BMJ Open Respiratory Research

Effectiveness, usability and acceptability of a smart inhaler programme in patients with asthma: protocol of the multicentre, pragmatic, open-label, cluster randomised controlled ACCEPTANCE trial

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To cite: van de Hei SJ, Poot CC, van den Berg LN, *et al*. Effectiveness, usability and acceptability of a smart inhaler programme in patients with asthma: protocol of the multicentre, pragmatic, open-label, cluster randomised controlled ACCEPTANCE trial. *BMJ Open Resp Res* 2022;9:e001400. doi:10.1136/bmjresp-2022-001400

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2022-001400).

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Received 10 August 2022
Accepted 8 December 2022

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ABSTRACT

Introduction Suboptimal asthma control is associated with incorrect inhaler use and poor medication adherence, which could lead to unfavourable clinical and economic outcomes. Smart inhaler programmes using electronic monitoring devices (EMDs) could support self-management and increase medication adherence and asthma control. However, evidence on long-term benefits and acceptability is scarce. This study aims to investigate the effectiveness of a smart inhaler asthma self-management programme on medication adherence and clinical outcomes in adults with uncontrolled asthma, to evaluate its acceptability and to identify subgroups who would benefit most based on patient characteristics.

Methods and analysis This open-label cluster randomised controlled trial of 12 months will be conducted in primary care in the Netherlands. General practices will be randomly assigned to either intervention or control group. We aim to include 242 patients. The intervention consists of (1) an EMD attached to the patient's inhaler that measures medication use; (2) a smartphone application to set medication reminders, receive motivational messages and track asthma symptoms; and (3) a portal for healthcare professionals to view data on medication use. The control group is passively monitored by the EMD but cannot view their inhaler data or receive feedback. Eligible patients are adults with suboptimal controlled asthma (Asthma Control Questionnaire score ≥0.75) with evidence of non-adherence established by the EMD during a 6-week run-in period. Primary outcome is the difference in mean medication adherence between intervention and control group. Secondary outcomes include asthma control, asthma-related quality of life, exacerbations, acceptance, cost-effectiveness and whether the effect of the intervention on medication adherence and asthma control is modified by patient characteristics (eg, self-efficacy, medication beliefs and eHealth literacy).

Trial registration number NL7854.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Smart inhaler programmes using electronic monitoring devices could support self-management and increase medication adherence and asthma control. However, evidence on long-term benefits and acceptability of smart inhaler programmes is scarce.

WHAT THIS STUDY ADDS

⇒ Our cluster randomised controlled trial will evaluate the long-term effectiveness and cost-effectiveness of a smart asthma inhaler programme in a real-world primary care setting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The outcomes of this pragmatic trial will provide evidence on the long-term effectiveness of smart inhalers in the treatment of asthma. Additionally, the study will contribute to the existing knowledge regarding the role of patient characteristics on medication adherence and the use of eHealth-based self-management interventions.

INTRODUCTION

Background and rationale

Asthma is characterised by chronic inflammation of the airways and affects more than 300 million adults and children worldwide.[1] Despite the availability of effective treatment, nearly half of all patients with asthma remain inadequately controlled.[2] Suboptimal control is associated with increased symptom burden, increased risk of exacerbations and reduced quality of life, and may lead to short-acting β-2 agonist (SABA) over-reliance.[3–7] Furthermore, an increased economic burden in terms of direct costs (healthcare use and medication)

and indirect costs (loss of productivity and absenteeism) is associated with poor control.[8 9] Poor medication adherence and incorrect inhaler use could lead to suboptimal asthma control.[10–13] Globally, medication adherence ranges from 13% to 52%.[14 15] Numerous factors contribute to poor medication adherence, including illness perceptions, medication beliefs (eg, concerns about side effects), forgetfulness, difficulty understanding specifics of the regimen (ie, inhaler technique), attitude towards the illness (ie, the patient's willingness to work with physicians to manage the disease) and self-efficacy (ie, the patient's confidence in his or her ability to contribute to the management of the disease).[16 17] As such, medication adherence interventions ask for a comprehensive and personalised approach, one that is tailored towards reasons of non-adherence.[18]

Having objective data on medication adherence is essential to inform interventions. Electronic monitoring devices (EMDs) can provide real-time data on medication adherence to both patients and healthcare professionals (HCPs). Insight on adherence data can support clinical decision making, for example, by being able to identify suboptimal adherence as reason for poor treatment response.[19] By combining the EMD with an application on the patient's smartphone, there is increasing potential for use in self-management of asthma.[20 21] These so called 'smart inhalers' are able to upload real-time data to the patient's smartphone. As such, patients can receive tailored audiovisual medication reminders and motivational messages, and gain insight on inhaler use. The use of an app makes it possible to integrate multiple self-management components such as the possibility to track symptoms and triggers over time. In addition, it is possible to provide tailored self-management care that can be delivered outside of office hours and scheduled appointments on a more timely manner.

Various studies have found that smart inhalers increase medication adherence,[19 22–26] but an improvement in asthma control is only shown in children.[27] However, those studies only evaluated the short-term effects (≤ 6 months) of smart inhalers. Also, evidence on the cost-effectiveness of smart inhaler-based self-management programmes is lacking. Furthermore, acceptance and eHealth usage have not been evaluated in prior studies on smart inhalers, whereas it is known that the effectiveness of an asthma smart inhaler based self-management programme may be compromised by adoption failure and poor adherence to the intervention.[28] Acceptance and eHealth usage depend on multiple patient characteristics, including illness perception, beliefs about medication and eHealth literacy.[29 30] By evaluating how these factors interact in affecting medication adherence and clinical outcomes, we will be able to identify which patients would benefit most from the use of a smart inhaler-based self-management programme. To our knowledge, this is the first pragmatic randomised trial to evaluate the long-term effects of a smart inhaler based asthma self-management programme on medication adherence and clinical outcomes, to collect data on patient characteristics and acceptance, and to perform a cost-effective analysis.

Aims

The primary objective of our study is to evaluate the effectiveness of a smart inhaler programme on medication adherence in adults with uncontrolled asthma compared with control (ie, passive monitoring with an EMD) over 12 months. Secondary objectives are to evaluate clinical outcomes (ie, asthma control, reliever use, exacerbations and asthma-related quality of life); to evaluate which patient groups would benefit most based on baseline patient characteristics (ie, self-efficacy and attitude, beliefs about medicine, illness perception and eHealth literacy); to evaluate usability and acceptability of the programme by patients and HCPs; and to evaluate the cost-effectiveness of a smart inhaler programme. The purpose of this paper is to describe the rationale and design of the trial.

METHODS

Study design

This is a pragmatic, multicentre, open-label cluster randomised controlled trial (RCT) of 12 months in primary care in the Netherlands. Primary care practices are eligible if they have access to a computer and internet. Eligible primary care practices that provided consent are randomised to either intervention (smart inhaler programme) or control (usual care+passive electronic monitoring). Participating patients receive either intervention or control, depending on the allocation of the cluster. Each patient is screened for eligibility and has follow-up measurements at 3, 6, 9 and 12 months from baseline. The baseline is preceded by a 6-week run-in period to assess whether patients are non-adherent. The study is run by three centres in the Netherlands (Leiden University Medical Centre, General Practitioners Research Institute and University Medical Centre Groningen). Practices and patients are recruited throughout the Netherlands. Since inclusion is ongoing during the COVID-19 pandemic, a number of amendments were made to continue inclusion, warrant the safety of the patients and the research team, and increase recruitment pace. All protocol amendments with reason are enlisted in online supplemental table E1. The design of the study and flow of practices and patients is depicted in figure 1. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[31] The SPIRIT checklist is provided in online supplemental table E2.

