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Title page

MyAirCoach – The use of home-monitoring and mHealth systems to predict deterioration in asthma control and the occurrence of asthma exacerbations; study protocol of an observational study.

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Keywords: mHealth, eHealth, asthma control, asthma exacerbations, self-management, home-monitoring

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
ACD	Asthma Control Diary
ACQ	Asthma Control Questionnaire
ASQ	After Scenario Questionnaire
BMI	Body Mass Index
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
EBT	Exhaled Breath Temperature
ER	Emergency Room
EU	European Union
FeNO	Fraction of exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in the first second
GA^2LEN FFQ	Global Allergy and Asthma European Network Food frequency Questionnaire
HADS	Hospital anxiety and depression scale
hEIQ	Health Education and Impact Questionnaire
IB	Investigator's Brochure
IC	Informed Consent
m-AQLQ	mini Asthma Quality of Life Questionnaire
MARS	Medication Adherence Report Scale
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)

NIHR	National Institute for Health Research
RR	Respiratory Rate
(S)AE	(Serious) Adverse Event
SES	Socio-economic status (SES)
SNOT-22	Sino-Nasal Outcome Test 22

ABSTRACT

Introduction: Asthma is a variable lung condition whereby patients experience periods of controlled and uncontrolled asthma symptoms. Patients who experience prolonged periods of uncontrolled asthma have a higher incidence of exacerbations and increased morbidity and mortality rates. The ability to determine and to predict levels of asthma control and the occurrence of exacerbations is crucial in asthma management. Therefore, we aimed to determine to what extent physiological, behavioural and environmental data, obtained by mHealth and home-monitoring sensors, as well as patient characteristics, can be used to predict episodes of uncontrolled asthma and the onset of asthma exacerbations.

Methods and analysis: In a one-year observational study, patients will be provided with mHealth and home-monitoring systems to record daily measurements for the first month (Phase 1) and weekly measurements during a follow-up period of 11 months (Phase 2). Our study population consists of 150 patients, aged ≥ 18 years, clinician's diagnosis of asthma, currently on controller medication, with uncontrolled asthma and/or minimally one exacerbation in the past 12 months, will be enrolled over three participating centres; Leiden, London and Manchester. Our main outcomes are the association between physiological, behavioural and environmental data and: i) the loss of asthma control; ii) the occurrence of asthma exacerbations.

Ethics: This study was approved by the Medical Ethics Committee of the Leiden University Medical Center in the Netherlands and by the NHS ethics service in the UK

Trial registration number: NCT02774772, available at https://clinicaltrials.gov/show/NCT02774772.

STRENGTHS AND LIMITATIONS

- This study will assess the early detection of periods of (un)controlled asthma and the occurrence of asthma exacerbations using a wide variety of novel parameters, such as home-monitoring systems, sensors and environmental factors
- Participants in this study are currently being treated in primary, secondary and tertiary care centres and the inclusion and exclusion criteria are relatively limited, resulting in substantial external validity
- In the design of this study not only clinicians were involved, but we also included engineers from technical universities, technical and pharmaceutical companies and representatives of patients' organisations, creating a unique environment of experts, sharing different insights into problems and potential solutions.
- A limitation of this observational study is that if we manage to establish points of early detection, a future randomised controlled trial is still required to assess whether it will improve asthma outcomes if treatment is adjusted accordingly.

- **INTRODUCTION**

Asthma is one of the most common chronic diseases worldwide, currently affecting approximately 300 million individuals.[1] According to the current asthma guidelines, treatment strategies should target minimisation of symptoms, optimisation of lung function and prevention of exacerbations whilst minimising medication related side-effects.[2] Despite wide availability of effective therapies for asthma, a considerable number of patients do not manage to achieve these proposed targets and experience a profound burden of disease,[3,4] with a significant impact on their quality of life and on society as a whole.[5]

There is a plethora of literature advocating the beneficial effect of self-management programmes on asthma control[2,6] and current guidelines suggest that all subjects with asthma receive education on asthma self-management.[2] Traditional self-management programmes involve a written plan of action of how to recognise and respond to worsening asthma. Despite significant benefits, the implementation of self-management programmes in clinical practice is low, with only one in five patients reporting that they receive a self-management programme[7] and patients' adherence to self-management programmes is poor and declines over time.[8]

Mobile healthcare (mHealth), whether involving mobile telephone-based interactive systems or internet-based systems, includes promising tools for supporting asthma self-management. There is increasing evidence that mHealth interventions lead to an important and sustained gain in quality of life, improved clinical outcomes and support informed and educated patient autonomy.[9-12] Thus far, mHealth approaches consisted of one or more of the following components: an individualised treatment plan including self-monitoring and goal setting; medication management (including alerts and reminders); case-specific education; a digital action plan; and integration with the electronic medical record of the health care provider.[13] A recent review suggests that current applications for asthma fail to combine these aspects

to a reliable supportive tool.[14] This might be due to the fact that asthma is a complex condition with a heterogeneous presentation, limiting the usefulness of current mHealth systems to specific groups of patients. With the advances in technology, it is possible to imagine that the next generation of mHealth systems could be personalised to different asthma phenotypes and endotypes, making the technology beneficial to a wider group of individuals. We envisage a system that is capable of providing personalised recommendations on asthma management (i.e., stepping up or stepping down treatment) based on patients' medical history and continuous/regular monitoring of their environment, physiology and behaviour.

To date, however, it is largely unknown which information would be useful in a personalised predictive model. Therefore, we aim to collect a wide range of clinical, physiological, behavioural and environmental data using current mHealth and home-monitoring systems to determine to which extent they can be used to predict asthma control and the occurrence of exacerbations. The results from this research may be used to develop tailored predictive models and personalised action points for self-management plans, which can be integrated into mHealth systems, to assist patients with the self-management of their asthma.

METHODS AND ANALYSIS

Study population

One hundred and fifty patients with a clinician's diagnosis of asthma will be recruited from outpatient clinics and general practices in the regions of London and Manchester in the UK and Leiden in The Netherlands (50 patients per region). The inclusion and exclusion criteria are provided in table 1.

Table 1 inclusion and exclusion criteria

Inclusion criteria (all of the following)

- Age 18+
- Confirmed diagnosis of asthma by either*:
  - Reversibility of 12% and/or 200 ml in a spirometry
  - Significant peak flow variability, defined as diurnal peak expiratory flow amplitude >8%
  - Positive bronchial challenge (any type of bronchial challenge (MCh, cold air, histamine, hypertonic saline) is allowed, and cut-offs depend on the selected type)
- Asthma treatment step 2-4†, need for regular treatment with controller medication (at least 6 months in the previous year)
- Either:
  - A course of oral prednisone for a minimum of three days, or an emergency department visit/hospitalisation for asthma, in the previous twelve months; or
  - Current uncontrolled asthma, based on the result of the Asthma Control Questionnaire‡

Exclusion criteria (any of the following)

- Comorbidities that cause overlapping symptoms such as breathlessness, wheeze, cough or other interfering chronic condition
- Unable to understand English or Dutch, as appropriate

* Participants without a positive result to any of the above mentioned tests will have the opportunity to complete these tests in order to meet the inclusion criteria.

† According to Global INitiative for Asthma (GINA) guidelines criteria.[2]

‡ Defined as an Asthma Control Questionnaire (ACQ)-result>1.5.[18]

Study design

This is an international, multicentre observational study that will occur alongside participant's normal asthma care, as part of the European Union Horizon2020 funded myAirCoach project. Participants will be asked to attend their GP and hospital appointments as usual, and continue to take their medication as recommended by their usual healthcare team. In addition to their usual care, participants will attend an introduction visit and complete a 12-month observational study with two phases (figure 1):

- Phase 1: 1-month period of daily monitoring of asthma
- Phase 2: 11-month period of weekly monitoring of asthma. During this phase, a second two-week period of daily monitoring will be randomly assigned between months 2-9, with the purpose to assess the influence of exposure during different seasons on patient's asthma.

The inclusion of the study is planned to start in September 2016 and the final patient is planned to finish January 2018.

Outcomes

Main study endpoints will be:

The association of physiological, behavioural and environmental data, alone and in combination, with;

- Phase 1: episodes of (un)controlled asthma (as determined by the Asthma Control Diary[15])
- Phase 2: occurrence of moderate and severe asthma exacerbations (as defined the European Respiratory Society and American Thoracic Society (ERS/ATS) Joint Task Force[16])

Secondary study endpoints

- User acceptance of mHealth and home-monitoring systems, as determined by user adherence to measurements and the After-Scenario Questionnaire (ASQ) feedback[17]
- The influence of seasonality on the primary endpoints

Measurements

Measurements will differ between phase 1 and phase 2 of the observational study and are summarised in table 2.

Questionnaires

Asthma control will be measured using the Asthma Control Diary (ACD)[15] for daily measurements or the Asthma Control Questionnaire (ACQ)[18] at screening and for weekly measurements. Medication usage will be measured using a custom designed questionnaire. The mini Asthma Quality of Life Questionnaire (m-AQLQ[19]) will be used to determine quality of life. Dietary information will be recorded using the GA^{2}LEN Food Frequency Questionnaire (FFQ[20]). Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS[21]), while health behaviour and insight will be determined using the health Education Impact Questionnaire (hEIQ[22]). Upper airway symptoms will be assessed via the Sino-Nasal Outcome Test (SNOT-22[23]) and the usability of all the devices using the after scenario questionnaire (ASQ[17]). For a detailed description of all questionnaires see the online supplement.

The occurrence of exacerbations will be assessed via a daily and weekly custom questionnaire, for phase 1 and phase 2 respectively. The following definitions of exacerbations will be used:[16]

- Severe Asthma Exacerbations: the occurrence of at least one of the following:
    - Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. (For consistency, courses of corticosteroids separated by 1 week or more should be registered as separate severe exacerbations.)
    - A hospitalization or ER visit because of asthma, requiring systemic corticosteroids.
- Moderate Asthma Exacerbations: the occurrence of at least one or more of the following:
    - deterioration in symptoms,
    - deterioration in lung function,
    - increased rescue bronchodilator use.

  These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization. ER visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids, will be also classified as moderate exacerbations.

Table 2. Study measurements.

