SADT in COPD and Oscillometry in obstructive airway disease in primary care. The SCOOP-study

Short title: SCOOP-study

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AC/DC	Asthma/COPD Differentiation and Classification
ACO(S)	Asthma/COPD overlap (syndrome)
ACQ	Asthma Control Questionnaire
AE	Adverse Event
ALDS	Ambulatory Lung Diagnosis System
AUC	Area Under receiver operation characteristic Curve
AX	Reactance Area
BMI	Body Mass Index
CCQ	Clinical COPD Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
ERS	European Respiratory Society
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
GP	General Practitioner
HCP	Healthcare professional
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
LABA	Long-Acting β-Agonist
LR+	Positive likelihood ratio
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
OAD	Obstructive airway disease
SAD	Small Airway Dysfunction
SADT	Small Airway Dysfunction Tool, where the suffix "-a" stands for asthma and "-c" stands for COPD, indicating the target population of SADT.
(S)AE	(Serious) Adverse Event
SCOOP	SADT in COPD and Oscillometry in obstructive airway disease in primary care
R5-R20	Resistance difference between 5 and 20 Hz

SUMMARY

Rationale: The Small Airways are a major site of obstruction in many respiratory diseases, including COPD. More insight into a diagnosis of Small Airways Dysfunction (SAD) in patients with COPD is clinically valuable as it might enable tailored pharmacotherapy. Currently, methods to diagnose SAD in COPD are not standardized and are not available in routine clinical practice. The Small Airways Dysfunction Tool (SADT) was developed to identify patients with asthma and SAD. Initially, the SADT included a comprehensive 63-item questionnaire. The number of items has been reduced to a SADT-asthma (SADT-a) questionnaire and key patient and disease characteristics for it to be feasible and implementable in clinical practice. Although there are many similarities between asthma and COPD, there might be differences in clinical characteristics and responses to small airways dysfunction between the two diseases.

The current study aims to adapt the original 63-item SADT questionnaire for dedicated use in COPD by reducing the number of items, and identifying COPD-SAD-specific items, to enhance its efficiency in identifying SAD when combined with key patient and disease characteristics in individuals with COPD (SADT-c). In addition, a comparison of diagnostic accuracy of spirometry and oscillometry will be made by interpretations by a panel of experts to provide a triage diagnosis. The previously developed machine learning AC/DC tool will be used to explore its diagnostic accuracy using oscillometry and spirometry results. This can contribute to standardizing oscillometry in clinical practice.

Objective:

Objectives	Endpoints
Primary	
1. To determine whether SADT-c can be used in patients with COPD to detect SAD.	The predictive value of SADT-c for detecting SAD in patients with COPD.
Secondary	
2. To determine whether the bronze model SADT-a is predictive for SAD in COPD.	Predictive value of SADT-a bronze model for SAD in COPD.
3. To develop SADT-c.	Agreement between SADT-c results and disease parameters. Content validity and reliability.
4. To evaluate how SADT-c compares to SADT-a.	Relative predictive value of SADT-a versus SADT-c for SAD in COPD defined as R5–R20 > ULN[1].
5. To determine whether oscillometry and spirometry are equally effective for triage	Agreement between triage diagnoses from oscillometry and spirometry. Relative usability of spirometry and oscillometry.

diagnosis in patients in primary care with respiratory symptoms.	
Exploratory	
Assess the diagnostic performance of the Asthma/COPD Differentiation Classification (AC/DC) Tool.	Diagnostic performance of AC/DC tool compared to expert panel diagnosis.

Study design: The study will take place in the Netherlands and aims to include 200 participants, targeting 50 with pre-existing COPD and 150 without diagnosis of which approximately 50 will be newly diagnosed with COPD. Participants, attending for usual or diagnostic care, will undergo an oscillometry test and complete a SADT-c questionnaire. The spirometry and oscillometry reports will be reviewed by a panel of experts (3-5 pulmonologists). In addition, 10-15 participants with COPD and SAD will be interviewed to assess if additional SADT-c questions are needed and to assess how participants process information to comprehend and respond to the question. If additional SADT-c questions are required, the questionnaire will be amended and completed by the same participants with COPD.

