"Breathlessness diagnostics in a Box" for primary care. A multi-country Quality Improvement Project using a randomized Stepped-wedge design

SHORT TITLE: Breathlessness diagnostics in a Box (BiaB)

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Coordinating investigator	Yoran Gerritsma Researcher General Practitioners Research Institute (GPRI) yoran@gpri.nl / breathlessness@gpri.nl
Product Owner	Marika Leving, PhD marika@gpri.nl
Principal investigator	Prof. J.W.H. Kocks, MD, PhD General practitioner Professor of Inhalation Medicine (OPRI institute, Singapore) Director of General Practitioners Research Institute (GPRI) janwillem@gpri.nl
Sponsor	General Practitioners Research Institute (GPRI)
Subsidising party	AstraZeneca Netherlands B.V.
Scientific Advisory Board	Prof. Ana María Cebrián-Cuenca (GP, Spain) Dr. Fiona Mosgrove (GP, UK) Prof. Rudolf de Boer (Cardiologist, the Netherlands) Prof. Chris Gale (Cardiologist, UK) Dr. Bernardino Alcázar-Navarrete (Pulmonologist, Spain) Prof. Huib Kerstjens (Pulmonologist, the Netherlands) Dr. Richard Russel (Pulmonologist, UK)

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor representative Jiska Meijer, MD, PhD General practitioner Director of General Practitioners Research Institute (GPRI)	 Jiska Meijer (Nov 8, 2024 08:57 GMT+1)	
Principal Investigator J.W.H. Kocks, MD, PhD General practitioner Director of General Practitioners Research Institute (GPRI)	 Janwillem Kocks (Nov 8, 2024 10:25 GMT+1)	8-Nov-2024
Coordinating Investigator Yoran Gerritsma Researcher General Practitioners Research Institute (GPRI)	 Yoran Gerritsma (Nov 6, 2024 12:59 GMT+1)	06-Nov-2024

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
ALDS	Ambulatory Lung Diagnosis System
BiaB	Breathlessness diagnostics in a Box
BiaB-algorithm	Breathlessness diagnostics in a Box algorithm, algorithm that forms part of the BiaB-app, contains a decision tree that combines all test results to a clinical interpretation for the BiaB report
BiaB-app	Breathlessness diagnostics in a Box app, software that is part of BiaB which guides the healthcare professional through the steps needed to complete the diagnostic procedures and provides the BiaB report
BiaB-box	Breathlessness diagnostics in a Box box, the yellow box containing all tests and equipment needed to perform the tests and interpretation
BiaB-procedure	Breathlessness diagnostics in a Box procedure, the process of conducting the individual tests in the BiaB-box, using the BiaB-app and receiving the BiaB-report by healthcare professionals
BiaB-report	Breathlessness diagnostics in a Box report, the report that is generated based on the tests performed as part of the BiaB procedure
BNP	B-type Natriuretic Peptide
COPD	Chronic Obstructive Pulmonary Disease
CONSORT	Consolidated Standards of Reporting Trials

CTPA	Computed Tomography (CT) Pulmonary Angiogram, a medical diagnostic test to obtain an image of the pulmonary arteries
CVD	Cardiovascular Disease
ECG	Electrocardiogram
eCRG	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-5L	EuroQol 5-Dimension 5-Level, standard layout for recording an adult person's current self-reported health state, consists of a standard format for respondents to record their health state according to the EQ-5D-5L descriptive system and the EQ VAS
ERS	European Respiratory Society
GDPR	General Data Protection Regulation
GP	General Practitioner
GPRI	General Practitioners Research Institute
ICF	Informed Consent Form
IRB	Institutional Review Board
HF	Heart Failure
HCP	Healthcare Professional
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
PE	Pumonary Embolism

PHQ-4	Patient Health Questionnaire
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SpO2	Peripheral oxygen saturation
SWGRT	Stepped-Wedge Group-Randomized Trial
VTE	Venous thromboembolism
WMO	Medical Research Involving Subjects Act
WPAI	Work Productivity and Activity Impairment questionnaire

SUMMARY

Rationale: Breathlessness has a prevalence of ~10% and is a common reason for people to consult their general practitioner. As breathlessness is a symptom in various conditions it is difficult to determine its cause, which hampers optimal treatment. There is a lack of quick and easy tests that can be used in primary care to diagnose the cause of breathlessness. Therefore, we have developed "Breathlessness diagnostics in a Box (BiaB)", an easy and reliable tool intended to support healthcare professionals with fast execution of diagnostic procedures required to diagnose the cause(s) of breathlessness. In 2023 a pilot study was performed to design and test BiaB. In the current study, we aim to investigate whether implementation of BiaB in primary care will shorten the time for the diagnostic process for patients presenting with breathlessness.

Objectives:

Objectives	Endpoints
Primary	
1. To demonstrate whether BiaB use shortens time to diagnosis as compared to usual care without BiaB use.	Days between presentation with or consultation for breathlessness and a diagnosis causing the breathlessness (usual care group versus BiaB intervention group)
Secondary	
2. To demonstrate whether BiaB use increases the number of new diagnoses of COPD and heart disease as compared to usual care without BiaB use.	Number of newly diagnosed patients with COPD and heart disease (usual care group versus BiaB intervention group)
3. To demonstrate usability and efficiency of BiaB.	Frequency of use of: • BiaB • Lung function tests • ECG measurements Frequency of: • Referral to specialist (and type) • Acute hospital admission • Emergency room visits

	Clinical outcomes Economic analysis Qualitative evaluation of the implementation of BiaB

Study design: In this study the implementation of BiaB in primary care will be evaluated. A total of 45 practices (900 patients) will be included in the Netherlands, Spain, and Portugal, with the option to expand to other countries. A stepped-wedge study design will be used with a randomised timing of BiaB implementation in general practices. The design includes a control period of 6-30 weeks, a transition period of 4 weeks, and a BiaB period of 3-30 weeks. Each practice will actively participate in the study for 40 weeks.

Study population:

1. Patients with undiagnosed dyspnea (breathlessness)
2. Patients who have existing diseases that could cause breathlessness but have residual or increasing breathlessness that could be caused by other not yet detected diseases. Or HCP has doubts or requires additional tests to confirm diagnosis or to suspect new, parallel, diagnoses. For example, breathlessness in patients assessed:
    a. within the framework of Cardiovascular Risk Management
    b. for COPD monitoring

Patients with acute worsening of previous diagnosed chronic disease where there is no suspicion of comorbidities (for example when a patient with clear COPD diagnosis has an exacerbation where typically the HCP will not perform additional tests) will be excluded from the study.

Intervention: All general practices will start with a control period, during which healthcare professionals will obtain consent from eligible participants to collect data and perform consultations as usual. At a certain timepoint, defined by randomisation, they will be assigned to use BiaB. From this moment on, visiting patients that meet inclusion criteria will be asked to partake in the study. After consent, healthcare professionals will use BiaB during patient

consultations/diagnostic workup. The BiaB-box contains questionnaires (YEARS, PHQ-4), point of care tests (NT-proBNP, D-dimer, pulse oximeter), an oscillometer and an ECG device. The BiaB-App will guide the healthcare professional (clinician, nurse, practice assistant) through the steps of diagnostic procedures within the BiaB-box. The BiaB-algorithm, developed by the GPRI team in collaboration with the international scientific advisory board, uses input from these tests to support the healthcare professional with interpretation of test results and generates the BiaB-report.

