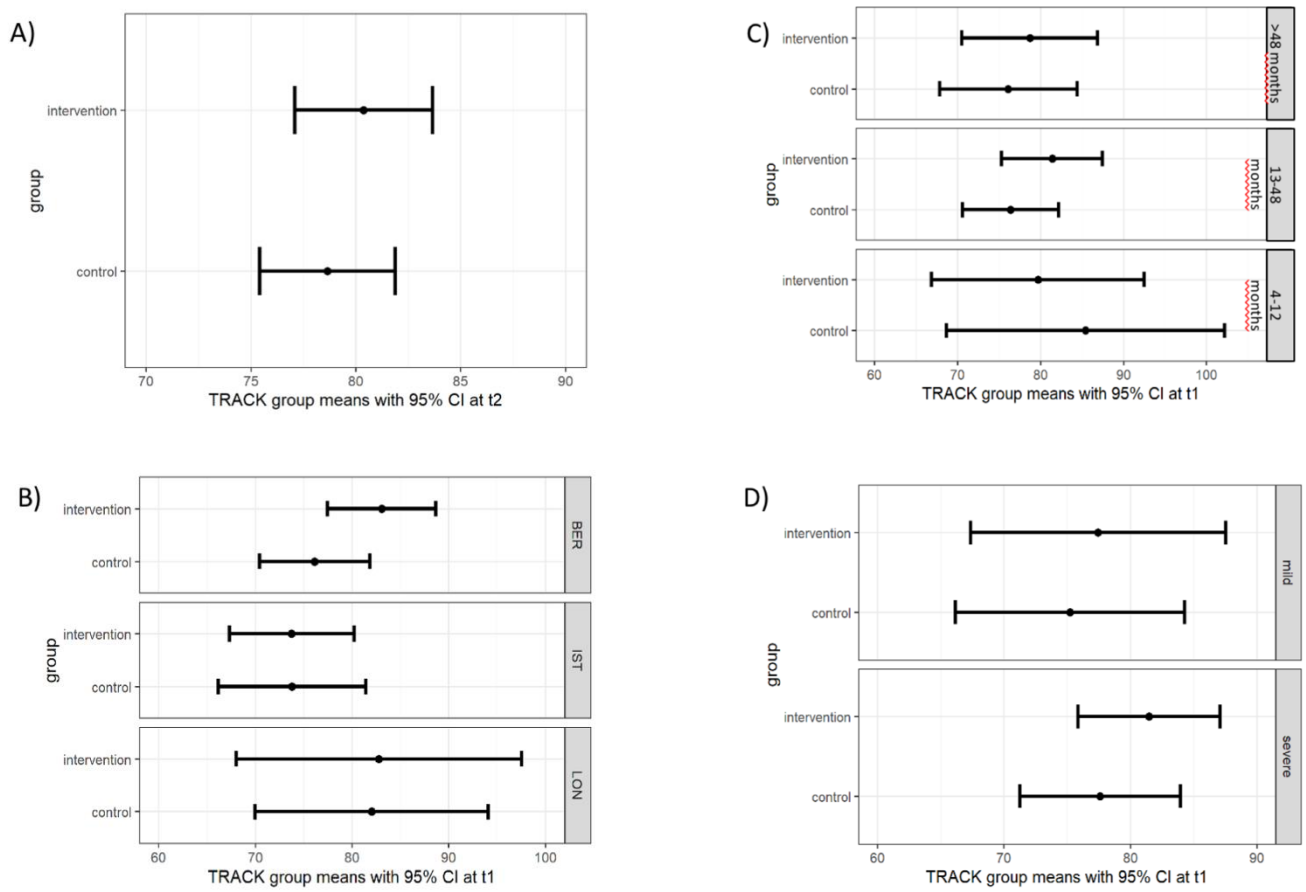

A)
intervention
control
group
70
75
80
85
90
TRACK group means with 95% CI at t2
B)
intervention
control
BER
IST
LON
60
70
80
90
100
TRACK group means with 95% CI at t1
C)
>48 months
13-48 months
4-12 months
TRACK group means with 95% CI at t1
D)
mild
severe
TRACK group means with 95% CI at t1