	Introduction visit	Phase 1	Phase 2	2 Week – Daily monitoring phase
Demographics				
Patient characteristics	**Once**	**-**	**-**	**-**
Questionnaires				
ACD	**-**	**Daily**	**-**	**Daily**
ACQ	**Once**	**-**	**Weekly**	**-**
Medication diary	**-**	**Daily**	**Weekly**	**Daily**
Exacerbation Question	**-**	**Daily**	**Weekly**	**-**
m-AQLQ	**Once**	**End of Phase 1**	**Monthly**	**-**
GA^{2}LEN FFQ	**Once**	**-**	**End of phase 2**	**-**
HADS	**Once**	**-**	**-**	**-**
hEIQ	**Once**	**-**	**-**	**-**
SNOT-22	**Once**	**End of Phase 1**	**Monthly**	**-**
ASQ	**-**	**End of Phase 1**	**Bi-annually**	**-**
Clinical tests & home monitoring/mHealth systems				
Allergy test	**Once ***	**-**	**-**	**-**
Reversibility test	**Once ***	**-**	**-**	**-**
Spirometry	**Once**	**Twice-daily**	**Weekly**	**Twice-daily**
FeNO	**Once**	**Twice-daily**	**Weekly**	**Twice-daily**
Breath temperature	**Once**	**Twice-daily**	**Weekly**	**Twice-daily**
HR and activity level	**-**	**Continuous**	**Continuous**	**Continuous**
Respiratory Rate	**-**	**Continuous**	**Continuous**	**Continuous**
Inhaler usage	**-**	**Continuous**	**Continuous**	**Continuous**
Environmental data	**-**	**Continuous**	**Continuous**	**Continuous**

* Performed if there is no previous test in medical notes. Atopy will be assessed by skin-prick tests,[24] or measuring levels of specific IgE in serum. FEV_1 before and after bronchodilation will be assessed using standardized spirometry according to the ERS criteria.[25]

Clinical tests & home monitoring/mHealth systems

Participants will perform spirometry measurements using the PIKO-1 device (© nSpire Health, Inc. Piko-1 device. Available at www.nspirehealth.com).

Fraction of exhaled Nitric Oxide (FeNO) will be measured in a 10 second exhalation manoeuvre using the NIOX-VERO (© Aerocrine. NIOX VERO device. Available at http://www.niox.com/en/). The device guides participants through the manoeuvre and gives an alert when it is performed incorrectly.

Exhaled Breath Temperature (EBT) will be performed at home by participants using the X-halo device (© Delmedica. X-Halo device. Available at http://www.x-halo.com/index.php). This device also includes detailed audiovisual feedback and alerts when used incorrectly.

The respiratory rate (RR) will be measured using the Spiro-device (© Spire 2015 inc. The Spire device. Available at www.spire.io). This device is worn on the belt or bra and requires no particular action other than wearing.

Physical activity and heart rate monitoring will be assessed using the Fitbit HR Charge (© Fitbit inc. Fitbit charge HR. Available at www.fitbit.com). This device is worn on the wrist and automatically collects data.

Medication adherence will be monitored using the Smartinhaler device (© Adherium (NZ) Limited 2013-2015. Smartinhaler device. Available at www.smartinhaler.com). The device records information on compliance with regular treatment and need of reliever medications.

Pollen concentrations are measured in the air at the Leiden University Medical Center. Additionally, it provides a daily, 5-day pollen forecast, based on pollen concentrations in previous years and weather forecast.[26,27] In the UK, the Meteorological Office (Met Office) manages a pollen count monitoring network, using information from their network, weather data and expertise from organisations such as the National Pollen and Aerobiological Unit and Pollen UK.[28-29] Daily pollen levels will be recorded at participants home and work postcodes.

The air quality will also be monitored. Measurements will be assessed in a similar manner in the UK and the Netherlands. In the UK, the Department for Environment, Food and Rural Affairs (DEFRA) provides in-depth information on air quality and air pollution.[28] In The Netherlands the air-quality monitoring network mainly hosted by the Netherlands National Institute for Public Health and the Environment (RIVM) provides information on measured air quality at many points throughout the Netherlands.[27] Based on postal codes of participant's home address and work address the appropriate measurement station will be selected. The following components will be monitored:

- *PM10.* PM10 is a collective term for suspended particles that can be inhaled, with a maximum diameter of 0.01 millimetres. The concentration of fine particulates is higher around the morning and evening rush hour. Weather and traffic emissions have a great impact on the concentration.
- *PM2.5.* PM2.5 is a collective term for suspended particles that can be inhaled, with a maximum diameter of 0.0025 millimetres. Similarly to PM10 the concentration of fine particulates is higher around the morning and evening rush hour and dependant on the weather and traffic emissions. As PM2.5 particles are even smaller than PM10

particles they are able to penetrate even deeper into the lungs and are therefore more harmful from a health perspective.

- *CO.* Carbon monoxide (CO) is formed when a substance is burned at low oxygen levels. Traffic is a main source of carbon monoxide in the air.
- *O3.* The concentration of ozone (O3) is an indicator of the level of smog. The concentration of O3 is dependant on sun-exposure, and therefore highest during good summer weather.
- *NO2.* The concentration of Nitrogen Dioxide is highly related to traffic exposure.

Weather conditions and forecast are also collected, including temperature, humidity, wind speed and forecasts. They will be measured at post code level.

Statistical analysis

Statistical methods

Collected data will be analysed with several tools such as cluster,[30] spectral and factor analysis,[31] in order to reveal which parameters allow for the prediction of periods of uncontrolled asthma. Additionally we will perform a similar analysis for phase two of the trial, where the dependent variable is the onset of (severe) exacerbations. Analyses will be performed in collaboration with the University of Patras and the Centre for Research and Technology Hellas (CERTH), who have previous experience in the handling of these types of continuous data.[32-35] In addition, the anonymised dataset will be input for a clinical state prediction engine and risk assessment, which will be used in future parts of the myAirCoach project. Furthermore, a spatial-temporal model will be generated using artificial intelligence methods and data related to user activity and physiological classification. Probabilistic techniques, i.e. Bayesian network, will be applied on a provided set of parameters to give probabilistic prediction of specific indicators. Different soft computing, probabilistic and data

mining techniques will be applied on the sensors' signals/data to provide least error prone analysis and decision support.

Sample size

This is a single-cohort observational study in which we aim to assess whether a wide variety of parameters, alone, or in combination, will be able to predict the occurrence of either uncontrolled asthma, or asthma exacerbations. As such, we were not able to perform an appropriate sample size calculation. However, with 150 patients daily monitoring for 6 (4+2) weeks we will obtain 150 * 6 * 7 = 6300 daily entries of measurements in this study. In addition to the daily monitoring, with 150 patients monitoring for 52 weeks we will obtain 150 * 52 weeks = 7800 weekly entries of measurements in this study. Furthermore, we also add the total number of daily/hourly/quarterly data that are automatically generated by the wearables, including the wristband and the respiratory rate monitoring device. These amounts of data should allow for a sufficiently confident prediction.

ETHICS AND DISSEMINATION

Data collection

Online questionnaires and home measurement data will be filled-in by the patient using the monitoring and research modules of the self-management support internet application PatientCoach.[36] A 'to do' list will be available in PatientCoach specifically designed for this research and will provide links to the appropriate questionnaires and data entry forms at the appropriate moment (figure 2a,b). This 'to do' list webpage will be pre-installed in an app on an iPod touch 6th generation (© 2015 Apple inc, iPod touch 6, available at www.apple.com). Applications for the Spire, Fitbit HR and Smartinhaler devices will be pre-installed on the iPod. Using Bluetooth and Wifi connections, the data stored on these devices will be regularly transmitted to and subsequently safely stored within the PatientCoach system.

Ethics

This study has been approved by the Medical Ethics Committee of the Leiden University Medical Center in the Netherlands and by the NHS ethics service in the UK. The subjects will be required to give signed informed consent. The study is registered in clinicaltrials.gov, available at https://clinicaltrials.gov/show/NCT02774772.

Dissemination

We plan to communicate final results to participants, healthcare professionals, policymakers, the funder, the public and other relevant groups via conferences, publication or other data sharing arrangements. A final study report will also be send to the Medical Ethics Committees within one year of finalisation.

DISCUSSION

Main expected outcome

In the present study we aim to determine the extent to which mHealth, home-monitoring sensors and environmental databases can predict (un)controlled asthma and exacerbations. Initially we will determine this ability for each individual device. However, more importantly, we plan to combine data in order to increase sensitivity and specificity, allowing us to determine optimal action points at which to intervene in order to prevent loss of control or exacerbations.

Choice of parameters

For the present study, we needed to make a selection of all currently available sensors and monitoring devices and for some, like spirometry, FeNO and pollen counts, this is based on evidence based criteria. However, our study aims to be innovative, therefore a lot of our devices are new in the management of asthma and are selected based on their potential value.

We added a spirometry measurement using Piko, since spirometry is one of the most commonly used measurements in asthma. Also, traditional asthma action plans aimed at predicting loss of control or asthma exacerbations, already involve regular measurements of peak flow or FEV1 and have been shown to be beneficial for asthma self-management.[37,38]

FeNO will be assessed since patients with allergic airway inflammation generally have higher than normal levels. By measuring FeNO, we aim to evaluate allergic airway inflammation in patients with underlying asthma. Measuring FeNO during regular control visits to assess current asthma control has been shown to be effective,[39-42] although there have been some contrasting results.[43-45] Daily monitoring of FeNO might prove to be of additional value. Van der Valk et al. analysed daily measurements of FeNO by different types of mathematical techniques in order to look at periods of exacerbations relative to reference periods in the same patient.[46] The analysis showed that there are changes in FeNO before the onset of exacerbations compared to reference periods. These findings support that regular FeNO measurements in the home setting could help to predict changes in asthma control.

Evaluation of exhaled breath temperature (EBT) has been suggested as a new method to detect and monitor pathological processes in the respiratory system. The putative mechanism of this approach is based upon changes in the blood flow in the conducting airways that are characteristic of different disease states, which influence the temperature of the exhaled gases. Thus far associations between EBT on the one hand, and bronchial blood flow, FeNO and sputum cellular content on the other have been demonstrated.[47]

The Respiratory Rate (RR) is one of the vital signs and has been an integral part of the assessment of asthmatic patients in an acute setting for decades.[2] Previous research

showed that variability of RR during sleep is different in asthmatics.[48] Additionally an increased resting RR during the day might also indicate loss of asthma control. Therefore, continuous analysis of RR both during the day and while sleeping might prove useful in the prediction of asthma control.