Ethical considerations and extent of the burden: Study specific involvement for patients presenting with breathlessness is limited to one visit for the patient and four follow-up questionnaires. The patients will receive medical care as determined by their physician. The BiaB-box contains non- and minimally invasive tests, limited to questionnaires, oscillometry which requires tidal breathing, an ECG and a finger stick point of care test. This test might cause a slight inconvenience for the patient but the risks of participating in the study are deemed to be negligible. Follow-up data will be collected by healthcare professional reported outcomes and patient reported outcomes in the form of short questionnaires up to one year for the patients.

1. INTRODUCTION

Breathlessness is a common reason for people to consult their healthcare professional (HCP) and can have various causes, including psychological factors. However, in most cases, the origin is pulmonary or cardiovascular.[1] HCPs (e.g., general practitioner, practice assistant, practice nurse, clinician) often find it challenging to distinguish between different causes of breathlessness because distinguishing dyspnea causes in primary care is hard with limited diagnostics. Referral to secondary care may be needed if the cause is unclear or initial treatment fails. A Danish study conducted in a hospital dyspnea clinic found that the initial diagnosis made by the HCP was correct in only 31% of patients referred to cardiologists and in 58% of patients referred to pulmonologists. This discrepancy may lead to delays in correct diagnosis and proper treatment. Moreover, there is considerable overlap between both causes of breathlessness, which requires an integrated approach. The Danish study revealed that heart failure was the sole cause in 17% of cases, pulmonary disease in 35%, and combined heart and lung disease in 14% of 284 patients examined.[2]

In a large study of a middle-aged Swedish population, the primary conditions contributing to breathlessness included respiratory disease, anxiety or depression, obesity, and heart disease or chest pain, with a high level of overlap (Figure 1).[3] Notably, 66% of the examined participants (n=1097) had two or more of these conditions.

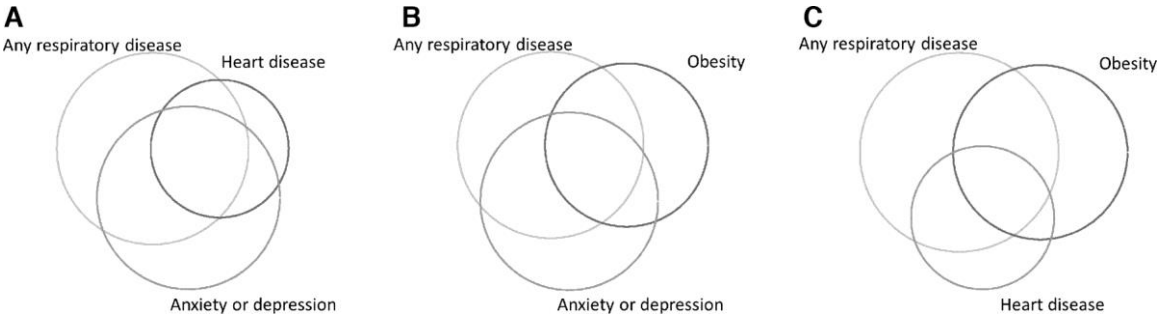

Figure 1. Overlap of underlying contributing conditions to breathlessness

Investigations into patients presenting with breathlessness in general practice often lack a structured approach and clear guidance. A study using a large UK electronic medical database, which analysed adults presenting with breathlessness, revealed that haemoglobin testing was

conducted in 69% of patients, though anaemia was diagnosed in only 5% of cases. Moreover, after two years, most patients (57%) still had no relevant diagnosis recorded.[4]

A Dutch study assessing the efficiency of integrated care provided by both a cardiologist and a pulmonologist found that patients received diagnoses nearly one month earlier than through consultations with non-integrated specialists. [1]

A recent literature review on incorporating clinical tools into a clinical decision support system for primary care, aimed at efficiently and accurately diagnosing chronic dyspnea, suggested a staged approach to testing. Initially, after history taking and physical examination, simple tests such as spirometry, pulse oximetry (SpO_2), and electrocardiography (ECG) should be performed.[5] If the diagnosis remains uncertain, the next step involves additional tests, including chest X-ray, full blood count, thyroid function tests, and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP test). Patients who remain undiagnosed are then referred for advanced testing, such as thoracic CT scans or echocardiograms (Figure 2).3[5]

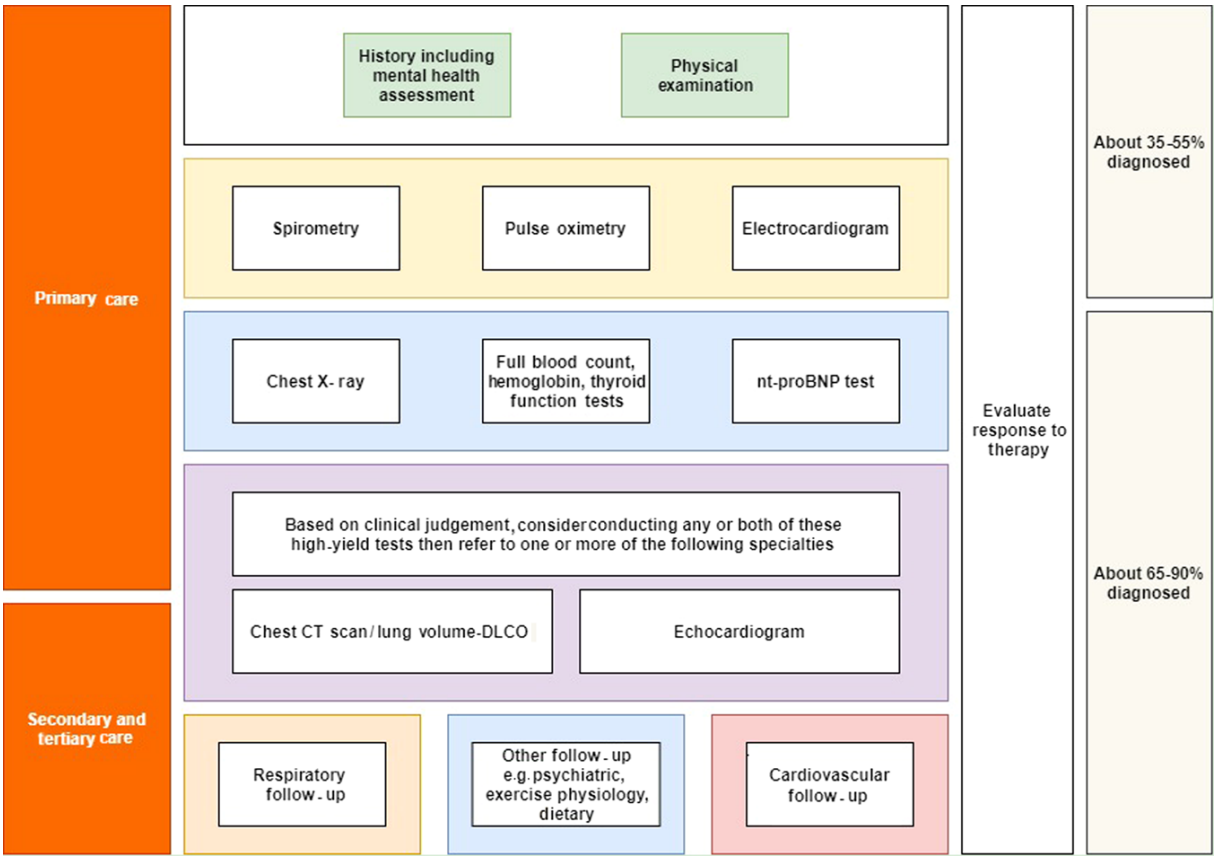

Figure 2. A summary of the stepwise approach for dyspnea assessment and the probability of elucidating the causal diagnosis based on included studies of the literature review of Sunjaya et al.[5]

Although the tests from the stepwise approach by Sunjaya et al. are available in many settings, the process of ordering, performing, and acquiring results often requires multiple appointments at different locations, leading to diagnostic delays.[6] There is currently a lack of quick and easy tests for HCPs to diagnose the cause of breathlessness. Therefore, we have developed "Breathlessness diagnostics in a Box (BiaB)", an easy and reliable tool intended to support HCPs with fast execution of diagnostic procedures required to identify the underlying cause of breathlessness (Figure 3).

