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Can electronic monitoring with a digital smart spacer support personalised medication adherence and inhaler technique education in patients with asthma?: Protocol of the randomised controlled OUTERSPACE trial

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ABSTRACT

Introduction Medication adherence and inhaler technique in patients with asthma remain suboptimal. A digital, smart spacer may support personalised adherence and inhaler technique education. The aim of this study is to assess the feasibility of undertaking a definitive randomised controlled trial of personalised, smart spacer data-driven education and explore clinical benefits.

Methods and analysis We present the design of the multicentre, randomised controlled OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE feasibility trial of 2 months. Patients will be recruited from four Dutch general practices. At t=−1, patients with asthma ≥18 years using inhaled corticosteroids±long-acting beta-agonists±short-acting beta-agonists administered with a pressurised-metered-dose-inhaler and spacer (n=40) will use a smart spacer for 1 month. The rechargeable CE-marked smart spacer (Aerochamber Plus with Flow Vu) includes a sensor that monitors adherence and inhalation technique to prescribed dosing regimen of both maintenance and reliever inhalers. After 1 month (t=0), patients are 1:1 randomised into two groups: control group (usual care) versus intervention group (personalised education). At t=-1, t=0 and t=1 month, the Asthma Control Questionnaire (ACQ), Work Productivity and Activity Impairment (WPAI) questionnaire and Test of Adherence to Inhalers (TAI) are administered and fractional exhaled nitric oxide (FeNO) is assessed. At t=0 and t=1, spirometry is performed. At t=1, usability and satisfaction will be analysed using the System Usability Scale and interviews with patients and healthcare providers. Primary outcome is the overall feasibility of a definitive trial assessed by patient recruitment speed, participation and drop-out rate. Secondary outcomes are patient and healthcare provider satisfaction and exploratory clinical outcomes are adherence, inhaler technique, TAI score, FeNO, lung function, ACQ and WPAI.

Ethics and dissemination Ethical approval was obtained from the RTPO in Leeuwarden, Netherlands (number: NL78361.099.21). Patients will provide written informed consent. Study findings will be disseminated through conferences and peer-reviewed scientific and professional journals.

Trial registration number NL9637.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled trial on the usability and potential clinical effects of using a smart spacer for personalised medication adherence and inhalation technique education in patients with asthma.
⇒ Inclusion and exclusion criteria are minimal in order to maximise the external validity of the findings.
⇒ The findings can be used to inform future larger studies and to further personalise asthma medication management.
⇒ An inevitable limitation of this study design is the impossibility to blind clinicians to the group allocation of the patients.

BACKGROUND

Asthma is a major cause of disability, healthcare services utilisation, work absence and quality of life impairment.[1–3] Asthma management aims to achieve good symptom control, minimise exacerbations and reduce side effects.[4] Although the majority of asthma patients can be effectively controlled, a substantial subset remains uncontrolled despite being offered optimal therapy.[4]

Poor adherence to treatment is one of the most common causes of poor control and is widely reported in patients with all severities of asthma.[5] Improving adherence can significantly reduce the disease burden. Yet, the biggest challenge facing physicians,

pharmacists and nurses treating patients with asthma is finding a way to ensure good adherence.[6] While elements of adherence, such as moment of inhalation, have been studied,[7–10] intervention studies of adherence to treatment between clinic visits, in daily life, including the vital domain of how devices are used are limited.[11]

Complete adherence for inhaled medications has two components: (1) 'implementation and persistence' and (2) inhaler technique.[12] Implementation and persistence in this context is the extent to which an individual uses the medication at the directed times for a chronic period. This can be measured using self-reported patient diaries, which are prone to reporting bias, or more accurately using electronic inhaler monitors.[13] Studies with these electronic devices show that persistence with treatment is relatively poor, but this may be improved by educational interventions. A recent UK study showed that average persistence for children with asthma was 49% for those who were monitored but received no reminders, and 70% for those who received reminders to take their treatment.[14] However, while the number of inhalations taken improved, asthma control did not improve, likely due to lack of inhaler technique improvement. While inhaler technique is regularly checked, in mostly primary care clinic visits, this aspect of adherence is much more difficult to monitor remotely.