Pulse rate can be easily measured by currently available wristbands. The Fitbit additionally assesses activity level**.** The added value of monitoring these parameters in asthma has not been established, yet they potentially provide relevant information about the clinical state of asthma including the severity of exacerbations when evaluated in combination with other clinical outcomes.[49]

Environmental factors and stimuli have a major impact on the clinical state of patients with asthma. There is a clear link between the amount of pollen and deterioration of asthma symptoms in allergic asthmatics.[50] Continuous data on exposure to pollen and associated feedback, especially in established allergies, might aid in preventing loss of control on asthma.[27,51] Furthermore, other environmental factors such as air pollution, also contribute to increased morbidity in asthma, and diminished lung function in children raised in a polluted environment.[52,53] Finally, certain weather conditions might also prove to be relevant for predicting asthma control.

Future implications

This study is part of the European Union Horizon2020 funded myAirCoach project. The final aim of this project is to develop a holistic mHealth personalised asthma monitoring system empowering patients to manage their own health by providing user-friendly tools to increase the awareness of their clinical state and effectiveness of medical treatment. To this purpose a large consortium of leading clinicians in the field of asthma, engineers from technical universities, technical and pharmaceutical companies and representatives of patients'

organisations was assembled, creating a unique environment of highly qualified experts, sharing different insights into problems and potential solutions a project such as this poses. In the present study data from a wide variety of measurements, including sensors, home-monitoring systems and environmental databases is collected and patients still need to manually report current symptoms and occurrence of exacerbations on questionnaires on their iPod. This requires intensive entry of questionnaires by patients in this phase of the entire myAirCoach project. This is needed to determine the correlation between symptoms/exacerbations and data from each of these measurements separately and combinations between measurements. However, if we manage to establish correlations, manual entry of questionnaires is no longer required. We might use these established correlations in our final model to predict asthma control and exacerbations, by real-time analysis of automatically collected continuous measurements from individual patients. We envisage a final system, where people with asthma will only be required to wear certain sensors and they will receive automated, personalised feedback via an app, for instance on their mobile phone. A "personal mHealth guidance system" will empower patients to customize their treatment towards personalised preset goals and guidelines, either automatically or driven by healthcare professional. In this context, myAirCoach will give to clinicians early indications of increasing symptoms or exacerbations, while making an important contribution in successful self-management of asthma.

Additionally, in another part of the myAirCoach study we are seeking to obtain end-user (people with asthma and healthcare professionals) opinions on the uses and applications of mHealth, in collaboration with patient-focused groups (asthma UK and The European Federation of Allergy and Airways Diseases Patients' Associations (EFA)), and will take these opinions into account in the design of the final prototype.

Besides the obvious necessity of the current study to ground the final myAirCoach framework with data, these results are also expected to lead to increased confidence in the myAirCoach

approach and in ICT decision support and self-management systems in general. The impact of such a holistic and innovative approach is huge and the foundations laid here are expected to result in a widespread adoption of sensor-based self-management systems not only in asthma, but also in other respiratory diseases.

REFERENCES

1. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59:469–478.

2. The Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: http://www.ginasthma.org/.

3. Wenzel S, , Denver D, Fahy J, et al. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions, American Thoracic Society. *Am J Respir Crit Care Med* 2000;162:2341-51.

4. Peters S, Ferguson G, Deniz Y, et al. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006;100:1139-51.

5. Dean BB, Calimlim BM, Kindermann SL, et al. The impact of uncontrolled asthma on absenteeism and health-related quality of life. *J Asthma* 2009;46:861-6.

6. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *The Cochrane database of systematic reviews* 2003;1:CD001117.

7. Haughney J, Barnes G, Partridge M, et al. The Living & Breathing Study: a study of patients' views of asthma and its treatment. *Primary Care Respiratory Journal* 2004:13;28–35.

8. Kaya Z, Erkan F, Ozkan M, et al. Self-management plans for asthma control and predictors of patient compliance. *Journal of Asthma* 2009:46;270–275.

9. McCurdie T, Taneva S, Casselman M et al. mHealth consumer apps: the case for user-centered design. Biomedical instrumentation & technology / Association for the Advancement of Medical Instrumentation 2012:Suppl2;49–56.

10. van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J, et al. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. Ann Intern Med 2009;151:110-20.

11. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database Syst Rev 2012;12:CD007459.

12. Reddel HK, Jenkins CR, Partridge MR. Self-management support and other alternatives to reduce the burden of asthma and chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2014;18:1396-406.

13. van Gaalen JL, Hashimoto S, Sont JK. Telemanagement in asthma: an innovative and effective approach. Curr Opin Allergy Clin Immunol. 2012;12(3):235-40.

14. Huckvale K, Car M, Morrison C, Car J. Apps for asthma self-management: a systematic assessment of content and tools. BMC Med 2012;10(1):144.

15. Juniper EF, O'Byrne PM, Ferrie PJ, King DR, Roberts JN. Measuring asthma control. Clinic questionnaire or daily diary? Am J Respir Crit Care Med 2000;162:1330-4.

16. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99

17. Lewis J.R. Psychometric evaluation of an after-scenario questionnaire for computer usability studies: The ASQ. SIGCHI Bulletin 1991:23;78-81.

18. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.

19. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.

20. Garcia-Larsen V, Luczynska M, Kowalski ML, et al. Use of a common food frequency questionnaire (FFQ) to assess dietary patterns and their relation to allergy and asthma in Europe: pilot study of the GA2LEN FFQ. Eur J Clin Nutr 2011;65(6):750–6.

21. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes 2003;1:29.

22. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns 2007;66:192-201.

23. Hopkins C., Gillett S., Slack R., et al. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009:34;447-454.

24. Bousquet J, Heinzerling L, Bachert C, et al. Practical guide to skin prick tests in allergy to aeroallergens. 2012;67(1):18–24.

25. Miller MR, Hankinson JL, Brusasco V, et al. Standardisation of spirometry. Eur. Respir. J. 2005;26(2):319–38.

26. de Weger LA, Beerthuizen T, Hiemstra PS, Sont JK. Development and validation of a 5-day-ahead hay fever forecast for patients with grass-pollen-induced allergic rhinitis.Int J Biometeorol. 2014;58:1047-55. doi: 10.1007/s00484-013-0692-5.

27. Luchtmeetnet. Available at: www.luchtmeetnet.nl (Accessed 2015).

28. Department for Environment, Food and Rural Affairs (DEFRA) is linked to the UK-AIR (Air Information Resource) webpages at: http://uk-air.defra.gov.uk/ (Accessed 2015).

29. National Pollen and Aerobiological Unit at: http://www.worc.ac.uk/discover/national-pollen-and-aerobiology-research-unit.html (Accessed 2015).

30. Haldar P, et.al. Cluster Analysis and Clinical Asthma Phenotypes. American Journal of Respiratory and Critical Care Medicine 2008:178;218-224.

31. Juniper E.F., et.al. Relationship between quality of life and clinical status in asthma: a factor analysis. European Respiratory Journal 2004:23;287-291.

32. Giakoumis D, Tzovaras D, Hassapis, G. Subject-dependent biosignal features for increased accuracy in psychological stress detection. International Journal of Human-Computer Studies 2013:71;425-439

33. Giakoumis D, Drosou A, Cipresso P, Tzovaras D, Hassapis G, Gaggioli G, Riva G. Using activity-related behavioural features towards more effective automatic stress detection. PLoS One 2012:e43571

34. SoltaniHeris T., Langarizadeh M., Mahmoodvand Z, Zolnoori M. Intelligent diagnosis of asthma using machine learning algorithms. International Research Journal of Applied and Basic Sciences 2013:4:4041-4046

35. Finkelstein J, Wood J. Predicting asthma exacerbations using artificial intelligence. Stud Health Technol Inform 2013;190:56-8.

36. Patient Coach platform. Available at: http://www.PatientCoach.nl/ (Accessed 2015)

37. Honkoop PJ, Taylor DR, Smith AD, Snoeck-Stroband JB, Sont JK. Early detection of asthma exacerbations by using action points in self-management plans. Eur Respir J. 2013 ;41:53-9.

38. Gibson PG, Powell H. Written action plans for asthma: an evidence- based review of the key components. Thorax 2004; 59: 94–99.

39. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352: 2163-73.

40. Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. Lancet 2011;378:983-90.

41. Honkoop PJ, Loymans RJ, Termeer EH, Snoeck-Stroband JB, van den Hout WB, Bakker MJ, et al. Symptom- and fraction of exhaled nitric oxide–driven strategies for asthma control: A cluster-randomized trial in primary care. JACI 2015;135:682-825.

42. Pavord ID, Shaw D. The use of exhaled nitric oxide in the management of asthma. J Asthma 2008;45:523-31

43. Szefler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline based treatment for inner-city adolescents and young adults: a randomized controlled trial. Lancet 2008;372:1065-72.

44. De Jongste JC, Carraro S, Hop WC, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. Am J Respir Crit Care Med 2009;179:93-7.

45. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med 2007;176:231-7.

46. van der Valk RJ, Baraldi E, Stern G, Frey U, de Jongste JC. Daily exhaled nitric oxide measurements and asthma exacerbations in children. Allergy. 2012 Feb;67(2):265-71.

47. Popov TA, Kralimarkova TZ and Dimitrov VD. Measurement of exhaled breath temperature in science and clinical practice. Breathe 2012;8:187-192

48. Campaa LM, Owens RL, Butler JP, Suki B, Malhotra A. Variability of respiratory mechanics during sleep in overweight and obese subjects with and without asthma. Respir Physiol Neurobiol 2013;186:290-5.

49. Lufti MF. Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability. Lung India. 2012;29:254-8. doi: 10.4103/0970-2113.99111.

50. Djukanović R, Feather I, Gratziou C, Walls A, Peroni D, Bradding P, Judd M, Howarth PH, Holgate ST. Effect of natural allergen exposure during the grass pollen season on airways inflammatory cells and asthma symptoms. Thorax 1996;51:575-81.

51. Pollen UK to produce forecasts that help support allergy and hay fever sufferers through the most difficult time of the year at: http://www.metoffice.gov.uk/health/public/pollen-forecast (Accessed 2015).