Study population: The study population will consist of patients referred by their General Practitioner (GP) when they are suspected to have asthma, COPD, asthma-COPD overlap (ACO) or when they present with pulmonary symptoms of unknown origin. Both patients invited for an initial diagnostic visit or a control visit can participate in the study.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participating in the SCOOP-study has minimal risks as it includes standard procedures, a non-invasive test, and a questionnaire. The study aims to assess if SADT-c can identify SAD in patients with COPD like SADT-a does in patients with asthma. It will conclude the test's suitability for COPD. Oscillometry, taking 45-60 seconds, could lessen the diagnostic burden and increase the access to lung function testing in primary care if proven equally effective.

1. INTRODUCTION AND RATIONALE

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of mortality and morbidity, imposing a high economic and social burden worldwide[2]. It is characterized by obstructed airways and significant inflammatory process. This inflammation affects the entire respiratory tract, from the central to the peripheral airways that are less than 2mm in internal diameter, also known as the small airways[3]. The small airways can be affected by inflammation, remodeling, and changes in the surrounding tissue, all of which contribute to small-airways dysfunction. Small Airways Dysfunction (SAD) is the major site of obstruction in many respiratory diseases, including COPD[4,5].

SAD is a widely recognized feature of COPD that extensively contributes to irreversible airway obstruction and findings from ex vivo studies showed that loss of small airways precedes emphysema[6]. Moreover, in patients with COPD, SAD may increase lung hyperinflation and lead to clinical deterioration of health status. The small airways are a central treatment target, especially in patients with COPD[7]. Patients with SAD may benefit from treatment with extra-fine inhaled corticosteroids (ICS), with or without a long-acting β-agonist (LABA), which has been shown to improve lung function, airway responsiveness, symptoms, and exacerbation rates. Hence, more insight into a diagnosis of SAD in patients with COPD is clinically valuable as it might enable tailored pharmacotherapy[8].

Currently, methods to diagnose SAD in COPD are not standardized and are not available in routine clinical practice[9]. The Small Airways Dysfunction Tool (SADT) was developed for patients with asthma as part of the ATLANTIS study, which utilized interviews, focus groups, and theories from research on patients with asthma, both with and without SAD[10]. Initially, the SADT included a comprehensive 63-item questionnaire, with items both suggestive (to include) and not suggestive for SAD (to exclude). After predictive modeling, and to be feasible and implementable in clinical practice, the number of items has been reduced to a SADT-a questionnaire[8].

The SADT-a predicts SAD in patients with asthma using a single criterion – wheezing at rest – along with certain basic patient characteristics, such as age, sex, age at diagnosis, and Body Mass Index (BMI); this is the bronze model (area under receiver operation characteristic curve (AUC) 0.74 and positive likelihood ratio (LR+) 2.3). Its ability to accurately identify SAD in asthma is greatly enhanced with the use of spirometry, which evaluates lung function by measuring air volume and flow during breathing; this represents the silver model (AUC 0.87, LR+ 5.0). The results from spirometry primarily include the FEV_1 % predicted. The diagnostic precision further improves with the incorporation of oscillometry, marking the gold model (AUC 0.96, LR+ 12.8). This technique assesses lung function by measuring airflow resistance and includes parameters like the resistance difference between 5 and 20 Hz (R5-R20) and reactance area (AX)[8].

The current study aims to adapt the original 63-item SADT questionnaire for dedicated use in COPD by reducing the number of items and enhance its efficiency in identifying SAD in individuals with COPD (the SADT-c). This process will follow the approach previously used for asthma[8]. We will assess the predictive value of SADT-c. Additionally, we will determine whether the bronze model of SADT-a is similarly predictive for SAD in COPD as is the bronze model of SADT-c.

Since oscillometry is not standardized in clinical practice, and the access and quality of spirometry is low[11], it would be of great value to determine whether oscillometry and spirometry are equally effective in the diagnostic work-up of respiratory symptomatic patients in primary care. Spirometry requires collaboration of the patient to perform a forced expiratory maneuver and well-trained

staff[12], whereas oscillometry is easy to perform as no training and limited effort of the patient is required (45 seconds of tidal breathing) and limited training of the staff[13]. In order to compare the effectiveness of spirometry and oscillometry, spirometry and oscillometry measurement will be interpreted by a panel of experts to provide a triage diagnosis. The previously developed machine learning AC/DC tool will be used to explore its diagnostic accuracy using oscillometry and spirometry results[14].

