# Diagnosing Obstructive Lung Disease with Point of Care Ultrasound- A Cross-sectional, Diagnostic Accuracy Test

Clinical Research Center, The Medical Intensive Care Unit, and Pulmonary Institute
Soroka University Medical Center,
Be'er-Sheva, Israel

Protocol SCRC23032
Version 1.2
September 2023

## 1 Investigator Signature Page

Study Title: Diagnosing Obstructive Lung Disease with Point of Care Ultrasound, A Cross-sectional, Diagnostic accuracy test

Protocol Version: Version 1.1

Protocol Date: 18 June 2023

**Investigator's Responsibility**

Prior to participation in the study, as the site principal investigator, I understand that I must obtain written approval from my local Ethics Committee (EC) and the hospital General Director. As the site Principal Investigator, I must also:

1. Ensure that the study is not commenced until EC and hospital General Director approvals have been obtained.
2. Ensure that written informed consent is obtained from each patient prior to any data collection using the most recent EC-approved Patient Informed Consent Form.
3. Provide all required data and reports and agree to source document verification of study data with the patient's medical records.
4. Allow EC representatives, to inspect and copy any documents pertaining to this clinical investigation.

**Investigator Signature**

I have read and understand the contents of the study protocol and agree to abide by the requirements set forth in this document.

| Dr. Lior Fuchs | Soroka University Medical Center |
|---|---|
| Investigator Name (print) | Investigative Site (print) |

| Dr. Lior Fuchs | June 18, 2023 |
|---|---|
| Investigator Signature | Date |

## 2 Protocol Summary

| | |
|---|---|
| **OBJECTIVE** | To assess the accuracy of the Point of Care Ultrasound (POCUS) exam in diagnosing obstructive lung diseases (OLDs) compared to the gold standard pulmonary function test (PFTs) |
| **STUDY DESIGN** | A cross-sectional diagnostic accuracy test |
| **INTERVENTION** | None |
| **SAMPLE SIZE CONSIDERATIONS** | We aim to enroll a total of 200 patients. The calculation stems from the speculation that the Se of the test will be 85%, with a confidence interval of 90% and the maximal width of the interval will be up to ±7%. |
| **INCLUSION CRITERIA** | • Age 18 or above<br>• Referral for full pulmonary function tests (PFTs)<br>• Patients are willing and able to sign a written informed consent form. |
| **EXCLUSION CRITERIA** | • Unable to give written informed consent.<br>• Unable to remain supine.<br>• Poor effort at PFTs<br>• Subcutaneous emphysema |
| **STUDY PROCEDURES** | We plan to conduct random POCUS scans at the respiratory institute of Soroka University Medical Center on patients who are sent for pulmonary function tests (PFTs) for any reason and provide each patient with a sonographic score, comprised of several criteria (table 1). |
| **DATA TO CAPTURE** | Aside from the sonographic data, we plan to collect descriptive data from the hospital's medical records (i.e., smoking history, comorbidities, past radiographic exams, BMI, etc.) and the PFTs results. |
| **OUTCOMES AND ANALYSES** | The diagnostic accuracy of the POCUS examination, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of obstructive lung diseases (OLDs) will be calculated using contingency tables with PFTs findings as the gold standard. |
| **DATA MANAGEMENT AND ANALYSIS** | The study will be overseen and managed by the Soroka Clinical Research Center. |

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## Abbreviations and Definitions

| Abbreviation | Term |
|---|---|
| A4C | Apical 4-chamber (view) |
| COPD | Chronic obstructive lung disease |
| DLCO | Diffusing capacity for carbon monoxide |
| GS | Gold standard |
| LV | Left ventricle |
| mMRC | Modified Medical Research Council (Dyspnea Scale) |
| OLD | Obstructive lung diseases |
| PFTs | Pulmonary function test(s) |
| POCUS | Point of care ultrasound |
| PLAX | Parasternal long axis (view) |
| SX | Subxiphoid (view) |

