Clinical Investigation Plan (CIP)

Title: APP-based medical device for education and training of inhalation technique (APPETITE)

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A.1 General

A.1.1 Introduction

Worldwide COPD and asthma are prevalent diseases causing death, health problems, impaired quality of life and high costs for individuals and society [1-4]. The common treatment goal of both these illnesses are to achieve quality of life and maintain symptom control with the lowest possible dose of control medication [5]. Pharmacological therapies for respiratory diseases are commonly delivered by inhalers allowing for lung deposition of the medication. Guidelines for chronic obstructive pulmonary diseases (COPD) [6] and asthma [7] address that patients should receive regular education and correction of inhalation technique [8]. Acceptable inhalation technique is an effective prevention of uncontrolled symptoms and exacerbations for asthma and COPD [9]. Therefore, education of inhalation technique is a prerequisite to ensure good treatment response. The education of inhalation technique is usually given by nurses, pharmacists or medical doctors and includes training and demonstration of inhaler use and correction of errors at clinical appointment, by observing if patient correctly can manage critical steps of getting the inhaler ready for inhalation by shaking the inhaler, remove the cap, execute the dose correctly and hold breath after inhalation.

Different inhaler devices have different properties with regards to inspiratory resistance and flow to ensure drug deposition in the lungs. Patient's ability to breath in and the internal resistance of the inhaler affects if drug particles will reach the inflammatory of lungs [10]. Particularly, children [11], and patients with reduced lung function, e.g. during acute exacerbation, risk not being able to inhale properly [12]. Furthermore elderly, irrespectively of COPD could also have compromised ability to generate a sufficient inspiratory flow [13]. Therefore, when prescribing a new inhaler for treatment it is important to evaluate the most appropriate inhaler device for the patient. Overall, there are two major groups of inhalers, dry powder inhaler (DPI) or metered dose inhaler (MDI), with different properties regarding inhalation technique. MDI requires the patient to breath in the drug slowly, and DPI require a more forceful inhalation. A critical challenge is therefore to assess if the inspiratory flow agrees with specific requirement of particular inhaler in use. Although different types of DPI exist (eg. Turbuhaler, Diskus, Novolizer, Breezhaler), generally an airflow is generated through the DPI during inhalation if the breath in flow is sufficiently strong the medication powder leaves the inhaler and enters the mouth and airway. When inhaling, the resistance of the DPI generates a pressure drop and the drug particle are released. The inspiratory outcomes determining optimized lung deposition are the peak inspiratory flow (PIF) [14], the inhalation time, as well as the time to PIF. Late PIF and low volume increases the risk that limited amount of drug particles reaches the lungs, instead, are deposited in the mouth, which can explain poor treatment response.

In view of available literature, clinicians are confronted to control that patient handle their inhalator and generate sufficient high inspiratory flow rate for optimal lung deposition before prescribing DPIs. Inspiratory flow rate can be assessed with the mechanical devices. This is a hand-held manual meter that enables assessment of PIF through adjustable resistance selected for a relevant inhalator (DPI or MDI) [14]. Additionally, app-based digital devices could provide even more extensive and detailed characterisation of patient's ability to perform acceptable inspiratory flows regarding pre-specified outcomes of PIF, time to PIF, and flow over time, to ensure optimal lung deposition of the inhaled drug and for evaluation of treatment response. App-based digital device may offer patient's a simpler support for education and training of inhalation technique. Therefore, we have developed an app-based medical device for improving inhalation techniques. The concept of the device consists of app-based materials for education and a CE-marked wireless spirometer (in this study, MIR AsthmaTuner) and CE-marked Airflow Trainer (MIR) to simulate the internal resistance of the common inhalers in

use (DPI or MDI). To determine if patient can fulfil acceptable inspiratory flows of millilitres (mL) per second (s), PIF (flow/min), time to PIF (s), inhalation time (s), but others such as area under the curve, and inhalation flow acceleration may be added in the future.

The investigational device is a separate module, inhalation app-module, embedded in the Cloud-based CE-marked system called AsthmaTuner. Our hypothesis is that provided education and training with the medical device measurement will improve the patients' ability to correctly use their inhalers over time. Thus, the aim of this study is to assess the effect of app-based medical device for education and training on inhalation techniques at 6-12 weeks follow-up visit in subjects with asthma and COPD. Secondary aim is to evaluate if the medical device is feasible to use in clinical practice. The study endpoints are peak inspiratory flow (PIF), time to PIF, flow (litre per min), inhalation time (seconds) and breath hold (seconds) divided by DPI and MDI, together with assessment of how the patient handles their inhaler according to a set of critical criteria. Patients treated for COPD or asthma in primary or secondary care will be invited to participate in a two-armed stratified randomised controlled blinded study (RCT) over 6-12 weeks.

The patient will download AsthmaTuner to their smartphone that connects to a Bluetooth spirometer (in this study, MIR AsthmaTuner). Inhalation test through Airflow Trainer, an adjustable resistance mounted on the home spirometer (Airflow Trainer), determines if the inhalation flow agrees with the endpoints for the inhaler used by study subject. The expected results of this trial will allow us to determine if app-based inhalation device improves inhalation technique compared with standard care. The goal of this project is to provide sufficient information for a CE-marked product of the inhalation app-module. The study will be performed by Karolinska Institutet (KI), B. Nordlund research group, also being the sponsor, but supported technically and intellectual expertise from Astra Zeneca and MediTuner AB (the owner of AsthmaTuner).

A.1.2 Identification of the clinical investigation plan

Title: App-based medical device for education and training of inhalation technique
Acronym: APPETITE
(Svensk titel): App-baserad medicinteknisk produkt för utbildning och träning av inhalationsteknik

Clinical investigation plan code: 02

CIV-ID: 23-06-043273

Study design: Two-armed, parallel-designed, individual single-blinded inhaler (MDI, DPI or both MDI and DPI) stratified randomised controlled trial with assignment (1:1) to (1) standard education and app-based education and training of inhalation technique or (2) standard education of inhalation technique.

Study ethics approved date: X record number XXXX
ClinicalTrials.gov Identifier: XX
Clinical Trial Regulation (CTR):

Identification of the investigational device: App-based medical device for education and training of inhalation technique. Will be called 'inhalation app module' in this CIP.

Summary of revision history according SS-EN ISO 14155:2020:

Revison	Date	Responsible	Status	Description
01	2024-02-15	B. Nordlund	First approved version	Clinical investigational plan v.1
02	2024-07-09	B. Nordlund	Second version	MPA submitted version

Total number of pages: 40

Abbreviations and acronyms	
AE	Adverse Events
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigational Plan
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organisation
DD	Device Deficiency
DPI	Dry Powder Inhaler
EC	Ethics Committee
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
IB	Investigator's Brochure
KTA	Karolinska Trial Alliance
RCT	Randomised Controlled Trial
MDI	Metered Dose Inhaler
MIR	Medical International Research
NCA	National Competence Authority
PIF	Peak Inspiratory Flow
SADE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Event

A.1.3 Sponsor

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A.1.4 Principal Investigator, coordinating investigator and investigation sites

Principal investigator:

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B. Nordlund is responsible for design and implementing the clinical investigation according to investigational plan. Further, he will ensure the management of the investigation at investigational sites, maintenance of information of study personnel, training and compliance of safety regulations and GCP. Additionally, conduct data analysis, compile and publish manuscript(s) and dissemination of results together with co-authors/investigators. The investigation will be funded by B. Nordlund's research group through various external sources, including Regio Stockholm (HMT-project, ALF Medicin) and Karolinska Institutet (FoU Statsbidrag). Research collaboration and data transfer agreements between Karolinska Institutet (KI) and MediTuner, as well as with the investigational sites, will be established upon approval from the Ethical Review Authority and the Medical Products Agency (MPA).
The research data will be securely stored at KI, managed by KI IT department. Sensitive data (personal information) will be pseudonymized, and the code list will be securely locked. Access to the code list will be restricted to a few affiliated members of B. Nordlund's research group. The code list will be stored at the research department of the KPE Lung Allergy Department, QB:84, ensuring strict confidentiality and compliance with data protection regulations.

Coordinating investigator:

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H. Ljungberg is responsible for data collection, documentation and conduct the study according to the investigational plan, report safety events to the sponsor, maintenance of the investigator site file, data analysis, compile manuscript and publish the results of the study.

Co-investigators:
Co-investigators are responsible for coordinating inclusion of subjects, data collection according to standardized operating procedures, analysis of data analysis, compile manuscript and publish results of the study according to International Committee of Medical Journal Editors (ICMJE) rules.

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Manufacturer of the investigational device, version 5.4.13.5, for education and training of inhalation technique connected to AsthmaTuner system is Medituner AB (org nr:556982-8295), Peter Myndes Backe 8, Stockholm. Contact: info@medituner.se

CRO: Karolinska Trial Alliance support. Visit address: Karolinska University Hospital in Solna, Princeton, Eugeniavägen 18C, Stockholm. Contact: Jenny Langels, jenny.langels@regionstockholm.se

Expert panel:
The panel supports the clinical investigational trial with expertise on the conception, design, conduction and translation of results of the clinical investigation:

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A.1.5 Overall synopsis of the clinical investigation

Primary aim: To investigate if app-based education and training of inhalation technique improves the rate of successful inhalation techniques compared with control group at 6-12 weeks follow-up visit.
Secondary aims: To evaluate the feasibility, usability, and safety of the investigational during the study period.
Study design: Two-armed, parallel-designed, individual single-blinded stratified randomisation by inhaler (DPI/MDI/both DPI and MDI) controlled trial with assignment (1:1) to (1) standard care and app-based education and training of inhalation technique or (2) standard education of inhalation technique over 6-12 weeks.
Subjects: Subjects from the age of 16 years with documented diagnosis of asthma and/or COPD, daily treated with dry powder inhaler (DPI) or metered dose inhaler (MDI), or both, will be invited to voluntarily participate. Exclusion criteria is age <16 years, no access to use BankID or similar electronic personal identification service, not using smartphone of type Android or iPhone, plan to stop use DPI and/or MDI the following 6-12 weeks from inclusion. No able to independently handle and inhale through DPI or MDI device.