2. OBJECTIVES

Primary Objective:

1. To determine whether SADT-c can be used in patients with COPD to detect SAD.

Secondary Objectives:

2. To determine whether the bronze model SADT-a is predictive for SAD in COPD.
3. To develop SADT-c.
4. To evaluate how SADT-c compares to SADT-a.
5. To determine whether oscillometry and spirometry are equally effective for triage diagnosis in patients in primary care with respiratory symptoms.

Exploratory Objective:

Assess the diagnostic performance of the Asthma/COPD Differentiation Classification (AC/DC) Tool.

3. STUDY DESIGN

The SCOOP-study will be executed in the Netherlands. The study consists of one visit during which all data will be collected. The aim is to include 200 participants in total. Of the 200 patients that will be seen for a visit, approximately 50 participants with previously diagnosed Chronic Obstructive Pulmonary Disease (COPD) and 150 participants without any diagnosis at the time of the visit will be invited. This should result in a total of 200 participants of which 100 are diagnosed with COPD: 50 with a pre-existing diagnosis and 50 newly diagnosed. An overview of the study flow is presented in figure 1.

Participants will visit the site for their usual care, which can be either a follow-up visit for those with an existing COPD diagnosis or a diagnostic visit. In addition to their usual care participants of the study will be asked to complete an oscillometry measurement and a Small Airway Dysfunction Tool for COPD (SADT-c) questionnaire. A panel of international experts will then review the oscillometry and spirometry reports of all 200 participants. Each report will be assessed by 3 to 5 independent pulmonologists in a randomized order. Finally, the triage diagnoses derived from oscillometry and spirometry assessments will be compared. The answers to the SADt-questionnaire items will be compared to the patients' respective SAD status to determine predictive value of SADT-c. Furthermore, ten to fifteen patients with COPD and SAD will be asked to participate in a cognitive interview to assess patient comprehension and necessity of additional questions. In case these are required, 100 COPD patients will be asked to complete the amended questionnaire.

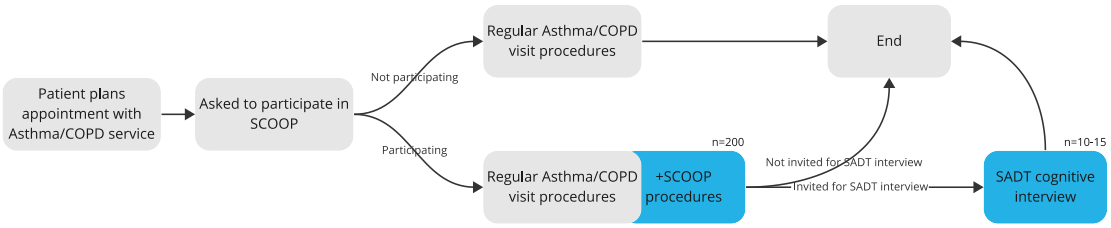

Figure 1: Study flow for patients

4. STUDY POPULATION

4.1 Population (base)

The study population for the SCOOP study will consist of patients referred by their General Practitioner (GP) to the Asthma/COPD service. Patients can be referred by their GP when they are suspected to have asthma, Chronic Obstructive Pulmonary Disease (COPD), asthma-COPD overlap (ACO) or when they present with pulmonary symptoms of unknown origin. After referral by the GP, patients will be invited by the Asthma/COPD service. Both patients invited for an initial diagnostic visit or a control visit can participate in the SCOOP study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- ≥35 years or older
- Suspected of having COPD, asthma or ACO as indicated by the referring GP
  OR a previous diagnosis of COPD

4.3 Exclusion criteria

A potential participant who meets the following criterium will be excluded from participation in this study:

- Inability to understand and sign the written informed consent form.

4.4 Sample size calculation

To determine whether Small Airway Dysfunction Tool for COPD (SADT-c) can be used in patients with COPD to detect Small Airways Disease (SAD) a prediction model will be used. To estimate the required sample size for a prediction study, a well-known rule of thumb is to ensure at least 10 events for each predictor parameter.

