MEDICO-ECONOMIC PROTOCOL

Supported by the General Administration of the offer of care

(Direction Générale de l’Offre de Soins)

Support for Costly Innovative Therapies – STIC 2012

Soutien aux Thérapeutiques Innovantes Coûteuses (STIC) 2012

REVOLENS

MEDICO-ECONOMIC EVALUATION OF ENDOBRONCHIAL

LUNG VOLUME REDUCTION WITH COILS.

(ÉVALUATION MÉDICO-ÉCONOMIQUE DE LA RÉDUCTION VOLUMIQUE PAR VOIE
ENDOBRONCHIQUE AU MOYEN DE SPIRALES)
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### 1. GENERAL INFORMATION

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<th><strong>ANSM Registration number</strong></th>
<th>2012-A01477-36</th>
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</thead>
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<tr>
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<tr>
<td><strong>Research Title</strong></td>
<td>Medico-Economic Evaluation of Endobronchial Volume Reduction Using Coils.</td>
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<tr>
<td><strong>Abbreviated Title</strong></td>
<td>REVOLENS</td>
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<tr>
<td><strong>Research Code</strong></td>
<td>STIC 2012</td>
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<td><strong>Research Category</strong></td>
<td>Superiority trial</td>
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<td><strong>Data and Safety Monitoring Board</strong></td>
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<td><strong>Anticipated study start date</strong>:</td>
<td>01/Jan/2013</td>
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<td><strong>Anticipated study completion date</strong>:</td>
<td>01/Jan/2015</td>
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<td><strong>Subject Follow-up</strong>:</td>
<td>12 months</td>
</tr>
<tr>
<td><strong>Number of study subject</strong>:</td>
<td>100 patients (50 per group)</td>
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**If YES, provide a brief description of the risk/benefit analysis**

Standard of Care for COPD emphysema patients provides limited improvement to breathing ability. Endobronchial volume reduction using coils is possible with a short hospitalization (48 hours) and provides benefits at least equal to Lung Volume Reduction Surgery, with less associated morbidity.
Summary

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Research Title

Medical Background:
Chronic Obstructive Pulmonary Disorder (COPD) is defined by permanent and progressive obstruction of airways, caused by reduction in the small airways (bronchioles) cross-sections and enlargement of the airspaces distal to the terminal bronchioles with destruction of airspace walls, without obvious fibrosis (emphysema). The most common cause of COPD is smoking. The primary clinical consequence of emphysema is exertional dyspnoea, which eventually can become very incapacitating, occurring during minimal efforts or even at rest.

Current available treatments for severe COPD with emphysema (smoking cessation, flu and pneumococcal vaccination, pulmonary rehabilitation short or long-acting bronchodilators, corticosteroids, supplemental oxygen, depending on the stage of COPD) have only limited impact on the respiratory functional impairment.

Lung Volume Reduction to treat emphysema was first developed as surgical techniques. The objective was to improve lung mechanics by reducing hyperinflation and resecting the emphysematous lung tissue. The functional benefits of Lung Volume Reduction Surgery (LVRS) were demonstrated, but at a price of significant morbidity and non-negligible mortality. Various endobronchial volume reduction methods have recently been developed, with the goal of attaining a clinical benefit as significant as Lung Volume Reduction Surgery, but with less mortality and morbidity.

Volume Reduction Using Coils was developed by PneumRx, Inc. (Mountain View, CA USA). The therapeutic concept is to provide a mechanical broncho-pulmonary compression using coils placed in the treated lobes, which causes a reduction in dead space and in hyperinflation.

Objectives
- Primary: demonstrate that volume reduction using coils provides a significant improvement in exercise capacity (improvement of at least 54 meters in the 6 Minutes Walk Test) at 6 months as compared to standard medical care in severe emphysema.
- Secondary:
  - Evaluate and compare the two groups in terms of clinical status (dyspnea, walking), lung functions and quality of life.
  - Evaluate the feasibility and the safety of endoscopic volume reduction using coils.
  - Evaluate and compare the two groups in terms of mortality and serious and non-serious morbidity at 12 months.
  - Perform a medico-economic study comparing the two strategies (cost-benefit and cost effectiveness).
### Material and Methods

**Study design:** superiority, prospective, randomized, multicentre (10 sites), open label trial.

**Study population / patients:**
The primary inclusion criteria are: severe bilateral emphysema (FEV1 <50%), symptomatic (dyspnea ≥2 on the mMRC scale).
The primary exclusion criteria are: anticoagulant therapy, post-bronchodilator improvement of FEV1>20%, frequent and serious respiratory infections, pulmonary hypertension, inability to perform the 6MWT (6 Minutes Walk Test), giant bullae > 1/3 of the lung volume, and contra-indications to general anaesthesia.
The group assignments will be randomized. Randomization will be centralized and done with a ratio of 1/1 by blocks of 4.
The population calculation to achieve the primary endpoint was made with the following hypotheses: 37% responder rate in subjects treated with volume reduction (data provided by PneumRx), and responder rate of 5% in subjects getting standard medical care. With a significance level of 5%, a power of 90% and a unilateral test, the Nquery software estimated that 32 subjects per group would be needed. Taking into account the expected number of non-evaluable patients at 6 months (30%), the number of subjects per group was estimated at 50, for a total number of subjects estimated at 100.

**Investigational Plan:**
- Subjects will be randomized after informed consent and checked the inclusion and exclusion criteria
- All subjects will be followed for 12 months after randomization, with systematic follow up evaluations at 1, 3, 6 and 12 months. The follow-up evaluations will consist in: complete medical examination, dyspnea and quality of life questionnaires, pPulmonary Function Tests (PFT), arterial blood gases on room air, 6MWT on room air, and a thoracic x-ray.
- All subjects randomized in the coil treatment group will be treated in the target lobe within 15 days after randomization (Treatment a). Treatment in the contralateral lung will be performed at least 1 month and no more than 3 months after the initial treatment (Treatment b).
- A Data and Safety Monitoring Board will be established. All Adverse Events (serious, non-serious, anticipated and unanticipated) will be collected.

**Study oversight:**
The different participating sites will collect their data. The data will be centralized and analyzed at CHU de Reims.

**Study calendar:**
Recruitment/enrolment will begin on January 1, 2013 and will last 12 months. With a 12 months patient follow-up, the end of the study is anticipated to be on January 1, 2015.

**Statistical Analysis Plan:**
- Comparison of the characteristics of the two groups.
- Analysis of the primary endpoint (Intention to Treat): comparison of the percentage of "responders" in the two groups by a Chi2 or exact Fisher test, study of other factors associated with the response to the treatment by a univariate analysis (Student, Wilcoxon, Chi2 or Exact Fisher test) and multivariate analysis (logistic regression) examining the factors associated independently from the response to treatment.
- Analysis of the secondary endpoints: comparison of the two groups regarding the progression of dyspnea, lung function, quality of life and morbidity and mortality.
- A medico-economic, cost-benefit and cost-effectiveness study will also be performed.
Expected results and Perspectives
The expected benefit of the research is to validate, by way of a multicentre, randomized study, the clinical effectiveness and the interest in terms of efficiency of endoscopic volume reduction using coils to treat severe emphysema. The expected benefit is to validate an innovative, minimally invasive technology requiring only a short hospitalization (48 hours), associated with a morbidity significantly inferior than Lung Volume Reduction Surgery. The medico-economic study will allow a precise evaluation of the economic impact of this innovative therapy and will estimate: 1) the cost of the innovative procedure, 2) the global cost of caring, and 3) the comparison of the cost to the cost of the standard of care. This study will allow a clear determination of the place of this innovation in the therapeutic caring of patients who suffer from severe emphysema.
2. SCIENTIFIC JUSTIFICATION OF THE RESEARCH