A Cochrane review of interventions to improve inhaler technique for people with asthma in 2017 concluded that 'Guidelines consistently recommend that clinicians check regularly the inhaler technique of their patients; what is not clear is how clinicians can most effectively intervene if they find a patient's technique to be inadequate, and whether such interventions have a discernible impact on clinical outcomes'.[15]

Effective treatment of asthma requires drug delivery to the airways and lungs. The devices which are used to achieve this include nebulisers, dry powder inhalers and pressurised metered dose inhalers (pMDI). The latter are most commonly used in combination with spacers (or valved holding chambers (VHC)) as recommended in many guidelines. There are several reasons behind the preference for pMDI and spacer use including: (1) they are usually the cheapest option and (2) pMDIs are also suitable for people that cannot generate sufficient inspiratory flow. However, also with a pMDI and spacer, many patients persist with critical errors in inhaler technique, leading to poorer disease control and poorer outcomes.[16] Until recently, spacer use has been difficult to measure. This study intends to use a newly developed prototype smart spacer, which simultaneously measures adherence and technique. This will generate significant new data and facilitate appropriate inhaler training by healthcare professionals. Understanding if critical errors in administration of inhaled medications are occurring is vital if healthcare professionals are to be able to effectively educate people with asthma.[17]

The aim of this OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE (OUTERSPACE) study is to assess the feasibility of undertaking a definitive randomised controlled trial (RCT) of smart spacer-based inhaler education and explore clinical benefits in adults with asthma.

METHODS

Study design and setting

The design of this feasibility study is a randomised trial of 2 months comparing smart spacer-based inhaler education vs usual care. Recruitment will take place in four primary care centres in the outreach area of the University Medical Center Groningen (UMCG) in the Netherlands. All practices consist of at least one general practitioner (GP), a pharmacy and multiple nurses. All practices have spirometry equipment available and have ample experience with spirometry as part of routine care. Practices will be provided with fractional exhaled nitric oxide (FeNO) devices (Niox Vero with NV TK 60-1 sensors) and trained. The study was reported according to the Standard Protocol Items: Recommendations for Interventional Trials checklist for study protocols of clinical trials[18] (online supplemental appendix A). The study is planned to take place between autumn 2021 and spring 2022.

Participants

Patients need to fulfil the following inclusion criteria: (1) adults≥18 years; (2) physician diagnosed asthma treated in primary care; (3) using inhaled corticosteroids (±long-acting beta agonists±short-acting beta agonists (SABA)), where at least the controller medication should be administered by pMDI and spacer (AeroChamber or Vortex, given their similar performance[19]) and (4) willing to sign written informed consent. The following exclusion criterium will be applied: (1) having had an exacerbation (defined by a short-course prednisone, emergency department [ED] visit or hospital admission due to asthma) in the last 30 days before potential inclusion.

Randomisation and blinding

At t=0, participants will be randomised in a 1:1 ratio to either the intervention (personalised smart spacer driven education) or the control group (usual care). All patients will be handed a smart spacer, but the data from the smart spacer will only be available to patients and healthcare professionals in the intervention group.

Smart spacer and inhaler error description

The smart spacer that will be used is based on the AeroChamber Plus with Flow Vu. The smart spacer (figure 1) is a rechargeable device and uses the same components as the existing Conformité Européenne (CE)-marked spacer, except for the adapter at the back of the spacer which has been modified to accommodate the sensing technology. To identify which inhaler a patients uses (eg, controller or reliever inhaler), an identifier is attached to each of the patient's inhalers.

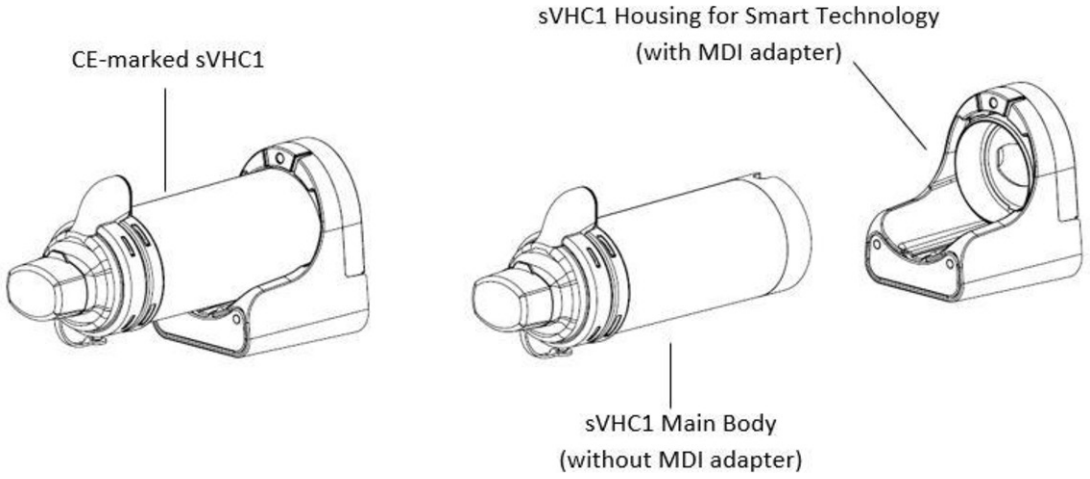

Figure 1 Smart spacer. CE, Conformité Européenne; MDI, metered dose inhaler; sVHC, smart valved holding chamber.