Figure e4

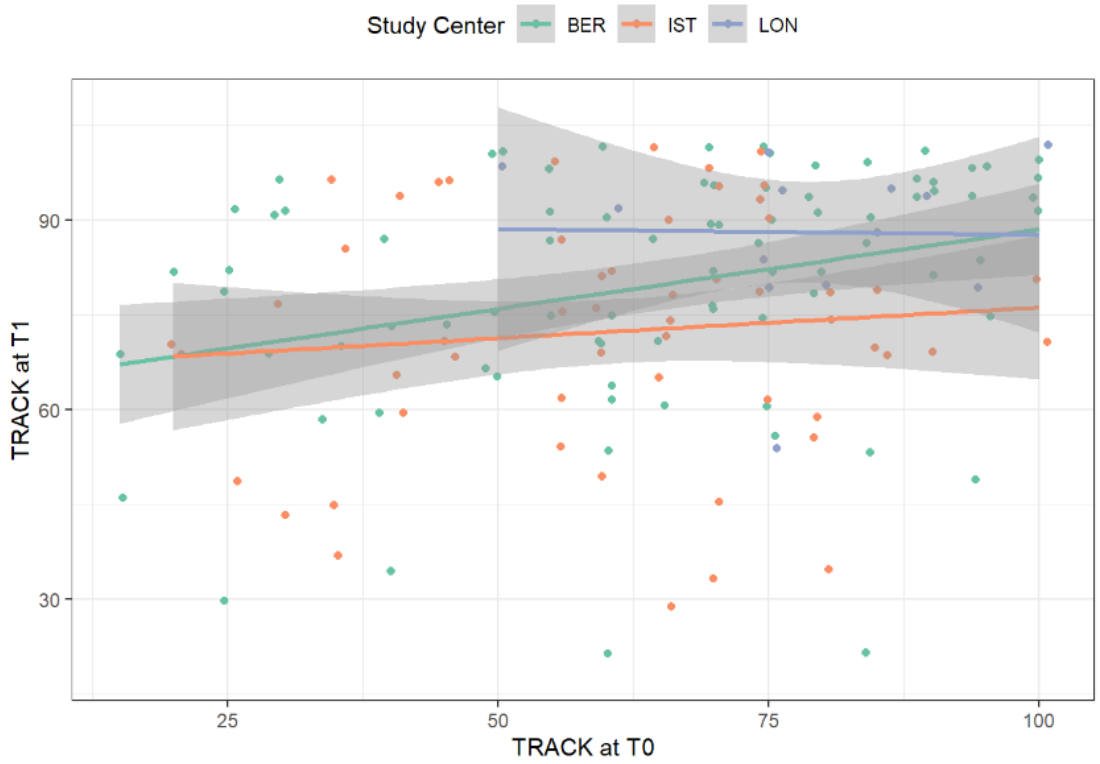

Study Center
BER
IST
LON
TRACK at T1
90
60
30
25
50
75
100
TRACK at T0

Figure e5

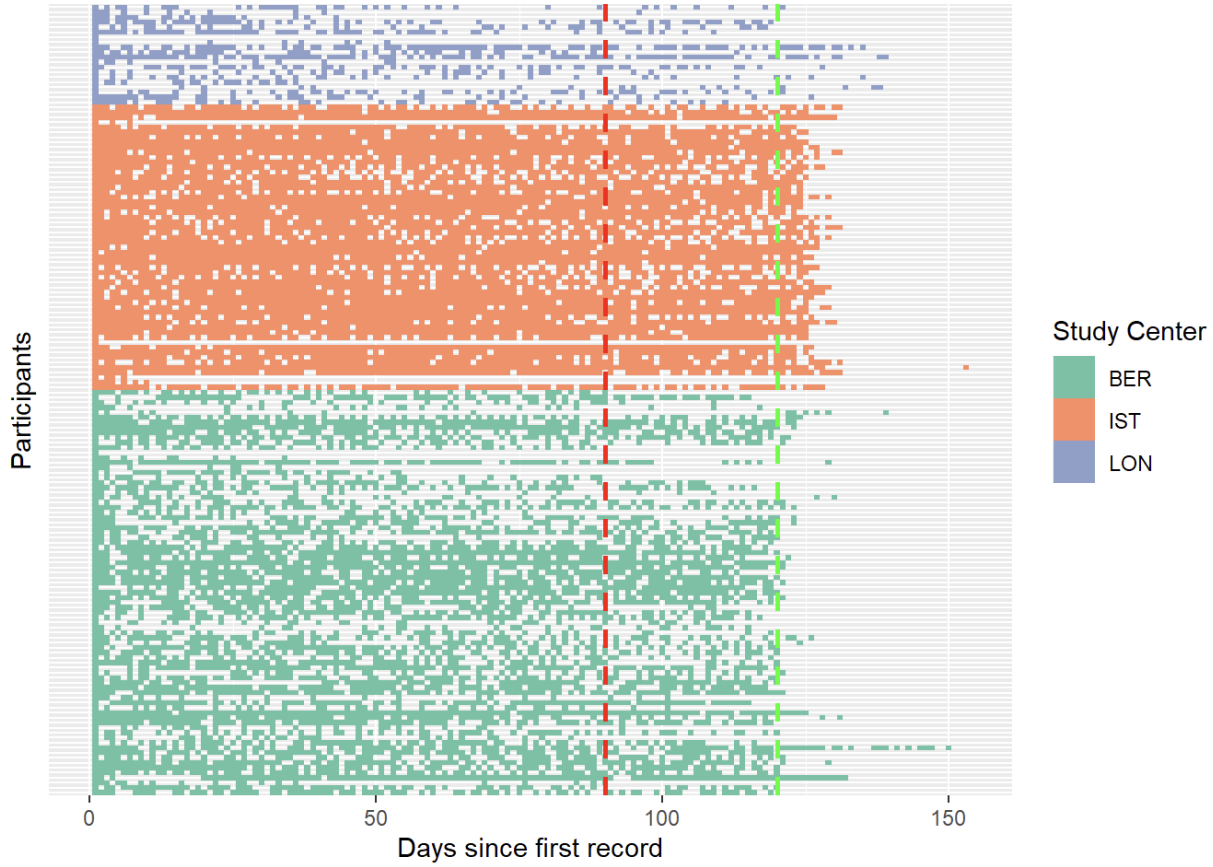

Participants
0
50
100
150