52. Gauderman WJ, Avol E, Gililand F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004;351:1057-67.

53. Wong GW, Lai CK. Outdoor air pollution and asthma. Curr Opin Pulm med 2004;10:62-66.

AUTHORS' CONTRIBUTIONS

PH is the main author of the study protocol and this manuscript. OU, FC, SF, and JKS secured the funding of this study. PH, AS, MB, JBS and SM obtained ethical and privacy approval. PH and AS drafted the manuscript. MB, JBS, SM, OU, FC, SF and JKS critically revised the manuscript. All authors approved the final version.

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COMPETING INTERESTS STATEMENT

Dr. Honkoop has nothing to disclose. Dr. Simpson has nothing to disclose. Dr. Bonini has nothing to disclose. Dr. Snoeck-Stroband has nothing to disclose. Dr. Meah has nothing to disclose. Dr. Chung reports personal fees from Advisory Board membership, grants for research, personal fees from payments for lectures, outside the submitted work. Dr. usmani reports grants from astra zeneca, personal fees from boehringer ingelheim, grants and personal fees from chiesi, personal fees from aerocrine, grants from glaxosmithkline, personal fees from napp, personal fees from mundipharma, personal fees from sandoz, grants from prosonix, personal fees from takeda, personal fees from zentiva, grants from edmond pharma, personal fees from cipla, outside the submitted work. Dr. Fowler has nothing to disclose. Dr. Sont reports grants from GlaxoSmithKline NL, grants from Chiesi NL, outside the submitted work.

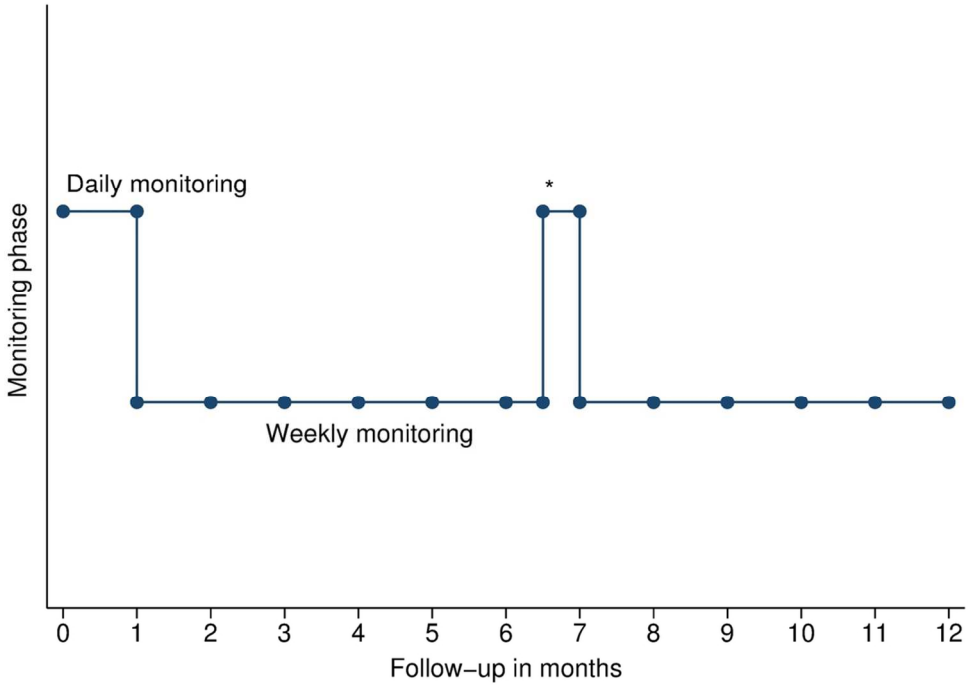
Figure legends

Figure 1. Schematic of study design.

In the first 4 weeks (phase 1) participants are monitored daily. Phase 2 consists of 11 months of weekly monitoring. Additionally in phase 2, blocks of patients will be randomised over month 2-9 for a second series of 2 weeks daily monitoring (in this example between month 6-7). Since participants will be included and commence the study over a four month period, all months will be covered, which allows the assessment of the influence of seasonality.

Figure 2a,b. A view of a participant's iPod

In figure 2a a general overview of the iPod-screen after turning it on and in figure 2b a screenshot of a "to do" list within the Patientcoach system.



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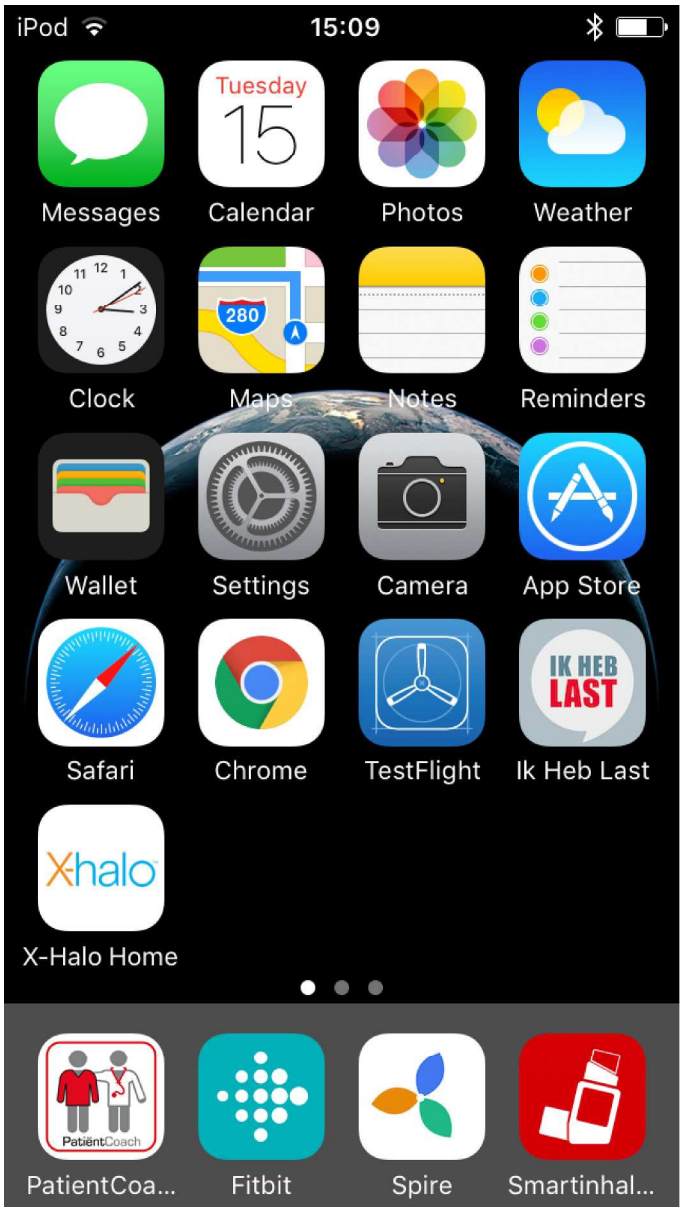
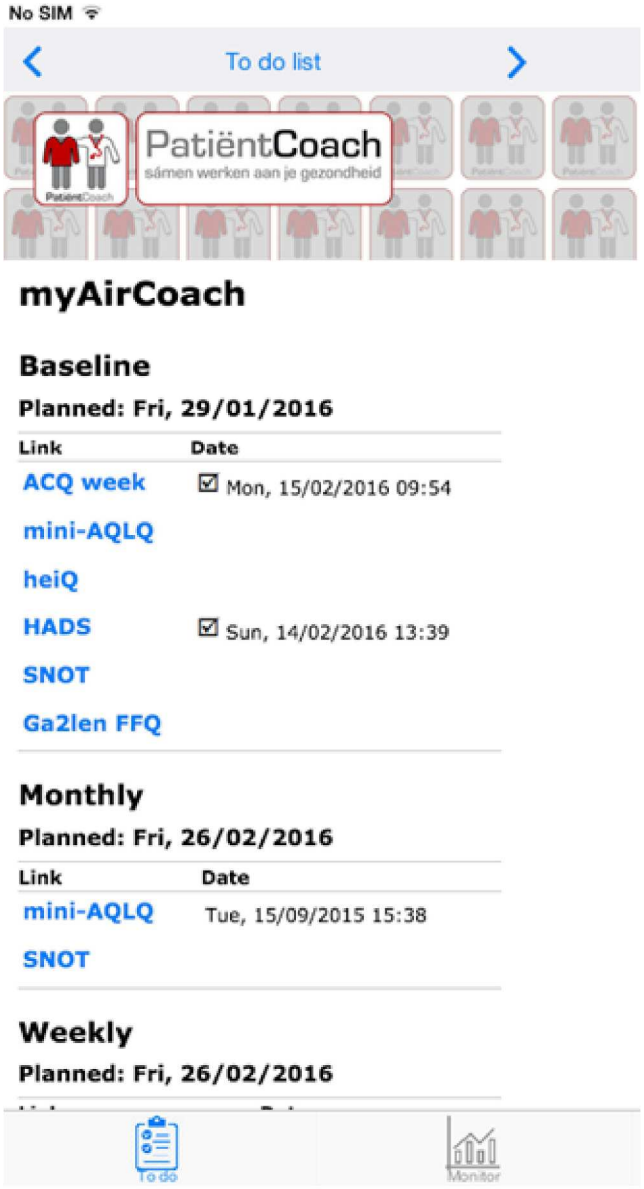


Figure 2a,b. A view of a participant's iPod

In figure 2a a general overview of the iPod-screen after turning it on and in figure 2b a screenshot of a "to do" list within the Patientcoach system.

400x711mm (300 x 300 DPI)



163x309mm (300 x 300 DPI)

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MyAirCoach – The use of home-monitoring and mHealth systems to predict deterioration in asthma control and the occurrence of asthma exacerbations; study protocol of an observational study.

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Secondary Subject Heading:	Diagnostics
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MyAirCoach – The use of home-monitoring and mHealth systems to predict deterioration in asthma control and the occurrence of asthma exacerbations; study protocol of an observational study.

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Keywords:asthma control, asthma exacerbations, eHealth, home-monitoring, mHealth, self-management.

