Universitair Ziekenhuis Brussel

Clinical Trial Center

Study Protocol

Study Title: Choice of Inhalation Device in Asthma and COPD
Study Acronym: CIDAC
Phase of Development: NA
Protocol Number:
Protocol Version and Date: Version number 1, 05/03/2021
EudraCT Registry Number: (ter info: zal gebeuren via studieloket UZ Brussel zodra ik goedkeuring ethisch committee heb)
ClinicTrials.gov Registry Number: (idem zie boven)
Indication: obstructive lung disease
Investigational product or Medical Device: NA
Sponsor: NA
Coordinating/Principal Investigator: Laure Vandermeersch

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PROTOCOL SIGNATURE PAGE

Protocol Version and date: Version number 1, 5 March 2021

Protocol Title: Choice of inhalation device in asthma and COPD patients

Sponsor: This study is an academic study and has no sponsor.

Principal Investigator: Laure Vandermeersch

I agree:

- to assume responsibility for the proper conduct of this study
- to conduct the study in compliance with this protocol and any future amendments
- not to implement any deviations from or changes to the protocol without prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
- that I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol
- to ensure that all persons assisting me with the study are adequately informed about the investigational drug and their study-related duties and functions as described in the protocol
- that I am aware of and will comply with the current good clinical practice (GCP) guidelines and ethical principles outlined in the Declaration of Helsinki
- to conduct the study in accordance with all applicable laws and regulations

Printed name Signature Date

Table of Contents

1 Trial Registration/Protocol Summary

Information	
EudraCT number: Date of registration:	Application for registration in a clinical trial registry will be done after obtaining approval from the ethics committee
ClinicalTrials.gov:	Please see previous line
Official Title:	Choice of inhalation device in asthma and COPD
Study Phase/Type:	Single center, single visit cross-sectional interventional study without device or investigational product.
Condition:	Asthma and COPD (Chronic Obstructive Pulmonary Disease)
Objectives:	To identify patient/inhalation device mismatch by using objective measurements.
Investigational Product or Medical Device:	NA
Interventions:	The intervention will be a three-step evaluation. Patients will perform a deep voluntary inspiration. This inspiration will be assessed by the investigator. Secondly, the peak inspiratory flow will be measured over 5 different resistances with an In-check Dial device. Subsequently, patients will receive education about good coordination technique, which is necessary for the optimal use of pressured metered dose inhalers (pMDIs). By using a placebo pMDI, the investigator will assess the coordination of the patient. The evaluation of voluntary deep inspiration, PIF's and coordination will be by pass or fail evaluation.
Endpoints:	To assess if the choice of inhaler device category differs when based on objective assessments, as compared to the choice made by the treating physician (during routine clinical practice), which is primarily based on subjective evaluation.
Study population:	Asthma and COPD patients treated with inhaled medications. Subjects will be recruited in the respiratory outpatient clinic in UZ Brussel after a scheduled consultation with their pulmonologist.
Number of patients:	40 COPD patients (GOLD II-IV); 20 patients with severe asthma, 40 patients with asthma aged ≥ 70y, 40 patients with mild-to moderate asthma aged < 70y
Overview of study design:	Single center, single visit cross-sectional interventional study without device or investigational product
Statistical Considerations:	Descriptive analysis will be used to describe the prevalence patient/device mismatch. Multiple regression analysis will be performed to identify patient characteristics associated with inability to use the 3 main classes of inhalation devices respectively. Due to the exploratory nature of this study, no formal power calculation can be performed.
Sponsor:	This study is an academic study and has no sponsor.
Inclusion Criteria:	- COPD patients (GOLD II-IV) - Patients with severe asthma - Patients with asthma aged ≥ 70y - Patients with mild-to moderate asthma aged < 70y
Exclusion Criteria:	- Patients with asthma or COPD not on inhaled therapy for maintenance treatment - Patients younger than 18y - Patients unable to give their informed consent due to mental or physical disability - Patients who don't speak Dutch or French
Target Date of first enrolment:	To be determined. Probably Q4 2021.