Days since first record
Study Center
BER
IST
LON

Figure e6

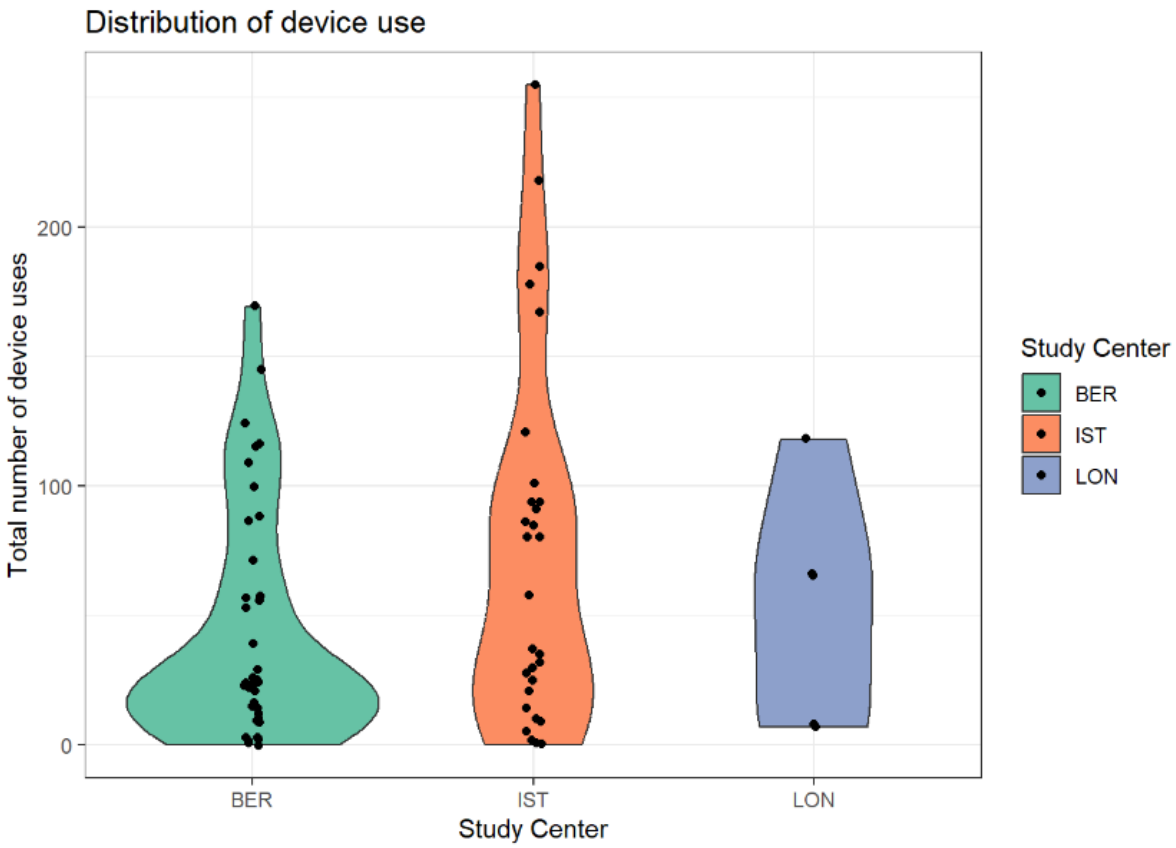

Distribution of device use
Total number of device uses
200
100
0
BER
IST
LON
Study Center
Study Center
BER
IST
LON