Practice recruitment

Practices are identified via a database search of all primary care practices in the Netherlands. Practices are invited to participate via a letter containing study information and

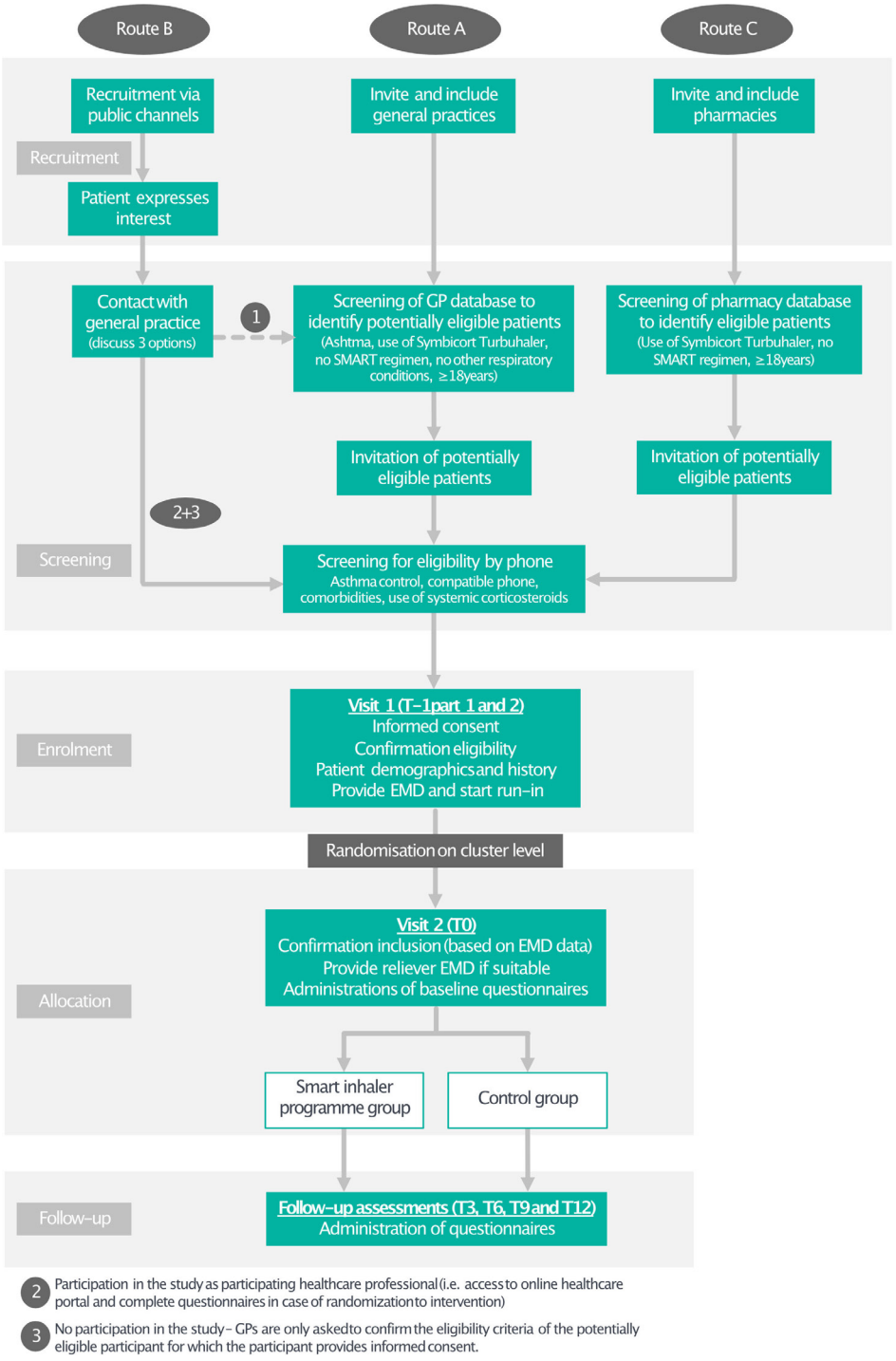

Figure 1 Study flow diagram. EMD, electronic monitoring device; GP, general practice; SMART, Symbicort as maintenance and reliever therapy.

an information folder. Practices are followed up via telephone contact and email. In addition to invitations, indirect approaches such as presentations at conferences, professional development events for HCPs and word of mouth are used to recruit practices. Before enrolment, practices sign a data processing agreement which allows selection and invitation of potentially eligible patients on behalf of the practice by research staff. This approach allows us to keep the burden for general practices to a minimum, and at the same time to reach an adequate patient sample.

Patient recruitment

Initially, patients are recruited only from enrolled practices. However, due to low inclusion numbers, mainly caused by the increased workload in primary care practices during the COVID-19 pandemic, we broadened the

recruitment strategy with recruitment via public channels (ie, social media and newspaper advertisement) and recruitment via pharmacies. Adding these two alternative recruitment strategies means that eligible patients recruited via these routes do not need to be registered at participating practices but do need to meet all further eligibility criteria. Also, inclusion criteria are checked by the general practitioner in each route. As such, patients can be recruited via the following three routes (partly overlapping at some stages).

Route A (recruitment via general practices)

Eligible patients are selected through electronic record screening by a research assistant or by the practice following an instruction sheet. Invitation letters with an expression of interest form and a reply envelope are sent on behalf of the general practitioner to all eligible patients. Patients can also express their interest via the study website with an identification code included in the letter. Non-responders are sent a reminder letter after 2–3 weeks. Furthermore, general practices are asked to contact non-responders.

Route B (recruitment via public channels)

Potentially eligible patients are recruited via public channels including (local) newspapers, social media channels and patient organisations by using a visual advertisement including a link to the study website containing more details on the study. Potentially eligible patients expressing their interest to participate are contacted and screened telephonically on eligibility. The general practice where the potential patient is registered is contacted to discuss participation of the general practice (ie, inviting all eligible patients from the practice following 'route A'). Practices that are not interested in study enrolment are asked to check the inclusion criteria only.

Route C (recruitment via pharmacies)

Pharmacies are identified via a database search of all pharmacies in the Netherlands. Pharmacies are invited to participate via email and are followed up via telephone or email. Pharmacies are also recruited via word of mouth. Potentially eligible patients are identified via pharmacy records. Pharmacies are asked to select and invite these patients following the steps outlined in route A. Patients who express their interest are screened on eligibility. Since pharmacies cannot identify patients by asthma diagnosis, the inclusion criterion 'doctor-diagnosed asthma' is checked by the general practice. The general practice is not asked to participate as a cluster, as we want to alleviate the burden that general practitioners face due to the COVID-19 pandemic (ie, an increase in absenteeism due to illness and a postponement of care due to several lockdowns). For the same reason, the inclusion criterion doctor-diagnosed asthma will be checked at 12 months of follow-up instead of at inclusion.

Inclusion and exclusion criteria

On expression of interest, all potentially eligible patients are screened by a research assistant telephonically for further eligibility. Patients aged 18 years and older, who have uncontrolled asthma (defined as an Asthma Control Questionnaire (ACQ)-5 score of ≥0.75), use budesonide/formoterol Symbicort Turbuhaler as maintenance therapy for at least 8 weeks before entering the run-in period, have a doctor-diagnosed asthma and are in the possession of a Turbu+ Insights application-compatible smartphone (ie, Android or iOS as mobile operating system) are eligible for inclusion. Patients can receive asthma treatment in primary care or (temporarily) in secondary care, and must provide digital (ie, via DocuSign) or written informed consent. Furthermore, patients should be classified as 'non-adherent', as observed during the run-in period, during which inhalation actuations are electronically monitored. Non-adherent is defined as an adherence rate of below 80% over the third and fourth weeks of the 6-week run-in period. The adherence rate is defined as the number of adherent days as a proportion of the total number of days. An adherent day is considered a day on which the patient takes at least the number of inhalations prescribed (less inhalations than prescribed means a non-adherent day). Validity of inhalation data can be compromised by change in adherence behaviour due to the knowledge on participating in a trial. To minimise impact, inhalation actuations from the first, second, fifth and sixth weeks of the run-in period are disregarded.