Previous studies indicated a prevalence of SAD in patients with COPD ranging from 74%[15] to 83%[16]. The final prediction model previously developed for patients with asthma included four variables in the bronze model and 7 variables in the gold model[8]. Therefore, we assume that we will have enough statistical power when we include 100 patients diagnosed with COPD in the current study.

5. SCOOP procedures

The SCOOP study will be integrated in the visits of the Asthma/COPD service for primary care at the study sites. General Practitioners (GPs) can refer individual patients (≥18 years of age) who are suspected to have obstructive airway disease (OAD) such as asthma, Chronic Obstructive Pulmonary Disease (COPD), asthma-COPD overlap (ACO) or present with pulmonary symptoms of unknown origin[17]. Visits can be for initial diagnosis of the OAD or for (yearly) follow-up of the disease.

In preparation for the regular asthma/COPD service visit the patient will receive questionnaires to complete, i.e.: the Asthma Control Questionnaire (ACQ), the Clinical COPD Questionnaire (CCQ) and a medical history questionnaire assessing gender, age, age of onset, family history, symptoms, exacerbations (oral corticosteroids or antibiotics use), allergy and other stimuli-provoking symptoms, medication, occupation, and smoking history.

During the visit the patient is assessed by a trained lung function technician. The following measurements are collected: Body mass index (BMI), evaluation and if needed instruction of inhalation technique (according to the Dutch Inhalation Medication Instruction School guidelines), spirometry (according to international guidelines).

Besides the regular assessments, the following assessments will be added for the SCOOP-study:

5.1 Small Airways Dysfunction Tool (SADT) questionnaire

The SADT questionnaire was developed for patients with asthma and consist of 63 items. SADT items were scored on a 3-point scale (no, yes, unknown)[10]. The items reflect specific signs and symptoms which could be suggestive for Small Airways Dysfunction (SAD) or could reflect signs and symptoms that are suggestive for less SAD.

A shorter version of the SADT for asthma with items more tailored to COPD patients will be devised as a part of study. Input from the scientific advisory board (in part the steering committee of the ATLANTIS study[18].) and patient interviews (described in chapter 5.4) will be used. The SADT for COPD (SADT-c) will contain approximately 15 questions.

5.2 Oscillometry

Oscillometry is a non-invasive technique for assessing lung function, as it requires only 45-60 seconds of tidal breathing to measure the mechanical properties of the respiratory system. This makes the measurement suitable for patients of all ages and with severe respiratory conditions. It also reduces the number of errors as compared to other methods (e.g., spirometry). Oscillometry can be used to evaluate airway resistance, reactance, and compliance, insights that are challenging to obtain with other methods. This quality makes oscillometry especially sensitive for obstructive diseases like asthma and COPD, and correlations with physiological small airways dysfunction have also been shown[8,18,19].

The Ambulatory Lung Diagnosis System (ALDS), manufactured by Lothar MedTec, can be used to perform oscillometry and spirometry (Figure 2). The ALDS follows the European Respiratory Society (ERS) technical standards for measurement and reporting of oscillometry.