2.1. Pulmonary emphysema

Chronic Obstructive Pulmonary Disorder (COPD) is defined by a permanent and progressive obstruction of airways, caused by an association, that varies among patients, of a reduction in calibre of the small airways (bronchioles) and an abnormal and permanent enlargement of airspace distal to terminal bronchioles (emphysema). (Recommendations of the French Language Pulmonary Society - SPLF- on the caring of COPD, 2010; GOLD, 2011; McDonough, 2011). The diagnosis of COPD relies on spirometric evidence of irreversible bronchial obstruction, defined by a post-bronchodilator Forced Expiratory Volume in one second (FEV1) on Forced Vital Capacity (FVC) ration of less than 70%. The level of spirometric severity of COPD is defined according to the recommendations of the Global initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD, 2011) by function of the value of FEV1: Stage 1 (mild): FEV1 between 80 and 100%; Stage 2 (moderate): FEV1 between 50 and 80%; Stage 3 (severe): FEV1 between 30 and 50%; Stage 4 (very severe): FEV1 <30% of <50% associated with chronic respiratory insufficiency. In the latest GOLD 2011 recommendations, a classification in 4 groups (A, B, C, D) was proposed, based on an evaluation combining the level of severity of bronchial obstruction, the level of exertional dyspnea, and the number of exacerbations per year, classifying the patients in groups more or less symptomatic and at more or less high risk. By way of example, a patient with an FEV1 less than 50% and with dyspnea at least equal to 2 on the mMRC scale is classified in Group D, corresponding to the group of patient most symptomatic and at high risk.

The physiopathology of emphysema is complex and multifactorial associating principally the mechanisms of inflammation, oxidation, and impairment in the protease/anti-protease balance, most often associated with inhalation of particles or toxic inhalations (Tarasevience-Stevart, 2008; Deslee, 2009, Bourdin, 2009, Fischer, 2011, Burgel, 2011). The most common cause of COPD associated with emphysema is smoking. Several professional or domestic exposures also constitute risk factors for emphysema (Salvi, 2009). The deficiency of alpha-1 antitrypsin (neutrophilic elastase inhibitor) constitutes a risk factor for the development of emphysema (Thabut, 2008).

Pulmonary emphysema causes a reduction in elasticity associated with hyperinflation that increases with effort, characterizing dynamic hyperinflation (Peunte-Maestu, 2006; Celli, 2008). The alveolar destruction decreases the The primary clinical consequence of emphysema is exertional dyspnoea, which eventually can become very incapacitating, occurring during minimal efforts or event at rest. The quality of life of severe COPD patients is severely impaired (GOLD stages 3 and 4). The limitation on exercise capacity contributes to global muscular and cardiovascular deconditioning, as well as to social isolation (Celli, 2008, Moy, 2009).

2.2. Standard of Care for Patients Suffering from Pulmonary Emphysema

In all stages of COPD, smoking cessation, influenza and pneumococcal vaccinations, and short acting bronchodilators as needed, are recommended. For stages 2, 3 and 4, pulmonary rehabilitation and long-acting bronchodilators (beta-2 agonist and/or
anticholinergic) are recommended (Recommendations of the French Society for Pulmonology Society – SPLF - for the management of COPD, 2010, Alifano, 2010, Roche, 2011). Inhaled cortico-steroids are not recommended with long-acting bronchodilators except for stages 3 and 4 (FEV1 < 50% or <60% with salmeterol/fluticasone association) with frequent exacerbations (≥ 2/year). Long-term oxygen therapy (LOT) is indicated in case of hypoxemia with a PaO₂ < 55 mmHg measured with two arterial blood gases at rest, in stable state, with medical treatment and performed at least 15 days apart. If 55 ≥ PaO₂ >59 mmHg, Lot is indicated in the presence of at least one of the following elements: pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg), clinical signs of chronic pulmonary heart, arterial O₂ desaturation during sleep in the absence of sleep apnoea, polycythaemia (hematocrit >55%).

It is important to highlight that available treatments for severe COPD/emphysema are of limited effectiveness on functional respiratory impairment.

The surgical treatments currently available for severe emphysema are LVRS (Nanheim, 2006, Criner, 2011), which is of limited application because of significantly associated morbidity and mortality; and lung transplantation (Quetant, 2010, Mal, 2011), which is limited by the number of available grafts. Currently in France there are no endoscopic lung volume options available outside of clinical trials.

### 2.3. Endoscopic Volume Reduction Using Coils

#### The concept of volume reduction

Lung Volume Reduction for emphysema was first developed as a surgical technique (Brantigan, 1957, Cooper, 1996). The objective was to improve lung mechanics by resecting the emphysematous lung tissue to achieve a reduction in hyperinflation. The functional benefits of surgical volume reduction have been demonstrated (Fessler, 1998, Geddes, 2002, Fessler, 2002, Ingenito, 2003) and confirmed by data from the NETT study (Nanheim, 2006, Criner, 2011), but at a cost of high morbidity and non-negligible mortality (7.9% death rate after 3 months in the NETT study). Due to the morbidity and mortality associated with LVRS, the technique is currently infrequently used.

#### Endobronchial volume reduction techniques

Several endoscopic volume reduction techniques have recently been developed, with the aim of providing a clinical benefit as significant as surgical techniques, but with less morbidity and mortality (Delage, 2011, Marquette, 2011).

Two endoscopic volume reduction techniques were evaluated in randomized studies, using the concept of regional change of airflow by using one-way valves (Sciurba, 2010) or by creating communication bypassing emphysematous zones and bronchi (Shah, 2011). The results of these randomized studies were disappointing, showing limited effectiveness for valves due to frequent inter-lobar collateral ventilation and the absence of effectiveness for the by-pass technique. The results at 6 months in the randomized valve study showed a different between the 2 groups (treatment/control) of +19.1 meters for the 6MWT and +1.9% in FEV1. In practice, two factors limit the effectiveness of the endobronchial valves: malposition of the valves and the existence of collateral ventilation between lobes, which is difficult to determine pre-treatment (Votruba, 2011) and very frequent with severe emphysema, which automatically excludes a large number of patients from being able to
benefit from this technique (Sandek, 2002; Marshall, 2012) Collateral ventilation detections
techniques currently allow a better response predictor for endobronchial valve treatment.
The ineffectiveness of the by-pass technique (Shah, 2011) is due essentially to the rapid
obstruction of the by-pass by reactive tissue.

Other endobronchial techniques are currently being developed, endoscopically introducing
to the bronchi biologic glues ("biological lung volume reduction") (Herth, 2011) or thermal
steam (Shell, 2011), which cause volume reduction by retracting the treated portion of the
lung. The results of these feasibility studies have shown their feasibility with low morbidity
and interesting clinical and functional effectiveness, but they still need to be demonstrated
by randomized studies.

**Description of the volume reduction technique using coils**

The technique of Volume Reduction with Coils was developed by PneumRx (Mountain
View, CA USA). The therapeutic concept is that of a mechanical effect of broncho-
pulmonary retraction caused by coils at the level of the treated lobes, leading to a
reduction of dead space and hyperinflation, two major factors responsible for respiratory
impairment in emphysema.

The treatment is performed using general anaesthesia and under fluoroscopic control.
The coils are deployed using a catheter through the working channel of a flexible
bronchoscope. After positioning a radiopaque guidewire in the target segment, the
catheter is placed using fluoroscopy. The coil is then inserted to the distal end of the
catheter. After retraction of the catheter, the coil, which was in a straightened
configuration in the catheter, regains its coil shape, causing a broncho-pulmonary
retraction effect. The treatment of one lung requires 8 to 10 coils implantation for optimal
effect. The average time of a procedure ranges from 30 to 60 minutes. One lobe is
treated per procedure; the contralateral lobe treatment is performed in a second procedure
one to three months later.