Total sample size: Eighty subjects (females and males) with daily treatment for COPD or asthma will be sufficient, based on the assumption of 25% percentage improvement in success rate of correct inhalation technique in the interventional group compared with control group (75% versus 50%) with 80% power at 5% significance level, including dropouts at 6-12 weeks follow-up visit.
Intervention: At the baseline visit patients will be randomised to app-based intervention consisting of education and training of inhalation technique of all inhalers used on daily basis (the inhalation app-module). Stratified randomisation based on type of inhaler(s); MDI, DPI or both MDI and DPI will be applied. The intervention is the inhalation app-module, which is a medical device that is embedded the AsthmaTuner app. The AsthmaTuner app is a CE-marked cloud-based system, provided by MediTuner AB in Stockholm, Sweden. The intervention group will be instructed to use the inhalation app-module on daily basis to improve their inhalation technique.
Control group: Standard education of inhalation technique using list of standardised criteria and non-app-based education of inhaler technique.
Endpoints: Primary endpoint is the rate of subjects with successful inhalation techniques based on subjective critical endpoints (CIP Table 2) and the following objective endpoints at the 6-12 weeks follow up visit:

- DPI: PIF $\geq$ 30 L/Min, time to PIF <0.5 seconds measured with the investigational device.
- MDI: inspiration time (> 3 seconds) and PIF less than 60 L/Min measured with the investigational device.

Procedures: At baseline, a trained respiratory nurse will subjectively assess and train each patient's inhalation technique according to defined criteria of device handling (standard education). The AsthmaTuner app is downloaded to a smartphone or tablet computer (Ipad) that is wirelessly (Bluetooth) connected to a home spirometer. In this study the Bluetooth spirometer AsthmaTuner from MIR will be used. Education and training of inhalation technique will include measurement of inhalation flow with an adjustable resistance mounted on the spirometer, Airflow Trainer (MIR). The app gives instruction to set the resistance, so it corresponds to the selected inhaler. Questionnaires and interviews will collect information about the feasibility, safety and experienced usability of the investigational device.
Analysis: The rate of subjects with successful inhalation technique at 6–12-week visit determined by fulfilling objective and subjective critical endpoints in intention-to-treat approach. The effect of using the inhalation app-module will be analysed with logistic regression analysis across randomisation groups. The secondary analysis of feasibility and the experienced benefit of using the inhalation app-module in clinical practice and for patient's education and training of inhalation technique is estimated on a Likert scale from 1 (not at all) to 5 (strongly agree) and presented as mean and median scores.

A.2 Identification and description of the investigational device

A.2.A Description of the investigational device

The investigational device is the inhalation app-module which will be investigated in this clinical study, version number 5.4.13.5 . In this study, it will be used in combination with the MIR AsthmaTuner spirometer and Airflow Trainer (adjustable resistance). The inhalation module starts with patients selecting their inhaler type (DPI or MDI), Appendix 1. This leads to written instructions which show patients how they should inhale their medication. The patient is then forwarded to the training part of the module, which allows a patient to inhale through their spirometer which is fitted with the Airflow Trainer (MIR). The patient will be able to see how their inhalation went and will pass or fail the training. A potential benefit of the app-based investigational device is the education patients receive about the medication they take. Patients cannot reach the status of 'medication

mastered' until they have also completed two quizzes. The first quiz teaches foundations of asthma or COPD (or both if patient has both diagnoses) while the second quiz touches on more advanced topics within the diseases and tips for effectively managing them daily. The inhalation flow is measured by the wireless spirometer (MIR AsthmaTuner), using connecter (Airflow Trainer) for creating inspiratory flow resistance that corresponds to resistance of the prescribed inhalator as presented in Appendix 2.

The inhalation app-module, embedded in AsthmaTuner version 5.4.13.5, is labelled as non-CE marked investigational device. The investigational device will be provided through a CE-marked digital system, AsthmaTuner.

The product description and regulatory classification of AsthmaTuner according to MDR is further described in investigational brochure (IB), Table 1, page 4 and IB appendix 1.

A.2.B Details concerning the manufacturer of the investigational device

Manufacturer	MediTuner AB
Address	Peter Myndes Backe 8 118 46 Stockholm Sweden
SRN	SE-MF-000028534
PRRC	Karlijn van Herpen
Email	Karlijn@asthmatuner.com
Phone	+46 72 853 80 46

A.2.C Identification numbers and model types

Inhalation app-module – version number 5.4.13.5 is the investigational device of this study.
An important note to make is on the versioning of the inhalation app-module. All testing (usability & regression testing, see IB) has been performed on version 5.4.13.5. No changes have been made to this version of the inhalation app-module. However, as the inhalation app-module is not intended to be a stand-alone device, but rather a module within AsthmaTuner, the version that will be used in the clinical investigation will be 5.4.13.12. The discrepancy in version numbers is due to the fact that minor releases are being done for AsthmaTuner, for example in the form of bug fixes or minor feature improvements. However, the inhalation app-module has not been altered from the 5.4.13.5 version, which is the one used in the pre-clinical testing.

AsthmaTuner – version number 5.4.13.5 is a CE-marked MDD, class 1 device, Appendix 8.

SpiroBank Smart or Smart One spirometer – Medical International Research (MIR) is CE-marked, Appendix 9.

Airflow Training - Medical International Research (MIR) is CE-marked, Appendix 10.

A.2.D Traceability

The serial numbers of AsthmaTuner spirometer (SpiroBank Smart/Smart One) are being used, can be traced through the backend of the AsthmaTuner system. The Airflow Trainers from MIR come in batches. Batch number 01 will be used in this clinical study.

A.2.E Intended purpose of the investigational device

The intended purpose of the investigational device is to support education, training, and assessment of inhalation technique for patients in clinical practice and in self-management to optimize response and adherence to self-treatment. However, the inhalation tool will be part of the AsthmaTuner system and will not be released as stand-alone device. Therefore, it will eventually be covered by the intended use of AsthmaTuner, which is:

The intended use of AsthmaTuner is to improve asthma control for adults and children over the age of 6. This is mainly done by providing information and treatment recommendations which are generated based on a patient's lung function, symptoms, and physician-prescribed treatment plan. Furthermore, AsthmaTuner facilitates the management of respiratory diseases by processing lung function and user-reported data and by providing information to adults and children over the age of 6. Any form of diagnosis of asthma or other respiratory diseases shall be done by a healthcare professional, so home use is only for indicative purposes

A.2.F Populations and indications

The populations and the indications for which the investigational device is intended is any subject above the age of 6 receiving pharmacological treatment through MDI or DPI devices, commonly for treatment of inflammatory respiratory conditions of asthma and/or COPD.

A.2.G Description of investigational device that will be in contact with tissue or body fluids.

The investigational device is software-only, and therefore will not be in contact with tissue or body fluids.

The MIR AsthmaTuner Spirometer with the Airflow Trainer attached to it, will be in contact with tissue in the mouth of the user. However, the Airflow Trainer, which simulates the resistance of the inhaler, is not in direct contact with human tissue. The mouthpiece of the spirometer is mounted on the Airflow Trainer. Both the spirometer and Airflow Trainer are CE marked and therefore have passed biocompatibility testing. Regarding the hygiene and risk of transmitting infections through the mouthpiece and the spirometer, instructions of disinfection of the mouthpiece and spirometer is further described in the instructions for use, appendix 11. Importantly, the spirometer is for personal use only and should not be used interchangeable between individuals as noted in the app and in the instruction for use.

A.2.H Necessary training based on risk assessment.

According to the risk analysis assessment there are no risks which require necessary training or experience to use the inhalation app-module. Additionally, the device has instructions embedded into the software, which have been deemed safe and effective through usability testing. See the IB for more information on usability testing.

A.2.I Description of the current state of the art in clinical care

Inhaled therapy with DPI or MDI is the cornerstone of asthma, COPD, and other respiratory diseases. Therefore, standard educational program should contain training about correct inhalation technique. The recommendations about choice and effective use of inhaler devices for educational program are presented in Table 1 according to Global Initiative for Asthma (GINA) [20].

Table 1: Recommendations of effective use of inhaler devices according to GINA – Global Initiative for Asthma guidelines.

CHOOSE: • Choose the most appropriate inhaler device for the patient before prescribing treatment. Consider the preferred medication, available devices, patient skills, environmental impact and costs. • Ensure that patient have no physical or functional barriers that limit use of the inhaler. • Avoid use of multiple different inhalers types where possible, to avoid confusion.
CHECK: • Check inhaler technique at every opportunity • Ask the patient to show how they use their inhaler (don't ask if they know how to use it) • Identify any errors using device specific checklist (Table 2).
CORRECT: • Show the patient how to use the inhaler correctly with a physical demonstrating, e.g. by using a placebo inhaler. • Check technique again, paying attention to critical steps putting patient at risk not receiving inhaled medication. You may need to repeat this process 2-3 times within the same session for the patient to master the correct techniques [21]. • Identify any errors using a device-specific checklist (Table 2). • Consider an alternative device only if patient cannot use the inhaler correctly after several training attempts. • Re-check inhaler technique frequently. After initial training, errors often recur within 4-6 weeks [22].
CONFIRM: • Clinicians should be able to demonstrate correct technique for each of the inhalers they prescribe. • Pharmacists and nurses can provide highly effective inhaler skills training [23, 24]

If the patient can't use the available device(s) correctly proper education, this could be related to factors of physical dexterity, coordination, inspiratory flow and cognitive status. Different inhaler types require different inhalation techniques, so it is preferable to avoid prescribing different types of inhalers for the same patient. Furthermore, incorrect inhaler technique increases risk of severe exacerbation of asthma or COPD. Additionally, Inspiratory flow rates can be assessed with the mechanical devices. These hand-held manual meters enables assessment of PIF, in some cases through adjustable resistance selected for a relevant inhalator (DPI or MDI) [14].
An educational and training device embedded in a patient smartphone app, shared with healthcare providers, offers novel and potentially cost-effective opportunities for healthcare providers to easily assess and monitor the performance of patients' inhalation techniques.