**Definitions**

## 3 Background

Point of care ultrasound (POCUS) is a valuable bedside tool for rapidly assessing multiple cardiorespiratory conditions (1). Its portability and ease of use make it particularly useful in acute care settings, where quick diagnostic information is crucial for optimal patient care (2). It has the advantage of immediate interpretation and clinical integration of the imaging results without radiation exposure. The POCUS assessment is considered quick and relatively simple even by non-radiologist novice trainees (3). It can closely monitor patients through repeatable exams in short periods, providing clinicians with an essential real-time image that can reinforce or weaken the initial diagnosis. Some even advocate its routine use as part of the physical exam and refer to it as the "new stethoscope" (4) The POCUS exam has been strongly validated as an accurate diagnostic tool in multiple lung pathologies such as pneumonia, pulmonary congestion, pleural effusions, and pneumothorax (5–8). It was found to be especially valuable in the acutely dyspneic patient, adding vital diagnostic information with great accuracy (9–11).

In contrast, POCUS has yet to be found as an efficient tool for diagnosing patients who suffer from obstructive lung disease (OLD) such as chronic obstructive pulmonary disease (COPD). This is probably due to air trapping in OLDs, considered the "great nemesis" of ultrasound. Nevertheless, based on multiple observations and personal clinical experience, we believe that POCUS can, in fact, efficiently recognize those patients with air trapping, mainly those with COPD.

In the last decade, we have used POCUS as part of the physical examination at the bedside regularly. We noticed that among COPD patients, we often detect very poor cardiac imaging on the parasternal long axis, apical four-chamber views (thoracal views), and relatively clear and noticeable cardiac imaging in the sub-costal view. In our experience, this group is characterized explicitly by multiple sonographic lung artifacts such as anterior predominant "A-lines" and the absence of "B-lines". We hypothesize that the poor thoracal visibility is due to air trapping which interferes with the ultrasound waves. On the other hand, the clear cardiac images seen from the sub-costal view might be explained by the hyperinflated lungs shifting the heart downward, causing better cardiac imaging than is usually seen.

We plan to perform a cross-sectional observational study at the pulmonary institute of Soroka university medical center. We will conduct random POCUS scans on patients who are sent for pulmonary function tests (PFTs) for different suspected lung diseases.

A presumptive diagnosis will be made on-site based on the sonographic data collected. The accuracy of the POCUS in identifying OLD will be compared to the full PFTs, considered the

gold standard for diagnosing OLD and air trapping. We believe that the POCUS exam, identifying poor thoracal and exceptionally good subcostal views will accurately identify those with confirmed OLD and air trapping.

Our goal is to assess whether the POCUS exam accurately diagnoses OLD and air-trapping compared to standard PFTs. If so, this finding will have great applicability for identifying OLD patients early, even in remote areas where full PFTs are not accessible and referring them for further diagnostic workup.

## 4 Method

### *Design*

In this cross-sectional study, we plan to conduct random POCUS scans at the respiratory institute of Soroka University Medical Center on patients who are sent for pulmonary function tests (PFTs) for any reason. The POCUS examiners will be blinded to the reason for referral or the patient's medical history in general. We plan to include all patients at the age of 18 or above who performed full PFTs and have signed the informed consent form. We intend to enroll 200patients who meet the inclusion criteria and none of the exclusion criteria.

The examiners performing the scans will be skilled POCUS instructors with at least two years of experience in the field of cardiac and lung POCUS. The ultrasound examination will be conducted at a supine position and will include 2 parts:

1. An anterior chest scan to detect A-lines versus B-lines in lung zone 1 (Figure 1)
2. A 3-part cardiac scan consisting of a parasternal long-axis view, an apical 4-chambers view, and a sub-xiphoid view. (Figure 2).

   Each patient will be met by the POCUS team once and scanned once, as described, in one lung zone and the three formal cardiac views.