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
ACD	Asthma Control Diary
ACQ	Asthma Control Questionnaire
ASQ	After Scenario Questionnaire
BMI	Body Mass Index
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
EBT	Exhaled Breath Temperature
ER	Emergency Room
EU	European Union
FeNO	Fraction of exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in the first second
GA^2LEN FFQ	Global Allergy and Asthma European Network Food frequency Questionnaire
HADS	Hospital anxiety and depression scale
hEIQ	Health Education and Impact Questionnaire
IB	Investigator's Brochure
IC	Informed Consent
m-AQLQ	mini Asthma Quality of Life Questionnaire
MARS	Medication Adherence Report Scale
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)

NIHR	National Institute for Health Research
RR	Respiratory Rate
(S)AE	(Serious) Adverse Event
SES	Socio-economic status (SES)
SNOT-22	Sino-Nasal Outcome Test 22

ABSTRACT

Introduction: Asthma is a variable lung condition whereby patients experience periods of controlled and uncontrolled asthma symptoms. Patients who experience prolonged periods of uncontrolled asthma have a higher incidence of exacerbations and increased morbidity and mortality rates. The ability to determine and to predict levels of asthma control and the occurrence of exacerbations is crucial in asthma management. Therefore, we aimed to determine to what extent physiological, behavioural and environmental data, obtained by mHealth and home-monitoring sensors, as well as patient characteristics, can be used to predict episodes of uncontrolled asthma and the onset of asthma exacerbations.

Methods and analysis: In a one-year observational study, patients will be provided with mHealth and home-monitoring systems to record daily measurements for the first month (Phase 1) and weekly measurements during a follow-up period of 11 months (Phase 2). Our study population consists of 150 patients, aged ≥ 18 years, clinician's diagnosis of asthma, currently on controller medication, with uncontrolled asthma and/or minimally one exacerbation in the past 12 months, will be enrolled over three participating centres; Leiden, London and Manchester. Our main outcomes are the association between physiological, behavioural and environmental data and: i) the loss of asthma control; ii) the occurrence of asthma exacerbations.

Ethics: This study was approved by the Medical Ethics Committee of the Leiden University Medical Center in the Netherlands and by the NHS ethics service in the UK

Trial registration number: NCT02774772, available at https://clinicaltrials.gov/show/NCT02774772.

STRENGTHS AND LIMITATIONS

- This study will assess the early detection of periods of (un)controlled asthma and the occurrence of asthma exacerbations using a wide variety of novel parameters, such as home-monitoring systems, sensors and environmental factors
- Participants in this study are currently being treated in primary, secondary and tertiary care centres and the inclusion and exclusion criteria are relatively limited, resulting in substantial external validity
- In the design of this study not only clinicians were involved, but we also included engineers from technical universities, technical and pharmaceutical companies and representatives of patients' organisations, creating a unique environment of experts, sharing different insights into problems and potential solutions.
- A limitation of this observational study is that if we manage to establish points of early detection, a future randomised controlled trial is still required to assess whether it will improve asthma outcomes if treatment is adjusted accordingly.

INTRODUCTION

Asthma is one of the most common chronic diseases worldwide, currently affecting approximately 300 million individuals.[1] According to the current asthma guidelines, treatment strategies should target minimisation of symptoms, optimisation of lung function and prevention of exacerbations whilst minimising medication related side-effects.[2] Despite wide availability of effective therapies for asthma, a considerable number of patients do not manage to achieve these proposed targets and experience a profound burden of disease,[3,4] with a significant impact on their quality of life and on society as a whole.[5]

There is a plethora of literature advocating the beneficial effect of self-management programmes on asthma control[2,6] and current guidelines suggest that all subjects with asthma receive education on asthma self-management.[2] Traditional self-management programmes involve a written plan of action of how to recognise and respond to worsening asthma. Despite significant benefits, the implementation of self-management programmes in clinical practice is low, with only one in five patients reporting that they receive a self-management programme[7] and patients' adherence to self-management programmes is poor and declines over time.[8]

Mobile healthcare (mHealth), whether involving mobile telephone-based interactive systems or internet-based systems, includes promising tools for supporting asthma self-management. There is increasing evidence that mHealth interventions lead to an important and sustained gain in quality of life, improved clinical outcomes and support informed and educated patient autonomy.[9-12] Thus far, mHealth approaches consisted of one or more of the following components: an individualised treatment plan including self-monitoring and goal setting; medication management (including alerts and reminders); case-specific education; a digital action plan; and integration with the electronic medical record of the health care provider.[13] A recent review suggests that current applications for asthma fail to combine these aspects

to a reliable supportive tool.[14] This might be due to the fact that asthma is a complex condition with a heterogeneous presentation, limiting the usefulness of current mHealth systems to specific groups of patients. With the advances in technology, it is possible to imagine that the next generation of mHealth systems could be personalised to different asthma phenotypes and endotypes, making the technology beneficial to a wider group of individuals. We envisage a system that is capable of providing personalised recommendations on asthma management (i.e., stepping up or stepping down treatment) based on patients' medical history and continuous/regular monitoring of their environment, physiology and behaviour.

To date, however, it is largely unknown which information would be useful in a personalised predictive model. Therefore, we aim to collect a wide range of clinical, physiological, behavioural and environmental data using current mHealth and home-monitoring systems to determine to which extent they can be used to predict asthma control and the occurrence of exacerbations. The results from this research may be used to develop tailored predictive models and personalised action points for self-management plans, which can be integrated into mHealth systems, to assist patients with the self-management of their asthma.

METHODS AND ANALYSIS

Study population

One hundred and fifty patients with a confirmed diagnosis of asthma (see Table 1 for criteria) will be recruited from outpatient clinics and general practices in the regions of London and Manchester in the UK and Leiden in The Netherlands (50 patients per region). The inclusion and exclusion criteria are provided in table 1.

Table 1 inclusion and exclusion criteria

Inclusion criteria (all of the following)

- Age 18+
- Confirmed diagnosis of asthma by either*:
  - Reversibility of 12% and/or 200 ml in a spirometry
  - Significant peak flow variability, defined as diurnal peak expiratory flow amplitude >8%
  - Positive bronchial challenge (any type of bronchial challenge (MCh, cold air, histamine, hypertonic saline) is allowed, and cut-offs depend on the selected type)
- Asthma treatment step 2-4†, need for regular treatment with controller medication (at least 6 months in the previous year)
- Either:
  - A course of oral prednisone for a minimum of three days, or an emergency department visit/hospitalisation for asthma, in the previous twelve months; or
  - Current uncontrolled asthma, based on the result of the Asthma Control Questionnaire‡

Exclusion criteria (any of the following)

- Comorbidities that cause overlapping symptoms such as breathlessness, wheeze, cough or other interfering chronic condition§
- Unable to understand English or Dutch, as appropriate

* Participants without a positive result to any of the above mentioned tests will have the opportunity to complete these tests in order to meet the inclusion criteria.

† According to Global INitiative for Asthma (GINA) guidelines criteria.[2]

‡ Defined as an Asthma Control Questionnaire (ACQ)-result>1.5.[18]

§ The decision whether or not a patient should be excluded due to significant comorbidity is to be made by the treating physician

Study design

This is an international, multicentre observational study that will occur alongside participant's normal asthma care, as part of the European Union Horizon2020 funded myAirCoach project. One hundred and fifty patients with a doctors-diagnosis of asthma will be recruited from outpatient clinics and from general practices in the region of London and Manchester in the UK and Leiden in The Netherlands (50 patients per region). Patients will be informed by their pulmonologist, general practitioner or practice nurse about the study. A member of the study group will be available for additional information.

Participants will be asked to attend their General Practitioner (GP) and hospital appointments as usual, and continue to take their medication as recommended by their usual healthcare team. In addition to their usual care, participants will attend an introduction visit and complete a 12-month observational study with two phases (figure 1):

- Introduction visit: all devices and study procedures are explained
- Phase 1: 1-month period of daily monitoring of asthma
- Phase 2: 11-month period of weekly monitoring of asthma. During this phase, a second two-week period of daily monitoring will be randomly assigned between months 2-9, with the purpose to assess the influence of exposure during different seasons on patient's asthma.

The study enrollment is planned to start in September 2016 and the final patient is planned to finish in March 2018.

Outcomes

Main study endpoints will be:

The association of physiological, behavioural and environmental data, alone and in combination, with;

- Phase 1: episodes of (un)controlled asthma (as determined by the Asthma Control Diary[15])
- Phase 2: occurrence of moderate and severe asthma exacerbations (as defined the European Respiratory Society and American Thoracic Society (ERS/ATS) Joint Task Force[16])

Secondary study endpoints

- User acceptance of mHealth and home-monitoring systems, as determined by user adherence to measurements and the After-Scenario Questionnaire (ASQ) feedback[17]
- The influence of seasonality on the primary endpoints

Measurements

Measurements will differ between phase 1 and phase 2 of the observational study and are summarised in table 2.

Questionnaires

Asthma control will be measured using the Asthma Control Diary (ACD)[15] for daily measurements or the Asthma Control Questionnaire (ACQ)[18] at screening and for weekly measurements. Medication usage will be measured using a custom designed questionnaire. The mini Asthma Quality of Life Questionnaire (m-AQLQ[19]) will be used to determine quality of life. Dietary information will be recorded using the GA^{2}LEN Food Frequency Questionnaire (FFQ[20]). Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS[21]), while health behaviour and insight will be determined using the health Education Impact Questionnaire (hEIQ[22]). Upper airway symptoms will be assessed via the Sino-Nasal Outcome Test (SNOT-22[23]) and the

usability of all the devices using the after scenario questionnaire (ASQ[17]). For a detailed description of all questionnaires see the online supplement.

The occurrence of exacerbations will be assessed via a daily and weekly custom questionnaire, for phase 1 and phase 2 respectively. The following definitions of exacerbations will be used:[16]

- Severe Asthma Exacerbations: the occurrence of at least one of the following:
  - Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. (For consistency, courses of corticosteroids separated by 1 week or more should be registered as separate severe exacerbations.)
  - A hospitalization or ER visit because of asthma, requiring systemic corticosteroids.
- Moderate Asthma Exacerbations: the occurrence of at least one or more of the following:
  - deterioration in symptoms,
  - deterioration in lung function,
  - increased rescue bronchodilator use.

  These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization. ER visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids, will be also classified as moderate exacerbations.