**Data from volume reduction using coils**

A prospective, cohort study (Slebos, 2011) validated the clinical effectiveness of volume
reduction using coils for treatment of severe emphysema. 16 patients were treated
unilaterally (n+4) or bilaterally (n=12) for a total of 28 procedures. The patients had severe
respiratory obstruction (mean FEV1: 28%) and heterogeneous emphysema. The
morbidities in the first 20 days after the 28 procedures were as follows: 1 pneumothorax
(4%), 2 pneumonias (7%), 6 COPD exacerbations (21%), 4 occurrences of thoracic pain
(14%), 21 minor haemoptysis, less than 5 cc/24 hours, (75%) and no haemoptysis greater
than 5 cc/24h. All events were resolved with standard care, without sequelae. The
effectiveness at 6 months was as follows: increased in exercise capacity, with an
improvement in 6MWT of 84 +/- 73 m, improvement in lung function (FEV1 + 14.9 +/- 17%,
Forced Vital Capacity + 13.4 +/- 12.9%, Residual Volume -11.4 +/- 9%), improvement in
quality of life measured by SGRQ (-14.9 +/- 12.1 points (p<0.05 for all endpoints).

PneumRx confidentially provided supplemental safety and efficacy data from international
feasibility studies sponsored by PneumRx in Germany, France and the Netherlands, and a
randomized trial performed in the UK (complete document provided by PneumRx is
attached in the annex).
With regard to safety, the Adverse Events reported in the first 30 days after the volume reduction using coil procedure in 138 patients who underwent a total of 250 procedures were as follows: 28 COPD exacerbations (11.2%), including 10 serious COPD exacerbations (4%), 67 haemoptysis (26.8%) including 2 serious haemoptysis (0.8%), 18 pneumonias (7.2%) including 12 serious pneumonias (4.7%), 19 episodes of dyspnea (7.6%) including 3 serious episode of dyspnea (1.2%), 13 pneumothorax (5.2%) including 2 serious pneumothorax (0.08%). To reduce the risk of puncturing the pleura and thus causing pneumothorax during the procedure, the IFU was revised to recommend a less distal placement of the coils: the catheter should not be extended more than 100 mm from the end of the bronchoscope, and should be kept least 3.5 cm from the pleura. The effectiveness data on 83 patients, in 166 procedures, shows the following for the evaluated patients: 1) 6 Minutes Walk Test (6MWT): +49 +/- 8 m at 6 months and +62 +/- 12 m a 12 months; 2) Residual Volume: -12 +/- 1.5% at 6 months and -10 +/- 2% at 12 months; 3) FEV1: +17 +/- 3% at 6 months and +12 +/- 4% at 12 months; 4) Quality of life questionnaire SGRQ: -11 +/- 1 points at 6 months, -12 +/- 2 points at 12 months (p<0.01 for all variables). The preliminary data from the randomized trial in the UK shows at 4 months a significant difference in favour of the treatment group for improvement in 6MWT (difference greater than 60 meters) and in reduction of residual volume (difference greater than 0.6L).

In addition, a post-hoc analysis looked at the correlations between the effectiveness results and the heterogeneity or homogeneity of the emphysema. Using a visual score for quantification of emphysema damages used in prior studies such as the NETT trial, there was no significant difference in effectiveness results between patients with homogeneous emphysema as compared to those with heterogeneous emphysema.

2.4. Justification of the research

The standard medical treatments for severe emphysema have very modest effectiveness on functional lung impairment. Lung Volume Reduction Surgery has shown clinical effectiveness, demonstrating the validity of the therapeutic concept, but the use of LVRS is limited because of elevated mortality, significant morbidity and prolonged hospital stay. The number of available grafts limits lung transplantation. The development of endobronchial techniques has risen in the past years, with the goal of achieving a significant lung volume reduction effect with lesser mortality and morbidity as compared to the invasive techniques. The endobronchial techniques that have been evaluated in randomized studies, such as one-way valves and the by-pass technique have shown limited effectiveness, necessitating the pursuit of research and innovation.

The technique of volume reduction using coils is a significant therapeutic innovation, using for the first time a mechanical effect of broncho-pulmonary retraction to treat severe emphysema. This technique has demonstrated its feasibility with a modest morbidity and has shown effectiveness on dyspnea, lung function and quality of life. This technique requires only a short, 48 hours, hospital stay per procedure.

The experience and the strong involvement of the French teams in the development of innovative therapies in the field of volume reduction for severe emphysema should be noted. All the teams involved in this STIC project were previously involved in a randomized study evaluating the effectiveness of one-way valves. Four teams (Reims, Nice, Strasbourg, Bichat) were involved in the feasibility study of endobronchial valves (15 patients treated in France). Two French investigators involved in the REVOLENS study...
are co-authors of the randomized study published in the New England Journal of Medicine regarding the evaluation of the valves (Sciurba, 2010). Being awarded the STIC would 1/ reinforce the place of the French teams in the development of innovative therapies in this field; 2/ allow the conduct the first medic-economic study on volume reduction using coils for severe emphysema. Information in terms of cost effectiveness would permit to determine the interest and the impact in terms of health costs of this innovative therapy.

**Choice of the primary endpoint**

Limitation in exercise capacity is a major element of the emphysema related respiratory impairment. The 6 Minute Walk Test is a simple, reproducible test that is well correlated to the maximal consumption of oxygen. It allows a "global" evaluation of the impact on exercise capacity.

The Minimally Clinically Important Difference (MCID) for the 6MWT is controversial. For a long time, a difference of 54 meters in the 6MWT has been considered as clinically significant for the therapeutic evaluation of COPD (Redelmeier, 1997; Puhan, 2005, Lacasse, 2006). More recently, a general review of the methods of evaluation of therapeutic studies on COPD defined the minimal clinical difference for the 6MWT between 25 and 71 meters, depending on the study (Martinze, 2011). Recent studies effectively suggested that an improvement of 35 meters (Puhan, 2008) or even 25 or 26 meters (Halland, 2010, Puhan, 2011) could be associated with a significant clinical benefit.

In this study, we deliberately chose to take a "hard" criterion for clinical effectiveness in defining as responder a patient with an improvement of 54 meters in the 6MWT. It is important for us to choose an irrefutable criterion for clinical effectiveness that will allow us to answer the question of the interest of this innovative technique. The analysis of the response for 6MWT will be associated with the follow-up of pulmonary function tests, as well as dyspnea and quality of life questionnaires. The medic-economic study will allow us to analyse the cost-benefit and cost-effectiveness of this technique.

**2.5. Bibliography**


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3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to demonstrate that endoscopic volume reduction using coils, together with usual medical treatment (standard of care) leads to a significantly higher improvement in exercise capacity at 6 months as compared to standard of care (SOC); significant improvement being defined as an improvement of at least 54 meters in 6MWT.

3.2. Secondary Objectives

The secondary objectives are:
- To evaluate and compare the two arms in terms of clinical evolution, lung function, and quality of life, according to the following parameters:
  - Dyspnea at 3, 6 and 12 months,
  - Lung function at 3, 6 and 12 months,
  - Quality of life linked to health at 3, 6 and 12 months,
  - 6 Minutes Walk test at 3, 6 and 12 months,
  - Rate of clinically significant improvement in 6MWT (improvement of at least 54 meters) at 3 and 12 months,
  - Rate of clinically significant improvement in 6MWT (improvement of at least 25 meters) at 3, 6 and 12 months,

- To evaluate the feasibility of endoscopic volume reduction using coils: percentage of failure of the procedure, number of coils placed per procedure, time required for procedure and percentage of patients who could only benefit from a unilateral treatment.

- To evaluate the safety of the technique: occurrence of death of major complication (pneumothorax requiring a chest tube for more than 7 days or a surgical procedure, haemoptysis greater than 150 ml, requirement of invasive mechanical ventilation for more than 24 hours) during and immediately after (within 24 hours) the volume reduction.