Patients who meet one or more of the exclusion criteria are excluded. Exclusion criteria are (1) use of Symbicort as Symbicort Maintenance and Reliever Therapy (SMART) (to be able to draw valid conclusions on the effect on the primary outcome medication adherence); (2) change in inhaled corticosteroids (ICSs) dose in the 4 weeks prior to the run-in period; (3) use of systemic corticosteroids in the 4 weeks prior to the run-in period, including maintenance therapy (ie, to exclude patients recovering from an exacerbation at study start); (4) current use of biologics, including anti-interleukin (IL)-5, anti-IL-4Rα or anti-IgE; (5) diagnosis of chronic obstructive pulmonary disease, interstitial lung diseases, bronchiectasis or other significant respiratory conditions; (6) malignancy with life expectancy of <1 year; (7) pregnancy; and (8) inability to understand Dutch. Patients with any other condition which, at the general practitioner's and/or investigator's discretion, is believed to potentially present a safety risk or impact the study results are also excluded from study participation.

Randomisation, sequence generation and allocation concealment

Primary care practices are block-randomised using a computer-generated permuted block scheme with random block sizes of 4 and 6, stratified by practice size (≤2500 patients or >2500 patients). The randomisation

code is recorded in the randomisation database, which is accessible only to the coordinating researcher and research assistants. Randomisation at practice level minimises the risk of contamination across intervention and control groups, as patients from the same practice are managed by the same HCPs. Randomisation takes place when the first patient of the general practice has finished the run-in period and will start the smart inhaler programme or enter the control group. Subsequently, practice staff are notified of the allocation of their practice. From this point, no additional patients from the same practice can be recruited. This minimises the risk of recruitment bias by practices based on knowledge on allocation. All patient participants that are registered to a participating practice receive the intervention or control, depending on the allocation of the practice. Each individual patient participant who is not registered in a participating practice (ie, part of the patients recruited via route B and all patients recruited via route C) is considered a separate cluster. The cluster will be randomised using the same randomisation scheme and procedures. Randomisation takes place after the 6-weeks run-in period when patients fulfil all inclusion criteria.

Study groups

All patients receive usual care according to the Dutch National Primary Care Asthma Guidelines.[32]

Intervention (smart inhaler programme)

Patients randomised to the smart inhaler programme will use an EMD, Turbu+ device (medical device class I, manufactured by Adherium (NZ), CE marked), which is a small battery-powered electronic data logger. This EMD has previously been used in a research context in the Netherlands.[25] The EMD is attached to the patient's inhaler (Symbicort Turbuhaler). The device automatically logs inhaler actuation data including an event stamp and a time-and-date stamp. A validation study on the detection of inhaler events as recorded by the Turbu+ device found an accuracy of 99.9% by bench testing over a 12-week period.[33] Logged actuation data are sent to an application on a smartphone (Turbu+ Insights). To enable upload of stored actuation data, the app needs to be installed on a smartphone and the device must be paired with the phone using a Bluetooth connection (instructions provided in the app). The upload of new data from the device to the app occurs automatically if the device is within range (<5 m) of the phone. When the phone is out of range, data will be stored on the device and uploaded to the app when the phone is within range. It is also possible to manually upload data to the app. The battery light-emitting diode (LED) on the device indicates the battery level. Battery life of the device is approximately 1 year. The app consists of several features which are detailed further. Patients in the intervention group receive instructions on how to use the EMD and how to download, log-in and navigate within the app. No specific instructions on the interaction with the device and application are given (ie, patients decide which features of the application they use and do not use and the frequency of interacting with the app) because we aim to mimic a real-world situation in which a wide range of user interactions is possible.

Logging and visualisation of actuation events

The app receives and stores inhaler actuation events recorded by the EMD and visualises inhaler use over time. Patients randomised to the intervention group are registered in the Turbu+ system. Registration includes medication regimen (eg, two inhalations two times a day). Changes in medication regimen are updated in real time and are visible for the patient in the app. Actuation events are plotted against the prescribed medication regimen on a timeline. In addition, patients can view the actuation events over a certain period (eg, last week or month).

Automatic reminder and messaging

The patient can opt in to receive medication reminder messages as push notifications that pop up on the screen. The application also provides preconfigured missed dose-engaging voice messages (30 min after a 'missed dose'). These short messages are based on known drivers and barriers of treatment engagement and treatment perceptions.[34] The application also sends overuse messages and weekly targeted motivational messages (eg, 'Great week. You've been following your prescription this week! Keep it up!').

Symptom and triggers

Patients can record their symptoms and triggers daily in the app by indicating the severity or presence of the symptom or trigger on a 5-point scale. The separate items are projected in the form of a flower (ie, a full flower is analogous to a happy flower, meaning a minimal presence of symptoms and triggers). The data can be viewed over time.

Web-based HCP portal

Inhaler actuation data are uploaded to the smartphone application and electronically linked to an online webportal (Turbu+ webportal), which can be accessed by the patient's HCP. Within the portal, HCPs can view real-time actuation data, including a date and time stamp. HCPs from participating practices receive a log in code to be able to set and change the medication regimen and to view the adherence data of their patients participating in the study. Furthermore, they receive instructions on how to access the online healthcare portal and navigate within the portal, but they do not receive specific instructions on the interaction with the healthcare portal and on the use of EMD data during or before patient consultations. Patients who are not registered in a participating

practice (ie, part of the patients recruited via route B and all patients recruited via route C) can use the app without participation of the HCP.

Control group (passive electronic monitoring)

Patients in the control group attach the same EMD (Turbu+) to their inhaler (Symbicort Turbuhaler) as the intervention group. However, the EMD is connected to a different smartphone application (Hailie Lite). Actuation data are not visible to patients in this app; the app only shows when the EMD last synchronised data with the smartphone (ie, 'Last synced: (date), (time)'). Inhalation data uploaded to the smartphone application will automatically be uploaded to an online portal (Hailie web portal) which is only accessible to the research team. As inhaler actuations are objectively monitored, without patients and HCPs being able to view their inhaler data, this is called 'passive electronic monitoring'.

EMD for reliever inhalers

A subgroup of patients, regardless of study arm, are provided with an EMD which is compatible with their reliever inhaler (Hailie sensor, medical device class I, manufactured by Adherium (NZ), CE marked). Compatible relievers are Bricanyl Turbuhaler (containing terbutaline) or Ventolin aerosol (containing salbutamol). As in the control group, the EMD will be attached to the patient's inhaler and passively monitor inhaler actuation data using the Hailie Lite smartphone application. Again, actuation data uploaded to the online Hailie portal will only be accessible to the research team.

Data collection and follow-up

Practices

Baseline data from the participating practices are collected at the time of enrolment using a standard data collection form. Data include information on practice size, number of patients and number of staff.

Patients

Considering the pragmatic nature of the study, data are collected during study visits at baseline and at 6 and 12 months after randomisation. At 3 and 9 months, data are collected via questionnaires sent to the patients. Initially, the study visits took place at the patient's home. Due to the COVID-19 pandemic, we decided to change to remote study visits using video consulting software to be able to continue the study and avert the risk of COVID-19 infection. As remote study visits allow a large flexibility and are perceived as useful by patients (ie, remote study visits could be easily combined with work), the remote study set-up is continued after social distancing measurements are lifted. In case of technical difficulties (eg, synchronisation problems) which cannot be solved remotely or when it is impossible for the patient to videocall, the visit proceeds via a home visit (only when COVID-19 measurements allow for home visits).