Target sample size:	No target sample size calculation could be performed due to exploratory nature of the study (please see above)

2 Protocol Version History

Version No.	Release Date	Summary of Changes

3 Sponsor/Coordinating Investigator Information

Coordinating Investigator (promotor): Prof. Dr. Eef Vanderhelst
Sponsor: NA
Principal Investigator Laure Vandermeersch
Co-investigators: Prof. Dr. Eef Vanderhelst, Dr. Shane Hanon (co-promotor), Mr Daniël Schuermans, Mss Cindy Zienebergh
Additional co-researchers: NA
Statistician
Laboratory (ies): NA
Pharmacy: NA
Study Coordinator; Daniël Schuermans
Study sites and co-investigators; respiratory outpatient clinic UZ Brussel

4 List of Abbreviations

COPD = Chronic Obstructive Pulmonary Disease
FEV1 = Forced Expiratory Volume in one second
FVC = Forced Vital Capacity
ICS = Inhaled corticosteroids
LABA = long acting beta-agonists
LAMA = long acting muscarinic antagonists
GOLD = Global Initiative for Chronic Obstructive Lung Disease
GINA = Global Initiative for Asthma

5 Introduction

5.1 Overview of Disease Pathogenesis

Pathogenesis of asthma

Asthma is a heterogeneous disease, which is normally characterized by the presence of chronic airway inflammation. Asthma is defined by the history of respiratory symptoms such as shortness of breath, wheeze, cough, chest tightness. These symptoms can fluctuate over time and in intensity in combination with a variable expiratory airflow limitation. (1)

Pathogenesis of COPD

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases

an influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.
The most common respiratory symptoms of COPD are cough and/or sputum production, dyspnea. Underreporting of these symptoms by patients can occur.
The most important risk factor for COPD is tobacco smoking. Other environmental exposures such as air pollution and biomass fuel exposure may contribute. (2)

5.2 Epidemiology

Epidemiology of asthma
Currently, 4.3% of the population worldwide has asthma. The prevalence of asthma in the United States is 8.4%. The prevalence of asthma is on the rise. Asthma is more prevalent in black than in white persons. It is remarkable that the prevalence of asthma decreases with each successive higher poverty level group. Asthma has a significant impact on morbidity and mortality. (3)

Epidemiology of COPD
The global prevalence of physiologically defined chronic obstructive pulmonary disease (COPD) in adults aged >40 years is approximately 9-10 per cent. (4)
The worldwide prevalence of chronic obstructive pulmonary disease (COPD) in adults older than 40 years old is approximately 9-10%. COPD is the fifth leading cause of years lost through early mortality or handicap (disability-adjusted life years). Country, sex and age are factors that influence the prevalence of COPD. (2)

5.3 Current Treatments

Treatment of asthma
The current pharmacological treatment of asthma consists of the stepwise approach by GINA. The goal is to optimize the personalized asthma management by assessing, adjusting and reviewing the response to treatment.
The treatment depends on the number of step of GINA. The 5 different GINA steps are characterized by different treatments. Inhaled corticosteroids (ICS), short acting β2- agonists (SABA) and long acting β2 agonists (LABA)
There are 3 different types of inhalers: dry powder inhalers (DPI), pressurized metered dose inhaler (pMDI) and soft mist inhalers (SMI).
SMI's and pMDI's can be used in combination with an inhalation chamber. (5)