Data from the medical records (i.e., smoking history, comorbidities, past radiographic exams, BMI, etc.) and the PFTs results will be collected by a third party, blinded to the POCUS exam. Eventually, the accuracy of the POCUS exam in identifying OLD will be compared to the gold standard of diagnosis, the full PFTs.

**Figure 1** – The ultrasound probe is placed at zone 1 on the anterior chest.

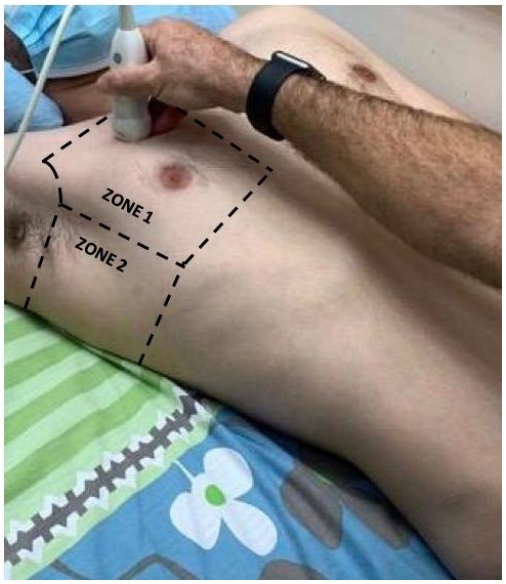
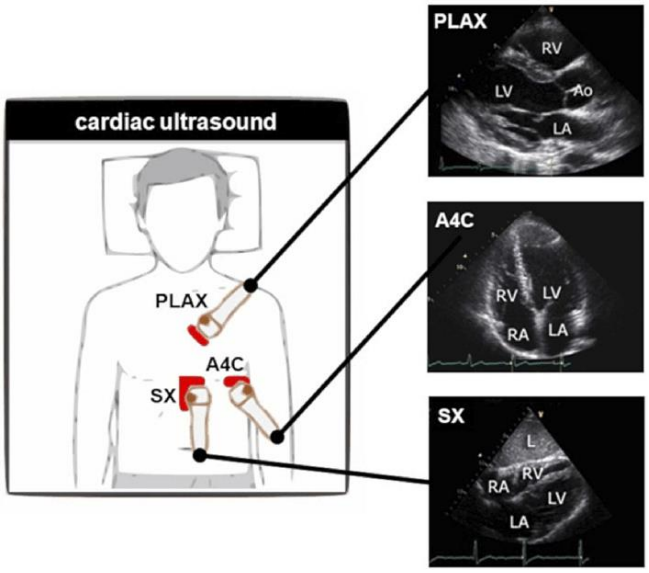



**Figure 2 –** The formal 3-part cardiac exam (Parasternal long axis view (PLAX), Apical four-chambers view (A4C), and the subcostal view (sub-xiphoid, SX)




*Diagnosis Considerations and Calculation*

*Chest scan grading*

The anterior chest (Zone 1) will be examined bilaterally (see Figure 1) searching for A-lines (meaning aerated "open" alveoli) versus B-lines (which suggest alveolar flooding). A sonographic scan consistent with multiple A-Lines on both sides of the chest strengthens the diagnosis of OLD. Patients with three A-Lines or more will claim the maximal grade of 2 points on the corresponding side, meaning that a "perfect" score regarding the anterior chest is 4 (see Table 1).

*Cardiac views grading*

We will use three formal echocardiographic views for scoping the heart: The PLAX, A4C, and SX views (see Figure 2). Each view will provide the patient with an image quality score ranging from 0-2 depending on the quality of the view (see Table 1). The score for the different cardiac views, from “No discernable anatomy” to “Great view”, is relied on the level of detection of the left ventricular endocardial border. This criterion applies to all three cardiac views. We expect that a scan consisting of OLD will be characterized by poor PLAX and A4C views and great SX views. Therefore, maximal cardiac score (=6) will be granted to a scan consisting of a great (i.e. when the left ventricle (LV)endocardial border is clear) SX view and no discernable anatomy noticed in the PLAX and A4C views.