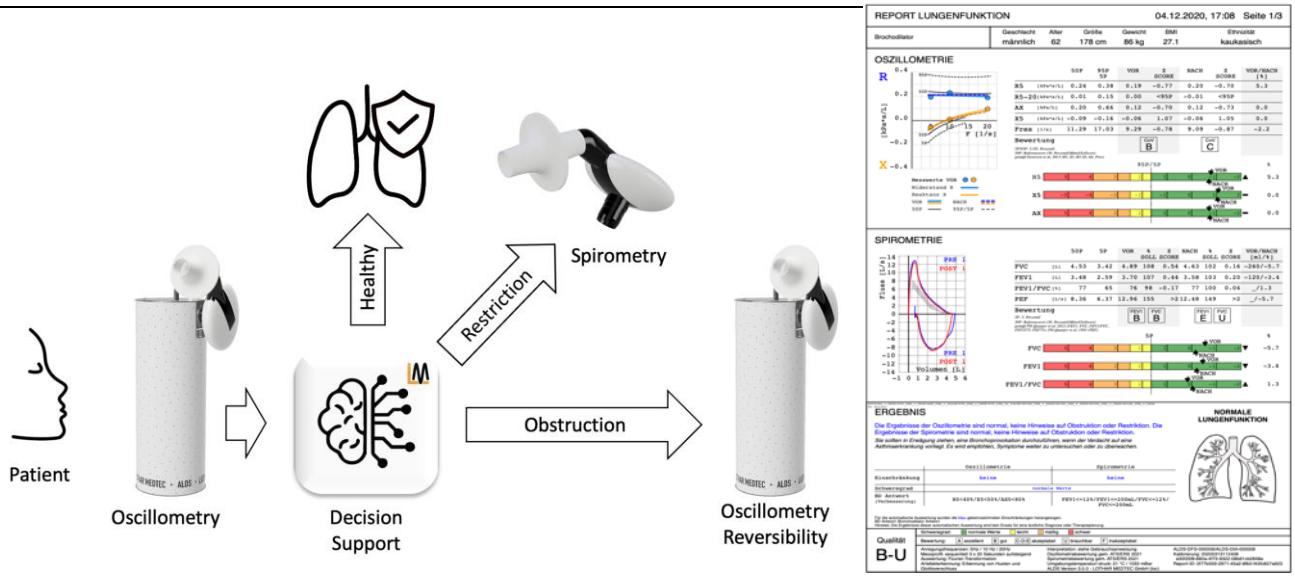

Figure 2. Oscillometry and spirometry performed with the ALDS system. A) Schematic overview of oscillometry process and decision support by the ALDS. B) Example of a report generated by the ALDS.

The measurement is performed using approximately 45-60 seconds of tidal breathing. Three measurements of 15 seconds will be performed, during which the patient will calmly breathe in and out while wearing a nose clip. This requires no specific training or effort from patients. The healthcare professional (HCP) can be trained within 15 minutes on how to perform the measurement and the requirements for accurate measurement. The ALDS has built-in quality control measures and provides feedback if quality is not sufficient.

Reversibility testing can also be conducted using the ALDS device, in addition to standard oscillometry measurements.

5.3 Additional AC/DC questions

The Asthma/COPD Differentiation Classification (AC/DC) tool is a machine learning algorithm for the differential diagnosis of asthma or COPD based on 12 variables. Except for two of the twelve variables, all information is already available in the data standard collected by the study sites. Two additional questions will be collected to be able to run the AC/DC algorithm. Namely:

1. Diagnosis of allergic rhinitis
2. Diagnosis of chronic rhinitis

5.4 Cognitive interviewing

The aim of cognitive interviewing is to assess how participants process information to comprehend, respond to the questions and to determine whether new items are needed to complete the SADT-c.

A total of ten to fifteen patients with COPD and SAD who are native Dutch speakers will be invited to participate in cognitive interviews about the SADT-c with a clinician. Patients are to be representative of the real-world population of patients with COPD as much as possible.
The interviewer will report the answers anonymously and will discuss the results of the interviews in a meeting with a member of the GPRI team.

The followings steps will be followed to conduct a cognitive interview:

1. The clinician will present a form with the patient-reported version of the questions under study to the patient and will ask the patient to read it and answer the question. The clinician will record the answer.
2. The clinician will ask the scripted questions.
3. The clinician will investigate whether there are additional items that could describe SAD.
4. The clinician will also report all other issues / comments that were raised during the interview.

The following scripted questions will be asked:

- In your own words, what do you think this question is asking?
- Was this question easy to understand? Are there any specific words that are difficult to understand?
- Was there anything else about the question that was unclear to you?
- Suppose you would be talking with others about /question/, which word or phrase would you use?
- Is there anything else you would like to share about this question?

6. METHODS

6.1 Study endpoints

6.1.1 Main study endpoint

The primary endpoint is the predictive value of SADT-c for detecting SAD in patients with COPD.

Required variables:

- Diagnosis of Asthma/COPD service
- SAD status defined as R5–R20 > upper limit of normal (ULN)[1]
- SADT question results
- Patient characteristics
    - Age
    - Sex
    - Height
    - Body Mass Index (BMI)
    - Age at diagnosis
- Oscillometry and spirometry results

6.1.2 Secondary study endpoints

The secondary endpoints are:

1. Predictive value of SADT-a bronze model for SAD in COPD.
2. Agreement between SADT-c results and disease parameters.
3. Content validity and reliability.
4. Relative predictive value of SADT-a versus SADT-c for SAD in COPD defined as R5–R20 > ULN[1]
5. Agreement between triage diagnoses from oscillometry and spirometry.
6. Relative usability of spirometry and oscillometry.

