STUDY PROTOCOL SYNOPSIS

Airway clearance therapy with SIMEOX technology in non-CF Bronchiectasis patients with Chronic Mucus Hypersecretion

A Multicenter Randomized Controlled Trial Pilot study

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Sponsor	**PhysioAssist** 31 Parc du Golf – CS 90519 13593 AIX-EN-PROVENCE Cedex 3 France

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TITLE	Airway clearance therapy with SIMEOX technology in non-CF Bronchiectasis (NCFB) patients with Chronic Mucus Hypersecretion (CMH). A Multicenter Randomized Controlled Trial Pilot Study
COORDINATING INVESTIGATOR	Prof. Wojciech PIOTROWSKI, MD, PhD
SPONSOR	Physio-Assist (France)
RATIONALE / CONTEXT	Non-cystic fibrosis bronchiectasis (NCFB) is a chronic respiratory disease with multiple etiologies characterized by an irreversible dilatation of bronchi and an impair mucociliary clearance. These alterations cause sticky mucus retention and leads to recurrent infections and chronic bronchial inflammations. Chest physiotherapy is one of the cornerstones of the management of NCFB patients, particularly to facilitate airway clearance. In NCFB patients with chronic mucus hypersecretion (CMH), it is recommended that airway clearance sessions be carried out daily or several times a day, which represents a very significant burden of care. Moreover, access to respiratory physiotherapy for patients can be limited due to several causes: geographical, time or healthcare professional availability constraints. In addition, few healthcare professionals are trained for bronchial drainage especially with airway clearance devices. SIMEOX® (Physio-Assist, Aix-en-Provence, France) is an innovative medical device (CE medical mark) for mucus clearance. The device is connected to patient mouth with an expiratory kit circuit. When the patient starts up the device during exhalation only, SIMEOX® disseminates a vibratory pneumatic signal in the bronchi that liquefies mucus and transports it from distal to central airways for sputum expectoration. After device training with respiratory physiotherapist, patients can be treated at hospital and use SIMEOX® in autonomy at home. Device training and patient follow-up can be performed also remotely with telecare with similar efficiency than face to face visits with health care professionals. The main objective of this Pilot study is to evaluate the effects of mid-term use of SIMEOX® in autonomy at home for 2 months in NCFB patients with CMH and pulmonary exacerbation (in- or outpatients) in comparison to standard of care.
METHODOLOGY	Multicenter, open-labelled, two-arm parallel groups, Randomized Controlled Trial Pilot study
OUTCOMES	Evaluate telecare feasibility and benefits of Simeox technology on lung function, respiratory symptoms, health-related quality of life, subjective efficiency, device adherence at home, Patient satisfaction, tolerance, and safety:

	i. To describe the self-reported adherence (collected during follow-up with telecare) evolution at home over follow-up (1week to 2 months) and rate of adherent patients (at least 4 sessions/week); ii. To describe Simeox therapy settings during follow-up; iii. To evaluate subjective efficiency of Simeox therapy during follow-up; iv. To evaluate session comfort and tolerability with the device during follow-up; v. To evaluate patient satisfaction with Simeox device after 2 months of use at home; vi. To determine factors associated with high adherence (at least 4 sessions/week); vii. Evaluate the feasibility of telecare during follow-up; viii. To evaluate the effect of Simeox on the health-related quality of life of NCFB patients after 2 months use at home; ix. To evaluate the effect of Simeox on respiratory function at home; x. To evaluate the effect of Simeox on dyspnea at home; xi. To evaluate the effect of Simeox on exercise capacity xii. To evaluate safety of Simeox
ENDPOINT MEASURES	The endpoint measures will be as follows: i. The evolution of device adherence will be described by % of self-reported sessions (0-1; 2-3; 4-7/week) by the patient over the 2-month FU (1 week, 2 weeks, 1 month and 2 months) ; ii. Simeox settings will be described by program selection, intensity, number of sessions per day and session duration; iii. Subjective device efficiency will be evaluated by mucus and breathing quality during follow-up; iv. Session comfort and tolerability with the device during follow-up will be described by the ease of exhaling, and pain and fatigue level; v. Patient satisfaction with the SIMEOX device will be estimated at 2 months during telecare by ease of use, ease of handle, like, preference, recommendation. vi. Correlations between self-reported adherence and baseline factors age, gender, bronchiectasis etiology, dyspnea, BSI, co-morbidities, and number of calls with telecare during follow-up; vii. Feasibility of telecare during follow-up will be estimated by number of call visit scheduled in the protocol and complete filling of the observation form; viii. The change in quality of life from baseline to 2-month FU will be measured with the Chronic Airways Assessment Test (CAT) questionnaire and the St Georges Respiratory Questionnaire. ix. The change in respiratory function from baseline to 2-month FU will be estimated on the following parameters between baseline and hospital discharge: Forced Vital Capacity % of predictive value