Figure e7

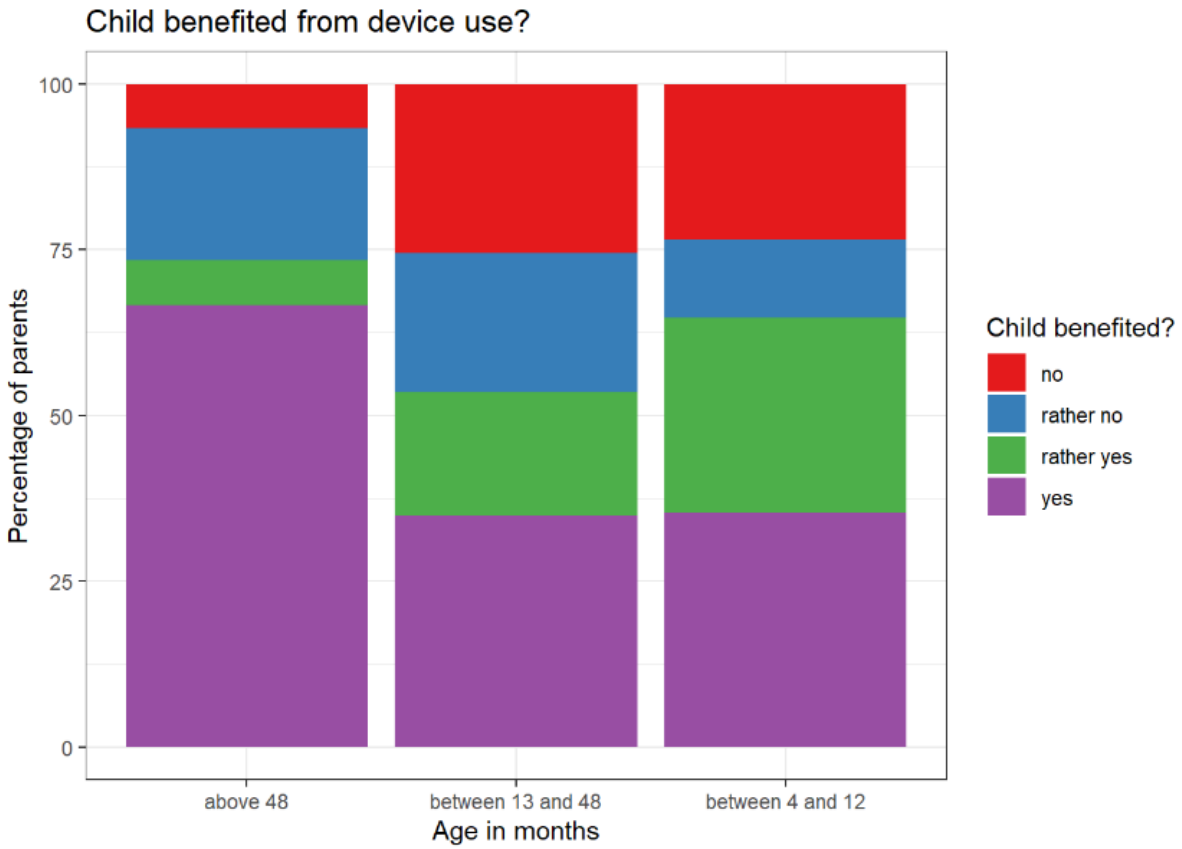

Child benefited from device use?
100
75
50
25
0
Percentage of parents
above 48
between 13 and 48
between 4 and 12
Age in months
Child benefited?
no
rather no
rather yes
yes