*Grading synthesis*

A sum of the cardiac and chest scans will give a final sonographic score between 0 to 10.
a scan most consistent with OLD will be given a score of 10.

In the case of any abnormal finding in the chest or the cardiac POCUS, direct notification to the pulmonologist and the primary caregiver will be given by the research team, as well as written notification in the patient's electronic medical record. The patient and the primary caregiver will be notified that this exam is not a diagnostic cardiac exam focused only on detecting the level of the endocardial imaging quality. If b lines or abnormal left ventricular function are detected, the information will be transferred to involved teams.

**Table 1**

The Sonographic Score Components for the Diagnosis of OLD

| | **Right-sided Anterior chest (A-lines)** | **Left-sided Anterior chest (A-lines)** | **Parasternal long-axis view** | **Apical four-chamber view** | **Sub-xiphoid view** |
|---|---|---|---|---|---|
| **0** | Multiple B-lines or No discernable A-lines | Multiple B-lines or No discernable A-lines | Great view (sub-endocardium noticed) | Great view (sub-endocardium noticed) | No discernable anatomy |
| **1** | 1-2 A-lines | 1-2 A-lines | Acceptable view | Acceptable view | Acceptable view |
| **2** | 3 or more A-lines | 3 or more A-lines | No discernable anatomy | No discernable anatomy | Great view (sub-endocardium noticed) |

*Obstructive lung disease (OLD definition)-*

An umbrella term for diseases characterized by airway obstruction, airflow limitation, and in severe cases air trapping. Within this group and specifically among the adult population, the most common is chronic obstructive pulmonary disease (COPD)(12). Since most adult patients with air trapping encountered have COPD, we will use the terms COPD and OLD interchangeably.

## 4.1 Working Hypothesis

We hypothesize that a high sonographic score (8-10 points) will have at least an equal diagnostic accuracy compared to the reference diagnosis with PFTs.

## 4.2 Objectives

4.2.1 Primary Objective

- To evaluate the validity (sensitivity and specificity) of the diagnostic accuracy of combined lung and cardiac ultrasound in obstructive lung disease (OLD), referring to PFTs as the diagnostic gold standard.

4.2.2 Secondary Objective

- To estimate the association between the sonographic score and the most recent (<5 years) computed tomography (CT) scan score (i.e., emphysema score).
- To estimate the association between the sonographic score and the patient's subjective severity of dyspnea (estimated by the mMRC scale)**.**
- To estimate the association between the sonographic score and the patient's diffusion lung capacity (DLCO).
- To determine the sonographic components that are the most sensitive for the diagnosis of COPD.
- To assess the additive value of the patient's smoking status to the diagnostic accuracy of the sonographic score**.**

## 4.3 Study Population

The study population will be screened at the respiratory institute of Soroka University Medical Center and will include patients who are referred for pulmonary function tests (PFTs) for any reason. The study population will be enrolled according to the following inclusion and exclusion criteria.

4.3.1 Inclusion Criteria-

- Age 18 or above
- Referral for full pulmonary function tests (PFTs)
- Patients are willing and able to sign the informed consent form.

4.3.2 Exclusion Criteria

- Unable to give written informed consent.
- Unable to remain supine.

- Poor effort at PFTs
- Subcutaneous emphysema

#### 4.3.3 Withdrawal Criteria

Participants who are unable or unwilling to complete the study procedures during their pulmonary institute visit or withdraw their consent for the researcher to access their electrical medical record and case report form within the following year after participation will be withdrawn from the study. Nevertheless, the results collected until the point of withdrawal will still be included in the study results as appropriate.

### *4.4* Enrollment

Before participating in this study, the Investigator must obtain written approvals from the ethics committee and other local regulatory bodies as appropriate approval for the protocol and the informed consent form. Failure to obtain a signed and hand-dated informed consent before the procedure constitutes a protocol violation, which is reportable to the EC.