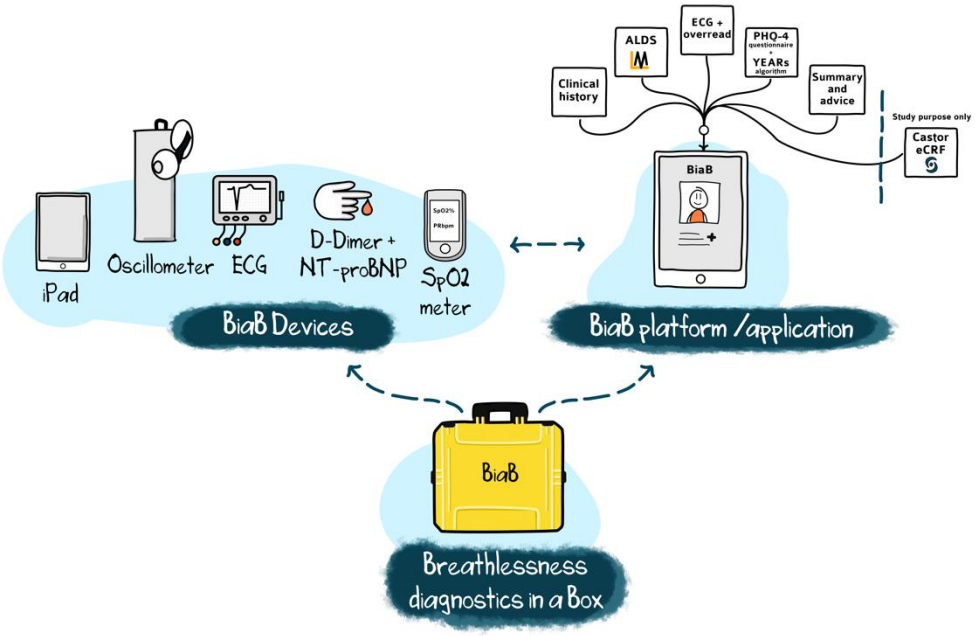

Figure 31. Content of the BiaB box

The BiaB-box includes the following devices: an iPad, an Oscillometer (the Ambulatory Lung Diagnosis System (ALDS)), an ECG, a point-of-care device to test D-dimer and NT-proBNP tests, and an SpO_2 meter. The BiaB-application (BiaB-app) guides the HCP through the necessary steps for conducting tests and collecting essential data, such as clinical history, questionnaires. The BiaB-app is also a platform of other applications (ALDS, ECG, ECG overread, Castor eCRF, point-of-Care), facilitating the interpretation and integration of the results of the tests that are included in BiaB. Upon completion of the BiaB steps, the application provides a report for the HCP as a guidance for the diagnosis in patients with breathlessness, based on the BiaB decision tree (section 5.1.7).

In 2023 a pilot study was performed to design and test BiaB. In this pilot study, 5 general practices and 122 patients were included. HCPs and patients co-designed the tool (unpublished data). The decision-tree within the BiaB-app successfully provided diagnostic reports based on input from the ECG, oscillometer and NT-proBNP tests to support HCPs. During the pilot study the BiaB-app and individual tests were positively perceived by HCPs and patients.

In the current study, we aim to investigate implementation of BiaB in more general practices in the Netherlands, Spain, and Portugal and potentially other countries (a total of 45 practices, 900 patients) to determine whether implementation of BiaB in primary care will reduce the time between presentation of breathlessness at the HCP and the diagnosis of a cause leading to the breathlessness.

2. OBJECTIVES

Primary objective:

- To demonstrate whether BiaB use shortens time to diagnosis as compared to usual care without BiaB use.

Secondary objectives:

- To demonstrate whether BiaB use increases the number of new diagnoses of COPD and/or heart disease as compared to usual care without BiaB use
- To demonstrate usability and efficiency of BiaB.

3. Study design

A prospective stepped-wedge study design will be used for this study (Figure 4). In every country, participating sites will be assigned randomly to one of the five sequences (3 sites per sequence) for timing of the intervention start. Each sequence starts with a usual care period (6 weeks or a multiple of 6) which will be followed by a transition period of 4 weeks prior to the BiaB intervention

period (6 weeks or a multiple of 6). During the transition period the healthcare professionals (HCPs) at the site will be instructed about the start date of the BiaB intervention and they will receive training for the use of BiaB. The study duration for sites is 40 weeks in total. The maximum study duration for patients is one visit followed by a maximum of 4 quarterly questionnaires (1 year).

There will be 15 sites per country, amounting to a total of 45 sites for The Netherlands, Spain and Portugal. Per site 20 patients will be included for analysis during the 40-week study period, amounting to 300 patients per country and 900 in total for 3 countries. Per site the number of patients seen in the usual care period and BiaB intervention period will differ, but at the end of the study this study design should yield a ratio of 1:1 (usual care or BiaB intervention).

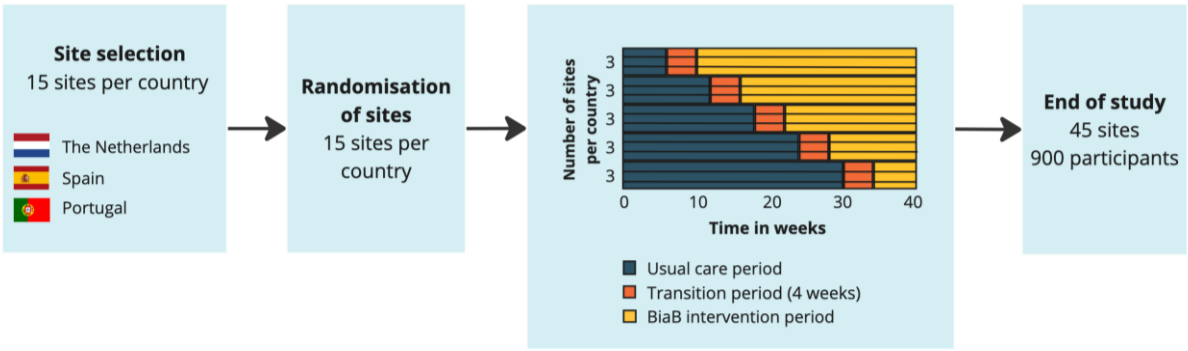

Figure 42. BiaB stepped-wedge study design. All sites (15 per participating country) will be randomly assigned to one of the sequences with set periods of usual care, transition, and BiaB intervention. In total 20 patients will be included per site, amounting to 300 patients per country and 900 patients in total.

Data will be collected (i) during the visit, and (ii) using questionnaires sent to patients and HCPs. Electronic medical data will be extracted from the participating GP practices before, during and at the end of the study. Data collected during the usual care period and, if possible, retrospective data will be used as a control to examine endpoints.