Required variables:

1.
    - Triage diagnosis of Asthma/COPD service
    - SAD status based on oscillometry test (R5-R20)
    - SADT question 8
    - Patient characteristics (bronze model)
        - Age
        - Sex
        - Height
        - Body Mass Index (BMI)
        - Age at diagnosis
2.
    - Triage diagnosis by Asthma/COPD service
    - SAD status based on oscillometry test (R5-R20)
    - Lung function results

- Asthma/COPD service collected questionnaires and patient characteristics (as described in chapter 5)
- SADT-c variables
- Patient characteristics bronze model

3.
- Cognitive interviews
- SADT-c results

4.
- Predictive value SADT-a different models
- Predictive value SADT-c different models

5.
- Panel expert diagnoses (spirometry)
- Panel expert diagnoses (oscillometry)
- Patient characteristics
- Difficulty to diagnose (scale)

6.
- Operator opinion
- Expert interpreter opinion
- Duration of measurement
- Patient burden

6.1.3 Exploratory study endpoints

Diagnostic performance of AC/DC tool compared to expert panel diagnosis.

Required variables:

- AC/DC tool
- FEV1
- FEV1/FVC
- Smoking pack-year
- Age at onset of respiratory disease
- Body mass index
- Dyspnea
- Wheeze
- Cough
- Diagnosis of allergic rhinitis
- Current smoker
- Never smoked
- Diagnosis of chronic rhinitis

6.2 Study procedures

Participants will be invited by the study site for a diagnostic or control visit to perform a lung function test. Together with the invitation for this visit, information about the SCOOP study is sent. The recipient will have the option to make their interest or disinterest in the study known before their visit (but this is not required). The study flow is presented in document E3.

During the regular diagnostic or control visit participants that did not reply to the initial information and participants that have shared their interest will be further informed about the SCOOP study and asked whether they would like to participate. In case a person does not want to participate in the study, the Asthma/COPD visit will continue as usual. In case a person does want to participate in the study, the study activities will be added to the regular visit.

After signing informed consent, the visit will include a (pre-)oscillometry measurement followed by a (pre-)spirometry measurement. In case of a diagnostic visit the participant will use Salbutamol followed by a post-oscillometry and post-spirometry measurement after a 15-minute wait time. During the wait time, or after the measurements in case of a control visit, the participant is asked to fill in the SADT-c questionnaire and two additional study questions.

10-15 participants with a triage diagnosis of COPD and SAD status defined as R5–R20 > ULN will be invited for a cognitive interview regarding the new SADT-c questionnaire. Purposeful sampling will be used, to have a widespread of patient characteristics. If new items are added to the SADT-c questionnaire as a result of the cognitive interviews, 100 COPD patients that had previously completed the SADT-c questionnaire will be asked to complete the updated questionnaire.

6.3 Determining the triage diagnosis using spirometry and oscillometry

To evaluate the spirometry and oscillometry results, a panel of ten experts on spirometry and oscillometry will review the pseudo-anonymized information from medical history, questionnaires and the respective lung function measurement. For each participant, three panel members (randomized) will initially review either the spirometry or the oscillometry reports, along with the medical history and questionnaires. After a minimum of four weeks, the same three panel members will review the remaining report (spirometry or oscillometry) for the same participant. The sequence of report delivery will be randomized to prevent panel members from recalling specific cases. This review flow is depicted in Figure 3.

Each of the 3 experts will individually determine a triage diagnosis for each patient. In addition, the expert will record the difficulty of diagnosis on a 6-point Likert scale from 0 to 5, in which 0 to 1 indicates easy to diagnose and 4 to 5 indicates hard to diagnose. In case only 2 out of 3 triage diagnoses are the same, the case will be reviewed by two additional experts. In case all triage diagnoses are different, the case will continue without additional review. In the statistical analysis those disagreements will be taken into account.