A.2. References to IB and IFU

IB Inhalation app-module.v1.2024.01.11
Appendix 5_Instructions for use.v1.24.01.11

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A.3 Justification for the design of the clinical investigation

The choice of inhalation device is crucial for the treatment of respiratory conditions or diseases like asthma and COPD [25]. Poor inhalation technique is a prevalent problem that makes treatment and management more difficult and costly [26].

The inspiratory flow is dependent on patient's technical skills and respiratory condition, as well as the resistance of the inhaler [27]. The use of MDI or DPI requires different inhalation techniques and flows, which makes correct inhalation technique more challenging if patient use different types of inhaler devices. Healthcare providers may assess inhalation technique by observation and in addition PIF may be measured by manual meter. However, this does not capture all relevant information about patient's ability to correctly inhale medication and handle prescribed inhaler(s) and do not give instant and automated feedback on the inhalation technique to user. For instance, DPI users should reached a sufficiently high PIF within the first 0.4 seconds [18] and MDI users inhalation time should exceed 4 seconds in adults (2-3 seconds in children) in order to optimize lung deposition of the aerosol during a low PIF [19]. The app-based inhalation medical device gives automated feedback on inspiratory flows that are specific DPI and MDI devices. Characterization inhalation flows may also support the personalized prescription of specific inhaler for a patient. That could have significant effect on treatment response and reduction of symptoms, healthcare utilization and costs that are associated with difficulty treated asthma or COPD [14]. Criteria acceptable inhalation technique according to DIP and MDI devices have been published elsewhere [18, 25, 27-30] and have been incorporated in the design and development of investigational medical device of AsthmaTuner.

The first prototype of the inhalation app-module was tested in a clinical pilot study assessed inhalation technique in 40 schoolchildren at Astrid Lindgren Children 's Hospital, Sweden. In the study population reported 27 (71%) of 40 that their inhalation technique was improved by visualizing the inspiratory flow curve during while measuring critical endpoints of PIF, time to PIF and inhalation time in relation to selected inhaler (Appendix 4). The respiratory nurses involved in the pilot study also reported that the automated feedback on training inhalation technique was a valuable support for education of inhalation technique in schoolchildren with asthma. The study has provided valuable information about feasibility that will be used for CE-marking the device. Therefore, we now plan for the next step to collect further information about the clinical effect on inhalation technique and the feasibility of using the device remotely in prospectively designed RCT including a larger study population with asthma and/or COPD. Integrating clinical results of the inhalation training tool in real life into a clinical evaluation and development plan as per MDCG 2024-3 section 3.4 ensures a systematic approach to validating its safety, performance, and usability. This alignment not only supports regulatory compliance but also enhances the potential for successful clinical adoption and impact on patient respiratory outcomes.

Content and relevant user interfaces of investigational device have been developed according to usability engineering to medical devices, IEC 62366-1:2015. The inventors Björn Nordlund and Henrik Ljungberg who have been involved in the design of investigational device and have also developed the AsthmaTuner, as well as founded the company MediTuner AB, which owns AsthmaTuner,

through innovation programs. They are clinical health care providers themselves, working with asthma patients on a daily basis as nurse and physician at Astrid Lindgren Children's Hospital, Karolinska University Hospital in Stockholm, Sweden.

A.4 Risks and benefits of the investigational device and clinical investigation

A.4.A. Anticipated clinical benefits

The added value of the investigational device compared with standard care is to make education and training of inhalation technique more accessible through an app module, which includes educational materials of film clips demonstrating correct inhalation technique, quiz and the inhalation training module assessing inspiratory flows of PIF (L/min), time to PIF (s) and inhalation time (s), which is regarded as critical endpoints for correct inhalation with DPI and MDI devices [18, 19]. The potential effect of the inhalation module is to reduce the number of common errors in inhalation technique among patients treated for asthma and/or COPD. The education and training can be done remotely or in clinical practice, both unsupervised or supervised by healthcare provider, on regular basis, or whenever patients or healthcare provider consider this is needed. Overall, this medical device can make patients with respiratory conditions more involved and supported in their self-care and improve their understanding on how to use their inhaler(s) and to avoid common pitfalls.

A.4.B. Anticipated adverse device effects

The signed risk analysis (IB Annex A) by the manufacturer MediTuner AB, indicates that no anticipated adverse device effects are expected from use of the investigational device.

A.4.C Risks associated with the participation in the clinical investigation

All risks have been considered and mitigated, see IB Appendix 5 for the risk analysis provided by the manufacturer. Risks relating to the clinical investigation, for example the risk of drawing a false conclusion based on the clinical data obtained, have also been considered and mitigated.

The CE-marked AsthmaTuner Spirometer is a device that requires little maintenance. However, there is a remote probability that subjects participating in the study experience transmission of infectious diseases through the spirometer when they do not adhere to the instructions for use on cleaning and hygiene. This risk has been mitigated by adding a warning in the inhalation app-module and study subjects will receive instructions regarding the following operations as described in the instruction for use, Appendix 5:

- investigational device is for personal use
- cleaning and disinfection of the turbine
- cleaning and disinfection of the mouthpiece
- cleaning of the device

A.4.D Possible interactions with concomitant medical treatments

No interactions with concomitant medical treatments are expected.

A.4.E Steps that will be taken to control or mitigate the risks

The signed IB including the risk analysis shows all risk control options that have been implemented to mitigate the risks associated with the inhalation module.

A.4.F Rationale for benefit-risk ratio

The assumption is that the benefits of using the investigational device to improve inhalation technique in subjects with asthma and/or COPD compared with standard education outweigh the risks. The nature of the risk control options makes that there are no unacceptable residual risks, as all risks are identified as low. The expected benefit of the investigational medical device is to make materials and methods for training and education of inhalation technique more available and feasible to use for patient and HCP. Additionally, to make the support for inhaler use more accessible for patients at home or whenever patients feel inhalation support is needed. It is therefore that the manufacturer believes that the investigational device has a positive benefit-risk ratio and is safe to use for patients. However, the results of this clinical investigation will be considered, and the benefit-risk ratio will be reassessed after the clinical investigation has been completed.

A.5 Objectives and hypotheses of the clinical investigation

Our hypothesis is that the app-based investigational medical device consisting is superior for education and training of inhalation techniques in patients with asthma and COPD compared with standard care. The pre-clinical evaluation indicated the use of the investigational device is a feasible and safe for patients using inhaler(s) for treatment. The study assumption is that the investigational medical device will improve the relative rate of successful inhalation technique with at least 25% compared with control group.

Primary aim: To investigate if app-based education and training of inhalation technique improves the rate of successful inhalation techniques compared with control group at 6-12 weeks follow-up visit.

Secondary aims: To evaluate the usability and safety of the investigational device during the study period.

The claim that this clinical data can substantiate is: the inhalation app-module in AsthmaTuner is superior for education and training of inhalation techniques in patients with asthma and COPD, when compared to standard care.

There are no identified risks or anticipated adverse events that will be studied in this clinical investigation.

A.6 Design of the clinical investigation

A.6.1 General

This confirmatory multicentre two-armed stratified randomised controlled blinded study analysing the effect of app-based education and training of inhalation technique compared with control group on subjective critical and objective endpoints of inhalation technique at 6-12 weeks follow-up visit. The study approach is intention to treat, including 80 subjects with daily therapy of DPI and/or MDI for asthma and/or COPD, Figure 2.

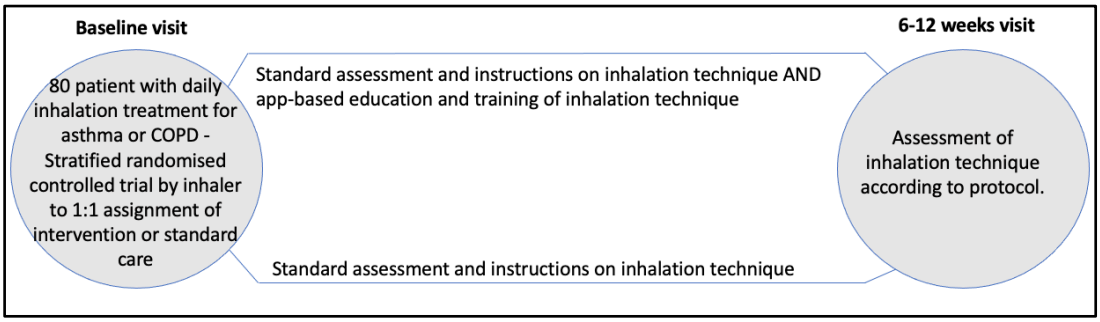


Figure 1 Two-armed, parallel-designed, individual single-blinded stratified randomised controlled trial.

The subjects will be randomly assigned to one of the following two arms (1:1):

1. Standard assessment and correction together with app-based education and training at baseline visit and at least every week or whenever needed during the following study period of 6-12 weeks.

2. Standard assessment and instructions on inhalation technique at baseline visit according to Table 2.

Table 2. Subjective assessment of handling and inhalation techniques, adopted from Aksu F. et al. [8]. If all criteria are not deemed to correction per inhaler, including objective endpoints defines primary endpoint of subject with successful inhalation technique.