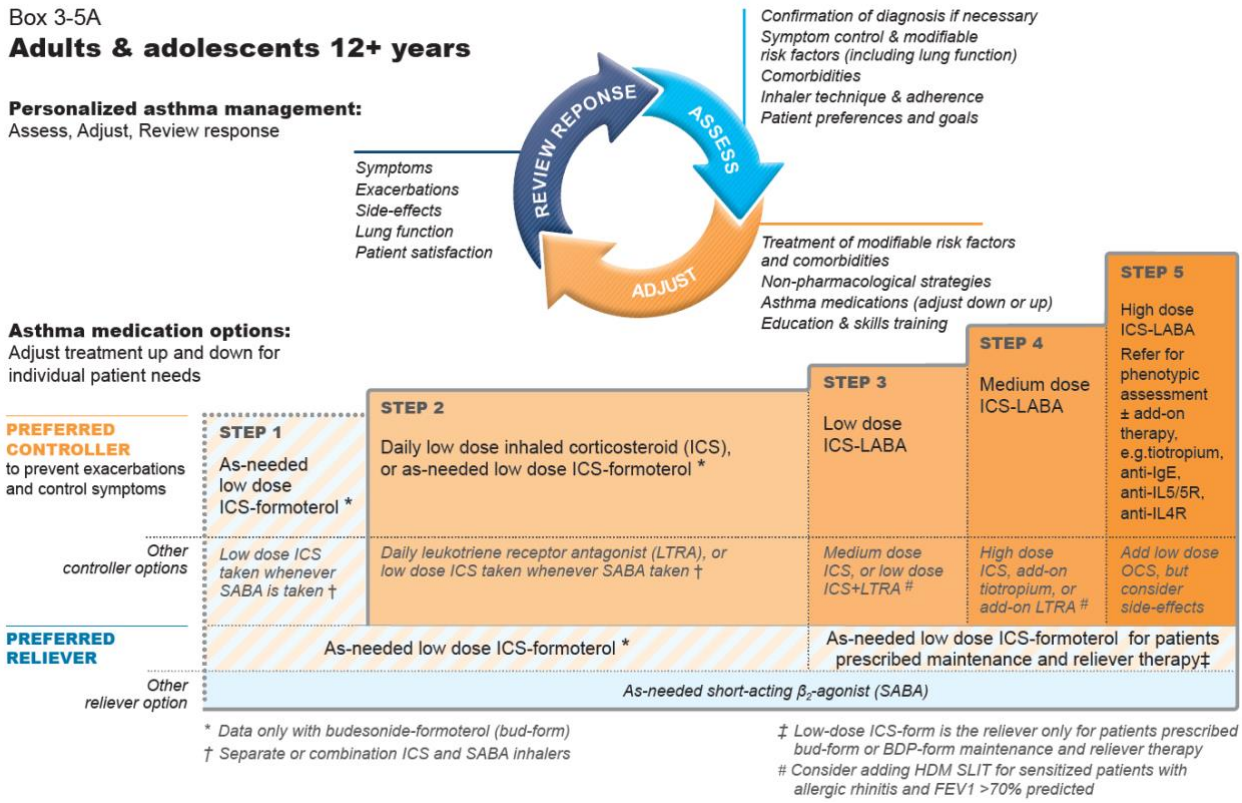

Figure 1: treatment of asthma

<u>Treatment of COPD</u>
The treatment of COPD depends on the group guided by GOLD: group A, B, C or D.
The corner stone of the pharmacological treatment consists of bronchodilatation: LABA (long acting beta-agonists), LAMA (long acting muscarinic antagonists). A triple therapy: ICS, LABA and LAMA, is recommended in COPD GOLD D patients. (6)

5.4 Study Rationale and Purpose

Inhalation therapy is the cornerstone therapy in asthma and COPD patients. Unfortunately, many errors are associated with the use of inhalers, which leads to poor outcome for patients. Problems with the use of pressurized metered dose inhalers were described shortly after the launch of pMDI and still persist today. The use of dry powder inhalers (DPI's) is also frequently associated with errors.
The most common errors in the use of pMDI's are incorrect coordination, insufficient depth and/or speed of inspiration and no postinhalation breath-hold in.
The post frequent DPI errors are no complete expiration before inhalation, incorrect preparation and lack of postinhalation breath-hold in.
The overall prevalence of poor technique was 31%, of acceptable technique 41% and of correct technique only 31%. It can be concluded that incorrect inhaler technique in asthma and COPD patients is unacceptably frequent. Over the past 40 years, the prevalence of correct inhaler technique has not improved. The lack of correct inhalation technique may be a major obstacle, which withholds patients from achieving optimal asthma or COPD control. (7)
Incorrect use of inhalers is associated with reduced disease control. The strongest associations have been found between incorrect inhaler technique and older age, lower schooling and lack of