T-1 (first visit) and run-in period

During the first visit, electronic or handwritten informed consent will be provided. Electronic signature was initiated during the COVID-19 pandemic and proceeds via DocuSign, an electronic signature software that meets all legal requirements for eSignatures according to the European Union (EU) law 'electronic identification, authentication and trust services'. After signing the informed consent, initial eligibility is confirmed according to the inclusion and exclusion criteria. Subsequently, demographics (date of birth, sex, education level, smoking history and pack years), medical history (age of asthma onset, number of exacerbations, asthma-related hospital admissions and emergency department visits in the prior year, and other comorbidities) and self-reported asthma medication use will be collected. Patients are provided the EMD (Turbu+ device), instal the app (Hailie Lite) on their smartphone following instructions from the researcher and then enter the 6-week run-in period in which inhaler actuations are objectively monitored.

T0 (baseline visit)

After the run-in period, final eligibility will be confirmed based on the actuation data collected with the EMD during the run-in period. Patients who are classified as non-adherent (see the Inclusion and exclusion criteria section for definition) will continue study participation. Before giving informed consent, patients are informed that an additional selection takes place after the run-in period, but they are not informed about what the additional selection entails (ie, selection based on the level of medication adherence). Awareness of patients hereof probably affects the adherence behaviour of patients and could lead to biased results, especially because the primary outcome measure of this study is medication adherence. During the baseline visit, baseline data are collected through questionnaires and structured interviews (see table 1). Furthermore, patients are informed of their assigned randomised condition (ie, intervention or control). The EMD of patients in the intervention group is replaced to ensure data collected in the run-in period are not visible in the intervention app, and instructions on how to download and use the intervention app are provided.

Follow-up visits (T6 and T12)

At visits T6 and T12, data are collected through structured interviews and questionnaires (see table 1), as this helps to keep patients involved, retain participation and reduce the amount of missing data. All patients receive a new EMD prior to visit T6 to ensure sufficient battery throughout the study.

Table 1 Overview of measurements

	Run-in	Intervention				
Contact moment	**1**	**2**	**3**	**4**	**5**	**6**
Month	**T-1**	**T0**	**T3**	**T6**	**T9**	**T12**
	Remote visit	**Remote visit**		**Remote visit**		**Remote visit**
Patient assessments						
Informed consent	X					
Eligibility assessment	X					
Demographic characteristics	X					
Medical history	X					
Provide EMD	X					
Confirmation inclusion		X				
Randomisation		X				
Asthma medication regimen	X	X		X		X
Healthcare use*		X		X		X
Exacerbations	X	X	X	X	X	X
(Severe) adverse events		X		X		X
Paper administered questionnaires						
Health use assessment*			X		X	
ACQ-5	X	X	X	X	X	X
Mini-AQLQ		X	X	X	X	X
WPAI Questionnaire		X	X	X	X	X
Electronic administered questionnaires						
KASE-AQ		X				X
BMQ-Specific		X				X
Brief IPQ		X				X
eHLQ		X				X
TAQ†			X			X
SUS†			X			X
Non-patient assessments						
Log data						X
Inhaler actuations (EMD)	Data collected over time interval T-1–T12					
Reliever inhalation actuations (EMD)‡	Data collected over time interval T0–T12					
Medication use§						X
Healthcare professional assessments						
TAQ†¶			X			X
SUS†¶			X			X

*At T0, T6, T12 structured interview, at T3 and T9 paper questionnaires (same questions). Healthcare use data covering the study period will be retrieved from the patient's general practice electronic health record system at study end.
†Questionnaires only administered to the intervention group.
‡Only patients that use an EMD compatible reliever inhaler.
§Medication use data during the study and the year prior to the study will be retrieved from the patient's main pharmacist dispense system.
¶Only for HCPs that participate in the study (option A, option B1 and B2).
ACQ, Asthma Control Questionnaire; BMQ-Specific, Beliefs about Medicine Questionnaire–Specific; eHLQ, eHealth Literacy Questionnaire; EMD, electronic monitoring device; IPQ, Illness Perception Questionnaire; KASE-AQ, Knowledge Attitude Self Efficacy-Asthma Questionnaire; Mini-AQLQ, Mini Asthma-Related Quality of Life Questionnaire; SUS, System Usability Scale; TAQ, Technology Acceptance Questionnaire; WPAI, Work Productivity and Activity Impairment.

Study outcomes

Primary outcome

The primary outcome of this study is medication adherence over 12 months, as measured objectively by electronic monitoring of inhaler actuations. The treatment effect will be expressed as the mean absolute difference in medication adherence between the smart inhaler programme group and the control group. Medication adherence is defined as the percentage of daily inhalations taken as prescribed (number of recorded

inhalations per day/number of maintenance inhalations prescribed per day×100), corrected for dose dumping. Dose dumping is defined as ≥6 actuations within a 5 min period. Daily adherence will be capped at 100% (ie, to avoid falsely increased values).

Secondary outcomes

Asthma control

Asthma control is measured with the ACQ-5.[35] The ACQ-5 is developed as a self-report measure to assess asthma control. The five items of the ACQ are each rated on a 7-point scale (0–6 points). The items assess sleep deprivation, symptoms on waking, activity impairment, dyspnoea and wheezing during the previous week. Patients with a score of ≤0.75 are considered as having controlled asthma; patients with a score of ≥1.5 are considered as having uncontrolled asthma.[36] A change of ≥0.5 is considered the minimal clinically important difference (MCID).[37]

Asthma-related quality of life

Asthma-related quality of life is assessed with the self-administered Mini Asthma-Related Quality of Life Questionnaire. Each of the 15 items is rated on a 7-point scale (1–7 points), and the questions cover four domains (symptoms, activities, emotions and environment).[38] A higher score indicates better asthma-related quality of life. The MCID is considered to be 0.5.[39]

Reliever use

Reliever use (SABA) is electronically monitored in a subgroup of patients who are in possession of a reliever inhaler which is compatible with an EMD. Reliever prescription data are retrieved from the patient's pharmacy at study end for all participating patients.

Exacerbations

The total number of severe exacerbations is collected through self-report (interview during visits and questionnaires at T3 and T9) and through the patient's pharmacist and general practice electronic health record system. The definition of a severe exacerbation is either the use of systemic corticosteroids or an increase from a stable inhaler maintenance dose for at least 3 days, or hospitalisation or an emergency department visit because of asthma requiring systemic corticosteroids.

Acceptance and usability of the smart inhaler programme

The usability and acceptance of the smart inhaler programme are assessed among patients and practices allocated to the intervention group using two questionnaires. Acceptance is measured with the Technology Acceptance Questionnaire, which consists of 22 items (eg, 'using Turbu+ makes it easier to manage my asthma' and 'I find Turbu+ easy to use') which are scored on a 5-point Likert scale. The items are based on the technology acceptance model and the unified theory of acceptance and use of technology and address the intended use and different factors determining the behavioural intention to use the smart inhaler programme.[40 41] Usability is assessed using the System Usability Scale.[42] This is a generic instrument to measure the usability of a technology or service and contains 10 items which are adapted to the specific technology or service. The items are rated on a 5-point Likert scale from 1 ('strongly disagree') to 5 ('strongly agree'). An additional free-text field allows for commenting on usability.

Patient characteristics

Asthma attitude and self-efficacy

The Knowledge, Attitude and Self Efficacy-Asthma Questionnaire (KASE-AQ) is used as a comprehensive tool to measure various aspects of attitude and self-efficacy regarding controlling asthma symptoms and disease.[43] Each domain consists of 20 questions with scores ranging from 20 to 100. Higher scores on the Self-efficacy Scale indicate more confidence in managing and controlling asthma. Higher scores on the Attitude Scale indicate a more positive attitude towards asthma. The Knowledge Scale will be omitted as it is oriented to the USA and is not in line with the current Dutch medical guidelines on asthma management. The KASE-AQ without the knowledge domain has successfully been used in previous studies.[44 45]

Medication beliefs

The Beliefs about Medicine Questionnaire–Specific (BMQ-Specific) is used to measure beliefs about asthma medication.[46] The BMQ-Specific consists of 10 items about the necessity and concerns of a patient's prescribed medication. The items are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree).