	DPI	MDI
1	Shook inhaler (critical for Easyhaler)	Shook the inhaler (critical for suspension)
2	Removed the cap of the inhaler correctly (critical)	Removed the cap of the inhaler correctly (critical)
3	Actuated one dose / loaded capsule correctly (critical)	Breathed out before slow inhalation
4	Inhaler kept in upright position (critical for some inhalers)	Breathed out and away from the mouthpiece of the inhaler
5	Breathed out and away from the mouthpiece of the inhaler	Placed the inhaler mouthpiece correctly in mouth
6	Inhaler correctly placed in mouth. Inhaled with lips sealed around the mouthpiece (critical)	Inhalation slow before or immediately when dose fired (critical)
7	Inhaled forcefully through the mouth after firing dose (critical)	Inhaled through the mouth after dose fired (critical)
8	Inhaled without interruption (critical)	Inhaler was correctly placed in mouth during the entire inhalation (critical)
9	Breath-holding more than 5 seconds after inhalation	Inhaled without interruption (critical)
10	Breathed out and away from the mouthpiece of the inhaler	Breath-holding more than 5 seconds after inhalation
11	For Handyhaler or similar, check powder drug rests in capsule, if necessary, inhale again	Breathed out and away from the mouthpiece of the inhaler

Each subject in both intervention and control arm will receive standard assessment and instruction on inhalation technique according to criteria in Table 2 at baseline visit. The study endpoints will be collected at the follow-up visit (6-12 weeks).

Randomisation and masking
Each of the 80 subjects is stratified to block of 4 numbers according daily used inhaler of (1) DPI, (2) MDI or (3) both MDI/DPI. Simple randomisation (1 to 1) will be applied in each block and at each study site. The randomisation will be blinded for the evaluator at 6-12 week visit, which practically means that not the same study personnel will do the baseline randomisation and the final 6-12 weeks assessment of inhalation technique.

Endpoints
Primary endpoint is number of subjects presenting successful inhalation techniques as defined by objective endpoints divided by:

- DPI: PIF $\geq$ 30 L/Min, time to PIF <0.5 seconds measured with the investigational device.
- MDI: inspiration time (> 3 seconds) and PIF less than 60 L/Min measured with the investigational device.
- Together with subjective critical endpoints at 6–12-week follow-up visit, assessed by study personnel, Table 2.

Secondary endpoints:

- Feasibility and safety of using the investigational device for education and training of inhalation technique based on questionnaire and interviews from subjects and healthcare personnel, Appendix 3.

Study personnel will get access and be trained in methods and procedures for informed consent, randomisation, investigational device, data collection and documentation. The study endpoints will be documented in electronic Case Report Form (CRF) provided by Karolinska Institutet. Data analysis will start at as soon as all 80 included subjects have completed or considered to be lost to follow-up at 6-12 week's visit by local investigator.

This RCT with multiple investigational sites consists of both primary and secondary level of asthma and COPD care to enabling generalizability of the results and implementation of the investigational device in different healthcare settings. Each study site has one local PI who is responsible for implementing and carry through the investigation. The local study team consist of experienced medical doctors and respiratory nurses in the field, who will receive support, training, and coordination in study procedures from the B. Nordlund's research group at KI. The KI research group will ensure the implementation and progress of the study follow the time plan, but also transparency, streamline the collaboration and find local solution that can prevent occurrence of problems. The study sites will be monitored by Karolinska Trial Alliance (KTA) to ensure compliance with study protocol, safety rules and securing the integrity of subjects. KTA will also train and educate study personnel in Good Clinical Practice (GCP).

Completion of study will be done after subjects have completed the 6-12 weeks follow-up visit, but not later than 12 weeks. Subjects who do not attend the follow-up visit within specified timepoint will be lost to follow-up, not replaced and withdrawn from the primary analysis. Information about feasibility and safety (secondary endpoints) will be collected by healthcare personnel at the

investigational sites after 12 weeks if the study subject has used the investigational device. The investigational device will be removed from the AsthmaTuner app after study completion by B. Nordlund research group at Karolinska Institutet. The stratified block randomisation 1:1 between intervention and control arm per study site will ensure the reliability and validity of study results by eliminating selection bias, balance confounding variables.

A.6.2 Investigational device and comparator

Investigational device:
The inhalation app-module is an integrated module of the AsthmaTuner application (iOS and Android). The investigational device is available for subjects by searching for the AsthmaTuner app in the AppStore or Google Play. The inhalation app-module will only be available for subjects in this clinical trial. The Airflow Trainer is made of the same type of plastic as the spirometer, by the same manufacturer (MIR), while not being in direct contact with the study subject mouth or skin during testing. The spirometer and Airflow Trainer will be sent to subject's home address or handed out at clinical visit.

App-based education and training of inhalation technique is a novel approach to improve respiratory health, which is to our best knowledge, is not used or implemented in clinical asthma or COPD care. The potential clinical benefit of using an app-based approach for education and training of inhalation technique is to make the support more accessible for patients to use at home or whenever patients feel inhalation support is needed. Another potential benefit and novelty are the objective assessment of inhalation techniques regarding PIF, time to PIF and inspiration time, which is not possible to precisely assess in standard assessment of inhalation technique. A limitation of the investigational device is the requirement of using it together with the CE-marked AsthmaTuner system (spirometer and app).

Handling MDI or DPI requires different techniques that are important to consider in education of inhalation techniques. DPI inhalers are dependent on inspiratory flow, which makes it an important outcome to consider in elderly and children due to lower muscle strengths and in patients with reduced lung function [13].

The comparator
The comparator is standard assessment and instructions of inhalation technique while healthcare personnel review patient using their inhaler (DPI or MDI) or similar training device without medication. Standard criteria for subjective review of inhalation technique as presented in Table 2.

To ensure optimal lung deposition of inhaled medication the inspiratory flow rate (PIF) could be assessed by manual meters. The CE-marked manual meter device In-Check Dial has the benefit that the inhaling resistance can be adjusted to certain inhalers. The device is limited to only measuring PIF and provides no other type of education and training of inhalation technique. This pragmatic RCT-study will allow use of manual meters in the control group if this is part of standard care at any of the investigational sites.

A.6.3 Subjects

Inclusion criteria

Subjects, age ≥16 years, willing to voluntarily participate in the study and give electronic written informed consent through BankID or similar service, with daily inhalation therapy through DPI and/or MDI for doctor's diagnosed asthma or COPD.

Exclusion criteria
Age <16 years, no access to use BankID nor use of smartphone of type Android or iPhone, plan to stop use treatment with DPI and/or MDI the following 6-12 weeks. Medical condition affecting the ability to independently inhale or use DPI or MDI device(s).

The total time for study participation is estimated to 40 min, 20 min per visit, over a period of 6-12 weeks. Severe asthma or COPD exacerbation or the severity of airway obstruction will affect inhalation technique, therefore, subjects will receive information to treat exacerbation and contact their healthcare provider in case of exacerbation. The study coordinator and medical doctor H. Ljungberg take individual decision if study subject should stop to use the medical device or due to medical condition unable to be treated with an inhaler. Although stopping the study is not expected, this can be done if on background of unexpected device deficiency, the decision will be taken by study coordinator and principal investigator B. Nordlund.

The ethical principal of this study is that subjects who wants to use the interventional device after study termination can do that when the device is CE-marked, as long as they are managed for asthma or COPD at any of the investigational sites or other healthcare provider who offers AsthmaTuner. Additionally, subjects will be informed at the time of study enrolment they are free to discontinue the study at any point, without any particular reason.

Lost to follow-up
Subjects lost to follow-up will not be replaced but the decision will be documented in the medical record. Subjects who not attend the follow-up visit 12 weeks after the baseline visit will be categorised as lost to follow-up. They will be asked through email, phone or letter to send in the medical device to the study centre with envelope they received when they received the device at baseline visit. Study sites will be informed about which subjects were lost to follow-up.

Point of enrolment and randomisation
At least 80 subjects will be invited to participate in the investigation, through phone, digital meeting (Teams or Zoom or similar) or at physical at the baseline visit. The study personnel at investigational site will contact the study centre through phone to receive the randomisation assignment and study ID. The anticipated distribution is a minimum of 10 subjects per each participating investigational site.

Expected duration of each subject's participation is 6-12 weeks after enrolment to the investigation. The follow-up visit will be booked 6 weeks after study enrolment but no longer than 12 weeks. Subjects unable to attend the 6-12-week follow-up visit will be withdrawn from the primary analysis of study. The number of subjects required to be included in the investigation is estimated on background of power calculation (see section A7). The timeline is to enrol subject to the investigation during the fall of 2024 and spring of 2025. No additional care is required after the investigation beyond what was initially planned for each subject.

Target and vulnerable populations

The target population for the medical device are patient treated for asthma or COPD or any other disorder requiring treatment with DPI or MDI in primary or secondary care setting. However, neither patient with other diagnosis or children under the age of 16 years will not be included in the study. Although schoolchildren below the age of 16 are considered as target populations for the medical device, we consider we have sufficient data from this population from the pilot study (Appendix 4). Vulnerable, pregnant and breastfeeding population fulfilling the inclusion criteria are welcome to participate, no adverse effects or events are expected in this vulnerable population as longs they will be able to attend the follow-up visit.

A.6.4 Procedures

The subjects will undergo the following procedures as summarized in Table 3.

Procedures	Baseline visit	6–12-week follow-up visit
Informed consent	X	
Randomization	X	
Questionnaires of medical history and usability	X	X
Spirometry test	X	
Standard review and correction of inhalation technique	X	X
Objective assessment of inhalation technique		X
Adverse events or device deficiency		X

Randomisation
Computer-based randomisation stratified for subjects' daily inhaler use into three groups of DPI, MDI or both DPI and MDI devices of four block numbers in each stratum per investigational site.

Interview and electronic questionnaires

- A structured health questionnaire completed at the first visit will provide information regarding medical history, health care utilization and experiences of inhalation education and training, Appendix 4.

Dynamic spirometry

- The lung function test will measure forced expiratory flow in one second (FEV_1), forced vital capacity (FVC), and FEV1/FVC according standardised procedures [31]. Applied percent of predicted reference values, adjusting for age, sex, height, weight and ethnicity, will be calculated based on continuous prediction equations of normal population [32].