4. Study population

This study aims to capture the real-world heterogeneity in primary care practices and patients. Therefore, inclusion and exclusion criteria are limited.

4.1 Inclusion criteria

Patients are eligible to be included in the study if the following criteria apply:

Age

1 Patient must be at least 18 years old at the time of signing the informed consent.

Type of patients and symptom characteristics

2a Patients that present with undiagnosed dyspnea (breathlessness); or

2b Patients who have existing diseases that could cause breathlessness, but have residual or increasing breathlessness that could be caused by other not yet detected diseases. Or HCP has doubts or requires additional tests to confirm diagnosis or to suspect new, parallel, diagnoses. For example, breathlessness in patients assessed:

a. within the framework of Cardiovascular Risk Management or
b. for COPD monitoring

4.2 Exclusion criteria

1. Acute worsening of previous diagnosed chronic disease where there is no suspicion of comorbidities (for example when a patient with clear COPD diagnosis has an exacerbation where typically the HCP will not perform additional tests).
2. Inability to understand and sign the written consent form.

4.3 Sample size determination

The sample size was determined to reliably demonstrate that there is a difference in the number of days between presentation with breathlessness in the clinic and diagnosis of a disease or disorder causing this breathlessness between usual care and the BiaB intervention.

For stepped-wedge clustered designs, the sample size is a combination of the number of clusters, the number of sequences, the number of time periods and the number of individuals per cluster period.[7] Research shows that the best method of estimating the required sample size for a

stepped-wedge design is to simulate the power based on the method of analysis proposed including time in the chosen model.[8,9] Therefore, for this study a sensitivity analysis has been performed using a desired power of 80% for the test of the intervention, with a type I (two-tailed) error rate of 0.05. The analysis was performed using the US National Institute for Health Stepped-wedge Group-Randomized Trials (SWGRT) Calculator software.[10]

The following assumptions were considered:

- The expected cluster autocorrelation (between two consecutive periods at the cluster level) was estimated 0.8, as healthcare professionals (HCPs) will use standard protocols or guidelines which are not expected to change between consecutive (6 week) periods within the study period.
- The intra class correlation was set to 0.03 based on previous data.[11]
- The expected individual autocorrelation (between two consecutive periods at the level of the patient) was estimated 0.8, as HCPs will use standard protocols or guidelines which are not expected to change between consecutive (6 week) periods within the study period.
- The decay-structure for over-time correlations is Block-exchangeable.
- The churn rate was set to 0.0, as the study consists of one visit for data collection and data essential for the primary objective can be retrieved from HCPs.
- The number of patients per sequence (3 practices) is 60.
- Variation in cluster size is not taken into account as 60 patients will be included per cluster for analyses.
- The expected distribution of the primary outcome, dichotomous was set to 0.3.
- There are 6 time periods (including usual care and BiaB intervention period).
- The hypothesized intervention effect as a difference of time to diagnosis from presentation with breathlessness between usual care and BiaB intervention is 0.2 (20% reduction of time to diagnosis (in days) based on data from the BiaB pilot study, assumed differences between countries the assumption that the average time to diagnosis in usual care will be 70 days and the assumption that a reduction of 14 days is assumed clinically relevant). The 70 day period is chosen after discussions with the scientific advisory board,

including general practitioners, pulmonologists and cardiologist from the Netherlands, Spain and the United Kingdom, because after an extensive literature search, no timed pathway could be found. This 70 days is based on knowledge of access times to several diagnostic tests and clinical experience.

Calculations showed that with 60 patients per cluster (20 patients per site, 5 sequences, 3 countries) and 3 sites per sequence per country we have sufficient power to detect an absolute difference in effect of 0.055 and a standardized detectable difference of 0.114 (i.e. 5.5-11.4%, respectively).

When assuming the outcome as a continuous effect of 0.2 with a variance of 0.1, we would have sufficient power to detect an absolute difference in effect of 0.0362 and a standardized detectable difference of 0.1144 (i.e 3.6 and 11.4%).

In terms of feasibility, Okkes et al. show an average of 2 to 3 patients present with breathlessness per primary care facility in the Netherlands monthly,[12] and other research shows the prevalence of breathlessness is even higher in Spain.[13] This means the determined study period is sufficient to find 20 patients to participate per site during the study.

5. BiaB procedures

A BiaB-app has been designed to create an efficient workflow and to guide the healthcare professional (HCP) through the diagnostic process, by instructing to perform several tests and subsequently providing automatic interpretation of the results. All test equipment (all CE marked) will be available in the BiaB-box (figure 3) and can be performed by an HCP following a consultation for breathlessness. The BiaB-procedures will take approximately 20 minutes in total (based on the pilot study) and require limited training as all separate tests and the BiaB-application (BiaB-app) have been designed with usability in mind. During a BiaB visit, the entire box with all its tests will be conducted, except for the D-dimer test and YEARS criteria, which will be administered only if pulmonary embolism is suspected.

Clinical history

General characteristics of the patient are collected in the BiaB-app, including gender, age, height, weight, duration of dyspnea symptoms, and whether pulmonary embolism (PE) is suspected. These characteristics are necessary input for the BiaB-algorithm to provide an accurate result.

The following tests are included:

5.1.1 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.[14–16]

The Ambulatory Lung Diagnosis System (ALDS), manufactured by Lothar Medtec, can be used to perform oscillometry and spirometry (Figure 5). The ALDS follows the European Respiratory Society (ERS) technical standards for measurement and reporting of oscillometry.

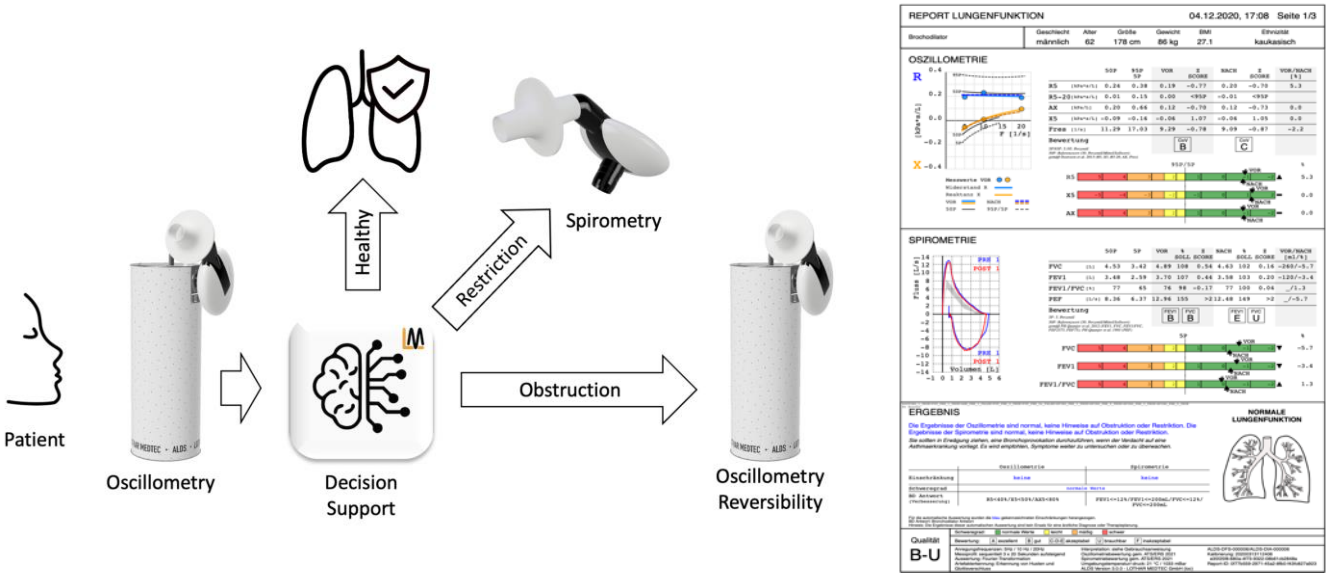

Figure 53. Oscillometry and spirometry performed with the ALDS system. A) Schematic overview of oscillometry process and decision support by the ALDS. B) Example of a report generated by the ALDS.