instruction about the correct inhaler technique by healthcare workers. These associations are independently of the inhaler type. Poor inhaler use is most common in older ages, but can occur at all ages. The misuse of inhalers is associated with an elevated risk of hospitalization, visits to the emergency department, treatments with oral corticosteroids and antimicrobials, and poor disease control. Instruction by healthcare workers about the correct use of inhalers is the only modifiable factor that can be useful to reduce the prevalence of inhaler misuse. (8)
The choice of inhalation device is an important decision and is often as important as the medication put in the device to achieve optimal outcomes for patients with asthma or COPD. The optimization of treatment could be established by switching between devices instead of increasing or changing the pharmacological therapy. There are multiple differences between the various devices such as particle size, release mechanism, drug deposition and required inspiratory flow. Switching devices should never be done without the patient consent. A patient should feel comfortable with their device in order to use it properly, which makes that switching of device is a careful process in which the patient has to be involved. (9)

In conclusion, the purpose of the study is to identify patient/inhalation mismatch by using objective measurements.

5.5 Rationale for Study Design

All assessments can be made on the spot following the consultation, which allows a cross sectional design.

5.6 Rationale for Dose and Regimen/Schedule Selection NA

6 Study Schematic and Schedule of Activities

6.1 Study Schematic

Characteristics of the study	
Informed consent procedure:	▪ Available in Dutch and French ▪ Signature and date written by participant
Inclusion criteria:	▪ COPD patients (GOLD II-IV) ▪ Patients with severe asthma ▪ Patients with asthma aged ≥ 70y ▪ Patients with mild-to moderate asthma aged < 70y
Exclusion criteria:	▪ Patients with asthma or COPD not on inhaled therapy for maintenance treatment ▪ Patients younger than 18y ▪ Patients unable to give their informed consent due to mental or physical disability ▪ Patients who don't speak French or Dutch
Collection of data form patient file:	▪ Choice of inhaler by physician (current inhaled maintenance treatment) ▪ GOLD grade and group (COPD patients) ▪ GINA treatment step (asthma patients) ▪ Smoking status ▪ Height ▪ Weight ▪ Age ▪ FEV_1, FVC, PIF if available ▪ Oral corticosteroid maintenance dose
Study assessments:	▪ Voluntary deep inhalation ▪ Peak inspiratory flows (PIF's) ▪ Coordination (through a placebo pMDI)
Reporting to treating physician in case of patient/device mismatch	▪ To avoid prescription of inappropriate inhaler

6.2 Study Activities

The study will take place in the respiratory outpatient clinic. Patients will be invited to participate in the study after the consultation with the pulmonologist. All pulmonologists have a flowchart regarding the optimal choice of inhaler at their disposition.

Patients will be provided sufficient time to read the informed consent file and to ask questions about the study. After giving their informed consent they will be screened for eligibility by an

investigator. Demographic data and characteristics will be retrieved from the medical record (EMD) of study participants.

The intervention will consist of three different steps.

First, the patient will perform a deep voluntary inspiration. The patient's ability to perform this inspiration will be assessed and scored by the investigator.

Secondly, the peak inspiratory flows (PIF) will be measured with an In-check Dial device over 5 different resistances.
The minimal and optimal peak inspiratory flow rates (PIFRs) differ by device. A minimum flow of 30 L/min is required for most DPI's. The optimal flow varies from 30 L/min to 35, 45, 50, 60 or 65 L/min. (10)
Due to the fact that there is still discussion about the effectiveness of PIF's going from 30 to 60 L/min, an arbitrary cut-off value will be set at 45 L/min. This cut-off value for sufficient PIF will be measured over a moderate resistance to distinguish subtherapeutic from therapeutic levels. (11) If the patient reaches a PIF lower than 45 L/min, the patient will be asked to make a second attempt.

Subsequently, the patient will receive education about the correct coordination, which is necessary in the use of dose inhalers. The patient will be evaluated for sufficient actuation-inhalation coordination, through a placebo pMDI.

The evaluation of the voluntary deep inspiration, PIF and coordination will be by pass or fail evaluation. Subsequently, the fitness of a patient to use any of the three inhaler classes will be determined by using a diagram designed by a Belgian expert group (unpublished to date; courtesy of Didier Cataldo, ULiège).

If a mismatch between prescribed inhaler and suitable inhaler types is found, the treating physician of the patient will be informed. By doing so, we wish to avoid patients receiving prescriptions for inhalers that they cannot use properly.