Table 2. Study measurements.

	Introduction visit	Phase 1	Phase 2	2 Week – Daily monitoring phase

Demographics				
Patient characteristics	**Once**	**-**	**-**	**-**
Questionnaires				
ACD	**-**	**Daily**	**-**	**Daily**
ACQ	**Once**	**-**	**Weekly**	**-**
Medication diary	**-**	**Daily**	**Weekly**	**Daily**
Exacerbation Question	**-**	**Daily**	**Weekly**	**-**
m-AQLQ	**Once**	**End of Phase 1**	**Monthly**	**-**
GA^{2}LEN FFQ	**Once**	**-**	**End of phase 2**	**-**
HADS	**Once**	**-**	**-**	**-**
hEIQ	**Once**	**-**	**-**	**-**
SNOT-22	**Once**	**End of Phase 1**	**Monthly**	**-**
ASQ	**-**	**End of Phase 1**	**Bi-annually**	**-**
Clinical tests & home monitoring/mHealth systems				
Allergy test	**Once ***	**-**	**-**	**-**
Reversibility test	**Once ***	**-**	**-**	**-**
Spirometry	**Once**	**Twice-daily**	**Weekly**	**Twice-daily**
FeNO	**Once**	**Twice-daily**	**Weekly**	**Twice-daily**
Breath temperature	**Once**	**Twice-daily**	**Weekly**	**Twice-daily**
HR and activity level	**-**	**Continuous**	**Continuous**	**Continuous**
Respiratory Rate	**-**	**Continuous**	**Continuous**	**Continuous**
Inhaler usage	**-**	**Continuous**	**Continuous**	**Continuous**
Environmental data	**-**	**Continuous**	**Continuous**	**Continuous**

* Performed if there is no previous test in medical notes. Atopy will be assessed by skin-prick tests,[24] or measuring levels of specific IgE in serum. FEV_1 before and after bronchodilation will be assessed using standardized spirometry according to the ERS criteria.[25]

Clinical tests & home monitoring/mHealth systems

The following devices will be used during the study: Piko-1 device, NIOX VERO, X-Halo, Spire, Fitbit HR Charge and the Smartinhaler.

Participants will use the PIKO-1 device (© nSpire Health, Inc. Piko-1 device. Available at www.nspirehealth.com) to perform spirometry measurements. .

Fraction of exhaled Nitric Oxide (FeNO) will be measured at home, in the morning and evening, in a 10 second exhalation manoeuvre using the NIOX-VERO (© Aerocrine. NIOX VERO device. Available at http://www.niox.com/en/). The device is provided to the participants for the duration of the study, and it guides participants through the manoeuvre audiovisually and gives an alert when it is performed incorrectly.

Exhaled Breath Temperature (EBT) will be performed at home by participants using the X-halo device (© Delmedica. X-Halo device. Available at http://www.x-halo.com/index.php). This device also includes detailed audiovisual feedback and alerts when used incorrectly.

The respiratory rate (RR) will be measured using the Spiro-device (© Spire 2015 inc. The Spire device. Available at www.spire.io). This device is worn on the belt or bra and requires no particular action other than wearing.

Physical activity and heart rate monitoring will be assessed using the Fitbit HR Charge (© Fitbit inc. Fitbit charge HR. Available at www.fitbit.com). This device is worn on the wrist and automatically collects data.

Medication adherence will be monitored using the Smartinhaler device (© Adherium (NZ) Limited 2013-2015. Smartinhaler device. Available at www.smartinhaler.com). The device records information on compliance with regular treatment and need of reliever medications.

Pollen concentrations are measured in the air at the Leiden University Medical Center. Additionally, it provides a daily, 5-day pollen forecast, based on pollen concentrations in previous years and weather forecast.[26,27] In the UK, the Meteorological Office (Met Office) manages a pollen count monitoring network, using information from their network, weather data and expertise from organisations such as the National Pollen and Aerobiological Unit and Pollen UK.[28-29] Daily pollen levels will be recorded at participants home and work postcodes.

The air quality will also be monitored. Measurements will be assessed in a similar manner in the UK and the Netherlands. In the UK, the Department for Environment, Food and Rural Affairs (DEFRA) provides in-depth information on air quality and air pollution.[28] In The Netherlands the air-quality monitoring network mainly hosted by the Netherlands National Institute for Public Health and the Environment (RIVM) provides information on measured air quality at many points throughout the Netherlands.[27] Based on postal codes of participant's home address and work address the appropriate measurement station will be selected. The following components will be monitored:

- *PM10.* PM10 is a collective term for suspended particles that can be inhaled, with a maximum diameter of 0.01 millimetres. The concentration of fine particulates is higher around the morning and evening rush hour. Weather and traffic emissions have a great impact on the concentration.
- *PM2.5.* PM2.5 is a collective term for suspended particles that can be inhaled, with a maximum diameter of 0.0025 millimetres. Similarly to PM10 the concentration of fine particulates is higher around the morning and evening rush hour and dependant on the weather and traffic emissions. As PM2.5 particles are even smaller than PM10

particles they are able to penetrate even deeper into the lungs and are therefore more harmful from a health perspective.

- *CO.* Carbon monoxide (CO) is formed when a substance is burned at low oxygen levels. Traffic is a main source of carbon monoxide in the air.
- *O3.* The concentration of ozone (O3) is an indicator of the level of smog. The concentration of O3 is dependant on sun-exposure, and therefore highest during good summer weather.
- *NO2.* The concentration of Nitrogen Dioxide is highly related to traffic exposure.

Weather conditions and forecast are also collected, including temperature, humidity, wind speed and forecasts. They will be measured at post code level.

Statistical analysis

Statistical methods

Collected data will be analysed with several tools such as cluster,[30] spectral and factor analysis,[31] in order to reveal which parameters allow for the prediction of periods of uncontrolled asthma. Additionally, we will perform a similar analysis for phase two of the trial, where the dependent variable is the onset of (severe) exacerbations. Analyses will be performed in collaboration with the University of Patras and the Centre for Research and Technology Hellas (CERTH), who have previous experience in the handling of these types of continuous data.[32-35] In addition, the anonymised dataset will be input for a clinical state prediction engine and risk assessment, which will be used in future parts of the myAirCoach project. Furthermore, a spatial-temporal model will be generated using artificial intelligence methods and data related to user activity and physiological classification. Probabilistic techniques, i.e. Bayesian network, will be applied on a provided set of parameters to give probabilistic prediction of specific indicators. Different soft computing, probabilistic and data

mining techniques will be applied on the sensors' signals/data to provide least error prone analysis and decision support.

Sample size

This is a single-cohort observational study in which we aim to assess whether a wide variety of parameters, alone, or in combination, will be able to predict the occurrence of either uncontrolled asthma, or asthma exacerbations. As such, we were not able to perform an appropriate sample size calculation. However, with 150 patients daily monitoring for 6 (4+2) weeks we will obtain 150 * 6 * 7 = 6300 daily entries of measurements in this study. In addition to the daily monitoring, with 150 patients monitoring for 52 weeks we will obtain 150 * 52 weeks = 7800 weekly entries of measurements in this study. Furthermore, we also add the total number of daily/hourly/quarterly data that are automatically generated by the wearables, including the wristband and the respiratory rate monitoring device. These amounts of data should allow for a sufficiently confident prediction.

ETHICS AND DISSEMINATION

Data collection

Online questionnaires and home measurement data will be filled-in by the patient using the monitoring and research modules of the self-management support internet application PatientCoach.[36] A 'to do' list will be available in PatientCoach specifically designed for this research and will provide links to the appropriate questionnaires and data entry forms at the appropriate moment (figure 2a,b). This 'to do' list webpage will be pre-installed in an app on an iPod touch 6th generation (© 2015 Apple inc, iPod touch 6, available at www.apple.com). Applications for the Spire, Fitbit HR and Smartinhaler devices will be pre-installed on the iPod. Using Bluetooth and Wifi connections, the data stored on these devices will be regularly transmitted to and subsequently safely stored within the PatientCoach system.

Ethics

This study has been approved by the Medical Ethics Committee of the Leiden University Medical Center in the Netherlands and by the NHS ethics service in the UK. The subjects will be required to give signed informed consent. The study is registered in clinicaltrials.gov, available at https://clinicaltrials.gov/show/NCT02774772.

Dissemination

We plan to communicate final results to participants, healthcare professionals, policymakers, the funder, the public and other relevant groups via conferences, publication or other data sharing arrangements. A final study report will also be send to the Medical Ethics Committees within one year of finalisation.

DISCUSSION

Main expected outcome

In the present study we aim to determine the extent to which mHealth, home-monitoring sensors and environmental databases can predict (un)controlled asthma and exacerbations. Initially we will determine this ability for each individual device. However, more importantly, we plan to combine data in order to increase sensitivity and specificity, allowing us to determine optimal action points at which to intervene in order to prevent loss of control or exacerbations.

Choice of parameters

For the present study, we needed to make a selection of all currently available sensors and monitoring devices and for some, like spirometry, FeNO and pollen counts, this is based on evidence based criteria. However, our study aims to be innovative, therefore a lot of our devices are new in the management of asthma and are selected based on their potential value.

We added a spirometry measurement using Piko, since spirometry is one of the most commonly used measurements in asthma. Also, traditional asthma action plans aimed at predicting loss of control or asthma exacerbations, already involve regular measurements of peak flow or FEV1 and have been shown to be beneficial for asthma self-management.[37,38]

FeNO will be assessed since patients with allergic airway inflammation generally have higher than normal levels. By measuring FeNO, we aim to evaluate allergic airway inflammation in patients with underlying asthma. Measuring FeNO during regular control visits to assess current asthma control has been shown to be effective,[39-42] although there have been some contrasting results.[43-45] Daily monitoring of FeNO might prove to be of additional value. Van der Valk et al. analysed daily measurements of FeNO by different types of mathematical techniques in order to look at periods of exacerbations relative to reference periods in the same patient.[46] The analysis showed that there are changes in FeNO before the onset of exacerbations compared to reference periods. These findings support that regular FeNO measurements in the home setting could help to predict changes in asthma control.