Illness perception

Illness perception specific to asthma will be measured using the Brief Illness Perception Questionnaire (Brief-IPQ). The Brief-IPQ assesses the emotional and cognitive representation of illness and consists of nine items rated on an 11-point scale.[47–49]

eHealth literacy

eHealth literacy is assessed using the eHealth Literacy Questionnaire, which is based on the eHealth Literacy Framework.[50] This framework consists of seven domains which include individual factors that are necessary to use eHealth (eg, engagement in own health), system factors (eg, access to digital services that work) and user–system interaction factors (eg, motivation to engage with digital services). The questionnaire consists of 35 items which are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). The eHLQ has been used in international research to help understand people's interaction with eHealth devices and has been translated into seven different languages. As validation studies of the

eHLQ into Dutch were ongoing at study start, the initial translated and culturally adapted version was used.

Healthcare use

Healthcare use is assessed at baseline (T0) and during all follow-up moments. Self-report data will be complemented with healthcare use data covering the study period, retrieved from the patients' general practice electronic health record system at study end. Use data include asthma-specific hospital admissions including intensive care unit days and length of stay, emergency department visits because of asthma, asthma-related visits and phone calls to the general practice, and medical specialist visits because of asthma. Data on medication use will be retrieved from the patients' main pharmacist dispense system at T12.

Absenteeism and presenteeism

The Work Productivity and Activity Impairment instrument will be completed by patients to measure absenteeism and presenteeism. The questionnaire consists of nine questions in three domains (work impairment, school impairment and activity impairment).[51 52] Outcomes on absenteeism, presenteeism, work productivity loss and activity impairment are expressed as percentages, with higher numbers indicating greater impairment and/or less productivity.

Cost-effectiveness analysis

The cost-effectiveness of the smart inhaler programme will be assessed by comparing the costs and benefits of the programme (ie, intervention group) with usual care (ie, control group) in a cost-effectiveness analysis.

Sample size

The power calculation is based on the primary outcome: medication adherence over 12 months, as measured by electronic monitoring of inhaler actuations. The treatment effect is expressed as the absolute difference in mean medication adherence between the intervention group and the control group. The sample size is based on an absolute difference in mean medication adherence between the groups of 15% (effect size), based on an expected adherence rate of 65% in the control group,[22 53 54] and the target of a mean adherence of 80% in the intervention group. An SD of 0.30 is used.[22] A design effect of 1.075 is used, which is based on an intracluster correlation coefficient of 0.025[55] and a cluster size of 4. The cluster size is based on (1) the average number of patients with asthma in a Dutch general practice; (2) data on age, asthma control level and medication use[56]; (3) the assumption that 40% of the patients are non-adherent; and (4) recruitment rates in previous primary care asthma trials.

To detect an absolute difference of 15% in mean medication adherence with 90% power and a 5% significance level, a sample size of 242 patients (121 per arm) across approximately 30 clusters in each arm is needed. Given the COVID-19 circumstances and the substantial impact on recruitment pace and strain on healthcare, it is difficult to predict recruitment and drop-out rates. Therefore, we explored different scenarios based on a power of 80% and varying drop-out rates based on literature (table 2).

Statistical analysis

The statistical analysis plan is presented in online supplemental file E3. Data will be analysed using the intention-to-treat principle. In addition, a per-protocol analysis will be performed for the primary outcome. Baseline demographic and clinical characteristics will be summarised using means and SD, or medians and IQRs, where appropriate. To test the effect of intervention condition on medication adherence and on changes in medication adherence over time, a multilevel linear mixed-model analysis will be performed. The model will include weekly adherence rates per patient from baseline to T12 (ie, recorded as a percentage). A precise definition and of medication adherence and how it is calculated is provided in the statistical analysis plan (online supplemental file E3). Medication adherence data around visits will be disregarded to minimise bias. The mixed model will include a random intercept per general practice. A correlation structure will be chosen for the repeated measurements on the level of patients by selecting the best fitting variance–covariance matrix. The model will include fixed effects for treatment (intervention or control), time, their interaction, age and baseline adherence. Assumptions for mixed models will be investigated beforehand to check that these are met. The mixed-effect model will provide valid statistical inferences in the presence of missing outcome data, which can be explained by covariates in the model (ie, treatment, age and time). To analyse the effect of intervention on secondary outcomes over time, a similar approach as for the primary outcome will be used. A linear mixed model will be used to assess whether the effect of the intervention on medication

Table 2 Scenario power calculations

	Drop-out rate			
	25%	18%[54]	16%[68]	10%[22]
Power 90%	121 per arm	111 per arm	108 per arm	101 per arm
Power 80%	91 per arm	83 per arm	81 per arm	76 per arm

adherence and asthma control at 12 months is modified by patient characteristics (ie, self-efficacy, attitude, medication beliefs, illness perception and eHealth literacy). Sensitivity analysis will be performed using all medication adherence data (ie, including medication adherence data measured around follow-up moments) and including patients with doctor diagnosed asthma only (see the Route C (recruitment via pharmacies) section). No interim analysis will be performed. Statistical analyses will be carried out using R V.4.1.1[57] and the R Studio IDE V.1.3.1073 (or higher versions of the programs).[58] P values below 0.05 are considered statistically significant.

Cost-effectiveness analysis

A cost-effectiveness analysis will be performed alongside the trial to compare the costs and outcomes of the smart inhaler programme with the control group. A cost-effectiveness model will be used to explore long-term effects. Cost-effectiveness will be assessed following the Dutch Guideline for Economic Evaluations in Healthcare.[59]

Blinding (performance and outcome assessment)

Due to the nature of the study, patients cannot be blinded to allocation. As unblinding may introduce performance bias (ie, a change in patient's behaviour caused by awareness of participation in a trial, especially around visits), the medication adherence data of 1 week before and 1 week after follow-up moments are disregarded to minimise the risk of bias. Outcome assessors cannot be blinded as it is important to carefully instruct patients on how to download and use the intervention app and to provide training to intervention practices on use of the online portal. The statistician who performs the data analyses and validates the results will be blinded to group allocation to avoid bias.

Data management

Data will be pseudonymised by using a code list during data collection. Collection of indirect and direct identifiable information will be minimised and will be only collected for the purpose of this study. Identifiable information will be stored separately from pseudonymised data. All data collected on paper are stored in locked filling cabinets at the study sites. Electronic data are collected using Castor EDC, an electronic data capture and management application.[60] Only investigators and research staff involved in the trial have access to participant data. For the logistic management of participants and the trial, a secured access database is used. Data handling and storage comply with the General Data Protection Regulation. Source documents, informed consent forms and investigator files are archived for 15 years at the study sites, according to the Dutch Medical Treatment Act. Video consulting software used during remote visits comply with security standards set by the study sites and applicable laws and features two-factor authentication and encrypted data. Data that are stored in the apps used in this study are encrypted, as well as data that are stored in a local database on the phone. This prevents other apps on the phone from accessing the data. Data are also encrypted when data are in transit to protect personal information. All the information supplied through the Turbu+ Insights application will be stored on secure servers in the EU (Ireland) and managed by the Turbu+ Insights program administrators. Data are pseudonymised when exported from the system. All data collected by Hailie Sensors and transmitted by Hailie Lite app, as well as data entered into the Hailie web portal in the course of the ACCEPTANCE study (Asthma Control through Cost Effective Primary care Treatment: AdhereNCe and E-Health feedback) by the study site personnel, are stored on secure servers in the USA: (1) on AWS servers, from study start date to 17 December 2020 and (2) on MS Azure SQL servers, from 17 December 2020 to the present, under data processing addendums including standard contractual clauses. Further data management procedures and operational details are specified in the data management plan.