### 4.5 Patient Screening

The screening will be performed at the respiratory institute of Soroka University Medical Center and will include patients who are sent for pulmonary function tests (PFTs) for any reason.

Soroka university medical center is a 1,000-bed university-affiliated referral center in Southern Israel, directly serving a population of over 700,000 and serving as a tertiary hospital for nearly 1 million people.

Patients who are sent for pulmonary function tests (PFTs) for any reason and fulfill all the inclusions and none of the exclusion criteria will be approached and offered participation by a study research member. A study research member will explain the study's purpose, procedures, and intent to each potential participant. Interested patients will be asked to provide written consent before performing any study procedure.

### 4.6 Study Procedures

The study will be performed in a fully paired fashion, i.e., a direct comparison in which all study participants receive the index test (sonographic assessment)and the reference standard (PFTs).

This should enhance the resulting precision relative to the number of study participants. The three following steps are planned to take place at the same visit:

1. Enrollment, including obtaining written informed consent.
2. PFTs, performed as planned.
3. A sonographic evaluation comprised of both lung and cardiac POCUS scans, performed by an experienced sonographer, blinded to the patient's medical history or PFTs results.

Steps two and three can be replaced in order as long as the POCUS operator is blinded to the PFTs results. The PFT technician is not part of the study team and will be blinded to the POCUS findings as well.

### *4.7* Study Duration

The evaluation is estimated to be around 10 minutes from the initial consent and will not interfere with the purpose of the patient's visit. We will collect the sonographic data prospectively based on the POCUS examination performed, while additional medical data will be collected retrospectively from the medical records (as specified below). We expect enrollment in the study to last for approximately twelve months.

## 4.8 Data to Capture

### 4.8.1 Required Data

We aim to collect the sonographic data as well as the PFT results for each participant. Furthermore, we plan to gather descriptive data from the medical records including –

1. Age -continuous variable. Values: above 18.
2. Gender - dichotomic variable (Female=1, Male=0).
3. BMI - continuous variable.
4. Smoking history (pack years)- continuous variable.
5. Comorbidities - nominal variable. Values: dichotomic variable (Yes=1, No=0)
6. Hypertension – ordinal variable. (0=Normal, 1=Elevated, 2= Stage 1, 3 = Stage 2, 4= Hypersensitive crisis). Values: 0=systolic<120 & diastolic<80, 1=systolic=120-129 & diastolic<80, 2=systolic=130-139 & diastolic 80-89, 3=systolic>140 & diastolic>90, 4= systolic>180 & diastolic>110.
7. Diabetes - dichotomic variable (Yes=1, No=0)
8. Other Lung diseases (such as cystic fibrosis, bronchiectasis, Interstitial lung disease, etc) - dichotomic variable (Yes=1, NO=0)
9. Ischemic Heart Disease - dichotomic variable (Yes=1, No=0)
10. Degree of dyspnea (based on the mMRC Dyspnea Scale) - ordinal variable (1=Grade 1 ,2= Grade 2, 3=Grade 3, 4 =Grade 4). See supplements for mMRC dyspnea scaling system.
11. Hemoglobin level (g%) - continuous variable.
12. Latest Venous/Arterial pH- continuous variable.
13. Latest Venous/Arterial HCO3- - continuous variable.
14. Latest Venous/Arterial pCO2- continuous variable.
15. Latest Arterial pO2 - continuous variable.
    a. The blood attributes under investigation will be derived retrospectively from the electronic medical record of the current hospitalization, and blood tests will not be performed as part of this trial.
16. Past computed tomographic scans (most recent and up to 5 years prior) - ordinal variable (0= no emphysema (score 0),1=≤25% emphysema (score 1),2=≤50% emphysema (score 2), 3=≤75% emphysema (score 3),4=>75% emphysema (score 4)).

All required data for this study will be collected via electronic case report forms (eCRF).