Evaluation of exhaled breath temperature (EBT) has been suggested as a new method to detect and monitor pathological processes in the respiratory system. The putative mechanism of this approach is based upon changes in the blood flow in the conducting airways that are characteristic of different disease states, which influence the temperature of the exhaled gases. Thus far associations between EBT on the one hand, and bronchial blood flow, FeNO and sputum cellular content on the other have been demonstrated.[47]

The Respiratory Rate (RR) is one of the vital signs and has been an integral part of the assessment of asthmatic patients in an acute setting for decades.[2] Previous research

showed that variability of RR during sleep is different in asthmatics.[48] Additionally an increased resting RR during the day might also indicate loss of asthma control. Therefore, continuous analysis of RR both during the day and while sleeping might prove useful in the prediction of asthma control.

Pulse rate can be easily measured by currently available wristbands. The Fitbit additionally assesses activity level**.** The added value of monitoring these parameters in asthma has not been established, yet they potentially provide relevant information about the clinical state of asthma including the severity of exacerbations when evaluated in combination with other clinical outcomes.[49]

Environmental factors and stimuli have a major impact on the clinical state of patients with asthma. There is a clear link between the amount of pollen and deterioration of asthma symptoms in allergic asthmatics.[50] Continuous data on exposure to pollen and associated feedback, especially in established allergies, might aid in preventing loss of control on asthma.[27,51] Furthermore, other environmental factors such as air pollution, also contribute to increased morbidity in asthma, and diminished lung function in children raised in a polluted environment.[52,53] Finally, certain weather conditions might also prove to be relevant for predicting asthma control.

Future implications

This study is part of the European Union Horizon2020 funded myAirCoach project. The final aim of this project is to develop a holistic mHealth personalised asthma monitoring system empowering patients to manage their own health by providing user-friendly tools to increase the awareness of their clinical state and effectiveness of medical treatment. To this purpose a large consortium of leading clinicians in the field of asthma, engineers from technical universities, technical and pharmaceutical companies and representatives of patients'

organisations was assembled, creating a unique environment of highly qualified experts, sharing different insights into problems and potential solutions a project such as this poses. In the present study data from a wide variety of measurements, including sensors, home-monitoring systems and environmental databases is collected and patients still need to manually report current symptoms and occurrence of exacerbations on questionnaires on their iPod. This requires intensive entry of questionnaires by patients in this phase of the entire myAirCoach project. This is needed to determine the association between symptoms/exacerbations and data from each of these measurements separately and combinations between measurements. However, if we manage to establish associations, manual entry of questionnaires is no longer required. We might use these established associations in our final model to predict asthma control and exacerbations, by real-time analysis of automatically collected continuous measurements from individual patients. We envisage a final system, where people with asthma will only be required to wear certain sensors and they will receive automated, personalised feedback via an app, for instance on their mobile phone. A "personal mHealth guidance system" will empower patients to customize their treatment towards personalised preset goals and guidelines, either automatically or driven by healthcare professional. In this context, myAirCoach will give to clinicians early indications of increasing symptoms or exacerbations, while making an important contribution in successful self-management of asthma.

Additionally, in another part of the myAirCoach study we are seeking to obtain end-user (people with asthma and healthcare professionals) opinions on the uses and applications of mHealth, in collaboration with patient-focused groups (asthma UK and The European Federation of Allergy and Airways Diseases Patients' Associations (EFA)), and will take these opinions into account in the design of the final prototype.

Besides the obvious necessity of the current study to ground the final myAirCoach framework with data, these results are also expected to lead to increased confidence in the myAirCoach

approach and in ICT decision support and self-management systems in general. The impact of such a holistic and innovative approach is huge and the foundations laid here are expected to result in a widespread adoption of sensor-based self-management systems not only in asthma, but also in other respiratory diseases.

REFERENCES

1. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59:469–478.

2. The Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: http://www.ginasthma.org/.

3. Wenzel S, , Denver D, Fahy J, et al. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions, American Thoracic Society. *Am J Respir Crit Care Med* 2000;162:2341-51.

4. Peters S, Ferguson G, Deniz Y, et al. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006;100:1139-51.

5. Dean BB, Calimlim BM, Kindermann SL, et al. The impact of uncontrolled asthma on absenteeism and health-related quality of life. *J Asthma* 2009;46:861-6.

6. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *The Cochrane database of systematic reviews* 2003;1:CD001117.

7. Haughney J, Barnes G, Partridge M, et al. The Living & Breathing Study: a study of patients' views of asthma and its treatment. *Primary Care Respiratory Journal* 2004:13;28–35.

8. Kaya Z, Erkan F, Ozkan M, et al. Self-management plans for asthma control and predictors of patient compliance. *Journal of Asthma* 2009:46;270–275.

9. McCurdie T, Taneva S, Casselman M et al. mHealth consumer apps: the case for user-centered design. Biomedical instrumentation & technology / Association for the Advancement of Medical Instrumentation 2012:Suppl2;49–56.

10. van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J, et al. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. Ann Intern Med 2009;151:110-20.

11. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database Syst Rev 2012;12:CD007459.

12. Reddel HK, Jenkins CR, Partridge MR. Self-management support and other alternatives to reduce the burden of asthma and chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2014;18:1396-406.

13. van Gaalen JL, Hashimoto S, Sont JK. Telemanagement in asthma: an innovative and effective approach. Curr Opin Allergy Clin Immunol. 2012;12(3):235-40.

14. Huckvale K, Car M, Morrison C, Car J. Apps for asthma self-management: a systematic assessment of content and tools. BMC Med 2012;10(1):144.

15. Juniper EF, O'Byrne PM, Ferrie PJ, King DR, Roberts JN. Measuring asthma control. Clinic questionnaire or daily diary? Am J Respir Crit Care Med 2000;162:1330-4.

16. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99

17. Lewis J.R. Psychometric evaluation of an after-scenario questionnaire for computer usability studies: The ASQ. SIGCHI Bulletin 1991:23;78-81.

18. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.

19. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.

20. Garcia-Larsen V, Luczynska M, Kowalski ML, et al. Use of a common food frequency questionnaire (FFQ) to assess dietary patterns and their relation to allergy and asthma in Europe: pilot study of the GA2LEN FFQ. Eur J Clin Nutr 2011;65(6):750–6.

21. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes 2003;1:29.

22. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns 2007;66:192-201.

23. Hopkins C., Gillett S., Slack R., et al. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009:34;447-454.

24. Bousquet J, Heinzerling L, Bachert C, et al. Practical guide to skin prick tests in allergy to aeroallergens. 2012;67(1):18–24.

25. Miller MR, Hankinson JL, Brusasco V, et al. Standardisation of spirometry. Eur. Respir. J. 2005;26(2):319–38.

26. de Weger LA, Beerthuizen T, Hiemstra PS, Sont JK. Development and validation of a 5-day-ahead hay fever forecast for patients with grass-pollen-induced allergic rhinitis.Int J Biometeorol. 2014;58:1047-55. doi: 10.1007/s00484-013-0692-5.

27. Luchtmeetnet. Available at: www.luchtmeetnet.nl (Accessed 2015).

28. Department for Environment, Food and Rural Affairs (DEFRA) is linked to the UK-AIR (Air Information Resource) webpages at: http://uk-air.defra.gov.uk/ (Accessed 2015).

29. National Pollen and Aerobiological Unit at: http://www.worc.ac.uk/discover/national-pollen-and-aerobiology-research-unit.html (Accessed 2015).

30. Haldar P, et.al. Cluster Analysis and Clinical Asthma Phenotypes. American Journal of Respiratory and Critical Care Medicine 2008:178;218-224.

31. Juniper E.F., et.al. Relationship between quality of life and clinical status in asthma: a factor analysis. European Respiratory Journal 2004:23;287-291.

32. Giakoumis D, Tzovaras D, Hassapis, G. Subject-dependent biosignal features for increased accuracy in psychological stress detection. International Journal of Human-Computer Studies 2013:71;425-439

33. Giakoumis D, Drosou A, Cipresso P, Tzovaras D, Hassapis G, Gaggioli G, Riva G. Using activity-related behavioural features towards more effective automatic stress detection. PLoS One 2012:e43571

34. SoltaniHeris T., Langarizadeh M., Mahmoodvand Z, Zolnoori M. Intelligent diagnosis of asthma using machine learning algorithms. International Research Journal of Applied and Basic Sciences 2013:4:4041-4046

35. Finkelstein J, Wood J. Predicting asthma exacerbations using artificial intelligence. Stud Health Technol Inform 2013;190:56-8.

36. Patient Coach platform. Available at: http://www.PatientCoach.nl/ (Accessed 2015)

37. Honkoop PJ, Taylor DR, Smith AD, Snoeck-Stroband JB, Sont JK. Early detection of asthma exacerbations by using action points in self-management plans. Eur Respir J. 2013 ;41:53-9.

38. Gibson PG, Powell H. Written action plans for asthma: an evidence- based review of the key components. Thorax 2004; 59: 94–99.

39. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352: 2163-73.

40. Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. Lancet 2011;378:983-90.

41. Honkoop PJ, Loymans RJ, Termeer EH, Snoeck-Stroband JB, van den Hout WB, Bakker MJ, et al. Symptom- and fraction of exhaled nitric oxide–driven strategies for asthma control: A cluster-randomized trial in primary care. JACI 2015;135:682-825.

42. Pavord ID, Shaw D. The use of exhaled nitric oxide in the management of asthma. J Asthma 2008;45:523-31

43. Szefler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline based treatment for inner-city adolescents and young adults: a randomized controlled trial. Lancet 2008;372:1065-72.

44. De Jongste JC, Carraro S, Hop WC, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. Am J Respir Crit Care Med 2009;179:93-7.

45. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med 2007;176:231-7.

46. van der Valk RJ, Baraldi E, Stern G, Frey U, de Jongste JC. Daily exhaled nitric oxide measurements and asthma exacerbations in children. Allergy. 2012 Feb;67(2):265-71.

47. Popov TA, Kralimarkova TZ and Dimitrov VD. Measurement of exhaled breath temperature in science and clinical practice. Breathe 2012;8:187-192

48. Campaa LM, Owens RL, Butler JP, Suki B, Malhotra A. Variability of respiratory mechanics during sleep in overweight and obese subjects with and without asthma. Respir Physiol Neurobiol 2013;186:290-5.

49. Lufti MF. Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability. Lung India. 2012;29:254-8. doi: 10.4103/0970-2113.99111.