Monitoring and quality assurance

The study will be monitored on annual basis according to a monitor plan by a monitor of the Leiden University Medical Centre who works in a department different from the research staff. A structured risk analysis is performed, whereby the risk of this study is considered negligible. Based on this risk, a data monitoring committee is not deemed necessary.

Trial status

The trial is in the recruitment phase at the time of manuscript submission. The first patient was enrolled on 16 December 2019. End of data collection is expected in March 2023.

Dissemination

Results of the trial will be submitted to peer-reviewed journals and presented at both national and international conferences, where possible. In addition, we plan to disseminate during public events for patients with asthma and caregivers.

Public and patient involvement

We set up a patient advisory panel consisting of four trained patient representatives with diverse backgrounds and experience as representatives. The patient advisory panel gives advice during several stages of the research. We received input from the advisory panel on study design, study materials, patient information, recruitment plans and burden to the patient. Alle study materials involving patients, such as the smart inhaler programme and videoconference systems, were checked and tested by the panel members. Regular meetings are held with the

advisory panel to inform, seek advice and evaluate the collaboration. No patients were involved in setting the research question or the outcome measures. We plan to disseminate the results of the research to all study participants and to interested audience during public events for people with asthma.

DISCUSSION

This study protocol details the evaluation of the effectiveness and cost-effectiveness of a smart asthma inhaler programme in primary care in the Netherlands. With a follow-up of 12 months, it is the first study to provide evidence on and insight in the effectiveness of a smart inhaler programme on the long term. To our knowledge, this is also the first RCT that longitudinally assesses the use of a smart inhaler programme in a real-world setting. It becomes increasingly acknowledged that eHealth and health innovations should be investigated in a real-world setting, meaning that the study resembles real practice as much as possible. In this trial, that means that study inclusion is inclusive and patients and participating HCPs do not receive instructions on how often to use the smart inhaler programme, allowing patients and HCPs to interact with the programme in a way it suits their needs. The outcomes of this large multicentre trial will add to the evidence on the effectiveness of EMDs in the treatment of asthma. Because of the pragmatic trial design, it will give important insights in the practical use and acceptability of a smart inhaler programme in clinical practice from the perspective of patients and HCPs. The study will also contribute to the existing knowledge regarding the role of patient characteristics in medication adherence and the use of eHealth based self-management interventions.

In the early months of the COVID-19 pandemic, study inclusion was paused for 6 months. In order to proceed with study activities and continue study inclusion, the study continued as remote research. Remote research methods, including video conference systems and postal delivery of questionnaires and devices, are innovative ways of performing research. As such, this study provides insight in how remote studies can be performed in an efficient way and how they may benefit participants and the research as a whole (eg, remote visits allow more flexibility and can easily fit into the participant's daily schedules), thereby adding to limited evidence on remote or decentralised trials.[61]

This study has some methodological challenges. First, due to the nature of the intervention, blinding of patients and participating practices is not possible, introducing the possibility of performance bias (ie, improved adherence behaviour due to knowledge on allocation). This challenge is often encountered in adherence trials. Changes in behaviour are mostly seen at study start and around study visits and result in increased medication adherence in both intervention and control groups. EMD data from the SYGMA two study showed an average improvement in adherence 1–2 weeks before and after a study visit, which normalised after a visit.[62] Consequently, frequent study visits may increase medication adherence, which can subsequently improve asthma control over a longer period of time (ie, more than 6 months). In order to reduce the impact of bias and improve internal validity, the study has a follow-up of 12 months and has a minimal number of research visits (ie, every 6 months resembling the check-up frequency of patients with suboptimal controlled asthma in the Netherlands). In addition, medication adherence data around visits will be excluded from the analysis to minimise the potential impact of performance bias.

Second, different modes of recruitment and study participation may have an influence on intervention compliance and delivery of the intervention (ie, delivered to one patient and delivered to all patients of the practice). However, having multiple recruitment strategies increases the reach and enhances the recruitment rate, which is necessary to reach the required study power. Sensitivity analysis will be performed where possible to identify any effects of recruitment ways on outcomes.

Finally, it is uncertain what proportion of patients will fulfil all inclusion criteria, especially the inclusion criteria 'having uncontrolled asthma' and 'being non-adherent'. In general, people with limited health literacy and/or a lower socioeconomic position are known to be less adherent to their medication and at higher risk of having suboptimal controlled asthma.[63–65] However, this patient population is also known to be less willing to participate in research, have difficulties understanding study content and be anxious towards research or the research team.[66] Hence, while patients with asthma with lower socioeconomic positions would probably benefit most from the intervention, people with lower socioeconomic positions are less likely to participate and complete participation in a clinical trial.[67] We attempt to deal with this by providing financial compensation for their time spent by involving the practice nurse, whom patients are familiar with, in recruitment, by creating a familiar face for the patients (ie, having the same research assistant perform all study visits with one patient) and through public recruitment channels which the target group interacts with on a daily basis.

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Acknowledgements We thank the members of the patient advisory panel (J Donkers, B Frankemölle, J Groenendijk and S Sturkenboom) for their valuable input in the set-up and execution of this study. We thank Nan van Geloven for statistical advice. AstraZeneca was provided the opportunity to review the manuscript; full editorial control remained with the authors.

Contributors SJvdH and CCP contributed equally to this paper. SJvdH, CCP, EM, JFMvB, MJP, LNvdB, BMJF-dB, NHC and JWHK made substantial contributions in the conception and design of the study. SJvdH and CCP wrote the first version and subsequent versions of this manuscript. All authors reviewed the article critically for important intellectual content and gave final approval of the version to be published.

Funding This study is funded by AstraZeneca following a research collaboration agreement. This funding body made suggestions for the design of this study, but final decisions regarding the design were made by the authors. The funding body is not involved in data collection and study management, and will not be involved in the analysis and interpretation of data. Reports will be reviewed for IP rights by the funding body, but the funding body has no influence on the decision to submit reports for publication.

Competing interests JWK reports grants, personal fees and non-financial support outside the submitted work from AstraZeneca; grants, personal fees and non-financial support from Boehringer Ingelheim and GSK; grants and personal fees from Chiesi Pharmaceuticals and TEVA; grants from Mundi Pharma; and personal fees from MSD and COVIS Pharma. JWK also holds 72.5% of shares in the General Practitioners Research Institute. JFMvB received grants and/or consultancy fees from AstraZeneca, Chiesi, European Commission COST (COST Action 19132), GSK, Novartis, Teva and Trudell Medical, outside the submitted work and all paid to his institution. BFdB was employed by General Practitioners Research Institute (GPRI) at the time of the study. In the past three years (2019–2021), GPRI conducted investigator-initiated and sponsor-initiated research funded by non-commercial organisations, academic institutes and pharmaceutical companies (including AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis and Teva).

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the medical research ethics committee of the Foundation 'Evaluation of Ethics in Biomedical Research' (BEBO, Assen, the Netherlands (reference NL69909.056.19). Results will be submitted for publication in peer-reviewed journals. Participants gave informed consent to participate in the study before taking part. The study was registered in the Netherlands Trial Register (NL7854) on 3 July 2019. In case of protocol modifications, the medical research ethics committee (and the study participants if necessary) will be notified. Since the smart inhaler programme is additional to usual care and patients will use their inhalation medication as prescribed, we do not expect any risk of participation for patients. Also, no risks on the use of the electronic monitoring devices have been reported previously nor are expected. Adverse events are recorded in the study database. Serious adverse events are reported to the sponsor and the medical research ethics committee without undue delay. Participants are informed that they can withdraw from the study at any time without giving a reason. Due to the pragmatic set-up of the study, participants may continue study participation when they switch from Symbicort to other inhaler medications during the study. Switching of inhalers will be documented and data collection will be continued, with the exception of medication adherence data. To promote participation and retention, patients will be financially compensated for their participation with a gift voucher. The compensation will be proportional to the number of visits completed (€20 per visit, maximum of €80). Participating general practices will be reimbursed with €200 for study participation and an additional €100 per patient (intervention group) or €34 (control group). Pharmacies will be reimbursed with €400 for study participation when the invitation letters to potential eligible patients are sent, and an additional €25 for each patient that is eligible. This compensates for the anticipated time a general practice and pharmacy will spend performing study-related activities and answering questions from patients regarding the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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Table E1: Summary of amendments