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 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.

Contingent on the results of the oscillometry testing, reversibility testing can also be conducted using the ALDS device, in addition to standard oscillometry measurements. When the ALDS suggests execution of a reversibility test, this is performed according to the ERS guideline with use of 400 μg Salbutamol as the bronchodilator.[17] If required, post-bronchodilator spirometry can also be performed using the ALDS device after training of HCPs.

The BiaB-app and the ALDS are integrated seamlessly. The complete ALDS output will be integrated in the BiaB-report. The resulting physiological interpretation, combined with the clinical BiaB-decision tree interpretation will be presented in the BiaB-report.

5.1.2 Electrocardiogram

A primary method of evaluating breathlessness, adjunct to pulmonary tests, is through an electrocardiogram (ECG). Breathlessness could well be a symptom of cardiovascular conditions, particularly heart failure.[18]

The CardioSecur Pro (Personal MedSystems GmbH, Frankfurt, Germany) will be used for ECG measurement as a diagnostic tool for cardiologic causes of breathlessness. The CardioSecur Pro is a 12+ leads ECG technology that uses 4 electrodes, which are placed on the thorax. This test is commonly used in diagnostic procedures in primary care. This technology is based upon the EASI lead standard and was clinically proven.[19,20] There is >99% agreement between the CardioSecur ECG and standard ECG for detection of myocardial ischemia.

The PMCardio algorithm (Powerful Medical, London, UK) is an AI powered diagnostic medical device for ECG assessments. The diagnostic performance of the device was examined in a study that encompassed more than 932,711 ECGs. High sensitivity, specificity and positive/negative

predictive values were demonstrated across all diagnostic categories. The findings indicate strong potential for the interpretation to enhance diagnostics.[21,22]

HCPs will retain the opportunity to use their own ECG device and run this through the PMCardio algorithm. PMCardio has the ability to interpret ECG results from all devices, allowing the HCP to be able to use their own ECG device. We have considered this option, because of health insurance reimbursements within the practices in primary care. Beside this, HCPs are often familiar with the equipment they have in their practice.

The PMCardio algorithm, a software application for interpretation of ECG results, will be integrated in the BiaB-app. The ECG interpretation, combined with the clinical BiaB-decision tree interpretation will be presented in the BiaB-report.

5.1.3 N-terminal pro-B-type Natriuretic Peptide (NT-proBNP)

B-type Natriuretic Peptide (BNP) is secreted by cardiomyocytes in response to any damage to the cardiovascular system. BNP and NT-proBNP in blood have been known as the gold standard, recommended by the American Heart Association and the American College of Cardiology, to identify heart failure (HF).[23] Of the two analytes, NT-ProBNP has a longer half-life and more consistent blood concentration.

The BiaB-box will include the LumiraDx point-of-care device (LumiraDx Ltd, London, UK) for quantitative assessment of NT-proBNP levels for point-of-care diagnostics of HF. This test is commonly used in diagnostic procedures in primary care. The measurement will be performed in approximately 20 µL of capillary blood obtained by a standard finger stick. HCPs will be instructed about use of the device but do not require training for the finger stick. For automated interpretation of quantitative values, cut-off values, depending on age, according to the paper by Gaggin et al. will be used.[24]

Results generated by the LumiraDx will be retrieved by the BiaB-app automatically. The BiaB-app will interpret the measurement according to guidelines taking into account the relevant dependencies. Results will be incorporated into the BiaB-report.

5.1.4 YEARS criteria and D-dimer test

Sudden breathlessness may be a sign of pulmonary embolism (PE), which requires urgent care. Therefore, it is important to investigate further when PE is suspected. This is a common method in primary care. This can be done using the YEARS criteria, which are derived from the most predictive items of the previously used Wells score. Compared to the Wells scores, with fixed D-dimer cut off values, the YEARS algorithm reduces the use of a CT pulmonary angiogram (CTPA) by 14%.[25] The YEARS algorithm has been shown to rule out PE (only 0.43% with a symptomatic venous thromboembolism (VTE) during 3 months follow-up) and has been incorporated in international guidelines.[25,26] The score derived from the YEARS algorithm dictates interpretation of the D-dimer test. D-Dimer, a fibrin degradation product, is a thrombotic biomarker used to exclude PE.[27]

In cases of suspicion of a PE, the YEARS criteria (Appendix A) and a D-dimer test will be advised in the BiaB-app. D-dimer can be tested on the same LumiraDx point-of-care device used to measure NT-proBNP levels with a different test cartridge. The measurement will be performed in approximately 10 µL of capillary blood obtained by a standard finger stick. PE can be ruled out if none of the YEARS items are applicable and D-dimer <1000 ng, or, if 1-3 YEARS items are applicable and D-dimer is <500 ng (Figure 6).[25,26]

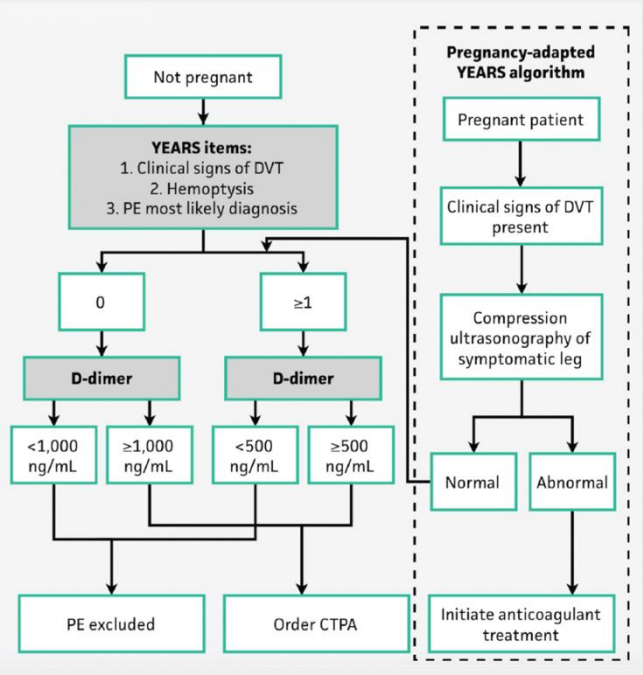

Figure 6. Decision tree for YEARS algorithm with binary d-dimer cut off values, adapted from Van der Pol 2019[28].

Results generated by the LumiraDx will be retrieved by the BiaB-app automatically. The BiaB-app will interpret the measurement according to guidelines taking into account the relevant dependencies. Results will be incorporated into the BiaB-report.

