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

Boudewijn H.J. Dierick1,2,3 Maria Achterbosch,1 Sandra Been-Buck,4 Titia Klemmeier,4 Susanne J. van de Hei,3,5 Paul Hagedoorn,6,7 Huib A.M. Kerstjens,3,8 Janwillem W.H. Kocks,7,9,10 Job F. M. van Boven1,3,7

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 undertaking 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.

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 inhaler 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. Asthma management aims to achieve good symptom control, minimise exacerbations and reduce side effects. Although the majority of asthma patients can be effectively controlled, a substantial subset remains uncontrolled despite being offered optimal therapy.

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. 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,\(^3\)–\(^10\) 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 AdherenceCE (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 practice. 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 \(\geq 18\) years; (2) physician diagnosed asthma treated in primary care; (3) using inhaled corticosteroids (long-acting beta agonistsshort-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 criterion 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 Aero-Chamber 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.
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 FlowVu. 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 recommendations16 (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

| Flowrate (L/min) | Pressure drop in Pa (mean of 2) |
|------------------|---------------------------------|
|                  | 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.
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), Work Productivity and Activity Impairment (WPAI) questionnaire and Test of Adherence to Inhalers (TAI) 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

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%.

Figure 2  Example data output smart spacer.
Usability Scale (SUS), 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).

**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. 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, 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 \( \chi^2 \) 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 al29 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 caretaker 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 ‘inhilation 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.

Author affiliations

1Department of Clinical Pharmacy & Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
2Department of General Practice & Elderly Care Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
3Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, The Netherlands
4Department of Pulmonology, Martini Hospital, Groningen, The Netherlands
5Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
6Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands
Medication Adherence Expertise Center of the northern Netherlands (MAECON), Groningen, The Netherlands
2Department of Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
3Observational and Pragmatic Research Institute, Singapore
4General Practitioners Research Institute, Groningen, The Netherlands

Acknowledgements The authors would like to thank Dr Wil Carroll (University Hospitals of the North Midlands, UK) lead of the OUTERSPACE paediatric asthma study, for his input during discussions on the study design of the OUTERSPACE programme.

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.

Funding This work was supported by an investigator-initiated grant from Trudell Medical International (grant number: 2020NO876).

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 Ingehelm, 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 Ingehelm, 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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Boudewijn H.J. Dierick http://orcid.org/0000-0001-6524-4290

REFERENCES
1 Dierick BJH, Flokstra-de Blok BMJ, van der Molen T, et al. Work absence in patients with asthma and/or COPD: a population-based study. NPJ Prim Care Respir Med 2021;31:9.
2 GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet Respir Med 2017;5:691–706.
3 Dierick BJH, van der Molen T, Flokstra-de Blok BMJ, et al. Burden and socioeconomic costs of asthma, allergic rhinitis, atopic dermatitis and food allergy. Expert Rev Pharmacoecon Outcomes Res 2020;20:437–53.
4 GINA report, global strategy for asthma management and prevention. From the global strategy for asthma management and prevention, global initiative for asthma (GINA), 2021. Available: http://www. ginaasthma.org [Accessed Sept 2021].
5 Dekhuizen R, Lavorini F, Usmani OS, et al. Addressing the impact and unmet needs of nonadherence in asthma and chronic obstructive pulmonary disease: where do we go from here? J Allergy Clin Immunol Pract 2018;6:785–93.
6 van Boven JFM, Ryan D, Eakin MN, et al. Enhancing respiratory medication adherence: the role of health care professionals and cost-effectiveness considerations. J Allergy Clin Immunol Pract 2016;4:835–46.
7 Chan AHY, Stewart AW, Harrison J, et al. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. Lancet Respir Med 2015;3:210–9.
8 Foster JM, Usherwood T, Smith L, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. J Allergy Clin Immunol 2014;134:1260–8.
9 Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. Eur Respir J 2018;51:1701836.
10 Moore A, Preece A, Sharma R, et al. A randomised controlled trial of the effect of a connected inhaler system on medication adherence in uncontrolled asthmatic patients. Eur Respir J 2021;57:2003103.
11 O’Dwyer S, Greene G, MacHale E, et al. Personalized Biofeedback on Inhaler Adherence and Technique by Community Pharmacists: A Cluster Randomized Clinical Trial. J Allergy Clin Immunol Pract 2020;8:635–44.
12 Vrijens B, Dirma AL, Van Gasse E, et al. What we mean when we talk about adherence in respiratory medicine. J Allergy Clin Immunol Pract 2016;4:802–12.
13 Jansen EM, van de Hei SJ, Dierick BJH, et al. Global burden of medication non-adherence in chronic obstructive pulmonary disease (COPD) and asthma: a narrative review of the clinical and economic case for smart inhalers. J Thorac Dis 2021;13:8346–64.
14 Morton RW, Elphick HE, Rigby AS, et al. STAAP: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax 2017;72:347–54.
15 Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. Cochrane Database Syst Rev 2017;3:CD012286.
16 Vincken W, Levy ML, Sculion J, et al. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res 2018;4:00065–2018–2018.
17 Price DB, Román-Rodríguez M, McQueen RB, et al. Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma control outcomes. J Allergy Clin Immunol Pract 2017;5:1071–81.
18 Chan A-W, Tetzlaff JM, Gratzke PC, et al. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.
19 Hagedoorn P, Bawary W, Frijlink HW, et al. A comparative analysis of changes in pMDI drug dose delivery before and after detergent coating using five antistatic valved holding chambers. J Allergy Clin Immunol Pract 2020;8:1124–5.
20 Juniper EF, O’Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;4:902–7.
21 Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–65.
22 Plaza V, Fernández-Rodriguez C, Melero C, et al. Validation of the Test of the Adherence of Inhalers’ (TAI) for Asthma and COPD Patients. J Aerosol Med Pulm Drug Deliv 2016;29:142–52.
23 van de Hei SJ, Dierick BJH, Aarts JEP, et al. Personalized medication adherence management in asthma and chronic obstructive pulmonary disease: a review of effective interventions and development of a practical adherence toolkit. J Allergy Clin Immunol Pract 2021;9:3979–94.
24 System usability scale (SUS). Available: https://www.usability.gov/how-to-and-tools/methods/system-usability-scale.html [Accessed 2021].
25 NTR. Available: https://www.trialregister.nl/trial/0037.
26 Additional guidance for applicants including a clinical trial, pilot study or feasibility as part of a personal Award application, 2021.
Available: https://www.nihr.ac.uk/documents/additional-guidance-for-applicants-including-a-clinical-trial-pilot-study-or-feasibility-as-part-of-a-personal-award-application/11702#Feasibility_studies [Accessed 2021].

27 Digital competence centre. Available: https://www.rug.nl/datafederationhub/portfolio/view?sid=dd74a696-aa8f-4ece-b2e2-63d07dfc60f2&lang=en

28 Román-Rodríguez M, Metting E, Gacia-Pardo M, et al. Wrong inhalation technique is associated to poor asthma clinical outcomes. is there room for improvement? Curr Opin Pulm Med 2019;25:18–26.

29 Bourdin A, Halimi L, Vachier I, et al. Adherence in severe asthma. Clin Exp Allergy 2012;42:1566–74.

30 Sanchis J, Gich I, Pedersen S, et al. Systematic review of errors in inhaler use: has patient technique improved over time? Chest 2016;150:394–406.