Standard review of inhalation technique

- All subject's ability to handle their inhaler(s) and inhalation technique will be reviewed and corrected at baseline visit and assessed at 6–12-week follow-up visit according to endpoints in Table 2.

Investigational device - app-based intervention for education and training of inhalation technique

1. Subjects randomised to intervention will receive instructions on using the investigational device, accompanied with written information (instructions for use) from study personnel at baseline visit. The subjects are instructed to use the investigational device 3-7 times per week to achieve the maximal effect.

2. Instruction for use manual on how to use medical investigational device will be available for subjects and study personnel at investigational sites (Appendix 5). Briefly, subjects follow the following procedure:
    a. Baseline visit: Download (Apple Store or Google Play) and login with BankID or similar to the AsthmaTuner app. Automatic Bluetooth connection will be established between the MIR AsthmaTuner and the app.
    b. Study personnel at Karolinska institutet set up login through BankID or SITHS card to AsthmaTuner Careportal for study personnel at investigational site.
    c. Enter patient information: Fill out patient's initial letters, study ID, height, weight and type of inhaler. Press "next" to start the test.
    d. The visual representations and explanatory text illustrating the step-by-step procedures within the app are displayed in Figure 3a-c, including the AsthmaTuner spirometer and the adjustable resistance and app-illustrations of training module of inhalation technique with DPI or MDI.

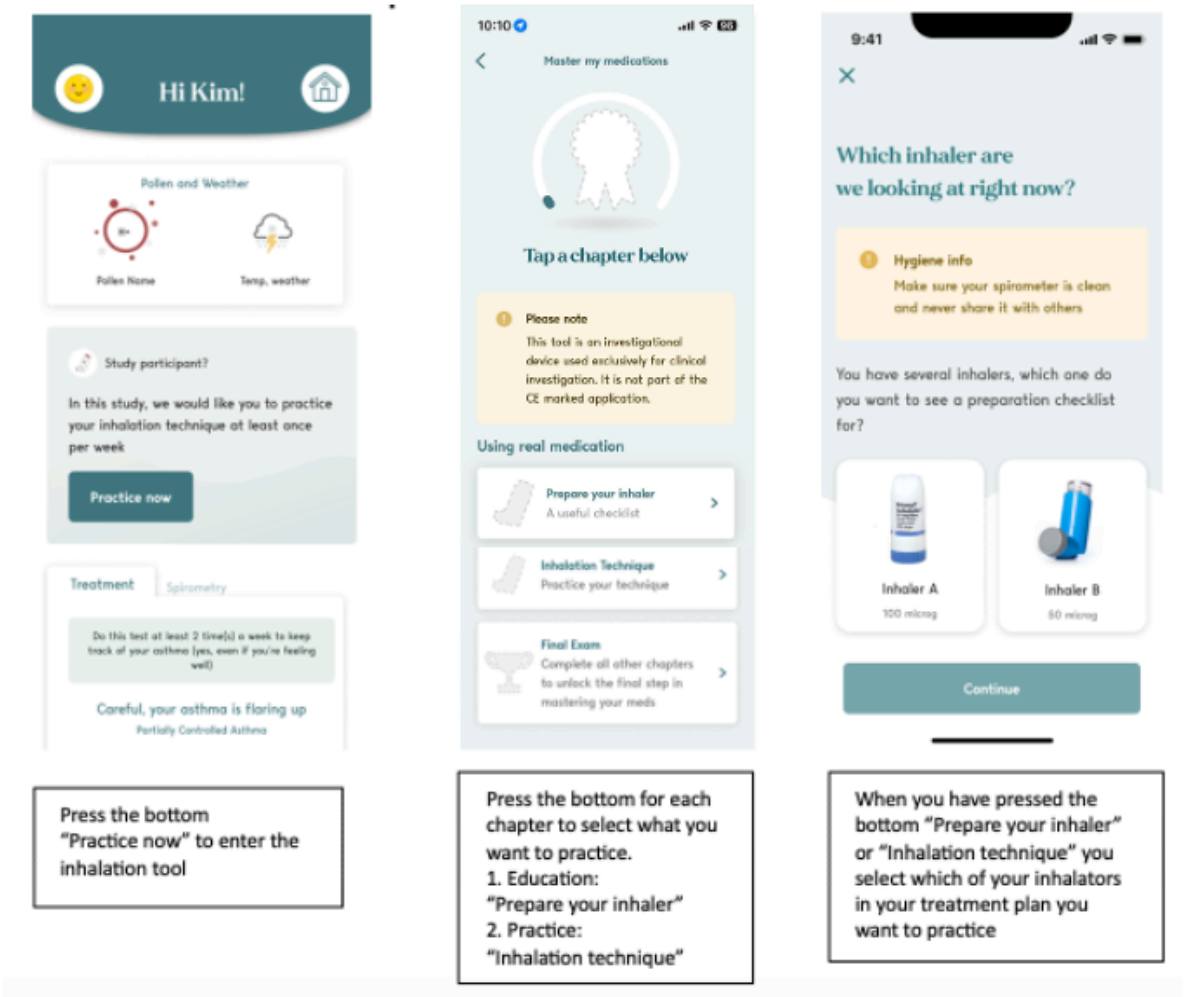


Figure 3a: Illustrations showing how to enter the app-based medical device in the CE-marked device AsthmaTuner.

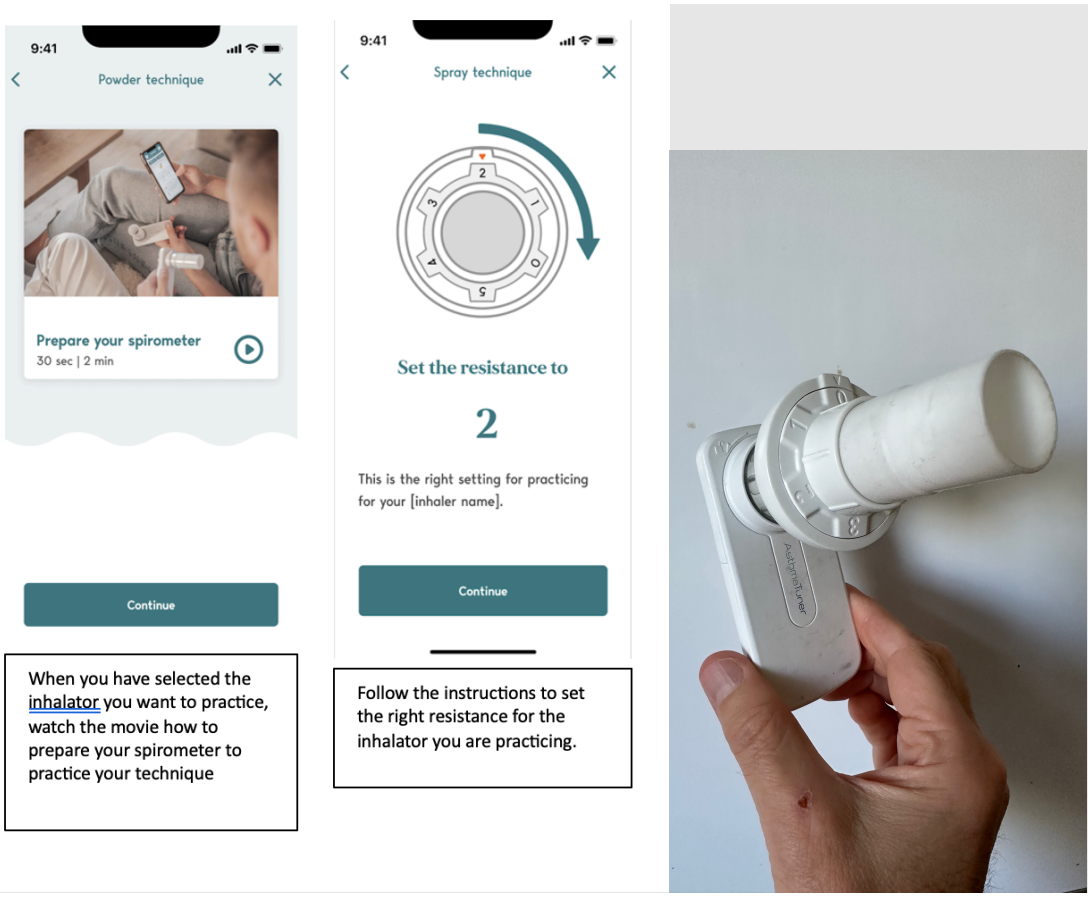
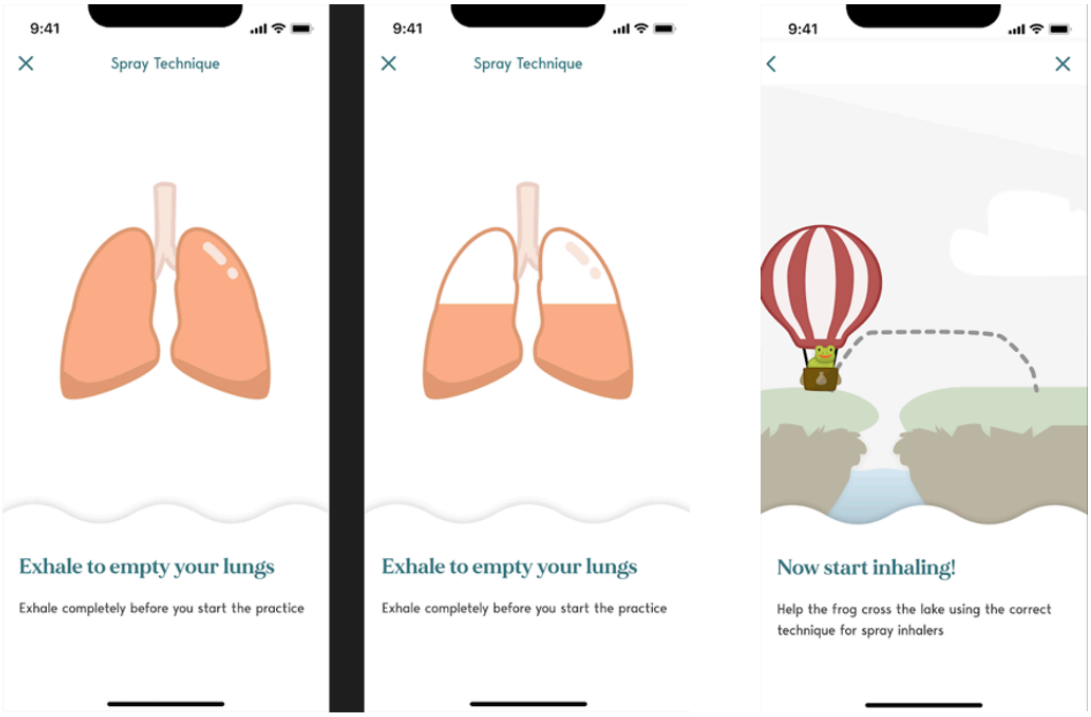