	(%FVC pred), Forced Expiratory Volume in 1 second % of predictive value (%FEV1 pred), FEV1/FVC ratio, Forced expiratory flow at 25% to 75% of forced vital capacity (%FEF 25-75 pred); Peak expiratory flow; residual volume % predictive value (% RV pred) x. The change in dyspnea from baseline to 2-month FU will be measured with the modified Medical Research Council (mMRC) xi. The change in walking distance from baseline to 2-month FU will be measured with the 6-min walking test (6MWT) xii. The safety of Simeox will be assessed by the rate and severity of Side effects
INCLUSION CRITERIA	✓ Patient with confirmed diagnosis of bronchiectasis confirmed by High Resolution Computed Tomography (HRCT): idiopathic, post-infective, systemic disease, ABPA, asthma, COPD, PCD… ✓ Overproduction of mucus (ie: estimated bronchorrhea >10mL/day). ✓ Pulmonary exacerbation (in- or outpatients) ✓ Age > 18 years old ✓ Patient able to understand the study and to perform the 2-month follow up visit
EXCLUSION CRITERIA	× Pneumothorax/pneumo-mediastinum in the six months prior hospitalization × Recent episode of severe haemoptysis × Unstable severe cardiac disease or hemodynamic instability × Cystic fibrosis or COPD as dominant diagnosis × Patient on lung transplant list × Severe lung injuries × Recent lung surgery × Inhalation support (continuous ventilatory support) × Tracheostomy × Uncontrolled GERD × Any contraindication to an instrumental bronchial clearance technique (up to the investigator) × Inability to perform PFT or 6MWT × Patient not available or wishing to move to a different region within 2 months of inclusion × Patient considered by the investigator to be physically or mentally inapt to use the device and/or to perform the study procedures. × Patient currently participating or having participated within one month prior to inclusion in a clinical intervention research trial that may impact the study, the impact of which is up to the investigator.
SAMPLE SIZE	50 patients will be recruited and randomized in the study (Simeox + Standard of care vs Standard of Care alone) Sample size calculation: Unanticipated issues with a prevalence of 5% will be identified (with 90% confidence) in this pilot study including 45 participants + 10% of lost to follow up, for a total of 50 patients.

<table>
<tr><td></td><td>Viechtbauer, W., Smits, L., Kotz, D., Budé, L., Spigt, M., Serroyen, J., & Crutzen, R. (2015). A simple formula for the calculation of sample size in pilot studies. Journal of Clinical Epidemiology, 68, 1375-1379.</td></tr>
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<tr><td>STUDY PROCESS</td><td>Data collection in:
- Inpatients (hospitalized for pulmonary exacerbation) or outpatients with Pulmonary exacerbation randomized in the study, treated with Simeox + SoC (Simeox group, n=25) or SoC alone (Control group, n=25)
AND then
- Trained/treated at home for 2 months in their respective study group (Simeox or Control)

Physio-Assist will provide Simeox devices and consumables needed for the study.