5.1.5 Patient Health Questionnaire-4 (PHQ-4)

As mentioned in the introduction, anxiety and depression are two of the primary underlying conditions contributing to breathlessness. Contributing to the necessary integrated approach needed for defining the cause of breathlessness, the PHQ-4 is incorporated into BiaB. The PHQ-4 is a brief self-report questionnaire that consists of a 2-item anxiety scale (GAD-2) and a 2-item depression scale (PHQ-2)[6] (Appendix B). This tool was found to be able to measure anxiety and depression reliably and validly in the general population.[29]

The GAD-2 is the short version of the 7-item Generalized Anxiety Disorder Scale (GAD-7), which was found to accurately diagnose the four most common anxiety disorders. The PHQ-2 focuses on depressed mood and loss of interest, thereby representing the DSM-5 diagnostic core criteria. A total score ≥3 for the first 2 questions will be used as cut-off to suggest anxiety and a total score ≥3 for the last 2 questions will be taken as cut-off to suggest depression.[29]

The patient fills out the PHQ-4 questionnaire, which is incorporated into the BiaB-app. The BiaB-app will interpret the questionnaire according to guidelines. Results will be incorporated into the BiaB-report.

5.1.6 Oxygen saturation measurement

The common causes of breathlessness can be divided amongst a cardiac, pulmonary, mental health or other category. Once cardiac, pulmonary, or mental health causations have been ruled out, focus on the 'other' category is necessary. Causes listed in this category are obesity, physical deconditioning, anaemia or long COVID. Unexplained reduction of peripheral capillary oxygen saturaitoin (SpO_2) or low SpO_2 levels during minimal activity can indicate sever acute breathlessness which upon review of the HCP can merit specialist assessment. Pulse oximeter is a non-invasive measurement of SpO_2. This test is commonly used in diagnostic procedures in primary care. As per guidelines, a cut-off value of ≥95% will be used for interpretation of the result. Results will be incorporated into the BiaB-report.[6]

5.1.7 Decision-tree for interpretation of test results

A decision-tree will be used for clinical decision support. This decision-tree combines all findings from the several assessments performed. The current version of the decision-tree is based on the pilot project (unpublished) and is now further optimized with the additional tests and new findings.

6. Methods

6.1 Study parameters/endpoints

For all study endpoints, the analysed population will include patients from usual care and the BiaB intervention period.

6.1.1 Primary study endpoint

The primary endpoint is days between presentation with or consultation for breathlessness and a diagnosis causing the breathlessness (usual care group versus BiaB intervention group).

Required variables:

- Date of presentation with breathlessness,
- Date of first consultation for breathlessness,
- Date of diagnosis, and
- Type of diagnosis.

Strategy: Data will be retrieved during patient consultation (presentation and consultation for breathlessness) and periodically (up to 12 months, to account for referral waiting times) from healthcare professional (HCP) reporting (date and type of diagnosis). The exact date of presentation with breathlessness, consultation and diagnosis will be recorded. If exact date of presentation is unknown, it will be set to [01/MM/YYYY], where MM is the month where symptoms started. If duration of presentation is >1 month and start date is unknown, it will be set to either [01/01/YYYY] or [01/07/YYYY] (whichever is most accurate). Date of diagnosis is defined as date of recorded diagnosis related to breathlessness by any HCP (either reported by

HCP or noted in referral documentation) or start of treatment related to breathlessness. If multiple diagnoses are recorded, all will be collected, and the first diagnosis is used to determine time to diagnosis. Patients with missing data will be censored. In countries where a preliminary diagnosis is entered int the medical records to make prescription of medication possible before diagnostic tests are performed, the date of diagnosis will be validated by the HCP to ensure final clinical diagnosis date.

6.1.2 Secondary study endpoints

6.1.2.1 First secondary endpoint

The first secondary endpoint is the number of new diagnoses of COPD and heart disease (CVD) in patients (usual care group versus BiaB intervention group).

Required variables:

- The number of newly diagnosed patients
- The number of new diagnoses
- The number of diagnoses per patient
- The number of patients presenting with breathlessness
- The type of diagnosis

Strategy: Data will be retrieved periodically (up to 12 months, to account for referral waiting times) from HCP reported outcomes (date and type of diagnosis). All types of diagnosis will be recorded. For determining the secondary endpoint, type of diagnosis will be categorized as either heart, respiratory, psychological, and other. In case no diagnosis is reported, this will be reported as late diagnosis. If multiple diagnoses are recorded, all will count towards the endpoint. In countries where a preliminary diagnosis is entered int the medical records to make prescription of medication possible before diagnostic tests are performed, the date of diagnosis will be validated by the HCP to ensure final clinical diagnosis date.

6.1.2.2 Second secondary endpoint

The second secondary endpoint is to demonstrate the usability and efficiency of BiaB.

Required variables:

- Number of lung function tests
- Number of ECG measurements
- Number of referrals to specialist
- Type of referral to specialist
- Number of acute hospital admissions
- Duration of hospital admission
- Number of emergency room visits

Strategy: Data will be retrieved from HCP reported outcomes. Anonymous data pertaining to the total number of lung function tests, ECG measurements and referrals are not limited to patients participating in the BiaB study.

- Clinical outcomes
    - Contents of BiaB report
        a) Test results
        b) Outcomes
        c) Advice
        d) Diagnosis
    - Change in breathlessness[30]
    - Number of cardiopulmonary events [31]
        a) COPD exacerbation
        b) Myocardial infarction
        c) Stroke
        d) Heart failure decompensation
        e) Arrhythmia
        f) Death due to any of these events
    - Change in prescribed medication

- Performed procedures (at visit and follow-up/referral)

Strategy: Change in breathlessness will be measured over time (0, 3, 6, 9, 12 months) as a patient reported outcome using the numeric rating scale (NRS)[32,33]. The number of cardiopulmonary events will be recorded at 3, 6, 9, 12 months, reported by HCP. Cardiopulmonary events are defined as COPD exacerbation, myocardial infarction, stroke, heart failure hospitalization, arrhythmia, and death due to any of these events[31]. COPD exacerbations are identified through use of oral corticosteroids irrespective of antibiotics use. Arrhythmia is defined as atrial and ventricular tachyarrhythmia. Change in prescribed medication will be determined by comparing medication prescribed before consultation for breathlessness to prescribed medication after consultation for breathlessness as reported by HCP. Data about procedures performed during visit, follow-up and referral will be collected through HCP reported outcomes.

- BiaB use
  - Number of times BiaB is started
  - Number of unique generated reports
  - State of generated reports
  - Number of times BiaB advice is followed
  - Prescribed treatment or referrals
  - Performed procedures

Strategy: The amount of newly generated participants IDs in the Electronic Data Capture (EDC) system and reports will be recorded automatically in the BiaB-application. The number of times BiaB advice is followed is determined by comparing generated advice to follow-up referrals, procedures, diagnosis and treatment, as reported by HCP.

- Economic analysis
  - WPAI questionnaire[34]
  - EQ-5D-5L questionnaire[35]
  - Mortality rates
  - Complications without treatment
  - Costs regular care and intervention

  - Costs of late or wrong diagnosis
  - Costs of specialists
  - Number of patients that would benefit from use of BiaB
  - Insurance costs and funding

Strategy: Questionnaires will be filled in by patients at 0, 3, 6, 9, 12 months. Mortality rates and complications will be reported by HCPs. Costs of late or wrong diagnosis will be calculated taking into account any treatment costs (necessary, unnecessary, and suboptimal). Cost of specialists, insurance and number of patients will be calculated. Available data will be used to calculate QALYs which will be used for economic analysis.

- Qualitative evaluation of the implementation of BiaB
  - Number of help requests
  - Type of help request
  - System usability scale
  - Interviews with healthcare professionals

Strategy: The number and type of help requests from HCPs related to BiaB use will be recorded by study personnel throughout the study period. Healthcare professionals will be asked to fill in the system usability scale after finishing the study.