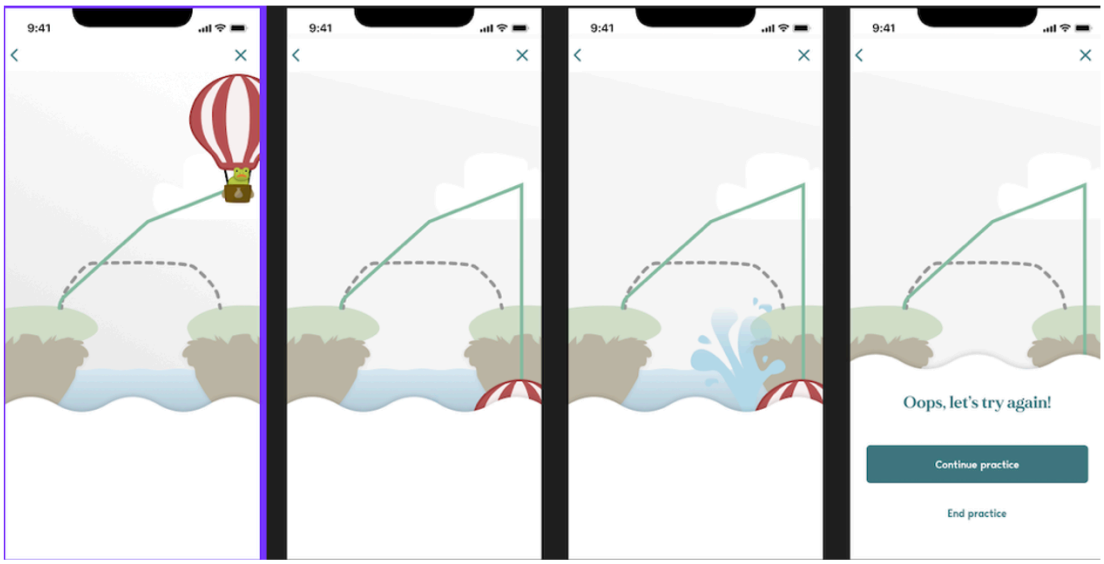
Figure 3b: Illustrations showing how to prepare for an inhalation test in the app-based medical device and the MIR AsthmaTuner spirometer with the adjustable resistance from 0 to 5 for measuring inspiratory flows.



Follow the instructions to practice your inhalation technique.

Follow the instructions to practice your inhalation technique.

Failed inhalation test:



Successful inhalation test:

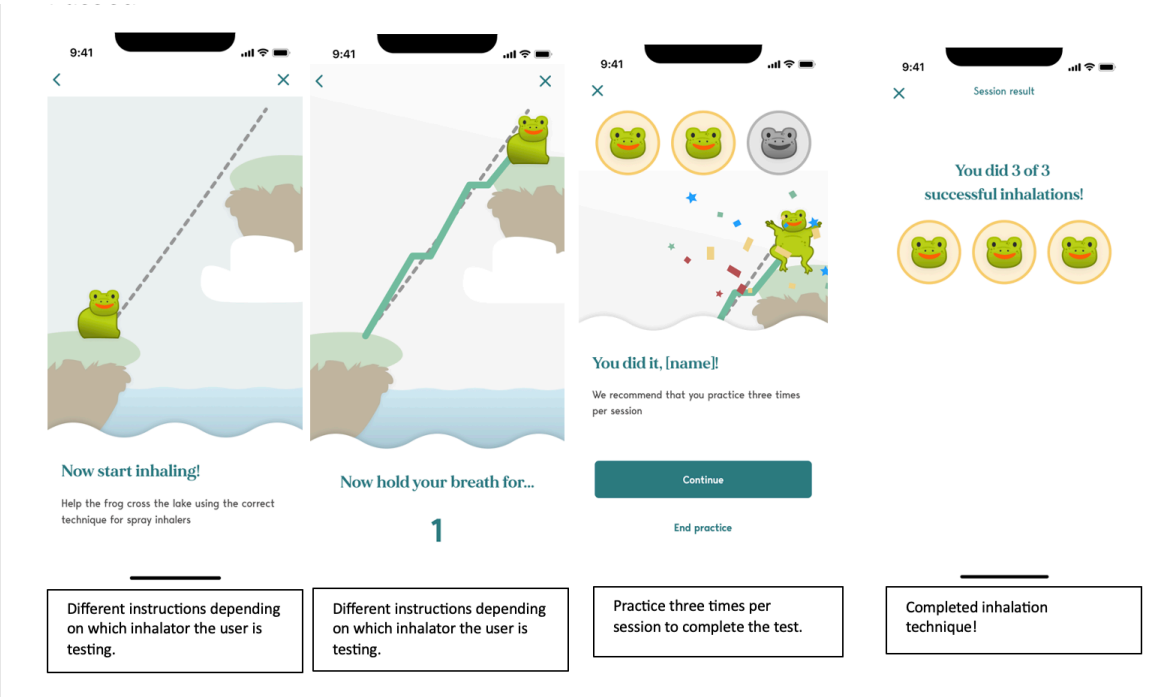


Figure 3c: Illustrations of failed and successful inhalation test with DPI and MDI inhalers from the app-based medical device.

While subjects enter the CE-marked “AsthmaTuner application”, subjects are presented with the option to enter the investigational device by selecting the “Practice now” button. It will be made clear to the subjects that they enter a non-CE marked part of the otherwise CE marked device. It will also be clear that the inhalation app-module is an investigational device only to be used in clinical study setting. Subjects are directed to the inhalation tool, which comprises educational resources and training materials for inhalation techniques. The tool is divided into four chapters: *Asthma quiz, COPD quiz, Prepare your inhaler*, and *Inhalation technique*. Education and preparation materials are specifically tailored to the inhalers included in the patient's treatment plan. The "Inhalation technique" chapter features a video demonstration and detailed instructions on preparing the spirometer prior to training sessions. Automated feedback is provided to subjects based on objective criteria for each selected inhaler, determining whether their inhalation technique meets the required standards. Subjects are encouraged to successfully training inhalation three times per session.

Follow-up visit 6-12 weeks
The subjective assessment of inhalation will be conducted ‘blinded’ by study personnel. The assessment will be filmed through Teams or Zoom to facilitate standardised review and judgment of inhalation technique according to Table 2. The film is stored on local hard disk of the computer and will be deleted after the “blinded” assessment is done.

The objective assessment will be performed in both groups according to Figure 3 a-c. Data is stored in the AsthmaTuner cloud.

Compromising factors that might affect the outcomes are i.e. ongoing exacerbation (asthma or COPD), the follow-up visit can therefore be rescheduled within the time frame of 6-12 weeks in case of any medical condition is deemed to affect the study endpoints. The coordinating investigator will

take the decision to withdraw subject in case of any not resolved medical condition, not present at baseline visit, is judged to significantly affect inhalation technique or subject's safety at the follow-up visit.

A.6.5 Monitoring plan

Before the beginning of the investigation, the Sponsor will appoint an independent monitor at Karolinska Trial Alliance (KTA). Monitoring will be performed before, during the study and after the study is completed in accordance with the ISO 141 55 GCP (Good Clinical Practice) standard. Study conductance, source data, device accountability, adherence to the study protocol, Good Clinical Practice, and regulatory requirements will be monitored.
Data to be monitored at site are e.g.

- Patient information and Informed Consent. That each patient included in the study has signed an Informed Consent and that no study procedures have begun before the date of the consent.
- That inclusion criteria are met for the included patients
- That all types of adverse events and serious adverse events, device related or not, as well as, those that might have led to SAE shall be reported, and even if those are listed as expected in this Clinical Investigation Plan.
- Check that all CRF data are entered
- Other CRF data will be source data verified against patient records according to a detailed Monitoring Plan (that will contain details regarding the overall monitoring) signed by the Sponsor prior to the start of the study. At least 20% of the patients will have data in the CRFs 100% source data verified.

The monitor and possible authorities must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the clinical study. In order to be able to do that, a written consent from each patient should be obtained. Additionally, a secrecy agreement between the monitor and the person responsible for patient records at the study site will be signed.

A.7 Statistical considerations

The analytical approach of this RCT is intention-to-treat, analyzing the effect of the investigational device across all randomized subjects with assessed inhalation technique at the 6–12-week follow-up visit. Additionally, a per-protocol analysis will be conducted on subjects who performed an inhalation test on average more than once per week during the study period, to evaluate the efficacy of education and training on inhalation technique between the intervention and control groups.