### 4.8.2 Data Collection

The final set of CRFs is designed to accommodate the specific features of the trial design. Modification of CRFs will only be made if deemed necessary by Soroka CRC. The CRFs will be filled out manually by the study personnel and or will be collected through the computer services database.

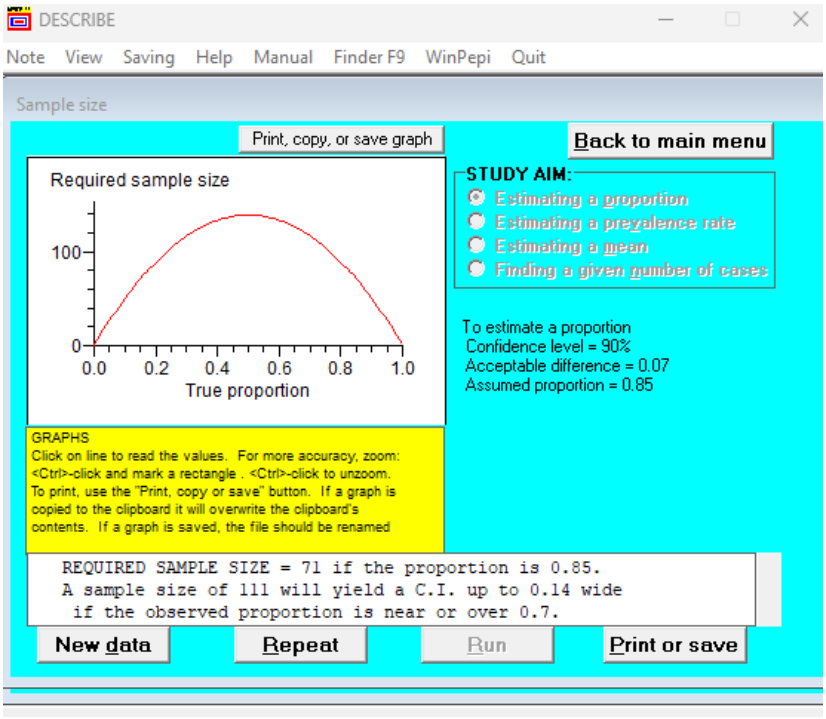
The following data will be collected:

- Demographic data: Age, Gender, BMI
- Detailed medical history, including smoking history, comorbidities, degree of dyspnea reported (based on mMRC score), and recent computed tomographic scan (up to 5 years prior).
- PFT results
- POCUS exam results

# 5 Statistical Considerations and Analysis Plan

## 5.1 Sample Size Considerations

In this study, the sample size calculation was aimed to ensure an accurate estimate of sensitivity (Se) and specificity (Sp) of the POCUS examination vs the gold standard PFTs. We aim to enroll a total of 200 patients. The calculation stems from the speculation that the Se of the test will be 85%, with a confidence interval of 90% and the maximal width of the interval will be up to ±7%.




## 5.2 Statistical Analyses

Data collected in this study will be documented using summary tables. Descriptive statistics will be provided. The statistics for continuous variables will include mean, standard deviation, minimum, maximum, and sample. Categorical variables will be described with numbers and percentages. Comparisons between the groups will be presented with Differences (with 95% Confidence Intervals) and/or P-values. Percentages will be rounded to one decimal place.

**Primary Objective Analyses**

To evaluate the diagnostic accuracy of the "sonographic COPD score" for COPD diagnosis, we will calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We will then construct a Receiver Operating Characteristic (ROC) curve based on the sensitivity and specificity values to evaluate the performance of the POCUS score compared to the gold standard test, the pulmonary function test. The area under the ROC curve (AUC) will be calculated to assess the accuracy of the POCUS score in diagnosing COPD. Performances are evaluated at two different operation points: the first one is at 80% of sensitivity, and the other is at knee-point, which represents the best point reached by the ROC curve, close to the upper left bond. The presence of obstructive lung disease (OLD) detected by both ultrasound and PFTs will be labeled as true positive, the presence of OLD detected only by ultrasound and not by PFTs will be labeled as a false positive, no OLD detected by both ultrasound and PFTs will be labeled as true negative, and the presence of OLD detected by PFTs and not by ultrasound will be labeled as a false negative.