- To evaluate and compare the two methods of care in terms of mortality and serious morbidity at 12 months taking into account a composite endpoint: occurrence of death, of massive haemoptysis (>150cc), of pneumonia requiring hospitalization, a pneumothorax requiring a chest tube for more than 7 days or a surgical procedure, requirement of mechanical ventilation for more than 24 hours or requirement of lung transplantation.

- To evaluate and compare the two methods of care in terms of morbidity and mortality at 12 months taking into account all adverse events (serious and non serious), related or not related to the procedure or the device.

- To conduct a medico-economic study comparing the two strategies (cost-effectiveness and cost-benefit):
  - To evaluate the cost related to the emphysema caring by endoscopic volume reduction coils and by standard of care;
To evaluate the relation between cost-effectiveness and cost benefit of volume reduction using coils compared to standard of care.

3.3. Objectives of ancillary studies, if applicable

Not applicable

4. ENDPOINTS

4.1. Primary endpoint

The primary endpoint will be the percentage of patients showing a clinically significant improvement (at least 54 meters) in 6MWT at 6 months.

4.2. Secondary endpoints

The secondary effectiveness endpoints will be:

- Dyspnea evolution at 3, 6 and 12 months will be evaluated by:
  - The mMRC questionnaire: evaluation of dyspnea by self-questionnaire on a scale 0-4,
  - The BDI/TCI Index (Baseline Dyspnea Index/Transition Dyspnea Index): index including a baseline questionnaire (BDI) and a follow-up questionnaire (TDI): index evaluating three component, functional impairment, amplitude of activity and amplitude of effort starting dyspnea with od score from 0 to 12,
  - The Borg scale at rest and during exercise after a 6MWT: evaluation on a scale from 0 to 10.

- Lung function evolution at 3, 6 and 12 months, will be evaluated by:
  - Pulmonary Function Tests (PFTs), including spirometry, plethysmography with a bronchodilatation test and a DLCO measurement. The following variables will be studies: FEV1, slow Vital Capacity (SVC), Forced Vital Capacity (FVC), FEV1/FVC, Total Lung Capacity (TLC), Residual Volume (RV), Forced Residual Capacity (FRC) and Carbon Monoxide Diffusion (DLCO).
  - Arterial blood gases at rest, at ambient temperature, in a seated position, taking into account PaO2, PaCO2 and pH.

- Quality of life evolution will be evaluated at 3, 6 and 12 months by:
  - St George Respiratory Questionnaire (SGRQ): self-questionnaire measuring quality of life on a scale from 0 à 100,
  - The EuroQoL 5D (European Quality of Life 5 dimensions): questionnaire measuring the quality of life on 5 dimensions..

- Exercise capacity evolution will be evaluated by:
  - Distance (in meter) performed at 6MWT at 3, 6 and 12 months,
  - The percentage of patients showing a clinically significant improvement in 6MWT (improvement of at least 54 meters) at 3 and 12 months,
  - The percentage of patients showing an improvement in 6MWT with an improvement of at least 25 meters at 3, 6, and 12 months.
The endpoints for safety and feasibility of endoscopic volume reduction will be:

- For safety: the occurrence of death or major complication (pneumothorax requiring a chest tube for more than 7 days or a surgical intervention, haemoptysis of more than 150 ml, requiring invasive mechanical ventilation for more than 24 hours) during or immediately after (within 24 hours) the endoscopic volume reduction procedure,

- For feasibility: the percentage of procedure failure, the number of coils placed for each procedure, the time required for the procedure, and the percentage of patients who could only benefit from a unilateral treatment.

The endpoints to evaluate the morbidity and mortality over 12 months will be:

- For mortality and serious morbidity, a composite judgment score is used consisting of: occurrence of death, regardless of cause, over 12 months, massive haemoptysis (>150 cc), pneumonia requiring hospitalization, pneumothorax requiring chest tube for more than 7 days or a surgical intervention, requirement of mechanical ventilation for more than 24 hours, requirement of lung transplantation.

- For global morbidity, all adverse events, serious or non-serious, expected and unexpected, related or not related to the procedure or the device that occur during the 12 months will be taken into account.

The endpoints for medico-economic evaluation will be:

- The cost of the endoscopic volume reduction,

- The difference between the cost of endoscopic volume reduction and standard medical care,

- An estimation of a cost-effectiveness ratio by relating the difference in cost between the strategies to the percentage of patients who achieved the primary endpoint in each arm,

- An estimation of the incremental cost-benefit ratio based on data collected from the EQ5D questionnaire.

5. MATERIAL AND METHODS

5.1. Study design

Open label, prospective, randomized, multicentre study based on superiority.

5.2. Investigational plan

5.2.1. Pre-screening (V0) and screening (V1) visits

A patient with pulmonary emphysema, who meets the inclusion criteria of the study, will have a consultation with the local pulmonary study investigator, who will propose the study to the patient (pre-screening visit V0). The investigator will inform the patient of the study objective, the two therapeutic strategies studied, the existence of a randomization scheme (by draw), the risks associated with the two therapeutic strategies, and the constraints related to participation in the study. The investigator will provide the patient with written Study Information brochure and a written Informed Consent Form. After time to consider the study, which would be a few days if necessary, the patient will provide the signed Consent Form to the investigator if he agrees to participate in the study.

If the patient agrees to participate in the study, the signed Informed Consent Form, signed by the patient, is collected and the investigator will schedule the screening visit (V1).
During the screening visit, the following examination will be performed:
- Medical, surgical and treatments history,
- Physical examination including lung and heart auscultation, heart rate measure, blood pressure, respiration frequency, saturation in ambient air,
- Dyspnea questionnaires: mMRC and BDI/TDI,
- Health related quality of life questionnaires: SGRQ and EuroQoL 5
- Pulmonary function tests including spirometry, plethysmography, DLCO and bronchodilatation test,
- Arterial blood gases at rest in a seated position and in ambient air,
- 6MWT in ambient air, with a BORG dyspnea test before and after the walking test, and measure of the saturation during the walking test
- Electrocardiogram,
- Echocardiogram with an evaluation of systolic pulmonary arterial pressure,
- Thoracic CT (except if the patient had a thoracic CT within 6 months before V1),
- Thoracic X-ray, from the front and from the side,
- Blood analysis with blood cells count, coagulation (PT, ACT), ionogram, creatinine, creatinine clearance), hepatic function (gamma-TG, TGO, TGP, bilirubin, alkaline phosphatases), C-reactive proteins (CRP) and pregnancy test for women of childbearing potential,
- Anaesthesia consultation to confirm the absence of any contraindication to general anaesthesia.

After the examinations performed during Visit 1, the inclusion and exclusion criteria will be evaluated. If the patient is eligible for the study, the investigator will call the coordinating site to perform randomization.

5.2.2. Hospitalization for the endoscopic procedure

For patients randomized to the treatment group, hospitalization will be scheduled within 15 days of randomization.

The procedure for endoscopic volume reduction with coils is as follows:
- The patient is hospitalized the evening before the procedure.
- Vital signs (pulse, blood pressure, breathing frequency, saturation in ambient air) and pulmonary examination data are collected
- A front-facing thoracic X-ray is performed.
- Prophylactic antibiotics will be provided according to French anaesthesia and reanimation society – SFAR – 2011 recommandations :
  - Amoxicillin – clavulanic acid 2 grams IV (single dose)
  Or
  - Clindamycin 600 mg + gentamicin 5 mg/kg (in case of allergy to betalactam antibiotics)
- The bronchoscopy will be performed under general anaesthesia, using fluoroscopy. The coils are deployed via a catheter that is inserted through the working channel of a flexible bronchoscope introduced in the endotracheal tube. After retracting the catheter, the coil, which was in a straightened configuration in the catheter, returns to its coil shape, causing a broncho-pulmonary retraction effect. Treatment of a lobe requires the placement of 8 to 10 coils to homogeneous retraction. One lobe is treated per procedure.
After the procedure, the patient is extubated and monitored in the recovery room for 2 hours. A chest x-ray is performed in the bed within 2 hours after the procedure.