The null hypothesis of this investigation is no difference in success rate of inhalation technique between subjects assigned to intervention or control group. If the number of patients with inhalation technique deemed for correction differ significantly between intervention and control group at 5% significance level, the null hypothesis will be rejected. Based on our cross-sectional pilot study, 50% of in 40 patients with asthma demonstrated successful inhalations technique (Appendix 3), assuming 25% relative improvement of correct inhalation technique in the intervention group compared with control group including 20% drop out rate, enrolment of at least 80 patients will be sufficient to reach 80% power at 5% significance level.

Primary analysis: The success rate of subjects with correct inhalation technique according to objective and subjective critical endpoints at the 6-12 weeks follow-up visit. The effect of the medical device on rate of successful inhalation technique will be determined across randomisation groups with logistic regression analysis as risk ratio (RR) with 95% confidence interval. No interim analysis will be performed.

Secondary analyses: The analysis of feasibility and the experienced benefit of inhlation education and training support will be estimated on a Likert scale from 1 (not at all) to 5 (strongly agree), and summarized as mean and median scores. Quality content analysis will assemble collected information from questionnaire and interviews of respiratory nurses together with comments from patients. Data will be presented as categories based on oral or written quotes.

Sensitivity analysis: Analyse the rate successful inhalation technique based on objective and all subjective (not only critical) endpoints.

Descriptive statistics of the study population will be presented across the randomisation groups including information of number of randomised subjects, sex, age, asthma/COPD diagnosis, tobacco smoking status, educational level and type of inhaler(s) used for daily treatment.

The purpose of stratified block randomisation per investigational site is to adjust for imbalance in subjects' acquired knowledge of inhalation technique, common errors related to DPI and MDI devices and assessor's review of inhalation technique.

The study and the data management will be monitored by CRO, Karolinska Trial Alliance. In addition, two independent researchers (Inger Kull and Tonje Reier Nielsen) will have full access to all study information for study quality evaluation.

A.8 Data management

A CRF is used for data collection, Appendix 7. Clinical data will be entered directly into the validated electronic CRF of Research Electronic Data Capture (REDCap), stored at Karolinska Institutet, by the study personal at each site. The REDCap CRF is an online password protected database provided for the KPE Lung and Allergy department, QB:84, by Karolinska Institutet. The data entered the CRF will be validated before the clinical investigation begins.

The source documents are to be defined at the site before inclusion of the first subject (please see the section below). The investigator must ensure that data is registered and any corrections in the CRF are made as stated in the clinical trial protocol and in accordance with the instructions. The investigator will ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The investigator signs the completed CRF. A copy of the completed CRF will be archived at the study site. All changes made to data entered into the eCRF will be recorded in a protected audit trail.

The Data management will be organized locally by data entry personnel and each investigational site. Data will be reviewed by the CRO, Karolinska Trial Alliance (KTA, principal investigator, study Coordinator at the KPE Lung AllergY, QB:84, with further checking and review of clinic records as

necessary. The external monitor will perform source data verification to confirm that data has been entered correctly in the data base.

The cloud based AsthmaTuner system stores information about objective endpoints, is traceable personal ID and labelled with time points, while subjective endpoints are entered directly in CRF sheet and electronic questionnaire through REDCap are stored at Karolinska Institutet. Procedures for data review will be conducted according to standards of GCP. Due to the nature design of the intervention the subjects cannot be blinded. Investigators or study personnel outside the research team will feed data into the computer in separate datasheets so that the researchers can analyse data.

Database cleaning and issuing data queries will be traceable and transparent with logs and data is stored at KI. Audit can be performed at later stage in relation to larger multi-centre study with by certified CRO to assure quality, and to verify the monitoring process and data as appropriate.

Study subject's identity are transcoded and listed in database and in the CRF's. A subject identification list will secure the identity of included patients, the list will be stored in safety deposit at Karolinska Institutet, KPE Lung and Allergy QB:84.
Monitors will on site do monitoring to review the data in the CRFs versus source data and issue queries to the Investigator to correct and clean data before CRF is sent to be entered into the database, stored and kept by the Sponsor.

The study database will be reviewed and cleaned prior to locking the study database and analysing the data, and a Clean File Report will be issued. During the course of the study the investigational team, and the monitor will have access to the study material, which will be kept in a locked place. Retention period for data storage is 10 years. All study documentation will be saved as paper copies and electronic files after the study has been published and reported. Participating investigators / Sponsor will be responsible for data collection, data processing and report writing.

Data security incidents are proactively mitigated though encrypted hardware and information, education of investigators in handling sensitive information and processing of personal data according to the General Data Protection Regulation (GDPR). The investigators will promptly report to KI IT department if an incident of personal data breaches occurs. The direct response will be mitigated effects by isolate affected systems to prevent unauthorized access or data leakage, revoked user access and information restored from backups. Support and inform affected individuals, we aim to mitigate the adverse effects of data security breach.

A.9 Amendment of CIP

The proposed investigation is not allowed to deviate from CIP, expect under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor. Such deviations shall be documented and reported to the sponsor and the ethical committee as soon as possible within 7 days.

Substantial modifications refer to significant changes that could affect the safety, performance, or scientific validity of a clinical investigation. These modifications typically require formal notification

and approval from regulatory authorities before implementation. However, non-substantial modifications that do not have a significant impact on the clinical investigation's safety, performance, or scientific integrity will typically not require approval but need to be documented and reported to the regulatory authorities of MPA. Examples include administrative changes of investigators and study staff, logistical adjustments that do not affect the study population or do not impact on data integrity or patients' safety, technical updates of software or data collections tools do not alter study data or minor technical adjustments to equipment or procedures, clarifications and enhancements to the study protocol or informed consent documents without altering the study scope. By clearly distinguishing between substantial and non-substantial modifications, and following the appropriate procedures for each, the investigators will ensure that the clinical investigation remains compliant with regulatory requirements while maintaining the integrity and validity of the study.

A.10 Deviation of clinical investigation plan

The proposed investigation is not allowed to deviate from CIP, expect under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor. Such deviations shall be documented and reported to the sponsor and the ethical committee as soon as possible within 7 days. The Sponsor is responsible for analysing any deviations and assessing their significance. Deviations from the protocol will be registered in the Study deviation form. Regular monitoring will be performed as a mean of corrective action and to avoid repeated deviations. The coordinating investigator or investigator at the site may be disqualified by the sponsor if he /she does not adhere to the protocol, fails to report this with good reasons and refrains from correcting his / her actions.

Occurrence of unscheduled visit is possible in this real-life study. An unscheduled visit that occurs between baseline visit 1 and the follow-up visit (6-12 weeks) will be noted as unscheduled visit in the medical record and in the unscheduled visit form in the CRF.

A.11 Device accountability

The investigational device is only used in this clinical investigation. Sponsor will keep records for subjects who downloaded the investigational device and Airflow Trainer for the spirometer. Furthermore, the dates of use, subject identification and dates on which the investigational product was returned from subject will be documented.

A.12 Statement of compliance

The trial will be performed in accordance with the World Medical Assembly Helsinki recommendations guiding physicians in biomedical research involving human subjects [33], and standards of GCP (ISO 14155:2020), with national legislation and MDR (MDCG 2024-3,3.9).

The clinical investigation shall not begin until required approvals ethical committee and Medical Products Agency of Sweden have been obtained.

Subjects participating in this study are insured through the LÖF - Landstingens Ömsesidiga Försäkringsbolag, according to Swedish law (Patientskadelagen, 1996:799), which includes clinical research.

Funding agreement is not applicable for this investigation between sponsor and investigation sites.

A.13 Informed consent process

In this real-life clinical study with intention-to-treat approach will include subjects diagnosed and managed for asthma or COPD at pre-specified the investigational site(s). The subjects will be asked if they want to participate by their nurse, study nurse, or medical doctor. Oral and written information will be delivered and patient and/or caregiver will sign informed consent on paper or through BankID or similar electronic service.

It is the responsibility of the investigators at each site to give the subject full adequate information regarding the trial and the procedures prior to study inclusion. The patient must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before study enrolment. In addition, it is the responsibility of the investigator to obtain signed informed consent from all subjects before they can be included in the study.

A.14 Adverse events, adverse device effect and device deficiencies

The definitions of adverse events comply with MDCG 2020-10 Rev 1 – Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 in this investigation.

Definitions
Investigational device
A device that is assessed in a clinical investigation
(MDR Article 2(46))
Note: An investigational device can be a non-CE marked device or a CE marked device. The definition in MDR Article 2(46) does not differentiate between different regulatory statuses of devices. However, the reporting requirements are different depending on whether the clinical investigation is done for purposes described in Article 62, 74 or 82. The definition is understood to cover also the devices investigated in PMCF investigations, even if they are not subject to notification per Art 74.1.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.
(MDR Article 2(57))
Note:
a. This definition includes events that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures.

Non-reportable adverse events include any adverse events that are anticipated as a natural part of asthma or COPD progression, and **not** caused by the investigational product or intervention.

Adverse device effect (ADE)
Any adverse event related to the use of an investigational medical device or a comparator.

Anticipated serious adverse device effect (ASADE)
Any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the last risk assessment document upon serious adverse device effect occurred.

Device deficiency (DD)
Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
(MDR Article 2(59))

Incident
Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.
(MDR Article 2(64))**.**

New Finding
New information discovered as the result of an inquiry/investigation/test based on the occurrence of the event. Follow-up from the event.

Serious Adverse Event (SAE)
Any adverse event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
i. life-threatening illness or injury,
ii. permanent impairment of a body structure or a body function,
iii. hospitalisation or prolongation of patient hospitalisation,
iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
v. chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Serious adverse device effect (SADE)
Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious incident
Any incident that directly or indirectly led, might have led or might lead to any of the following:
a) the death of a patient, user or other person,
b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,

c) a serious public health threat.

Unanticipated serious adverse device effect (USADE)
Any serious adverse device effect, the nature, severity or outcome of which is not consistent with the reference safety information.

Reportable events
For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with MDR Art. 80(2):
a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b).