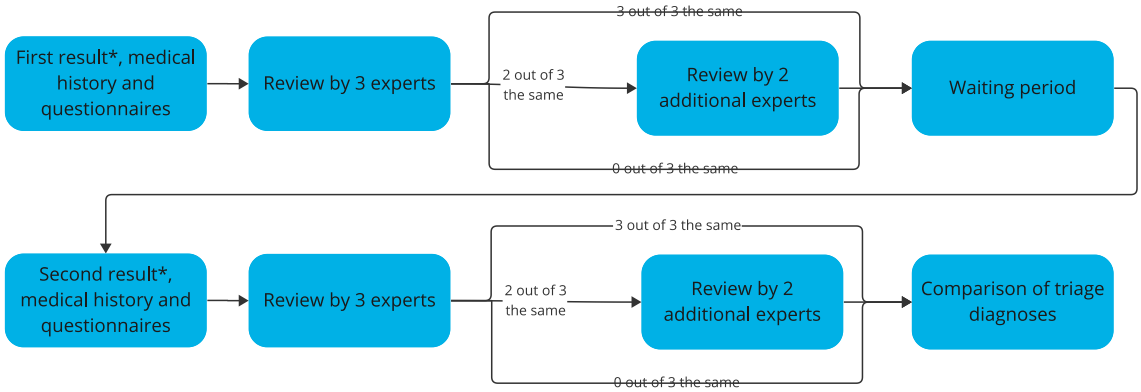

*Figure 3. Flow of spirometry and oscillometry assessments by expert panel. * The result can be either a spirometry or oscillometry measurement. The order will be randomly determined.*

6.4 Withdrawal of individual participants

Participants can leave the study at any time for any reason if they wish to do so without any consequences.

6.5 Replacement of individual subjects after withdrawal

Participants that left the study will not be replaced.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of participant safety

In accordance with section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participants health or safety. The sponsor will notify the accredited METC (Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)) without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all participants are kept informed.

7.2 AEs and SAEs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study visit, whether or not considered related to trial procedure. Only adverse events during the visit will be considered and reported as (serious) adverse events.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

Only SAEs occurring during or directly after the visit will be considered and reported as SAEs.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

- Events related to the indication of the Asthma/COPD consultation and not related to the SCOOP procedures performed during the visit, as interpreted by the investigator.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported in line listings after study closure.

8. STATISTICAL ANALYSIS

The statistical analysis plan will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section serves as a summary of the planned statistical analysis and the most important endpoints.

8.1 Primary study parameter(s)

The primary endpoint is the predictive value of SADT-c for SAD in COPD. The statistical hypothesis for the primary objective is that the predictive value of SADT-c is above the lower limit of the confidence interval of predictive value of SADT-a (AUC 0.74, LR+ 2.3 for the SADT-a bronze model). The hypothesis will be tested at a 2-sided significance level of 0.05.

For the analysis of this primary endpoint, the following population is defined:

- All participants that have a prior or novel COPD (triage) diagnosis, and
- Do not have an asthma, asthma-COPD overlap syndrome, missing or other diagnosis, and
- Have filled in the SADT-c questionnaire.

The presence of SAD will be based on oscillometry results. A resistance difference between 5 and 20 Hz (R5-R20) cutoff of 0.07 kPa x s x L^{-1} will be used to define the presence of SAD[15].

Analysis will be performed as done earlier for the development of SADT for asthma[8]. In short, to assess the predictive value of SADT-c we first will select the most important SADT items (secondary study parameter). Regression analysis will be used to select SADT items that show a relation with SAD in the expected direction based on the content validity of the items. In a next step the most important SADT items for SAD group will be selected by using logistic regression models. Prediction models using bootstrapping resampling will be used. In addition to the individual SADT items, also patient characteristics, such as age, sex, and height, BMI, will be considered as independent predictors in the model.

Selected key SADT items will be used together with available clinical information to build logistic regression models to predict the SAD group. Three levels of clinical information will be considered resulting in three regression models:

- Bronze: Basic patient characteristics (such as age, sex, age at diagnosis, BMI, or other)
- Silver: Spirometry test results (FEV_1 % predicted)
- Gold: Oscillometry test results (R5-R20 and reactance area (AX)).

For each model the area under the receiver operating characteristic curve (AUC), positive likelihood ratio (LR+) and sensitivity and specificity will be calculated, using a probability cut-off of 0.5 to indicate predicted SAD.