Performance of the smart spacer

Design verification testing was performed by the manufacturer of the device (Trudell Medical International) in order to support the CE mark declaration of the prototype smart spacer in Europe. The design process was compliant to ISO13485 and included the verification that the adherence and technique measurements were accurately and reproducibly transferred into data outputs. Note that this prototype device is being used for evaluating the clinical value of capturing this type of inhaler and spacer usage data. Usability (including industrial design), data visualisation and connectivity will all need to follow and be optimised within a commercial device. Our own testing (table 1) confirmed that the smart spacer meets flow performance specifications and aerosol drug output specifications, compared with the original spacer. The department Pharmaceutical Technology and Biopharmacy of the University of Groningen has performed calibrations to verify the effect of the Smart Technology Housing in comparison with the original AeroChamber Plus Flow Vu. A flow-pressure drop test was performed which demonstrated that the Smart Technology Housing has no effect on the internal resistance of the original AeroChamber in combination with the maintenance and reliever inhalers. These tests were performed with differential pressure gauges from Hottinger Baldwin Messtechnik, type PD1, Darmstadt, Germany and a calibrated mass flow metre from Brooks Instrument, type 5863S, Veenendaal, the Netherlands.

Definitions of adherence and inhaler errors

The prototype smart spacer monitors inhaler use in terms of adherence to prescribed dosing regimen and inhalation technique.

The adherence to dosing can range from 0% to 100% and is calculated based on the number of controller (ie, long-acting medication) doses taken divided by the prescribed dose (eg, two puffs twice daily). To achieve a 100% score, discrete doses must be at least 8 hours apart.

The score for inhalation technique, ranging from 0% (poor) to 100% (good), is calculated for each actuation of the controller or rescue inhaler. To define inhalation technique, five different errors are defined based on previous research and recommendations[16] (table 2). Each error is initialised to 100% for each actuation and adjusted after the inhalation. Scores take into account the type of pMDI connected to the smart spacer.

Data output smart spacer

Figure 2 shows an example of the output of the smart spacer data visualisation. To assess this output, the memory card from the smart spacer needs to be manually removed and the data file should be transferred to a computer to be analysed using a Microsoft Excel file. Together with the patient, the adherence report is then analysed by the nurse. Using this output, tailor made inhalation education can be given. As such, patients will be asked to bring their smart spacer to the study visits.

Table 1 Flow-pressure differential relationship of the smart spacer in relation to the standard Aerochamber

	Pressure drop in Pa (mean of 2)			
Flowrate (L/min)	Smart+reliever pMDI	Standard+reliever pMDI	Smart+controller pMDI	Standard+controller pMDI
30	82	82	100	100
60	160	160	220	216
90	320	320	438	438

pMDI, pressurised metered dose inhaler.

Table 2 Technique error summary, as measured by the smart spacer

Technique error #	Technique error name	Description	Possible values
1	Multiple actuations	Multiple actuations before a full breath has occurred	*0%, 100%
2	No inhalation	No inhalation within 30 s of an actuation	*0%, 100%
3	Delayed inhalation	Based on time between the actuation and start of inhalation	0%, 25%, 50%, 75%, 100%
4	Excessive flow	Inhalation flow >120 L/min,>80 L/min or <80 L/min	50%, 75%, 100%
5	Low volume	Based on volume (in mL) within 15 s of an actuation	0%, 25%, 50%, 75%, 100%

*If technique error 1 or 2=0%, technique score for the entire actuation is 0%.

Study visits

An overview of the study visits is provided in figure 3.

Training of study sites

To learn how to handle the smart spacer, interpret its data and standardise the education, the nurses received a protocolled 2-hour training from a specialised respiratory nurse who had experience with the smart spacer.

The study has three visits, further detailed below.