7 Study Objectives and Endpoints

7.1 Primary Objective

To study the prevalence of patient/device mismatch based on objective assessments.

7.2 Secondary Objectives

To assess the proportion of patient/device mismatch per patient subgroup.

To assess the fail rates for each objective measurement separately for the entire study population and per patient group.

To correlate the fail rates for each objective measurement separately with patient's characteristics per patient subgroup and overall (age, sex, height, weight, FEV_1, FVC, PIF, GOLD grade and group, smoking status, GINA treatment step, oral corticosteroid dose).

To correlate fail rates for each objective measurement with patient's characteristics.

7.3 Endpoints

Cfr 7.1 and 7.2

8 Investigational Plan

8.1 Overall Study Design

Cross sectional study design

8.2 Study Duration for Subjects

8.2.1 Screening

Patients will be recruited following their consultation with their pulmonologist. The recruitment of the patients will take place in the respiratory outpatient clinic of UZ Brussel.

8.2.2 Treatment Period NA

8.2.3 Unscheduled Visit(s) NA

8.2.4 Early Study Termination NA

8.2.5 End of Study

The duration of the study for each individual patient will be around 5 to 10 minutes. Participation ends when the patient leaves the pulmonology division at the outpatient clinic.

9 Selection of Subjects

9.1 Selection of Study Population

The selection of study population will take place in the respiratory outpatient clinic in UZ Brussel. The patients will be recruited following their consultation with the pulmonologist.

9.2 Inclusion Criteria

- COPD patients (GOLD II-IV)
- Patients with severe asthma included in the Belgian Severe Asthma registry aged <70
- Patients with asthma of any severity aged ≥ 70y
- Patients with mild-to moderate asthma aged < 70y

9.3 Exclusion Criteria

- Patients with asthma or COPD not on inhaled therapy for maintenance treatment
- Patients younger than 18y

- Patients unable to give their informed consent due to mental or physical disability
- Patients who don't speak French or Dutch

9.4 Contraception/Pregnancy Avoidance NA

10 Screening and Randomization

10.1 Screening and Enrollment

Patients who gave their informed consent will be screened for eligibility by an investigator.

10.2 Randomization NA

10.3 Blinding Procedures NA

11 Interventions/Treatment

11.1 Treatments Administered

The intervention consists of physiological measurements. No treatment, drug or product will be administered. No device will be tested. The In-check-dial-device and placebo pMDI are merely tools to perform the physiological measurements.

11.2 Product Characteristics NA

11.3 Randomization and Stratification NA

11.4 Direction of Administration NA

11.5 Dosing Regimen NA

11.5.1 Dose Modifications and Dose Delay

11.5.2 Treatment Interruption and Treatment Discontinuation

11.6 Treatment Compliance NA

11.7 Study Drug or Medical Device Accountability NA

11.8 Storage, Packaging and Labeling NA

11.9 Blinding NA

11.10 Prior and Concomitant Medication NA

11.11 Non-Drug Therapies NA

11.12 Prohibited Medication NA

11.13 Prohibited Procedures NA

11.14 Other Interactions NA

11.15 Study Disposal and Destruction NA

11.16 Known Undesirable Effects of Study Drug NA

12 Study Assessments and Procedures

Please see section 6.2: study activities

12.1 Study Assessments:

12.1.1 Screening
cfr supra (6.2 and 10.1)

12.1.2 *Baseline: NA*

12.1.3 Run-In: NA

12.1.4 Treatment Period: NA

12.1.5 Follow-Up

12.1.6 End of Study

The study will end when the anticipated number of participants will be reached.

12.1.7 Re-screening NA

12.1.8 Early Termination NA

12.1.9 *Unscheduled Visits* NA

NA= not applicable for this cross-sectional study

12.2 Assessment Types

This study will assess physiological data (ability to perform a voluntary inhalation, PIF, and actuation-inhalation coordination with a pMDI). Cfr supra.

12.2.1 Efficacy Assessment NA

12.2.2 *Safety and Tolerability Assessments* NA

12.2.3 *Physical Examination* NA

12.2.4 Vital Signs, Height, Weight…

The height and weight of patients will be collected from the patient file.