8.2 Secondary study parameter(s)

SADT-c

To determine whether bronze model SADT-a is predictive for SAD in COPD, the steps described in section 8.1 will be followed. The AUC, LR+ and sensitivity and specificity will be calculated and reported.

To assess the agreement between SADT-c and disease parameters, the steps described in section 8.1 will be reported. Logistic regression analysis results will be reported.

To assess the content validity and reliability of the SADT-c, 10-15 patients with COPD and SAD will be invited for a cognitive interview. Results will be presented in a descriptive way.

To evaluate how SADT-c and SADT-a compare in detecting SAD in COPD the predictive values of the various SADT-c and SADT-a models will be compared.

In case the SADT-c has a significantly reduced predictive value as compared to the SADT-a, new items derived from the cognitive interviews will be added, if any. The amended questionnaire will subsequently be reinvestigated using the same protocol, in the same population (ie. 100 patients with COPD participating in the SCOOP study).

Oscillometry vs spirometry

To assess the agreement between oscillometry and spirometry, triage diagnoses as determined by the expert panel will be compared. Cohen's kappa or comparable statistics will be used to compare the outcomes. Additional analysis will be done adjusted for difficulty of diagnosis and the agreement between panel members. In addition, subgroup analysis will be performed based on the level of agreement between panel members.

8.3 Other study parameters

To assess the diagnostic performance of AC/DC tool, the diagnoses based on the tool will be compared to the diagnoses given by the expert panel. Results will be compared using logistic regression analysis.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted in accordance with the principles of the declaration of Helsinki (version October 2013).

9.2 Recruitment and consent

The informed consent process will follow the principles outlined in the current version of the Declaration of Helsinki.

Prior to the visit, when the Asthma-COPD service sends the initial invite to patients, potentially eligible participants will be invited by the study sites through an information leaflet (document "E3. Flyer"). It will be made clear that the study is not part of the Asthma-COPD service regular care and that choosing to participate (or not) will not influence the patient's care. The information leaflet specifies different ways in which participants can obtain additional information, ask questions, or indicate their interest in participating the study.

The Healthcare Professional (HCP) from the Asthma/COPD service will explain the nature of the study with the participant after they have shown interest in participating. Participants will then receive either a digital or hard copy of the Patient Information Sheet and Informed Consent Form (ICF) (Document E1/2. ICF). Participants must be informed that their participation is voluntary, and they are free to refuse participation and may withdraw their consent at any point during without any consequences.

Before signing, participants will have the opportunity to ask any questions they might have. Upon satisfactory clarification of all questions, participants will be given the option to sign the ICF. The signing will be done in person at the study site by both the participant and the HCP. Following the signing process, one copy of the ICF will be kept at the site in line with Good Clinical Practice (GCP) standards, and the other copy will be given to the participant.

9.3 Benefits and risks assessment, group relatedness

The risks associated with participating the SCOOP-study are negligible because besides the usual procedures at the Asthma/COPD service, the study concerns a non-invasive test and questionnaire.

The overall aim of the study is to evaluate whether the SADT-c can be used to determine SAD in patients with COPD, similarly to how the SADT-a is used in patients with asthma. The analyses at the end of the study will conclude its applicability for patients with COPD.

Additionally, oscillometry is a non-invasive technique that requires only 45-60 seconds of tidal breathing. Should the results demonstrate equivalent effectiveness in the diagnostic work-up of respiratory symptoms, patients in primary care might experience a reduced burden during diagnostic testing in the future.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data handling and storage will comply with the General Data Protection Regulation (GDRP). The investigator will ensure protection of participant's personal data in compliance with the Personal

Data Protection Act and that all reports, publications, and any other study disclosures do not reveal the identity of the participant, except where required by laws. Participants are identified only by a participant identification number or site identification number to maintain participant confidentiality. All participant study records will be kept safely in an access-controlled area. Identification code lists linking participant names to participant identification numbers will be stored separate from participant records. In case of data transfer, the sponsor or its representative will maintain high standards of confidentiality and protection of participant personal data. Clinical information will not be released without the written permission of the participant, except for monitoring by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.2 Public disclosure and publication policy

Findings of the study will be presented as an abstract at (inter)national conferences and published. In our publications, the identity of the patients will not be disclosed in any way.

11. REFERENCES

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