**Secondary Objective Analyses**

- To estimate the association between the sonographic score and the most recent (<5 years) computed tomography (CT) scan score (i.e., emphysema score) - we will use a Spearman's rank correlation coefficient.
- To estimate the association between the sonographic score and the patient's subjective severity of dyspnea (estimated by the mMRC scale)- we will use the Mann-Whitney U test to determine the association between the sonographic score and the mMRC scale.
- To estimate the association between the sonographic score and the patient's diffusion lung capacity (DLCO) - We will use the Mann-Whitney U test to determine the association between the sonographic score and DLCO.
- To determine the sonographic components that are the most sensitive for the diagnosis of OLD - we can use a logistic regression analysis. The regression will provide estimates of the effect of each sonographic component on the probability of being diagnosed with OLD. In this analysis, we can use the sonographic components as predictor variables and OLD diagnosis as the outcome variable.
- To assess the additive value of the patient's smoking status to the sonographic score's diagnostic accuracy- will be based on a logistic regression analysis. In this analysis, we can use the sonographic score and smoking status as predictor variables and OLD diagnosis as

the outcome variable. The regression will provide estimates of the effect of each predictor on the probability of being diagnosed with OLD, as well as an estimate of the additional effect of smoking status beyond the sonographic score.

All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha$=0.05 (2-sided) or $\alpha$=0.025 (1-sided), except for those specified otherwise. All p-values reported will be rounded to three decimal places. All statistical analyses will be conducted using SPSS 29.0 statistical software (IBM Corp Armonk, NY, USA).

### 5.3 Primary Endpoints

Our primary endpoint is to diagnose OLD with POCUS examination (compared to the PFT which is considered the gold standard).

## 6 Adverse Events

There are no known adverse events to the point-of-care ultrasound exam.

### 6.1 Adverse Event Definition

#### 6.1.1 Adverse Event

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical events) occurring to a subject, that is considered related to the investigational treatment regimen prescribed as part of the clinical protocol, predefined in the clinical protocol, and/or Instructions For Use, that is identified or worsens during a clinical study.

#### 6.1.2 Treatment-related Adverse Event

A treatment-related adverse event is defined as any adverse event, for which a causal relationship between the treatment and the event is at least a reasonable possibility, i.e., the relationship cannot be excluded.

#### 6.1.3 Serious Adverse Event

A serious adverse event is considered one of the following: Death, Life-threatening, Hospitalization (initial or prolonged), Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/ structure, physical activities, or quality of life, Congenital anomaly or requires intervention to prevent permanent impairment or damage.

In the event of a serious adverse event, the investigational site must inform the EC up to 48 hours after becoming aware of the event. An initial written report will be provided to the EC within 2 working days after the investigator learns of an unanticipated adverse treatment effect. All unanticipated adverse effects are to be reported throughout the entire time that the patient remains active in the study.

### 6.2 Intensity of Adverse Event

The following categories of the intensity of an adverse event are to be used:

- Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment, and with no sequelae;
- Moderate: Interferes with the subject's usual activity, but the subject is still able to function.
- Severe: Events that interrupt a subject's usual daily activity and generally require a systemic device therapy or other treatment.

### 6.3 Anticipated Adverse Event

In this study, we do not anticipate adverse events.

### 6.4 Outcome

The clinical outcome of the event at the time of the last observation will be characterized as follows:

1. Not Recovered/Not Resolved
2. Recovered/Resolved
3. Recovered/Resolved with Sequelae
4. Recovering/Resolving
5. Fatal
6. Unknown

### 6.5 Treatment or Action Taken

The Principal Investigator will decide whether the subject needs any additional treatment or withdraw the subject from the study. In any case of detection of any cardiac or lung abnormality, a formal notification- verbal as well as written will be placed. The notification of any abnormal finding will be transferred to the pulmonologist as well as to the medical team from the referral unit.