Amend-ment number	Protocol version	Month/ year	Changes
	1.0	Apr-2019	
	2.0	Jun-2019	Resubmission (no major changes)
1	3.0	Jul-2019	Sponsor changed from University Medical Center Groningen to Leiden University Medical Center
Start recruitment practices (August 2019)			
2	4.0	Oct-2019	- Location of where consent forms will be saved added to patient information. - Randomisation will proceed via Castor EDC instead of sealed envelopes - Only adverse events related to asthma, asthma medication or investigational product will be inquired and documented.
First patient enrolled and first cluster randomised (16 December 2019)			
Recruitment and inclusion paused from March to August 2020 due to COVID-19 pandemic			
3	5.0	May-2020	- Expansion of recruitment area to the whole country - Inclusion criterion 'patients should receive asthma treatment in primary care' was removed. In this way, patients with higher symptom burden are able to participate, which increases the reach and enhances the recruitment rate. Also, patients that receive treatment from a pulmonologist will still visit their general practitioner during exacerbations or between pulmonologist consultations. - Participants will be financially compensated for their participation with gift vouchers, to promote participation and retention.
4	6.0	Jul-2020	- Replacement of home visits by remote visits, in order to proceed with study inclusion during the covid-pandemic. - Replacement of face-to-face instructions about the intervention portal for health care professionals to remote instructions.
Restart recruitment and inclusion (September 2020)			
5	7.0	Jan-2021	- Broaden recruitment strategy with recruitment via public channels (general practitioner can choose how to participate)
6	8.0	Aug-2021	- Broaden recruitment strategy with recruitment via pharmacies. Due to this change, patients will be included based on a self-reported diagnosis of asthma. The diagnosis will be checked at study end by the general practice. - Possibility added to electronically sign the informed consent form using Docusign®.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	Supplementary Table E1
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16-17

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4–5
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6–7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7–8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9–10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11–12, 17–18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12–15, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11–12, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6–7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8–9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8–9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8–11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11–14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17–18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16–17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15–16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Supplementary
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Supplementary
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STATISTICAL ANALYSIS PLAN (SUMMARY)

A cluster Randomised Controlled Trial of the effectiveness, usability and acceptability of a smart inhaler programme in asthma patients: the ACCEPTANCE study

Short title:	ACCEPTANCE study
Protocol ID:	NL69909.056.19
Sponsor:	Leiden University Medical Centre (LUMC)
Funding party:	AstraZeneca B.V.
Protocol version, date:	v8.0, 24 August 2021

This is a summary of the Statistical Analysis Plan version 1.0, dated 13 July 2022. The full Statistical Analysis Plan has been approved and signed by the principal investigator and reviewed by the subsidising party.

1. Statistical Analysis Plan

1.1. General principles

Unit of analysis will be patient level. Following the pragmatic goal of the study, the final analysis will be carried out on an intention-to-treat basis: patients will be analysed in the trial arm they are randomised to, regardless of whether or not they are exposed to the intervention (e.g. use of the Turbu+^{TM} Insights application, switch of inhaler type) and regardless of compliance to the intervention by their HCP (e.g. use of the Turbu+^{TM} Health care portal) or involvement of their HCP (e.g. general practices that do not participate). The exposure, delivery and result of the intervention (use of Turbu+^{TM} health care portal in clinical decision-making) may depend on the clusters. Therefore, the clustering of patients in the general practices will be taken into consideration in all analyses performed. In addition, a per protocol analysis will be performed for the primary outcome. A two-sided significance level of 0.05 will be used for the primary outcome, medication adherence. Due to the nature of the study, patients cannot be blinded to allocation. Furthermore, outcome assessors that perform visits with patients cannot be blinded as it is important to carefully instruct patients and practices on the use of the intervention app and portal. To reduce bias, validated questionnaires that are administered on paper or electronically will be used. Furthermore, the trial analysist that performs the data analyses will be kept blind to practice allocation until all analyses have been completed to avoid bias.
Data will be presented by intervention group. Continuous variables will be summarised as number of observed values, number of missing values, mean and standard deviation, median and interquartile range and minimum and maximum. Categorical data will be summarised as number of observed values, number of missing values, number and percentage in each category.
Analyses will be carried out using R version 4.1.1.[1], in the R Studio IDE version 1.3.1073[2] or higher versions of the programmes.

1.2. Study Populations

The intention-to-treat (ITT) population consists of all randomised clusters excluding clusters that were randomised in error (i.e. a cluster not containing participants that passed the T0 visit). Per protocol (PP) population consists of all participants who have any data available for the outcome of interest and do not have any other major protocol violation identified prior to database lock. Reasons for exclusion from PP population will be summarised.

1.3. Study Status and Consort diagram

A consort diagram will be created to graphically depict the flow of practices and patients and the phases of the trial.

1.4. Visit Attendance

For each visit, the number and percentage who attended the visit, missed the visit, had withdrawn from follow-up or had died before the visit will be reported.

1.5. Baseline Characteristics

Baseline characteristics will be descriptively summarised overall and by treatment group to check for imbalances in randomisation and to provide an overview of the study population overall on practice level and patient level. The following characteristics will be presented:

- Practice level:
  - GP participating clusters only: size of practice (continuous), number of HCPs employed (categorised)
  - GP participating clusters and non-GP participating clusters: cluster size (categorised as 1/2/3/>3)
- Patient level:
  - Age (continuous), sex (categorised), BMI (continuous), education level (categorised), smoking history including status (never, current, former) and pack years (number of cigarettes smoked per day/20*number of years smoked);
  - Medical history: age of asthma onset (continuous), exacerbations in the year prior to the study (categorised as 0/1/2/>2), comorbidities (categorised), SABA prescription (yes/no), concomitant medication use (categorised as none/1/>1)
  - Baseline medication adherence in % (continuous, adherence is defined as the number of adherent days as a proportion of the total number of days during the third and fourth week of the run-in period);
  - Baseline asthma control (ACQ-5), asthma related quality of life (mini-AQLQ), level of self-efficacy regarding the patient's perceived ability to control asthma and attitude about asthma (KASE-AQ), medication beliefs about the necessity of prescribed medication and concerns about prescribed medication (BMQ-specific), illness perception (brief-IPQ) and eHealth literacy (eHLQ).

1.6. Primary outcome

The primary outcome of this study is medication adherence over twelve months, as measured by electronic monitoring of inhalation actuations. The treatment effect of the intervention on medication adherence will be expressed as the mean absolute difference in medication adherence. Medication adherence is defined as the percentage of daily inhalations taken as prescribed (number of recorded inhalations/number of maintenance inhalations prescribed*100), corrected for dose dumping. Dose dumping is defined as ≥6 actuations within a 5-minute period. Daily adherence will be capped at 100% (i.e. to avoid falsely increased values). Adherence rates will be calculated for each week and recorded as a percentage. Medication adherence data of one week before and one week after (follow-up) visits (T0, T6, T12) and of one week after other follow-up moments (T3, T9) will be disregarded to minimize performance bias (i.e., caused by awareness of participation in trial around visits).