12.2.5 ECG…. NA

12.2.6 Laboratory Evaluation NA

12.2.6.1 Clinical Chemistry

12.2.6.2 Hematology

12.2.6.3 Urine Analysis

12.2.6.4 Pharmacokinetics….

13 Safety Monitoring and Reporting

Patient safety during the assessments is monitored by the investigators. In the highly unlikely event of an adverse event (AE) or severe adverse event (SAE), this will be reported in the CRF and the treating physician will immediately be notified by the investigator.
The assessments of a deep inhalation, PIF maneuvers over a resistance and the use of a placebo pMDI do not differ from the maneuvers performed in daily life, when inhaler therapy is used by patients.

13.1 Adverse Events NA

13.1.1 Definitions and Reporting

Reporting in the CRF

13.1.2 Reporting Period

Duration of the study for the individual patient

13.1.3 Laboratories Test Abnormalities: NA

13.2 Serious Adverse Events

13.2.1 Definitions

13.2.2 Immediate Reporting

Immediate reporting in the CRF and to the treating physician by the investigator

13.3 Suspected Unexpected Serious Adverse Events (SUSAR) NA

13.3.1 Definitions

13.3.2 Reporting

13.4 Other safety data requiring an immediate declaration NA

13.5 Procedures for Handling Special Situations NA

13.5.1 Pregnancy

13.5.2 Overdose Management

13.6 Annual Safety Report NA

14 Data Collection and Management

14.1 Monitoring

14.1.1 Composition of data monitoring committee: NA

14.1.2 Interim analysis: NA

14.2 Data Collection

By the investigator (from medical records and study assessments).

14.3 Database Management and Quality Control

The promotors and investigators from UZ Brussel's respiratory division assume database management and quality control.

14.4 Statistical Considerations and Data Analysis

The promotors and investigators from UZ Brussel's respiratory division will perform the statistical analysis, with the help of VUB statistician Professor Kurt Barbé.
The statistical plan was discussed during a meeting with professor Barbé (see below).

Sample size calculation

This is a purely explorative study, since there is no a piori hypothesis to be confirmed. Hence, no formal sample size calculation is possible.
The findings of this study could later on be confirmed and assessed more extensively in larger dedicated studies.
For this study however, it is important that the patient groups be stratified according to their occurrence in society. We believe this will be the case when the in-and exclusion criteria for this study will be applied.

Statistical analysis

Descriptive statistics will be used to describe the prevalence of patient/device mismatch for the entire study population.
The comparison of the prevalence of patient/device mismatch between patient subgroups and the comparison of the fail rates for each objective measurement separately between patient subgroups will be done by means of the Chi-square test and will be visualized in cross-tables.

To study correlations between patient characteristics (independent variables) and pass or fail rates for each of the three test criteria (dependent variables), box-plots will be used for continuous variables (for example weight and length), whereas the Chi-square test will be used for categorical variables (for example diagnosis, age expressed in years, GOLD stage and GOLD group).

15 Ethical Considerations

15.1 Ethical conduct of the study

15.1.1 Declaration of Helsinki

The study will be conducted in accordance with the principles and guidelines of the declaration of Helsinki.

15.1.2 Ethics Committee

Application for approval of this protocol by UZ Brussel's ethics committee is being prepared.

15.2 Informed Consent

Patients will sign an informed consent before participating in the study. The informed consent will be available in Dutch and French.

15.3 Patient and Study Data Protection

This study will be performed in accordance with the standards applied by the UZ Brussel's Data Protection Officer.
Paper CRF's (source data) will be stored only in UZ Brussel's respiratory division. Anonymized data (excel file) will be stored on UZ Brussel's S-drive.

15.4 Subject Identification

Data will be anonymized before storage.

16 Finance and Insurance

The conduct of this academic study will be financed by UZ Brussel's respiratory division. An insurance will be taken out for this study.

17 Reporting and Dissemination

The principal investigator will report the results of the study in her master thesis. The results may also be presented at a scientific conference or be published. The investigators hold all publication rights.

18 Conflict of Interest Statement

The investigators have no conflicts of interest related to this study.