50. Djukanović R, Feather I, Gratziou C, Walls A, Peroni D, Bradding P, Judd M, Howarth PH, Holgate ST. Effect of natural allergen exposure during the grass pollen season on airways inflammatory cells and asthma symptoms. Thorax 1996;51:575-81.

51. Pollen UK to produce forecasts that help support allergy and hay fever sufferers through the most difficult time of the year at: http://www.metoffice.gov.uk/health/public/pollen-forecast (Accessed 2015).

52. Gauderman WJ, Avol E, Gililand F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004;351:1057-67.

53. Wong GW, Lai CK. Outdoor air pollution and asthma. Curr Opin Pulm med 2004;10:62-66.

AUTHORS' CONTRIBUTIONS

PH is the main author of the study protocol and this manuscript. OU, FC, SF, and JKS secured the funding of this study. PH, AS, MB, JBS and SM obtained ethical and privacy approval. PH and AS drafted the manuscript. MB, JBS, SM, OU, FC, SF and JKS critically revised the manuscript. All authors approved the final version.

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COMPETING INTERESTS STATEMENT

Dr. Honkoop has nothing to disclose. Dr. Simpson has nothing to disclose. Dr. Bonini has nothing to disclose. Dr. Snoeck-Stroband has nothing to disclose. Dr. Meah has nothing to disclose. Dr. Chung reports personal fees from Advisory Board membership, grants for research, personal fees from payments for lectures, outside the submitted work. Dr. usmani reports grants from astra zeneca, personal fees from boehringer ingelheim, grants and personal fees from chiesi, personal fees from aerocrine, grants from glaxosmithkline, personal fees from napp, personal fees from mundipharma, personal fees from sandoz, grants from prosonix, personal fees from takeda, personal fees from zentiva, grants from edmond pharma, personal fees from cipla, outside the submitted work. Dr. Fowler has nothing to disclose. Dr. Sont reports grants from GlaxoSmithKline NL, grants from Chiesi NL, outside the submitted work.

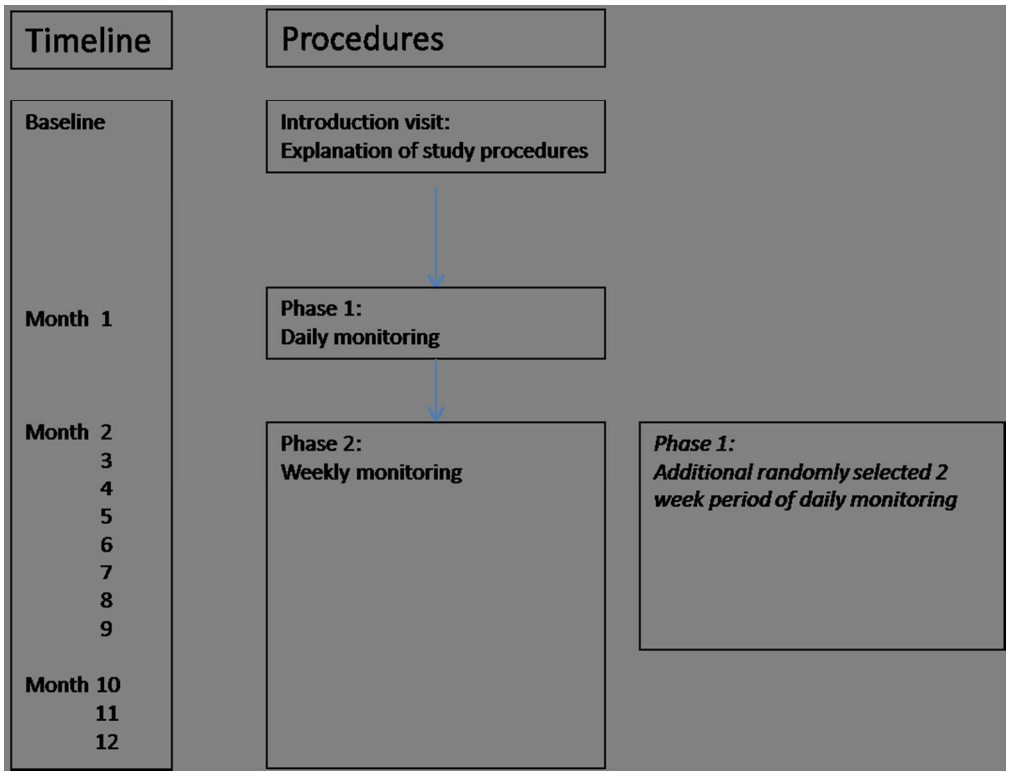
Figure legends

Figure 1. Schematic of study design.

At the baseline visit all study procedures are explained. In the first month (phase 1) participants are monitored daily. Phase 2 consists of 11 months of weekly monitoring. Additionally in phase 2, blocks of patients will be randomised over month 2-9 for a second series of 2 weeks of phase 1 daily monitoring. Since participants will be included and commence the study over a four month period, all months will be covered, which allows the assessment of the influence of seasonality.

Figure 2a,b. A view of a participant's iPod

In figure 2a a general overview of the iPod-screen after turning it on and in figure 2b a screenshot of a "to do" list within the Patientcoach system.



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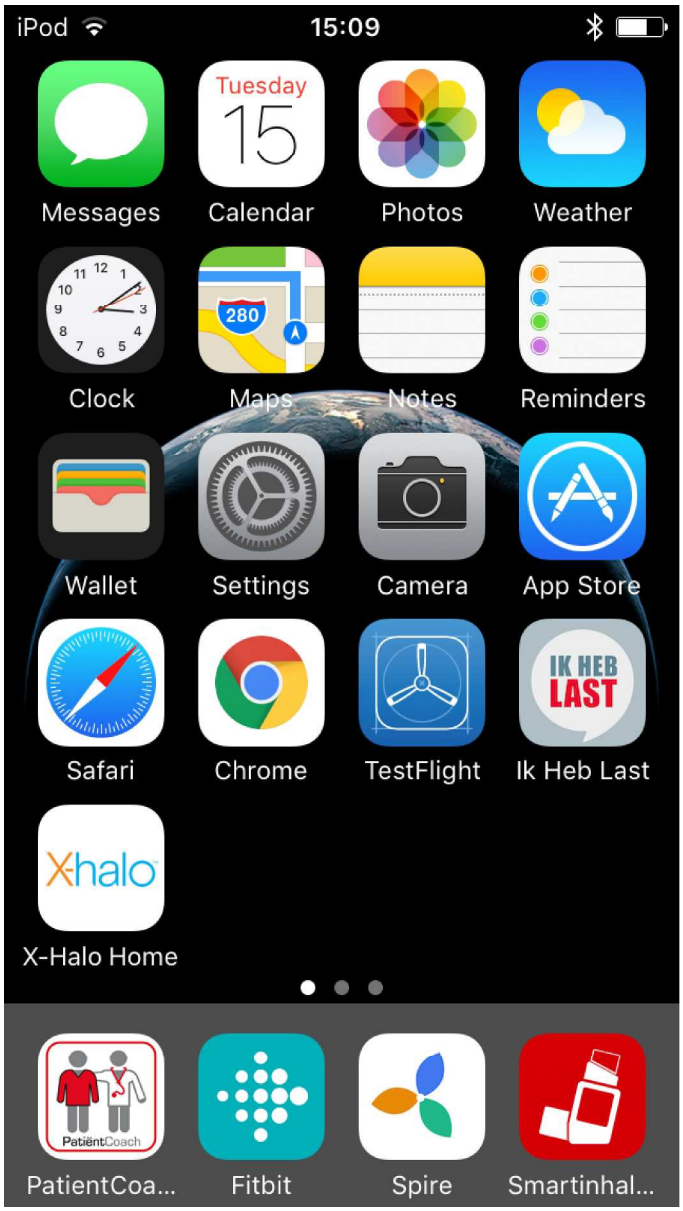

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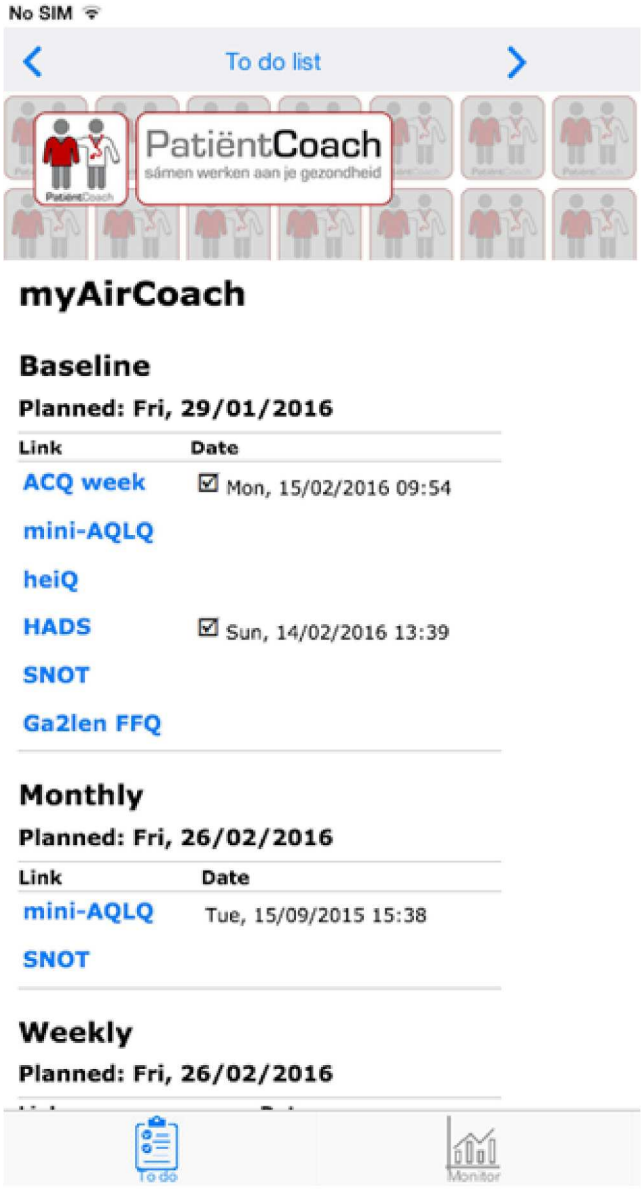

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