First visit (t=−1 month)

At baseline during the first visit, all participants' demographics and medical history are recorded (age, sex, weight, height, smoking status, comorbidity, date of last exacerbation, prescribed medication), a FeNO test is performed, and the Asthma Control Questionnaire (ACQ),[20] Work Productivity and Activity Impairment (WPAI)[21] questionnaire and Test of Adherence to Inhalers (TAI)[22] are administered. Pharmacy dispense records from the previous year will be extracted to assess 1-year history of medication use, including oral steroid and antibiotics short-courses. Patients receive the smart spacer with user instruction.

Second visit (T=0)

One month after the first visit, the second visit takes place where a lung function test is performed (forced

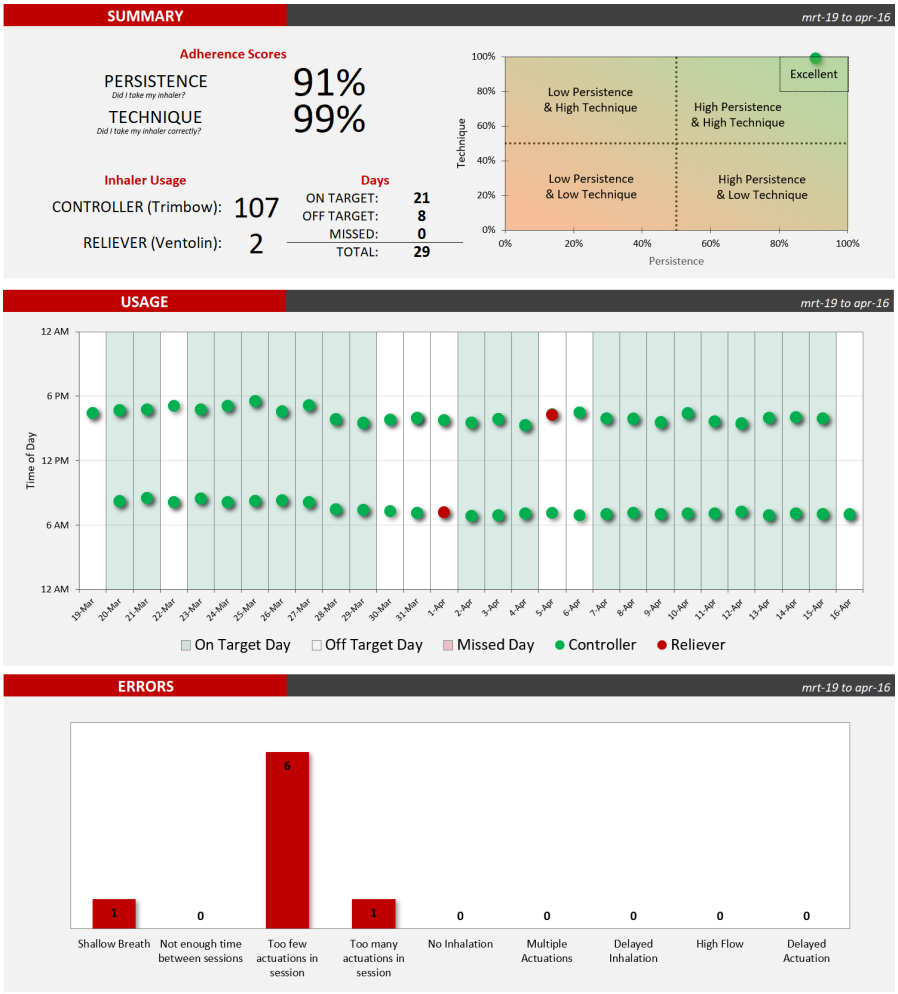

Figure 2 Example data output smart spacer.

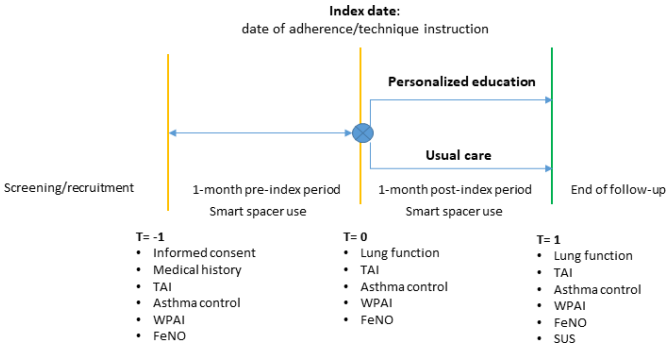

Figure 3 Study design and visits of the OUTERSPACE study. FeNO, fractional exhaled nitric oxide; OUTERSPACE, OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE; SUS, System Usability Scale; TAI, Test of Adherence to Inhalers; WPAI, Work Productivity and Activity Impairment.

expiratory volume in 1 second [FEV1], peak expiratory flow [PEF]), FeNO will be reassessed and the ACQ, WPAI and TAI will be readministered.