19 Tables and Figures

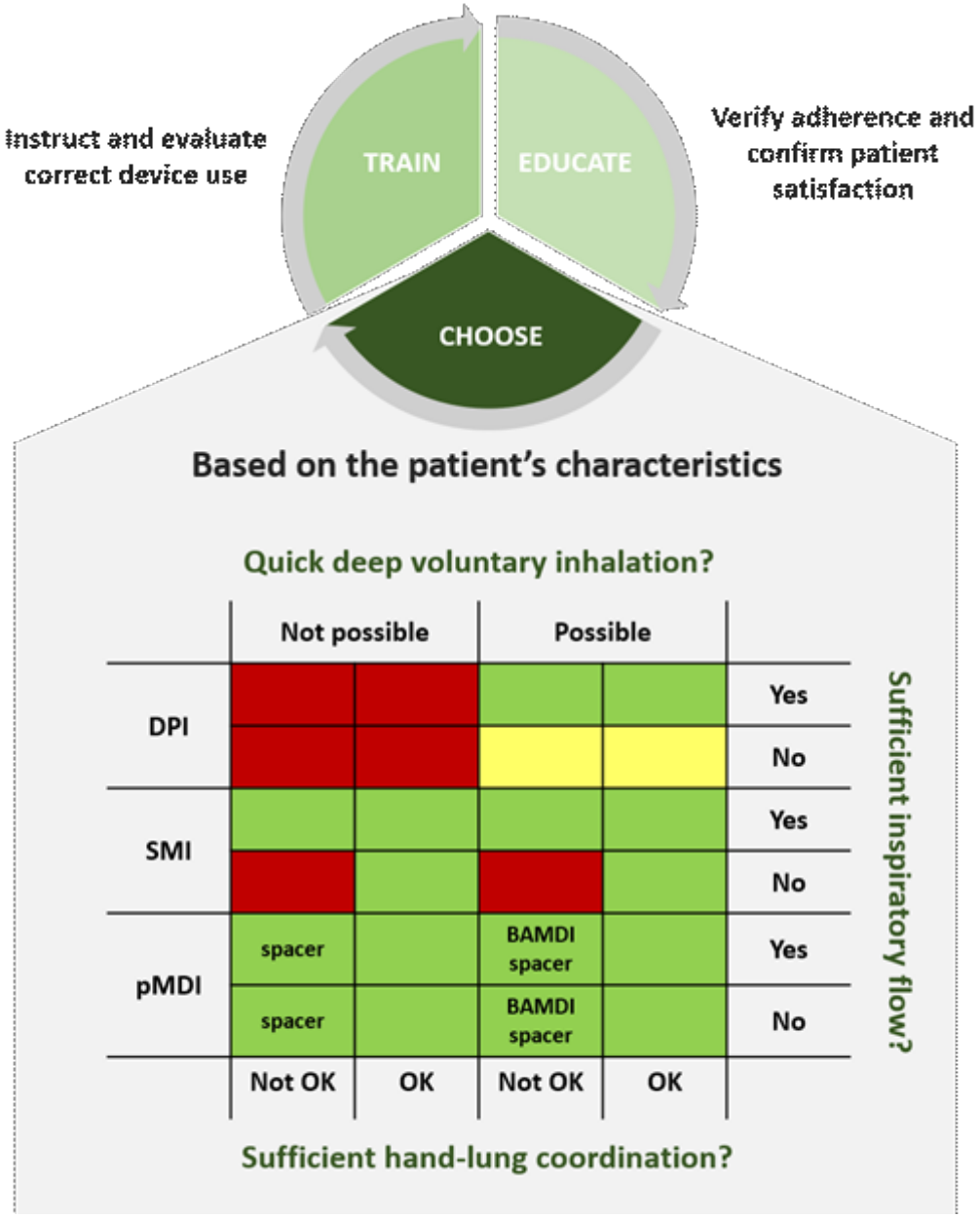

Figure 1: Diagram designed by a Belgian expert group: unpublished to date; used under permission of Prof. Dr. Didier Cataldo and courtesy of Prof. Dr. Didier Cataldo, University of Liège.

Legend of the used colours in this diagram:
Green = optimal indication
Yellow = not indicated
Red = not indicated

20 References

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