Serious adverse events related to a CE marked device which is part of the investigation procedure (for example a CE-marked implanting tool used in combination with a non-CE marked investigational device) are reportable per MDR Article 80(2) if there is a causal, (or reasonably possible) relationship to the device, the comparator or the investigation procedure. The reporting procedures described in this guide should then be followed in addition to the normal vigilance reporting procedures for CE marked devices.

All causality assessments should be made using the guidance in section 9. Only causality level 1 (i.e. “not related”) is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.

Exceptions for PMCF investigations falling under MDR Article 74.1
Following Article 74.1 the SAE reporting for these PMCF clinical investigations is governed by Articles 80(5) and 80(6). Thus the provisions of vigilance laid down in Articles 87-90 and acts adopted pursuant to Article 91 shall apply. However, the SAEs where a causal relationship between the serious adverse event and the preceding investigational procedure has been established shall follow the reporting procedures of clinical investigations as outlined in Article 80.
This means that:

- **For the purpose of this guidance** (safety reporting in clinical investigations) reportable events in PMCF clinical investigations are those serious adverse events where a causal relationship between the serious adverse event and a preceding investigational procedure has been established. The other relationship categories i.e. not related, possible and probable do not need to be reported **in the context of the clinical investigation** under Article 80.
- **In the context of vigilance**, articles 87-90 need to be taken into account and this concerns the Serious Incidents where a relationship between the incident and the device or a procedure stated in the IFU is at least reasonably possible. Also not related, possible and probable events need to be reported in the context of vigilance (Art. 87-90).

It is thus possible that events occurring in such clinical investigations need to be reported to both the competent authorities in charge of SAE in clinical investigations AND to the competent authorities in charge of vigilance, as outlined above, including a relationship to a procedure stated in the IFU.

"Preceding investigational procedure" shall be understood as a procedure which is imposed by the Clinical Investigation Plan and which has taken place before (or coincided in time) with the serious adverse event. This includes both the investigational device application procedure and any additional burdensome or invasive procedure(s) which defines whether the study is subject to notification requirements following MDR article 74(1).

Transition period for reportable events in pre-market clinical investigations initiated under directives legislation
It is acknowledged that the MDR implies changes to the reporting requirements compared to the directives' requirements where all SAEs should be reported regardless of relatedness. Under MDR sponsors are no longer obliged to report SAEs that are "not related" to the clinical investigation procedures or the investigational device. At the date of application for MDR there will be ongoing events for clinical investigations initiated under directives legislation. As from the 26th of May 2021 sponsors are no longer expected to submit follow-up reports to NCAs for events that have been deemed "not related" (see section 9 of this document for guidance on causality assessment). For ongoing events that have a causality assessment other than "not related" follow up reports will still have to be provided.

To facilitate the transition and give time for sponsors to update Clinical Investigation Plans and study procedures in clinical investigations a sponsor may continue to report all SAEs to NCAs until Eudamed reporting is mandatory (see section 4.1 Transition to reporting via Eudamed). This applies only to studies which have started to be conducted5 in accordance with Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC prior to 26 May 2021.

Transition for reportable events in PMCF clinical investigations initiated under directives legislation
In case of PMCF studies which required SAE reporting according to the Pre-MDR national legislations, MDR article 80 (5) and 80(6) shall apply from May 26th, 2021.

Report by whom
Reportable events have to be reported by the sponsor of the clinical investigation, which could be the manufacturer, the legal representative or another person or entity.

Report to whom
Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the Appendix 6.
A list of clinical investigation contact points within the NCAs is published at the Commission's homepage.
For the purpose of this guidance, an investigation is considered to have commenced in an individual Member State:
• For investigations under the directives: When the sponsor is authorized to start the investigation in accordance with the notification procedures in that Member State.
• For investigations started under the MDR: When the sponsor is authorized to start the investigation in that Member State in accordance with the provisions laid out in the MDR.

Member States may also require separate reporting to the Ethics Committee(s).

Reporting timelines
Report by sponsor to NCAs.
The sponsor must report to all NCAs where the clinical investigation is authorised to start:
• For all reportable events as described in section 5 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.**

This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.
These concerns may be identified by either the NCA or the manufacturer.
• Any other reportable events as described in section 5 or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

In some cases, a different periodicity or different modalities may be agreed between the participating NCAs and the sponsor according to the investigation's design and to the pathology under clinical investigation. This would allow implementation of adequate provision for clinical investigations in which SAE frequency is expected to be high due to the natural progression of the disease (e.g. palliative oncology).

Report by the investigator to the sponsor
The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events as defined under chapter 5 will be provided by the investigator to the sponsor immediately, but not later than 3 calendar days after investigation site study personnel's awareness of the event.

Causality assessment
The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.
During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there8. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.
The above considerations apply also to the serious adverse events occurring in the comparison group.
For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:
1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.
1. Not related: Relationship to the device, comparator or procedures can be excluded when:
- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis9, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
o the investigational device or procedures are applied to;
o the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis10, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device.
Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.
The relationship between a serious adverse event and the procedure or the device, needs to be assessed separately. This does however not mean that they are mutually exclusive, a serious adverse event can be related to both the procedure and the device, or it can be related only to the procedure or only to the device. When it is unclear whether an event is related to the device or to the procedure, the investigator should:
• set the Relationship to device to possible (or higher)
AND
• set the Relationship to procedure to possible (or higher)

Since it is the healthcare provider who performs the procedures and manages/handles the medical device(s), the causality assessment of this healthcare provider should prevail.
In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting not be delayed.
Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

Reporting form
The reporting form template for the summary SAE tabulation is given in the Appendix 6 (Appendix7_.10-2 MDCG 2020-10-2 Clinical Investigation Summary Safety Report Form v1.0).
The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan. English is the recommended language for the reporting form. The report form can be modified in any applicable software (not only Microsoft Excel) but the file needs to be compatible with Microsoft Excel when sent to the participating NCAs.
The template form contains inserted filters and functionality to facilitate use of preferred terminology in the reporting. These are important for the analysis and should be maintained. Sponsors who generate the excel report file by automated processes may implement other technical features in their systems for excel file generation to ensure the preferred terms listed in metadata are used.
The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual study specific reporting form (see further section 4.3 Collecting reports from investigators).

Contact details for sponsor and coordinating investigator:

1. Björn Nordlund, RN, PhD, Associate professor, KPE Lung Allergi QB:84, Karolinska University Hospital, and Department for Women's and Children's Health, Karolinska Institutet. Phone: +46 703234414
2. Henrik Ljungberg, MD and PhD, Astrid Lindgren Children's Hospital, Lung-Allergy Department and Department for Women's and Children's Health, Karolinska Institutet. Phone: +46 706628642

A.15 Vulnerable population

Vulnerable populations in this study are considered to be adolescents and elderly. Informed consent requires from child's legal caregiver and the child herself, children from the age 15 years to 17 years can leave their own informed consent if they understand what the research means for him or her. However, the medical device is designed and developed for children from the age of 6 years. Children and elderly patients are particular important groups to approach with inhalation technique support since symptom fluctuations constitute a difficult challenge to young patients' ability to self-manage their disease, fundamentally different from more predictable illness patterns [34] and in elderly with multimorbidity and practitioners [35].

The informed consent process initiated by nurse or medical doctor at the investigational site should approach vulnerable populations at site or through letter or phone, and in case of adolescent also legal caregiver. Basic understanding of the Swedish language is required to understand the purpose and the procedures of study and also access to BankID or similar digital service for signing informed consent and login to the AsthmaTuner app. Therefore, are subjects without BankID (or similar service) will be excluded. The subjects will get sufficient time to consider study participation, this could be anything from 5 min to 1-2 weeks depending on the subject individual needs. After consideration of study participation, the subject will leave signed informed consent before randomisation. The subjects can continue to use the investigational device after the clinical investigation without any costs. They will be supported to do at the investigational site.

A.16. Suspension or premature termination of the clinical investigation

The sponsor, principal investigator or regulatory authority may suspend or prematurely terminate either a clinical investigation or an individual investigation site or the entire investigation for significant reasons as follows:

- Suspicion or confirmation of an unacceptable risk to subjects arises during the investigation
- Serious or repeated deviations on the part of an investigator or study site

If suspension or premature termination occurs the sponsor agree to follow up all included subjects enrolled in the clinical investigation according to CIP. Principal investigator will prompt inform all collaborators, and all enrolled subjects involved will be informed at each investigational site, and report the occurrence to *MDR-IVDR Swedish Medical Products Agency 'Läkemedelsverket' Department of Medical Devices*
Box 26, SE-751 03 Uppsala,
E-mail: registrator@lakemedelsverket.se
Web site: https://www.lakemedelsverket.se/sv

To maintain the overall quality and legitimacy of the clinical trial, code breaks should occur only in exceptional circumstances when knowledge of the actual management is absolutely essential for further treatment of the patient. The investigator is encouraged to maintain the blind as far as possible. The actual allocation must NOT be disclosed to physician and investigators, nor should there be any written or verbal disclosure of the management period in any of the corresponding patient documents. The investigator will report all code breaks (with any reason) as they occur on the corresponding CRF and medical record. Unbliniding should not necessarily be reason for discontinuation of the trial.

If unblinding is deemed to be necessary, the investigator should ask the patient directly or the study nurse, alternatively contact principal investigator directly on phone number: B. Nordlund + 46 703234414 or H. Ljungberg + 46 706628642.

Subjects will continue to receive standard care irrespective of participation or randomization.

A.17 Publication policy

Independently of results of this clinical investigation the result is aimed to be published in academic peer-reviewed journal of high impact. The plan is to publish data within 12 months of end of data collection. The authors will be based on contribution according to standards from international committee of medical journal editors (http://www.icmje.org).
The results of clinical investigation will be reported according to ISO 14155:2020, Annex D *Clinical investigation report*, by sponsor within one year after the end of the investigation to MPA.

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