### 6.6 Documentation

All adverse events, from signing the informed consent until EOS, whether observed directly or reported by the patient, will be collected and recorded. Non-serious adverse reactions or events are not required to be reported in an expedited manner but will be recorded on the data collection forms.

Serious Adverse events must be listed on the appropriate CRF. All SAEs will be characterized by the following criteria:

1. Relatedness
2. Outcome
3. Treatment or action taken.

All SAEs must be recorded on the SAE Form within 48 hours of the research staff becoming aware of the event.
For each SAE, the following information will be collected: full details in medical terms with a diagnosis, if possible, its duration (start and end dates; times, if applicable), action taken, outcome and causality in the opinion of the investigator (must be made by a doctor).

### 6.7 Expedited Reporting of Serious Adverse Events

The procedure for reporting any Serious Adverse Event is as follows:

1. Report any serious adverse event to the EC according to the investigational site's EC procedures.
2. Complete appropriate Event Form(s) for any complication and/or serious adverse events.
3. Submit physician/nurse notes or discharge summaries related to the reported event, as requested.

4. Report of a subject death must be along with a brief statement of the pertinent details, and the death records/certificate or autopsy report, if available/performed.

Clear pathways have been developed for the reporting and analysis of serious adverse events. Study site personnel are responsible for SAE identification. SAEs are reported by the site to the local EC, the sponsor within 48 hours of becoming aware of the event.

# 7 Ethical and Regulatory Considerations

# 8 Subject Confidentiality

Subject confidentiality will be maintained throughout the study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows the identification of all data reported for each subject.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the subject's privacy is guaranteed.

## 8.1 Sources of Materials

No tissue or any other physical specimen will be taken from the patients.

All of the data obtained for this study will be obtained prospectively.

Copies of data obtained as part of the study will be retained by the clinical research center, with appropriate source documentation, on all subjects that sign informed consent. The data utilized in this study are described above and consist of information from medical records or study-specified measures and interventions.

## 8.2 Maintaining Records

The principal investigator will maintain copies of all study-related correspondence, regulatory documents, data, shipment of supplement accountability logs, adverse supplement effects and

other records related to the clinical study. The principal investigator will maintain records related to the signed Investigator Agreements.

### 8.3 Site Record Retention Policy

All core laboratories and clinical sites will maintain study records until the principal investigator notifies them and the reviewing regulatory authorities that research is completed or terminated under the clinical investigation in compliance with national law. Record retention dates will be provided to study sites by the principal investigator at the onsite closeout visit.

### 8.4 Informed Consent and Ethics Committee

All subjects must provide written informed consent in accordance with the local clinical site's EC. A signed Informed Consent must be obtained from each subject prior to commencing screening/baseline evaluations. One copy of the Informed Consent document will be given to the subject and another retained by the Investigator.

### 8.5 Protocol Deviation

Any incident in which the investigator or site personnel did not conduct the study according to the clinical protocol or the investigator' agreement.
Protocol deviations are classified to three categories:

- Major deviation: Any deviation from subject inclusion and exclusion criteria or subject informed consent procedures.
- Critical finding: any deviation that can affect the wellbeing of the participant, or the reliability of the data collected is compromised.
- Minor deviation: Deviation from a clinical protocol requirement such as incomplete/inadequate testing procedures, follow-ups performed outside specified time windows, etc.

## 9 References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## 10 Supplements

- Modified Medical Research Council (Dyspnea Scale)

| Grade | Degree of breathlessness related to activities |
|---|---|
| 0 | I only get breathless with strenuous exercise. |
| 1 | I get short of breath when hurrying on the level or walking up a slight hill. |
| 2 | I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level. |
| 3 | I stop for breath after walking about 100 m or after a few minutes on the level. |
| 4 | I am too breathless to leave the house or I am breathless when dressing or undressing. |