Intervention group

Those randomised to the intervention group will, in addition to usual care, be given personalised inhalation education with detailed information about how and when they used their inhaled medications based on smart spacer data. Data from the smart spacer will be downloaded by the nurse and discussed with the patient. If errors in medication use are identified with data from the smart spacer, protocolled inhaler instructions will be provided to help eliminate errors, following standardised Dutch Lung Alliance Netherlands inhaler use protocols. To protocolise the adherence interventions, the TAI Toolkit[23] will be used.

Control group

The control group receives usual care, that is, a regular review of their asthma according to Dutch primary care asthma guidelines.

All participants will be given a fully charged smart spacer to use for the remainder of the study period (a further month).

Third visit (t=1 month)

After another month, at the third visit, all patients will complete a second lung function test (FEV1, PEF), FeNO test, ACQ, TAI and WPAI and return the smart spacers. Patients and study nurses will complete the System Usability Scale (SUS),[24] will be asked to report any difficulties encountered with the devices to the study team, and views will be specifically sought about how the device and training could be improved.

Outcomes

This primary outcome of this study is the feasibility of performing a definitive study of a personalised educational approach to improve disease control in adults with asthma using a smart spacer. Feasibility outcomes include (1) patient recruitment speed, (2) participation rate and (3) sample size calculation for a definitive trial.

Secondary outcomes include patient and healthcare provider satisfaction with the smart spacer (assessed by the SUS and interview) and feasibility of study procedures in the general practice as well as time investment (assessed by end-of-study interviews with nurses). Furthermore, exploratory outcomes include the changes in distribution of medication adherence patterns (total number of inhaler errors, overall inhaler technique score, individual error distribution and adherence (number of controller actuations divided by the prescribed dose)) and clinical outcomes (lung function, ACQ, WPAI, TAI, SABA use, oral steroid bursts) as compared between the intervention and the control group.

Treatment fidelity

To ensure GPs and nurses fidelity to study protocol, the nurses will be trained and supported directly by the project leader and by a specialised pulmonary nurse from the Martini hospital in Groningen who has experience with the smart spacer (OUTERSPACE-chronic obstructive pulmonary disease [COPD] study).[25]

Sample size calculation

This is a feasibility trial to inform a larger definitive RCT. We lack the data for a formal power calculation to determine study size. Recommended sample sizes for feasibility RCTs vary between 24 and 50. The recruitment target of 40 has been pragmatically chosen based on National Institute for Health and Care Research recommendations.[26] It should provide us with sufficient information to determine SD to inform a formal sample size for a larger definitive outcome RCT.

Planned statistical analysis

Continuous variables (eg, age, adherence, inhaler errors, ACQ, WPAI, TAI, FEV1, FeNO, SUS) will be descriptively summarised as number of observed values, number of missing values, mean and SD, or median and IQR and minimum and maximum, where appropriate. Categorical data (eg, gender, comorbidity) will be summarised as number of observed values, number of missing values, number and percentage in each category.

For statistical comparison between study groups: when continuous data are normally distributed, the student T-test will be used. For non-normally distributed data, the Mann-Whitney U test will be used. Categorical data will be compared using χ^2 or Fisher exact test, where appropriate.

Data management

In this study, the data will be collected, processed and archived in accordance with the General Data Protection Regulation and the Findable, Accessible, Interoperable, Reusable principles under the responsibility of the principal investigator. A research data management plan has been drawn up to describe the further operational details and procedures.

All study data will be with a patient pseudonymised number, safely and structurally captured using a study folder and stored electronically in the UMCG REDCap system. Individual study maps will be stored in a locked cabinet.