Figure e8

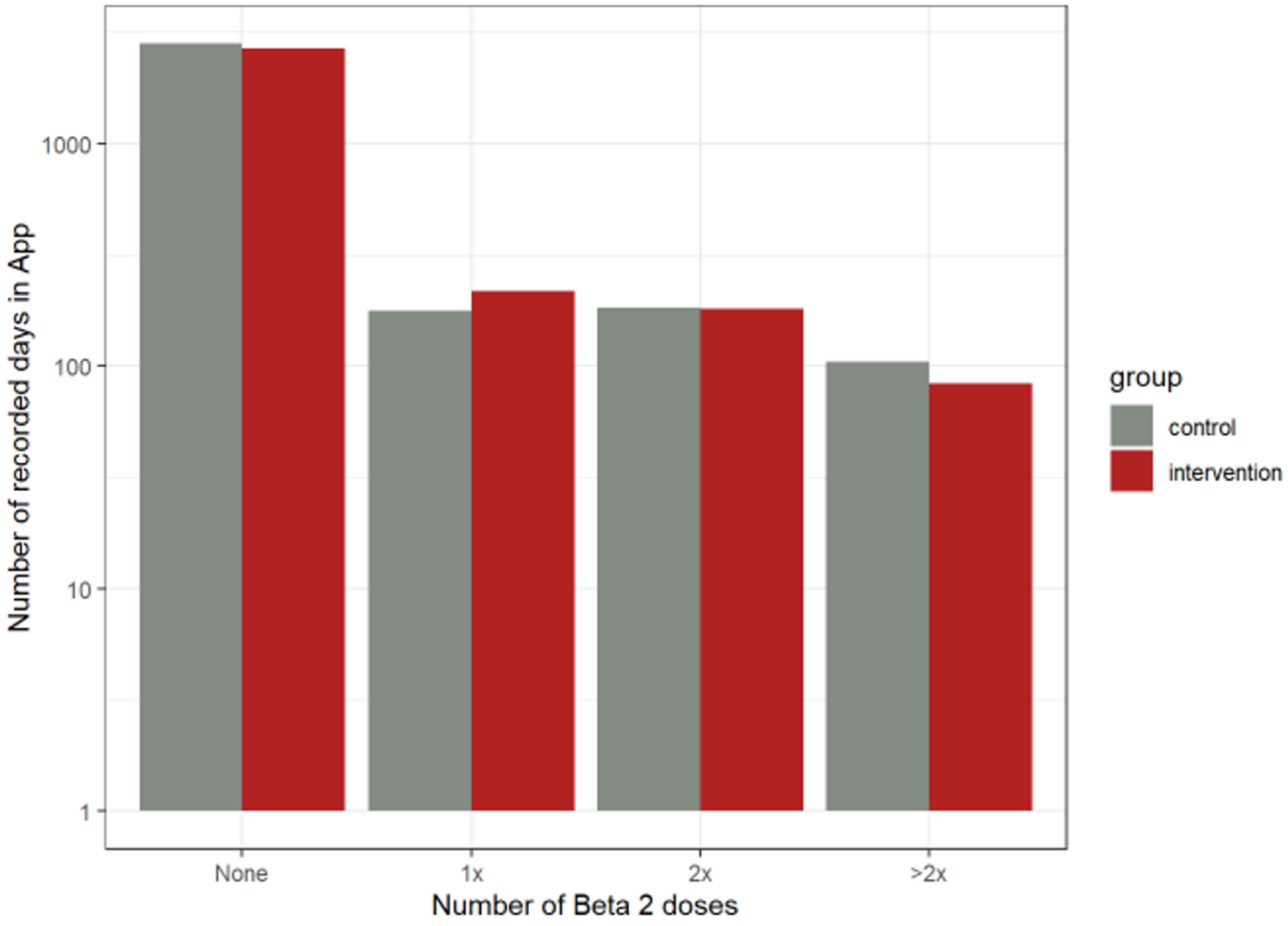
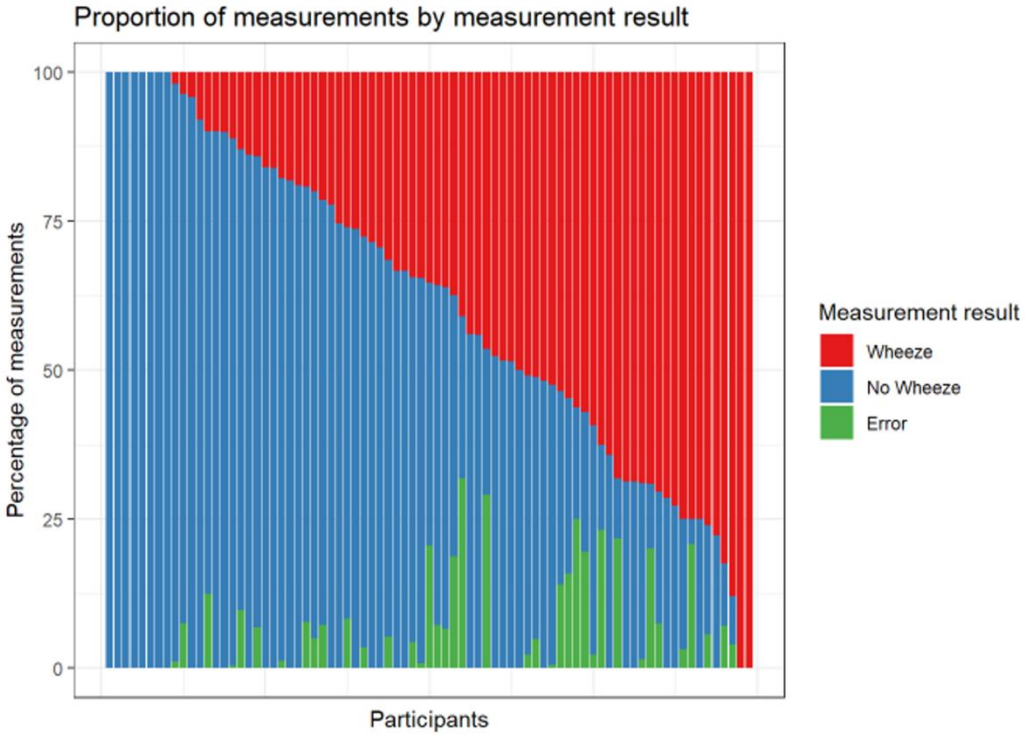

Number of recorded days in App
1000
100
10
1
None
1x
2x
>2x
Number of Beta 2 doses
group
control
intervention

Figure e9

A)


Total number of measurements by measurement result
Total number of measurements
200
100
0
Participants
Measurement result
Error
No Wheeze
Wheeze

B)


Proportion of measurements by measurement result
Percentage of measurements
100
75
50
25
0
Participants
Measurement result
Wheeze
No Wheeze
Error