To test the effect of intervention condition on medication adherence and on changes in medication adherence over time a multilevel linear mixed-model analysis will be performed. The model will include weekly adherence rates per patient over 12 months. The mixed-model will include a random intercept on the level of general practices. A correlation structure will be chosen for the repeated measurements on the level of patients by selecting the best fitting variance-covariance matrix (e.g., autoregressive or exchangeable). The model will include fixed effects for treatment (intervention or control), time (i.e., week 1-52 as a continuous variable), their interaction, age and baseline adherence. Primary evaluation of the outcome will be based on comparing the estimated marginal means between the two treatment groups; we will further report on the other included variables in the model. Assumptions on mixed models will be investigated beforehand to check that these are met (i.e., normality of residuals and potential transformation of data to meet assumptions of

normality). The mixed-effect model will provide valid statistical inferences in the presence of missing outcome data, that can be explained by covariates in the model (i.e. treatment, age, time). A figure will be created in which mean adherence will be plotted against time in weeks, based on raw data.

1.7. Secondary Outcomes

To analyse the effect of intervention on secondary outcomes over time, a similar approach as for the primary outcome will be used. However, this data will not consist of daily/weekly observations, as they were obtained at several fixed time points (see Table 1 for an overview of measurements). In case of missing data, the participant will be expelled from the analysis, unless stated otherwise.
In case of missing data at one or more follow-up moments, only the completed measurements will be included in the analysis, unless stated otherwise.

For continuous secondary outcomes, comparative analyses between the intervention and the control group will be performed as for the primary outcome. These outcomes are:

- Asthma control as measured by ACQ-5 (model will be adjusted for baseline ACQ-5).
- Asthma related quality of life as measured by mini-AQLQ (model will be adjusted for baseline mini-AQLQ).

Binary secondary outcomes will be analysed using a multilevel logistic regression model, allowing for the clustered nature of the data and repeated measurements. Binary secondary outcomes are:

- Proportion of patients with a change of ≤ -0.5 (MID) from baseline to T12 in ACQ-5 compared between treatment groups.
- Proportion of patients with a change of ≥0.5 (MID) from baseline to T12 in mini-AQLQ compared between treatment groups.
- Proportion of patients that shift in asthma control category as measured by ACQ-5 (<0.75 vs. ≥0.75) from baseline to T12 compared between treatment groups.
- Proportion of patients that shift from being adherent to non-adherent and vice versa, from baseline to T12, compared between treatment groups. Being adherent is defined as ≥80% adherence.

Count data will be analysed using a Poisson regression model and will include a random intercept on the level of general practices. In case of zero inflated data, a negative binomial regression model will be used. These outcomes are:

- Total number of self-reported exacerbations from baseline to T12, as recorded every three months, compared between treatment groups.
- Number of exacerbations from baseline to T12, as retrieved from the general practices' electronic health records system at study end, compared between treatment groups.
- Number of prescribed reliever medication inhalers (SABA) from baseline to T12, as retrieved from the compared between treatment groups. The number of prescribed inhalers during the study period will be retrieved from the patient's main pharmacist.

Other secondary outcomes:

- Usability (as measured by the System Usability Scale (SUS) at T3 and T12) and acceptability (as measured by the Technology Acceptance Questionnaire (TAQ) at T3 and T12) of the Turbu+ Insights application (intervention patients) and Turbu+ Insights health care portal

(intervention general practices) will be summarised. Furthermore, scores at T3 and T12 will be compared, using a parametric (t-test) or nonparametric test (Mann Whitney U) depending on distribution of data. In case of missing data, the participant will be expelled from the analysis.

- Absenteeism, presenteeism, work productivity loss and activity impairment as measured by WPAI will be descriptively summarised for both groups. Scores will be compared between the two groups, using a parametric (t-test) or nonparametric test (Mann Whitney U) depending on distribution of data.
- Zero adherent days (when patients have taken no inhalations) and underuse days (when patients have taken less inhalations than prescribed) in both groups will be descriptively summarised.

1.8. Sensitivity analyses

- To determine the robustness of our conclusions on primary outcome, a sensitivity analysis for the primary outcome will be performed following the same method as previously described, but using all measured medication adherence data, i.e. including medication adherence measured around follow-up moments.
- If substantial baseline imbalances are observed that have not already been adjusted for in the primary analysis, sensitivity analysis will be performed, by including the respective variable as additional covariate in the model, to assess the robustness of the primary analysis.
- A sensitivity analysis will be performed to assess the effect of intervention on the primary outcome including only those patients with doctor-diagnosed asthma.
- If more than 5% of the study population will be prescribed add-on therapy during the study (i.e. anti-IgE, anti-IL5, systemic corticosteroids), a sensitivity analysis will be performed to assess the effect of the smart inhaler programme on the primary outcome, including only those patients without add-on therapy.

1.9. Subgroup analyses

The interaction between intervention conditions (smart inhaler vs. control) and patient and disease characteristics on the dependent variables medication adherence and asthma control will be analysed using a linear mixed model (same approach as for the primary outcome), to assess whether the effect of the intervention on medication adherence and asthma control is modified by patient characteristics (i.e. self-efficacy, attitude, medication beliefs, illness perception and eHealth literacy). We will examine the effect of each interaction term (e.g. intervention condition * eHealth literacy) on the outcome, corrected for the main effects of the intervention condition, the respective moderator variable (e.g. eHealth literacy) and covariates. Separate analyses will be performed for medication adherence and asthma control and for the different interaction terms. A Bonferroni correction will be applied to correct for multiple testing,

1.10. Exploratory analyses

Medication adherence

- An exploratory analysis will be performed to test the effect of intervention condition on medication adherence and on changes in medication adherence over time, in which

medication adherence is defined differently than in the primary outcome analysis. Medication adherence will still be calculated as the percentage of daily inhalations taken as prescribed and corrected for dose dumping, but will be corrected for intervals between doses (i.e., correct time of use is twice a day, in a period of >6 hours and <18 hours between doses). Furthermore, a 24-hour period will be defined as 03:00-02:59. The same model as for the primary outcome will be used. As for the primary analysis, daily adherence will be capped at 100% (i.e. to avoid falsely increased values), adherence rates will be calculated for each week and recorded as a percentage and medication adherence data of one week before and one week after (follow-up) visits (T0, T6, T12) and of one week after other follow-up moments (T3, T9) will be disregarded to minimize performance bias.

Reliever use

- A subgroup of patients will have an EMD attached to their short-acting beta agonist (SABA) inhaler (i.e. reliever inhaler). An exploratory analysis will be performed on the effect of the intervention condition on electronically monitored SABA use, as a more accurate measure for reliever use. Reliever use defined as number of inhalations as measured by EMD, averaged over the monitoring period of twelve months, will be compared between the two groups, using a parametric (t-test) or nonparametric test (Mann Whitney U) depending on distribution of data.

Delivery and use of intervention

- Due to the pragmatic nature of the trial (i.e. patients and HCPs decide on how and how often they interact with the Turbu+^{TM} Insights application and Turbu+^{TM} HCP portal respectively), we expect that there will be differences in exposure to the intervention that may impact the magnitude of effect. In other words, we expect that use of the app (as measured by the log-rate) will be associated to medication adherence. Therefore, further exploratory analysis will be performed on the correlation between intervention use (single measure over the study period) and medication adherence. Medication adherence is defined as described for the primary outcome. Depending on distribution of data, a parametric (Pearson) or nonparametric test (Spearman) will be used.
- We also expect that there will be differences in intervention delivery, as participants in GP-participating clusters will receive the full intervention, whereas participants in non-GP participating clusters will receive only part of the intervention. This difference in delivery may impact the effect of the intervention. Therefore, further exploratory analysis will be performed on the correlation between intervention delivery (yes/no) and medication adherence. Medication adherence is defined as described for the primary outcome. Depending on distribution of data, a parametric (Pearson) or nonparametric test (Spearman) will be used.

1.11. Safety Outcomes

- Numbers withdrawn from the study and the main reasons for withdrawal will be summarised by treatment group.
- The number and characteristics of serious adverse events and adverse events will be summarised by treatment group.

2. References

1. R Development Core Team. *R: A language and environment for statistical computing*. (R Foundation for Statistical Computing, 2020).
2. Rstudio team. *Rstudio: Integrated Development for R*. (RStudio PBC, 2020).