The patient will then be monitored for 24 hours in the hospital. Vital signs (heart rate, pulse, temperature, blood pressure, respiration frequency, saturation in ambient air) and the data from a pulmonary auscultation are collected at 24 hours. A chest x-ray will be performed 24 hours post procedure.

In the absence of complication, the patient returns home 1 day after the procedure.

The volume reduction procedure is done sequentially, in two steps, with one procedure for each treated lobe, with both procedures being performed in the same way. The second procedure is performed at least 1 month and no more than 3 months after the first procedure.

5.2.3. 1 Month follow-up visit

The visit will take place, for all patients, one month (+/- 7 days) after randomization. During this visit, the following examinations are performed:
- Notation of medical and surgical events, and medical treatments,
- Complete physical examination including lung and heart auscultation, heart rate, blood pressure, respiratory frequency, saturation in ambient air,
- Dyspnea questionnaire: mMRC and BDI/TDI scale,
- Health-related quality of life questionnaires: SGRQ and EuroQoL 5,
- Spirometry, plethysmography and DLCO measurement bronchodilatation test,
- Arterial blood gases, at rest in a seated position, in ambient air,
- 6 MWT in ambient air with Borg dyspnea scale before and after the walking test and saturation measurement during the test,
- Front facing and profile thoracic X-ray.

5.2.4. 3 months follow-up visit

The visit will take place, for all patients, three months (+/- 15 days) after randomization. During this visit, the following examinations are performed:
- Notation of medical and surgical events, and medical treatments,
- Complete physical examination including lung and heart auscultation, heart rate, blood pressure, respiratory frequency, saturation in ambient air,
- Dyspnea questionnaire: mMRC and BDI/TDI scale,
- Health-related quality of life questionnaires: SGRQ and EuroQoL 5,
- Spirometry, plethysmography and DLCO measurement bronchodilatation test,
- Arterial blood gases, at rest in a seated position, in ambient air,
- 6 MWT in ambient air with Borg dyspnea scale before and after the walking test and saturation measurement during the test,
- Front facing and profile thoracic X-ray.

5.2.5. 6 months follow-up visit

The visit will take place, for all patients, six months (+/- 15 days) after randomization. During this visit, the following examinations are performed:
5.2.6. 12 months follow-up visit

The visit will take place, for all patients, twelve months (+/- 15 days) after randomization.

During this visit, the following examinations are performed:

- Notation of medical and surgical events, and medical treatments,
- Complete physical examination including lung and heart auscultation, heart rate, blood pressure, respiratory frequency, saturation in ambient air,
- Completion of two dyspnea questionnaires: mMRC and BDI/TDI scale,
- Completion of two health-related quality of life questionnaires: SGRQ and EuroQoL 5,
- Spirometry, plethysmography and DLCO measurement bronchodilatation test,
- Arterial blood gases, at rest in a seated position, in ambient air,
- 6 MWT in ambient air with Borg dyspnea scale before and after the walking test and saturation measurement during the test,
- Front facing and profile thoracic X-ray.

At the end of the 12-month visit, patients in the SOC group (i.e., Control) group who so desire may ask to be treated with volume reduction using coils.

5.2.7. Emergency visits (Unexpected visits)

In the event that a non-study scheduled visit or hospitalization is required, a study investigator will see the patient. The nature of the event requiring the consultation or hospitalization and the findings of the totality of the exams performed during that visit or hospitalization will be collected.
The entire study schedule is described in the table below:

<table>
<thead>
<tr>
<th>V0 Pre-screening</th>
<th>V1 Screening Randomization</th>
<th>V2 Ta *</th>
<th>V3 M1</th>
<th>V4 Tb *</th>
<th>V5 M3</th>
<th>V6 M6</th>
<th>V7 M12</th>
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<tr>
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<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Dyspnea questionnaires mMRC, BDI/TDI</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
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<td>Anesthesia consultation</td>
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<tr>
<td>Blood samples</td>
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<td></td>
</tr>
</tbody>
</table>

Ta : initial treatment ; Tb : bilateral contralateral treatment

* only for patient treated with lung volume reduction using coils
The investigation plan for each group is represented in the figure below:

5.3. Study logistics

Before the commencement of the study, PneumRx will train all of the pulmonologists participating in the study on the lung volume reduction using coils technique. In addition, throughout the duration of study enrolment, PneumRx will make available to the investigators a technician (full time technician, dedicated to this study) who can respond to any questions or any potential problems.

At the beginning of the study, a local coordinating investigator will be designated for each site participating in the study. A national coordinating investigator will be responsible for coordinating the set up and the conduct of the study, with the help of a full time clinical research coordinator. Data collection will be performed in each centre by a clinical research technician.

To facilitate the enrolment, PneumRx has committed to establish an informational website intended for patients and their referring physicians. The cost of this website, estimated at 45,000 Euros for two years, is entirely funded by PneumRx. A strategy of communication
on this project, targeting medical societies as well as patient associations will also be undertaken in parallel.

5.4. Randomization

The treatments, coils vs SOC will be randomized. Randomization will be centralized. Randomization will be performed with a ratio of 1:1 in blocks of 4.

Once the patient is enrolled (signed informed consent form) and the inclusion/exclusion criteria have been confirmed, the investigator will phone to the coordinating site to confirm enrolment. He/she will also fax the enrolment form to the coordinating site. The coordinating site will then proceed with randomization and will provide the investigator with the patient's enrolment number and treatment group by phone and by fax. The patient will be informed verbally by the investigator of the group in which the patient was randomized.

5.5. Study Duration

The study total duration will be of 24 months:
- 12 months for enrolment: from January 1, 2013 to January 1, 2014
- 12 months for patient's follow-up: last 12 months follow-up of the last patient enrolled on January 1, 2015.

5.6. Temporary or permanent stopping rules

5.6.1. Terminating the participation of a subject from the study

All patients may terminate their participation in the study (withdrawal of content) at any time during the study without any consequences regarding their relationship with their doctor.

5.6.2. Partial or total termination of the study

The study may terminate temporarily or permanently:
- By the principal investigator, the sponsor, or ANSM,
- In the event of data indicating an undue safety risk for the patients,
- In the recommendation of the Data and Safety Monitoring Board based on the occurrence of Adverse Events deemed to be serious and established or suspected to be related to the research (i.e., the device or the procedure).

The study Data and Safety Monitoring Board can recommend the termination of the study for safety reasons. To perform this task, the Data and Safety Monitoring Board will have access to data relating to the failure of the treatment and to adverse events. These analyses are not requiring adjustment of statistical significance level for the primary endpoint. The Data and Safety Monitoring Board may recommend the termination of the study for safety reasons if the board believes that the frequency and/or the severity of the adverse events is excessive in view of the expected benefit of the treatment. In this case, the sponsor will inform the CPP and ANSM of the early termination of the study.
5.7 Identification of all the data to be collected directly on the case report forms, which will be considered as source data

All data will be noted on the case report form. The case report form will include especially:

- Patient’s socio-demographic information,
- Patient’s medical and surgical history,
- The history of the patient’s lung disease: commencement date, treatments received,
- All inclusion and exclusion criteria,
- All data related to the treatment received in the study:
  o For the « reduction volume using coils » group: dates of the procedures, number of coils implanted, any associated treatment etc.,
  o For the « standard of care » group: treatment received, posology, etc.,
- Findings of the tests performed at each visit: physical exam, 6MWT, dyspnea evolution, health-related quality of life questionnaire, thoracic X-Ray, lung function, arterial blood gases (ambient air).
- Notification of all adverse events (serious, non serious, anticipated, or unanticipated).