- Practice characteristics
  - Number of current patients
    - Number of COPD diagnoses in last year
    - Number of cardiac disease diagnoses in last year
  - Mean age of patients
  - Gender ratio of patients
  - Number of HCPs
  - Access to spirometer and ECG
  - Region
  - Local wait time (days) for secondary care

Strategy: Information about the practice will be captured as reported by HCP before and after the study. In countries or practices where this information is not easily available from the medical records, it will not be collected.

6.1.3 Other study parameters

During the consultations the HCP will collect medical history and perform physical examination (or take from the medical record if the BiaB visit is not performed by the general practitioner) The following parameters will be collected:

- Reason for the BiaB box:
  - New breathlessness, with no previous diagnosis
  - Breathlessness in existing diseases that could cause breathlessness, but have residual or increasing breathlessness that could be caused by other not yet detected diseases
- Differential diagnosis prior to BiaB tests (yes, no, type)
  - Suspected heart failure
  - Suspected ischemic heart disease
  - Suspected asthma
  - Suspected COPD
  - Suspected anxiety/depression
- Patient information (age, sex, height, weight, smoking status)
- Reason for visit
- Medical history (COPD, Asthma, allergy/hyperreactivity, eosinophilia, cardiac disease, anxiety, depression, chest operations, rhinosinusitis)

6.2 Randomisation

In each participating country, participating sites will be assigned randomly to one of the five sequences (3 sites per sequence) for timing of the intervention start. A computer-generated list of random assignment will be created. A researcher not involved in the site recruitment and intervention delivery/implementation at the sites will generate the allocation sequence after all

sites in the country have been recruited. The allocation sequence will be available to the national coordinating investigators in each country in order to prepare the rollout of BiaB in the transition period.

6.3 Study procedures

Data collection will take place during the BiaB visit, retrospectively, and after the visit during the follow-up period. See the Schedule of Assessments with an overview of all performed procedures (Table 1).

Table 1. Schedule of assessments for usual care and BiaB intervention period.

Schedule of assessments (usual care period)						
Visit	Visit 0[1]	Visit 1[1]	Follow up 1	Follow up 2	Follow up 3	Follow up 4
Time (months)	0	0	3 (+14 days)	6 (+14 days)	9 (+14days)	12 (+14 days)
Invitation + Informed consent						
Invitation and informed consent provided	X					
Informed consent procedure		X				
Patient reported outcomes (electronic)[2]						
WPAI		X	X	X	X	X
EQ-5D-5L		X	X	X	X	X
Healthcare utilization		X	X	X	X	X
NRS dyspnea		X	X	X	X	X
Diagnosis questionnaire		X	X	X	X	X

Schedule of assessments (BiaB intervention period)						
Visit	Visit 0[1]	Visit 1[1]	Follow up 1	Follow up 2	Follow up 3	Follow up 4
Time (months)	0	0	3 (+14 days)	6 (+14 days)	9 (+14days)	12 (+14 days)
Invitation + Informed consent						
Invitation and informed consent provided	X					
Informed consent procedure		X				
BiaB visit						
Patient characteristics		X				
YEARS questionnaire + D-dimer test (optional)		X				
SpO2 measurement		X				
NT-proBNP test		X				
PHQ-4 questionnaire		X				
ECG		X				
Oscillometry		X				
Patient reported outcomes (electronic)[2]						
WPAI		X	X	X	X	X
EQ-5D-5L		X	X	X	X	X
Healthcare utilization		X	X	X	X	X
NRS dyspnea		X	X	X	X	X
Diagnosis questionnaire		X	X	X	X	X

1 V0 and V1 can be at the same moment if regulations allow
2 (electronic) patient reported outcome ((e)PRO), see section 6.3.2

6.3.1 BiaB-application

Information required to run the BiaB-algorithm and create the report will be collected via screens on the study/BiaB iPad during the BiaB intervention visit. Study specific data collection will take place in Castor EDC via automatic transfer from the BiaB application.

6.3.2 Patient reported outcomes

During the follow-up period, every three months for up to a year, patients will be asked to fill out questionnaires (WPAI, EQ-5D-5L, healthcare use, numeric rating scale (NRS), and diagnosis)

(Appendix C-F). The preference for the study is to make use of electronic questionnaires. Patients can receive the questionnaires by email or will be invited at the study site. Patients which are hesitant or unable to complete information using electronic questionnaires will be provided with paper copies. Data will then be entered into the eCRF using double data entry.

6.3.3 HCP reported outcomes

During Visit 1 and the follow-up period, every three months for up to a year, HCPs will be asked to provide details on patient characteristics, medical information, diagnosis, medication, and referrals.

6.3.4 Specialist questionnaire

A link and a QR-code will be included on the BiaB report, which will be shared with the specialist. These will direct the specialist to a specific questionnaire for the referred patient, where they can enter details on the procedures/tests performed, the outcomes, and the diagnosis made.

6.3.5 Qualitative evaluation of BiaB

A qualitative evaluation of the implementation of BiaB will be performed via semi-structured face-to-face (either on-site or online) interviews or focus groups with HCPs who participated in the study. At the end of the study period, HCPs from the participating sites will be invited for an interview or to join a focus group, with the format being chosen based on the preference of the local researcher. The discussions will focus on the following topics:

- Experiences with BiaB: including its advantages and disadvantages.
- The feasibility and acceptability of BiaB for future use in general practice.
- Initial expectations versus actual experiences with the performance of BiaB.

6.3.6 Overread service

For each HCP participating in the BiaB study, we offer an overread service that involves a group of specialists who can provide advice on the output and potential next steps if needed.

6.4 Withdrawal of individual patients

Patients will visit their HCP once for the BiaB study. Afterwards, patient reported outcomes will be collected using questionnaires. Patients can leave the study (stop answering questionnaires) at any time for any reason if they wish to do so without any consequences.

6.5 Replacement of individual patients after withdrawal

Patients that left the study will not be replaced.

6.6 Follow-up of patients withdrawn from study

There will be no follow-up of patients withdrawn from the study.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of patient 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 patients health or safety. The sponsor will notify the accredited Institutional Review Board (IRB) 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 IRB. The investigator will take care that all patients are kept informed. The investigators perceive the occurrence of this risk as very low.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Since the current study is a quality improvement project only adverse events occurring while using BiaB will be considered and reported as (serious) adverse events. Adverse events occurring during the follow-up period of a patient will not be recorded or reported as such.

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 use of the BiaB-box will be considered and reported as SAEs.

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

- Events related to the indication of the HCP consultation and not related to the procedures performed with the BiaB-box, as interpreted by the HCP.

The National coordinator will report the SAEs through the national applicable way to the accredited IRB 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 formal statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

8.1 Primary study parameter

8.1.1 Statistical hypothesis

Use of BiaB reduces time to diagnosis as compared to usual care.

8.1.2 General considerations

To demonstrate whether BiaB use shortens time to diagnosis as compared to usual care, the time from presentation with breathlessness to diagnosis for breathlessness will be compared between the usual care group and the BiaB intervention group.

Time between presentation and diagnosis will be summarised as number of days (median with interquartile range) for patients in the usual care group and BiaB intervention group.

Additionally, analyses will be performed stratified per country and will be presented for the different study populations. The stepped-wedge study design, including potential clustering effects, will be considered in the analysis.