- Tooling (eg, software and procedures) used for collecting, processing, analysing and storing data will be compliant with the UMCG policy and Standard Operating Procedures in the UMCG Research Toolbox.[27]
- Data will be pseudonymised by use of a code list during data collection.
- Indirect and direct identifiable information collected will be minimised and only collected for the purpose of this study.
- Direct identifiable information (eg, contact details, code list/encryption key/subject identification log) will be stored separately from pseudonymised data.
- Direct identifiable information can only be accessed by the principal investigator and study delegates after authorisation by the principal investigator.
- Pseudonymised/anonymised data can only be accessed by the Principal Investigator and study delegates after authorisation by the principal investigator.
- Data roles, responsibilities, access and authorisation—during the study and after study completion—will be managed and documented.
- Digital data will be archived on the UMCG network complying with strict UMCG security and back-up policy.
- Paper source data and study files will be archived within the UMCG facilities.
- Source data, study files and digital data will be stored 15 years after the study is completed.

Patient and public involvement

Before this study, a pilot study (N=12) applying the same concept of smart spacer-data driven education was carried out in patients with COPD.[25] Feedback from these patients was used to inform the current trial protocol. After the study, a qualitative evaluation will take place with patients participating in this study. Results from this study will actively be communicated to patients involved in the study and beyond.

Ethics and dissemination

Ethical approval was obtained from the RTPO MCL in Leeuwarden, The Netherlands (Number: NL78361.099.21). All patients will provide written informed consent before participation in this study. Findings of this study will be disseminated through national and international conferences and peer-reviewed scientific and professional journals.

DISCUSSION

Proper adherence to inhalation medicines is a topic of major concern in patients with asthma. Numerous studies have been performed trying to find means to improve adherence to inhalation medicines. These studies can roughly be divided into two groups: studies that aimed to improve adherence and studies that aimed to improve inhaler technique.[28] Most studies are however confronted with the same problem: how to gain insight into the continuous daily use of the inhalation medicines.

To assess adherence, patients are often asked if they used their medicine often enough at the correct time of the day. Yet, overestimation and socially desirable answers are common. Indeed, Bourdin *et al*[29] state in their review: 'Most of the severe asthma patients overestimate their level of observance because of memory recall, defence or desire to please their health care provider. As a result, most of the physicians tend to overestimate their severe asthma patients' adherence too'.

To assess inhaler technique, patients are usually asked by their caregiver to show how they use their inhalation device. This only provides insight into how patients use their device in a clinical setting knowing that they are being observed. These studies do, however, not give an understanding of the actual inhalation technique at home.[30]

Data from the OUTERSPACE programme (that also includes smart spacer studies in patients with COPD and paediatric asthma) can bring us to the next level: not only can we objectively monitor intake of inhalation medicines, we also obtain continuous data on inhaler technique at of multiple inhalers in the home setting. With this data, the caregiver can interact with the patient and personalise their education. The caregiver can give the patient an insight into his or her 'inhalation behaviour' during their usage at home. For these data to be optimally used for educational purposes, further real-world validation of the smart spacer data is required. Although design verification was performed by the manufacturer, including the verification that the adherence and technique measurements were accurately and reproducibly transferred into data outputs, the clinical validation to drive clinical decisions should be further tested.

With the data of this smart spacer study, we not only hope to improve adherence to inhalation medicines and outcomes, we also hope that this data will help to improve the 'ownership' of patients to their own adherence and to their own responsibility of achieving an optimal asthma control.

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Contributors BD wrote the first draft of this protocol. BD, JFMvB, HAMK, PH and JK participated in the design of the study and contributed to the revision of the study protocol. PH tested flow performance specifications and aerosol drug output specifications of the smart spacer. TK and SB-B piloted the devices. SvdH and MA piloted the educational materials. All authors provided comments and approved the final manuscript.

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Competing interests HAMK reports a fee for a one time consultancy outside the realm of this study, and grants and fees for consultancy or advisory board participation from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Novartis all outside of the submitted work. All were paid to his institution. JK reports grants, personal fees and non-financial support from AstraZeneca, grants, personal fees and non-financial support from Boehringer Ingelheim, grants and personal fees from Chiesi Pharmaceuticals, grants, personal fees and non-financial support from GSK, grants from Mundi Pharma, grants and personal fees from TEVA, personal fees from MSD, personal fees from COVIS Pharma, outside the submitted work; and Janwillem Kocks 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, Lung Alliance Netherlands, Novartis, Teva, and Trudell Medical, outside the submitted work and all paid to his institution. Other authors declare no relevant conflicts of interest.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix A.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Reported on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	11
	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	11

	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)	11
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
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5 / 8
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)	5
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	5
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)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	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)	

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7 / 8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	8
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)	
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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	
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	

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
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	9
	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	
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	9
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	

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	9
	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	
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	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	

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	9 / 10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	9 / 10
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	
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	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	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	

*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.