6. PATIENTS SELECTION

6.1. Inclusion criteria

To be eligible, the patient must meet all the following criteria:

- Bilateral emphysema as conformed by thoracic CT-Scan,
- Post Bronchodilators FEV1 < 50%,
- Residual volume (RV)> 220%,
- Total Lung Capacity (TLC) > 100%,
- Dyspnea score between 2 and 4 on the mMRC scale,
- Tobacco cessation for at least 8 weeks,
- Completion of a pulmonary rehabilitation within 12 months prior to V1
- Signature of the informed consent form,
- Patient entitled to French social security.

6.2. Exclusion criteria

The patient will be excluded from the study if any of the following conditions apply:

- FEV1 < 15 %,
- Increase of FEV1 > 20% post bronchodilators,
- Serious frequent respiratory infection having required more than 2 hospitalizations during the year prior to enrolment,
- Severe COPD exacerbation having required hospitalization within 3 months prior V1,
- Pulmonary hypertension (right ventricular systolic pressure > 50mmHg on echocardiogram),
- Patient unable to perform a 6 Minutes Walk Test in ambient air,
- Giant bullae > 1/3 lung volume, based on CT-Scan,
- Severe homogeneous emphysema, based on CT-Scan,
- Clinically significant bronchiektasis,
- History of lobectomy, lung volume reduction surgery or lung transplant,
- Any non-pulmonary disease that would compromise survival and/or possibility of study follow-up; severe heart disease, renal disease, cancer etc.,
- Lung cancer or suspect pulmonary nodule requiring imaging control in less than a year,
- Contra-indication to general anaesthesia,
- Anticoagulant therapies (e.g. vitamin K antagonists)
- Participation in another clinical trial evaluation pulmonary medications,
- Patient protected by law,
- Patient with known allergy to nitinol.

7. TREATMENTS ADMINISTERED TO STUDY SUBJECTS

7.1. Description of the procedure under investigation

By creating a broncho-pulmonary retraction in treated lobes, Lung Volume Reduction using Coils reduce dead space and hyperinflation, two elements primarily responsible for respiratory impairment in patients suffering from emphysema.

The treatment is performed under general anaesthesia, using fluoroscopy. The coils are deployed via a catheter through the working channel of a flexible bronchoscope. 8 to 10 coils per lobe are required to achieve an optimal effect. After being released from the Catheter, the Coil, which was delivered in a straight configuration through the catheter, resumes its coil shape, creating a broncho-pulmonary retraction effect. A single lobe is treated per procedure; the contralateral side is treated in a second procedure 1-3 months later (a complete description of the technique can be found on the Innovarc website in Annex 1).

7.2. Description of standard of care

Standard medical treatment for severe emphysema includes smoking cessation, influenza and pneumococcal vaccinations, pulmonary rehabilitation, bronchodilators, inhaled corticosteroids for frequent exacerbations and oxygen therapy for chronic, severe respiratory failure. Surgical options are Lung Volume Reduction Surgery, which is infrequently performed due to high morbidity and mortality, and lung transplantation, which is limited by the number of available grafts. Randomized studies evaluating endobronchial treatments modifying airflow by blocking a region of the lung using one-way valves (Scirube, N Engl J. Med. 2010) or by creating a communication using a by-pass between the emphysematous zones and the bronchi (Shah, Lancet, 2011) have demonstrated only limited effectiveness for the valves, due to the frequency of collateral ventilation, and a lack of effectiveness for the by-pass technique.

7.3. Authorized and forbidden study treatments

No treatment is forbidden for this study. All treatment administered to patients will be noted.
8. SAFETY EVALUATION

8.1. Procedures for collection and notification of Adverse Events

8.1.1. Collection of Adverse Events

The term "Adverse Event" means any harmful event occurring to someone participating in biomedical research, which or not it is related to the study and/or the product under investigation.

A Serious Adverse Event is an Adverse Event:
- That leads to death,
- That is life threatening to the person participating in biomedical research, corresponding to an immediate threat of death, at the moment of the onset of the Adverse Event, independent of the consequences of a corrective or palliative therapy,
- That requires hospitalization or a prolongation of hospitalization,
- That leads to incapacitation, including any clinical significant handicap, temporary or permanent,
- That results in a congenital abnormality or malfunction,
- Any other event considered to be « potentially serious » in the investigator’s judgment.

Adverse Events that occur during the study have to be reported in the case report forms, in a section specifically dedicated to AEs. The following information must be recorded for each AE: patient identification, date of onset, a clear and detailed description of the event (diagnosis, clinical symptoms, the chronology, any exams performed as a result of the AE and the findings of those exams, the duration of the event, severity, consequences, and the treatment) and its follow-up. AEs must be reported within 24 hours to the study sponsor. The initial report will be followed up with additional information within 15 days for Adverse Events and within 8 days for Serious Adverse Events.

8.1.2. Responsibilities of the Investigator for Serious Adverse Events

In the event of a Serious Adverse Event, the investigator must complete the report form and immediately inform the sponsor by phone, email and/or fax within 24 hours. The initial report must be supplemented with all information of interest within 8 days. The report will include all information concerning the Serious Adverse Event and the study procedure or device.

The investigator must determine whether there is a causal relationship between the Serious Adverse Event and the study procedure or device.

The factors to consider determining the relationship between the Event and the study procedure or device are:
- The chronology of events,
- The disappearance of the Adverse Event when the medication(s) is stopped and/or the re-appearance in case of re-administration,
- The pharmacodynamics and the pharmacokinetics of the medications,
- The possibility of history of a similar event associated with the administration of the medication or a medication of the same category,
- The existence of another cause of the Adverse Event.

The investigator must follow-up the patient until the Serious Adverse Event is resolved.
8.1.3. Sponsor Responsibilities

The sponsor will establish a procedure allowing the collection of all the Adverse Events, particularly the Serious Adverse Events. A database containing all the Adverse Events will be maintained.

The sponsor must also determine the causal relationship between a Serious Adverse Event and the study procedure or device. In the event of a possible causal relationship, the sponsor will classify the events as anticipated events or unanticipated events, depending on whether the adverse events are identified and listed in the manufacturer’s IFU.

The sponsor will report all the unanticipated Serious Adverse Event as well as new information concerning the safety of the device within the regulatory timeframes.

The notice shall be made to Eudrac Vigilance/Clinical Trial section, to ANSM, to the CPP who approved the study, and to study investigators. Notification must be made within 7 calendar days for fatal or life threatening unanticipated adverse events and within 15 calendar days for other Serious Adverse Events. In either case, additional information regarding the follow up of the Serious Adverse Event must be investigated and reported within an additional 8 days timeline.

The sponsor will provide an annual safety report including a list of all of the Serious Adverse Events (anticipated or unanticipated) and a concise critical analysis of patient safety relating to the study and will provide such report to ANSM, the CPP (to provide advice concerning this study), and to study investigators.

The sponsor will provide any additional information requested by the CPP who approved the study or by ANSM.
8.2. Anticipated Adverse Events

The followings are anticipated Adverse Events, whether or not connected with the procedure and the device (anticipated frequency within 30 days based on previous studies conducted by PneumRx):

1. COPD Exacerbation: 11.2%, which 4% were serious,
2. Haemoptysis: 26.8%, which 0.8% were serious,
3. Pneumonia: 7.2%, which 4.8% were serious,
4. Dyspnea: 7.6%, which 1.2% were serious,
5. Pneumothorax: 5.2%, which 0.8% were serious (seriousness defined by the need for a chest tube for more than 7 days or for surgical intervention)
6. Thoracic pain: 14%

Considering the severity of the COPD and the requirement of a bronchoscopy for the coils placement procedure, under general anaesthesia with intubation, the following Adverse Events, not mentioned above, are likely to occur:

1) Related to coil placement:
   a. Local bleeding,
   b. Tissue hyperplasia or other tissue reaction at the site of coil implantation,
   c. Perforation or dissection of tissue.