8.2 Secondary study parameter(s)

8.2.1 Statistical hypothesis

Use of BiaB increases the amount of new COPD and/or heart disease diagnoses as compared to usual care.

8.2.2 General considerations

All secondary analyses will be stratified per country and results will be presented for the different study populations. All results will be compared between the usual care group versus the BiaB intervention group. Data will be summarised as descriptive statistics (number of observations, mean, SD, median, interquartile range, minimum and maximum) where appropriate. The stepped-wedge study design, including potential clustering effects, will be considered in the analysis.

- To evaluate the number of newly diagnosed patients with COPD and/or heart disease (CVD) in patients with breathlessness, the following outcomes will be reported: frequency and cumulative incidence of new (working) diagnosis of COPD and/or heart disease.
- To demonstrate usability and efficiency of BiaB the following statistics will be reported:
  - Frequency of use of: BiaB, Lung function tests, ECG measurements,
  - The distribution of working diagnosis outcomes from the BiaB box,
  - Frequency of: Referral to specialist (and type), Acute hospital admission, Emergency room visits,
  - Clinical outcomes; BiaB report and advice, patient characteristics,

    And:
  - Economic analysis will be performed; reporting either cost-benefit or budget impact.

8.3 Other study parameters

8.3.1 Qualitative: Interviews with healthcare professionals

Audio recordings of interviews will be transcribed and analysed with qualitative content analysis. Transcripts will be analysed at fragment levels using content analysis by the research team. Content analysis will be conducted with Dedoose or comparable software. Data will be coded and analysed by two researchers and consensus will be reached about potential discrepancies. Results will be systematically discussed with the Scientific Advisory Board.

9. ETHICAL, DATA PRIVACY, AND LEGAL ISSUES

9.1 Regulation statement

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

9.2 Informed consent

9.2.1 Informed consent procedure

The healthcare professional (HCP) will explain the nature of the study to the patient after he or she has expressed interest in participating. Patients or their legally authorized representative

will receive either a digital or hard copy of the Patient Information Sheet and Informed Consent Form (ICF). Patients must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study without any consequences. Depending on the specific regulations in patient's country, the informed consent procedure may either be directly initiated or after the minimum consideration period. If applicable, before signing, the HCP will explain the study again. Patients can ask any questions they may have. Upon satisfactory clarification of all questions, patients will be given the option to sign the ICF. Signatures can be provided either on paper or digitally.

9.2.2 Paper-based consent

The patient and HCP will sign the ICF on paper at the site. Following the signing process, one ICF will be retained at the site in accordance with Good Clinical Practice (GCP) standards, while the other will be provided to the patient.

9.2.3 Electronic Consent

Signing the ICF electronically will be facilitated through the eConsent module of the designated Electronic Data Capture (EDC) system. The patient and HCP will sign the ICF using the study tablet. The eConsent module will comply with 21 CFR Part 11 regulations for electronic signatures and will incorporate encryption measures. HCP's will undergo two-factor authentication prior to signing the ICF. Upon completion of the signing process, the patient will receive a digital copy of the signed ICF.

9.2.4. Electronic Data Capture System

The HCP will either conduct a usual care visit or, during the intervention period, perform the BiaB. Regardless of whether the ICF signature is electronic or paper-based, visits data will be collected in an EDC system.

The medical record must include a statement that informed consent was obtained for the BiaB study and the date it was obtained. If new information requires changes to the ICF, it should be assessed whether patients need to undergo re-consent. If re-consent is deemed necessary, it

must be done using the most up-to-date version of the ICF available during their participation in the study.

The ICF will contain a separate section detailing the storage and utilization of data gathering during the study, aimed at selecting and potentially inviting patients to participate in other research studies. Patients will be informed of their freedom to decline participation in this additional use of their data in the future and retain the right to withdraw consent at any time and for any reason without any consequences.

9.3 Benefits and risks assessment, group relatedness

The risks of participating in the BiaB study are negligible because the box only contains non-invasive tests. The diagnostic test which are included in the box are all validated and approved tests, adding no elevated risks to this one study visit, when compared to usual care. There might occur a minor inconvenience for the patient, because of the finger stick necessary for the NT-proBNP test.

The overall aim of the study is to test whether the use of the BiaB box reduces the time to clinical diagnosis, and consequently earlier treatment. The cost effectiveness assessments (including the quality of life questionnaire) will at the end conclude whether this has benefitted the patient, however the hypothesis is that it will.

Besides direct benefit for the specific patients that will be included in the study, we hope that raising awareness for breathlessness will indirectly influence the health of patients by inspiring the healthcare professionals in primary care.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data

Data collection in the BiaB-app

Data from the BiaB-app will be stored according to the medical information regulation by Lothar Medtech which complies with class IIa for continuous operation according to Annex IX of the Directive, also complies with the essential requirements according to EN ISO 13485:2016. medical devices - quality management systems - requirements for regulatory purposes. Certification authority: TUEV SUED (CE0123) Certificate numbers: G10 102194 0002 Rev. 1

Data collection in electronic Data Capture system

All research data will be directly entered into an Electronic Data Capture system (EDC). The data collection software Castor or a comparable vendor will be used to ensure the adequate entry, management, and storage of the collected data. The selected EDC system will have an audit trail that enables the tracking of changes. Furthermore, the system enables the application of validation rules (e.g. halts when a value is incorrectly filled out e.g. an age value that is smaller than 18 or when a data field is accidently skipped). This will minimize errors and missing values on questionnaires. The selected EDC system should comply with all applicable laws and regulations, including ICH E6 Good Clinical Practice (GCP), 21 CFR Part 11, EU Annex 11, General Data Protection Regulation (GDPR), HIPAA (US), ISO 9001 and ISO 27001.

Data handling and storage will comply with the General Data Protection Regulation (GDRP). The investigator will ensure protection of patient's personal data in compliance with the Personal Data Protection Act and that all reports, publications, patient samples and any other study disclosures do not reveal the identity of the patient, except where required by laws. Patients are identified only by a patient identification number or site identification number to maintain patient confidentiality. All patient study records will be kept safely in an access- controlled area. Identification code lists linking patient names to patient identification numbers should preferably be stored separate from patient records. In case of data transfer, the sponsor or its representative will maintain high standards of confidentiality and protection of patient personal data. Clinical information will not be released without the written permission of the patient, 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 Study registration

The study will be registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

10.3 Monitoring and Quality Assurance

Monitoring will be done following the written monitor plan. Monitoring will be conducted remotely using the Castor and BiaB environment.

10.4 Remuneration

General practices will be remunerated for their services, based on the time spent on study procedures and the number of patients included in the study.

The specific remuneration for each country can be found in appendix H.

11. DISSEMINATION

11.1 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. Results will be reported following the Consolidated Standards of Reporting Trials (CONSORT) extension for the stepped-wedge cluster randomised trial.

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13. Appendix

All questionnaires are added as separate appendices to the submission folder.

Appendix A. YEARS Algorithm

English version:

1. Signs of deep vein thrombosis
2. Hemoptysis
3. Pulmonary embolism most likely diagnosis

Dutch version:

1. Klinische tekenen van trombosebeen
2. Bloed ophoesten (hemoptoe)
3. Longembolie meest waarschijnlijke diagnose

Appendix B. PHQ-4 questionnaire

Appendix C. WPAI questionnaire

Appendix D. EQ-5D-5L questionnaire

Appendix E. Healthcare utilization questionnaire

Appendix F. Numerical Rating Scale (NRS) Dyspnea

Appendix G: Diagnosis questionnaire

Appendix H: Remuneration per country

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