• Baseline visit at hospital discharge
• Telecare visits at 1 week, 2 weeks and 1 month after hospital discharge;
• Hospital visit at 2 month (last FU visit)
<table>
<tr><th>Visits</th><th>Baseline</th><th>1-week</th><th>2-week</th><th>1-month</th><th>2-months</th></tr>
<tr><td>Randomization</td><td>x</td><td></td><td></td><td></td><td></td></tr>
<tr><td>PFT</td><td>x</td><td></td><td></td><td></td><td>x</td></tr>
<tr><td>6MWT</td><td>x</td><td></td><td></td><td></td><td>x</td></tr>
<tr><td>mMRC</td><td>x</td><td></td><td></td><td></td><td>x</td></tr>
<tr><td>CAT, SGRQ</td><td>x</td><td></td><td></td><td></td><td>x</td></tr>
<tr><td>Telecare</td><td></td><td>X</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td><td></td><td></td><td>x</td></tr>
<tr><td>Sub efficiency</td><td></td><td>X</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Simeox tolerance</td><td></td><td>X</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Simeox adherence</td><td></td><td>X</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Side effects</td><td></td><td>X</td><td>x</td><td>x</td><td>x</td></tr>
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<tr><td>RANDOMIZATION</td><td>Sealed envelopes will be distributed to all study centers.
Randomization will be stratified according to participating study centers to avoid center effect.</td></tr>
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DATA ANALYSIS	**General statistics:** Descriptive statistics will be presented for all the variables collected. Qualitative variables will be presented by percentages and counts, quantitative variables by means and standard deviations, or by medians and first and third quartiles according to their distribution. Unpaired t-test or Wilcoxon-Mann-Whitney test (according to the distribution) will be used to assess: - Comparison between groups of the change in health-related quality of life, from baseline to 2-month follow-up with the CAT and SGRQ questionnaires - Comparison between groups of the change in lung function from baseline to 2-month follow-up, estimated by the following parameters: Forced Vital Capacity (FVC), Forced expiratory Volume in 1 second (FEV1), FEV1/FVC ratio, forced expiratory flow at 25% to 75% of forced vital capacity (FEF 25-75). - Comparison between groups of the change in mMRC from baseline to 2-month FU - Comparison between groups of the change in 6-min walking distance from baseline to 2-month FU Fisher test will be used to assess comparison between groups of adverse events and new pulmonary exacerbations over 2-month FU High adherence will be described by the % of patients performing on average at least 4 sessions/week between phase training and follow-up (self-reported adherence by the patient at 1 week, 2 weeks, 1 month and 2 months). The relationship between high self-reported adherence with the SIMEOX® device (>4 sessions/week versus <4 sessions/week) and age, dyspnea, BSI and number of telecare will be studied using the Mann and Whitney test. The links between high adherence to the SIMEOX® device and gender, BE etiology and co-morbidities will be studied using the Fisher test. Statistical Plan of the study will be described before the end of last patient follow-up.
MEDICAL DEVICE UNDER EVALUATION	SIMEOX® device (Physio-Assist, France)
CALENDAR	Anticipated start of the study: October 2023 Anticipated length of study: 12 months Anticipated end of the study: November 2024
EXPECTED OUTPUTS	Telecare is a key element in improving access to healthcare and the quality of care. If the solution Simeox and telecare proposed in this project is feasible (regular telecare by a physiotherapist for Simeox device training and follow-up), safe and efficient, it could be implementing more largely in health care organization for telecare in patients with chronic respiratory disease like non-cystic fibrosis bronchiectasis. Physio-Assist wishes to implement a large-scale European trial using the solution proposed in this project. This pilot study will allow, on the one

	hand, to make a sample size calculation based on these data, on the other hand, to evaluate and adapt, if necessary, the procedures for carrying out the future trial.