2) Related to general anaesthesia or intubation:
   a. Tracheal stenosis related to intubation,
   b. Any complication associated with the administration of general anaesthesia, including and without limitation of other potential complication: bronchospasm, acute respiratory failure, shock, cardiac arrhythmia, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, death. All the procedures will be performed according to good anaesthesia practice, using procedures designed to minimize the risk of complication.

3) Related to severe COPD:
   a. Cough, expectoration
   b. Bronchial infection,
   c. Acute respiratory failure,
   d. Death.

8.3. Procedure and duration for Adverse Events follow-up

Patients who experience Adverse Events will be cared for in accordance with Good Clinical Practice and will be followed until resolution of the Adverse Event.

8.4. Data and Safety Monitoring Board

The mission of the Data and Safety Monitoring Board (DSMB) is to follow and analyse Adverse Events, and particularly Serious Adverse Events. The DSMB will take all actions necessary to guarantee the safety of enrolled patients and will advise the Sponsor on the conduct of the study. For this study, the DSMB will be comprised of four doctors and will meet once every four months. Their meetings will be held by videoconference, except in the case of a major complication, in which case the members will meet in person. The
The coordinating investigator will notify the DSMB of all Adverse Events. The DSMB will inform the team of investigators of the decisions made after each meeting.

The composition of the Data and Safety Monitoring Board, comprised of independent members is the following:
- Prof. HACHULLA, Internist
- Prof. FOURRIER, Intensivist, Past President of the French Intensive Care Society (SRLF - Société de Réanimation de Langue Française)
- Prof. DUSSER and Prof. ROCHE, pneumologists, experts in the field of COPD but not practicing interventional pulmonology.

9. STATISTICS

9.1. Number of study subjects, with statistical justification

The primary endpoint is the percentage of patients showing a clinically significant improvement in 6MWT (improvement of at least 54 meters) at 6 months. A patient who demonstrates such an improvement is defined as a "responder."

The calculation of the number of subjects required is determined with the help of the Nquery 7.0 software using the following hypotheses:
- A 37% responder rate among subject receiving the lung volume reduction with coils procedure (percentage calculation based on data provided by PneumRx from 79 treated patients),
- A predicted 5% responder rate among subjects treated with standard of care.

With a level of significance of 5%, a power of 90% and a unilateral test, the Nquery software predicted that it was necessary to include 32 patients per group to demonstrate a statistically significant difference between the two groups.

Taking into account the anticipated number of subjects who will not be evaluable at 6 months, due to loss to follow up or patients who will be unable to complete a 6MWT (30%) the number in subjects enrolled in each group was estimated to be 50 for a total of 100 patients to be enrolled in the study.

9.2. Statistical analysis method for the endpoints

The level of significance will be 0.05. There is no intermediate analysis planned.

The baseline characteristics of the patients will be described using means and standard deviation for quantitative variables, and using percentages for qualitative variables.

The characteristics of the two groups ("standard of care" and "volume reduction using coils") will be compared using Student tests, Chi2 tests or Fishers exact tests depending upon the application modalities.

9.2.1. Primary endpoint

With regard to the primary endpoint, the percentage of patients with a significant improvement in 6MWT will be calculated for each groups and these percentages will be compared using a Chi2 test of an exact Fisher's test, depending upon the application modalities. The other factors associated with this improvement will be evaluated using a
univariate analysis, using Student tests, Wilcoxon tests, Chi2 tests or Fisher's exact tests, depending up on the application modalities. A multivariate analysis (logistic regression) to evaluate the factors associated independently from significant improvement in 6MWT will also be performed.

9.2.2. Secondary endpoints

With regard to the mMRC scale, the BDI/TDI index, the Borg scale at rest, the Borg scale after exercise, Pulmonary Function Tests and arterial blood gases:
- The differences between the values at baseline and the values at 3, 6, and 12 months will be calculated within each group and will be compared using a Student test,
- The other factors associated with these differences will be evaluated using univariate analyses, using Student tests, Wilcoxon tests, Pearson correlation tests and Spearman correlation tests, depending upon the application modalities,
- Multivariate analyses (linear regression) to evaluate the factors associated independently from these differences will be performed,
- Repeated measures analyses will also be performed.

With regard to the Saint Georges Respiratory Questionnaire (SGRQ) concerning health-related quality of life, the differences between the global score and 3 sub scores (symptoms, activity, impact) at baseline and the scores at 3, 6 and 12 months will be calculated for each group and will be compared using Student tests. The other factors associated with these differences will be evaluated using univariate analyses, using Student tests, Wilcoxon tests, Pearson correlation tests and Spearman correlation tests, depending upon the application modalities. Multivariate analyses (linear regressions) to evaluate the associated factors independently from these differences will be performed. Repeated measures analyses will also be performed.

With regard to the EuroQoL, which evaluates health-related quality of life, the differences between the scores of each dimension at baseline and the scores of these dimensions at 3, 6 and 12 months will be calculated for each group and will be compared using Student tests. The other factors associated with these differences will be evaluated using univariate analyses, using Student tests, Wilcoxon tests, Pearson correlation tests and Spearman correlation tests, depending upon the application modalities. Multivariate analyses (linear regressions) to evaluate the associated factors independently from these differences will be performed. Repeated measures analyses will also be performed.

The mean and standard deviation of the difference in 6MWT values at baseline and at 3, 6 and 12 months will be calculated for each group and will be compared using Student tests. The other factors associated with these differences will be evaluated using univariate analyses, using Student tests, Wilcoxon tests, Pearson correlation tests and Spearman correlation tests, depending upon the application modalities. Multivariate analyses (linear regressions) to evaluate the associated factors independently from these differences will be performed. Repeated measures analyses will also be performed.

The percentage of patients with a significant improvement in 6MWT (improvement of at least 54 meters) at 3 and 12 months will be calculated in each group and these percentages will be compared using Chi2 or exact Fisher tests, depending upon the application modalities. The other factors associated with these improvements will be evaluated using univariate analyses, using Student tests, Wilcoxon tests, Chi2 or exact
Fisher tests, depending upon the application modalities. Multivariate analyses (logistic regressions) to evaluate the associated factors independently from these significant improvements in 6MWT at 3 and 12 months will be performed.

The percentage of patients with an improvement in 6MWT of at least 25 meters at 3, 6 and 12 months will be calculated in each group and these percentages will be compared using Chi2 or exact Fisher tests, depending upon the application modalities. The other factors associated with these improvements will be evaluated using univariate analyses, using Student tests, Wilcoxon tests, Chi2 or exact Fisher tests, depending upon the application modalities. Multivariate analyses (logistic regressions) to evaluate the associated factors independently from these significant improvements in 6MWT at 3 and 12 months will be performed.

With regard to the safety of the procedure, the percentage of patients who die during the surgical intervention or who have had a major complication during or within 24 hours of the procedure will be calculated.

With regard to the feasibility of the procedure, the percentage of failed procedures, the mean number of coils placed in each treated lobe, the mean procedure time and the percentage of patients who can only benefit from a unilateral treatment will be calculated.

With regard to morbidity and mortality:
- The percentage of patients who experience an event of death, massive haemoptysis, pneumopathy, pneumothorax requiring a chest tube for more than 7 days, or need for mechanical ventilation for more than 24 hours will be calculated in each group and the percentages will be compared using Chi2 or exact Fisher’s tests, depending upon the application modalities. The other factors associated with this composite morbidity-mortality criterion will be evaluated using a univariate analysis, using Student tests, Wilcoxon tests, Chi2 or exact Fisher tests, depending upon the application modalities. Multivariate analyses (logistic regressions) to evaluate the associated factors independent from this morbidity-mortality composite criterion will be performed.
- The percentage of patients who experience an Adverse Event (serious or non-serious) will be calculated in each group and the percentages will be compared using Chi2 or exact Fisher’s tests, depending upon the application modalities. The other factors associated with an Adverse Event (serious or non-serious) will be evaluated using a univariate analysis, using Student tests, Wilcoxon tests, Chi2 or exact Fisher tests, depending upon the application modalities. Multivariate analyses (logistic regressions) to evaluate the associated factors independent from the incidence of adverse will be performed.

9.2.3. Management of modifications to the Statistical Analysis Plan

Section 9.2 describes the principal elements of the Statistical Analysis Plan. This plan can be revised during the course of the study in light of protocol amendments or the occurrence of unanticipated events. These modifications to the Statistical Analysis Plan will be made before the database is locked.

9.3. Management of missing data
The study will be conducted to minimize the amount of missing data. For each variable, the number and the percentage of missing data will be described. No method for data imputation is envisaged.

9.4. Choice of the subjects to include in the analyses

After randomization, patients will remain in their original group and Intent to Treat (ITT) analysis will be performed. For this analysis, the totality of the patient cohort will be taken into account. The patients that were only able to undergo one lung volume reduction with coils procedure (unilateral treatment) will be taken into account. An analysis per protocol, taking into account only the patients who underwent bilateral lung volume reduction with coils treatment will also be performed.

9.5. Medico-economic evaluation

The medico-economic evaluation objectives are (1) to estimate the cost of the lung volume reduction with coils technique with the purpose of pricing, and (2) to evaluate the impact of the technique on patients (medical effectiveness and quality of life) and for health-care system.

The economic evaluation consists of the following stages:
- To estimate the cost of the technique by micro-costing,
- To estimate the cost of treatment of treated patients,
- To compare the costs of caring with and without the lung volume reduction with coils treatment,
- To compare the morbidity and health-related quality of life with and without lung volume reduction with coils treatment (gross comparison).

9.5.1. Micro-costing

The micro-costing study will be performed from the point of view of the institution. The resources used for the intervention will be collected by direct observation from 5 interventions performed at the highest recruiting sites (so as to minimize the costs linked to the researcher travel). It would be theoretically useful to include all of the sites, but this option would require additional travel costs that we have elected to avoid.

The plan is to standardize as much as possible the interventional techniques.

The resources considered for collection by direct observation are:
- The number and kind of site personnel present during the procedure,
- The important equipment used: devices
- In addition, the other resources utilized during the intervention will be identified by the hospital's analytical accounting department:
  - Financial amortization of the equipment,
  - Overhead costs.

Valuation:
The cost in personnel will be estimated based on median salaries for each category of personnel (taken from national databanks), the equipment will be valued according to...
purchase price (with a sensibility analysis taking into account the potential reduction in price that could be negotiated in certain sites). The fixed costs and the overhead costs will be calculated by looking at the annual costs of the operating room related to the duration of the intervention (using a daily cost of use for the operating room based on local conditions).

The mean cost of each procedure will be estimated by valuing the mean quantity of resources by the unitary costs available at the end of the study, so as to provide the decision makers with necessary information to make a prospective choice.

One could also discuss, in the context of micro-costing, the opportunity to estimate the capitalized cost for a team. Capitalized costs are calculated according to the training time for the technique, as described in the preceding paragraphs. We expect to document the time spent by the teams and to value it according to the salaries of the personnel involved. These data will not be included in the economic evaluation, but could provide useful information to the institutions who might adopt this strategy.

9.5.2. Estimation of the cost of lung volume reduction with coils strategy

This cost will be estimated from the point of view of Health Insurance for the follow up period (1 year), without discounting due to the study duration.

The resources that will be valued are:

- Hospitalizations (during the follow-up),
- Transportations,
- Medical and paramedical consultations,
- Amount of day-off from work for medical reasons for the patient in professional activity will also be collected.

Data Collection:
Hospitalizations will be collected during the follow-up visits in the case report forms. Patient consultations and day-off from work can be collected in a diary, given to the patient at discharge. Each page of the diary would record a one-month period, to be sent to participating sites every two months. A pre-addressed, stamped envelope will be provided to each patient to send the "patient diary entries" to the site principal investigator, and a new monthly sheet and a new envelope will then be sent to the patient.

Valuation:
- Hospitalisations: we will note the totality of the elements that go into a medical unit so as to be able to code the hospitalizations using the most recent version of T2A,
- Transportations: mean health insurance allowance in urban area,
- Medical and para-medical consultations: nomenclature charges,
- Days off from work for health reasons: mean value of per diem allowance (data from health insurance).

9.5.3. Balance between costs and medical findings

The primary endpoint is the percentage of patients having an improvement in 6MWT. We can estimate a ratio defined by the over-costs for a lung volume reduction with coils treatment in comparison to the percentage of improvement. This ratio is not traditional and
is not comparable to ratios existing in the literature, but it would seem difficult, based on the clinical criteria, to model a gain in life expectancy.

On the other hand, data from the EQ5D at the beginning and end of the study could be used to estimate (over 1 year) an improvement in quality of life and to estimate a cost-effectiveness ratio.

10. ACCESS TO DATA AND TO SOURCE DOCUMENTS

In compliance with the applicable laws and regulations, notably Articles L.1121-3 and R.5121-13 of the CSP (Code de la Santé Publique), individuals with direct access (investigators, sponsor Clinical Research Associate, CRA responsible for quality control, non-physician researchers participating in the research and all other persons duly authorized by the sponsor) are bound to professional secrecy. In addition, these persons will take all necessary precautions to ensure the confidentiality of the information related to experimental medications (as applicable), to the tests, to the study subjects and particularly with regard to identity of study participant or results.

Note: The data collected during the course of quality control or audits will be anonymized.

11. QUALITY INSURANCE AND CONTROL

In each participating site, a clinical study technician (TEC) will be designated to ensure the data collection for enrolled patients. This person will complete the Case Report Forms for the patients from their medical records. The TEC should contact the investigator in case of data not contained in the medical records and in the event of inconsistent or surprising data. This methodology for completing Case Report Forms should lead to the collection of good quality data.

A Clinical Research Associate (CRA) mandated by the sponsoring site will visit each site (one visit per six months). This person will verify the inclusion and exclusion criteria with the patient's medical records. The CRA will verify the informed consent forms and that the compliance to the protocol. Finally, the CRA will verify that the CRFs are completed so as to minimize the amount of missing data.

Two secretaries working independently will perform double data entry manually. An automated comparison of the two databases will be performed and the data will be corrected. This will be repeated until there are no differences between the two databases. Quality control of data entry will also be performed on 10% of the Case Report Forms (comparison between the paper Case Report Forms and the data entered into the data base).

12. ETHICAL CONSIDERATIONS

12.1. Law of Biomedical Research or of Bioethics

This study is conducted in compliance with the biomedical research law of August 9, 2004.

Sponsor: CHU of Reims (University Hospital of Reims).

Principal Investigator: Prof. Gaëtan Deslée

Ethic Committee (Comité de Protection des Personnes- CPP): If the project is accepted, it will be submitted to the Ethic Committee.
**Competent Authority:** If the project is accepted, it will be submitted to AFSSAPS (*Agence Française de Sécurité Sanitaire des Produits de Santé*).

In case of protocol amendments, they will be submitted to the CPP. The sponsor will also submit each amendment to AFSSAPS.

### 12.2. Risk/Benefit Analysis

The published feasibility studies and the data provided by PneumRx demonstrate the feasibility and safety of the endobronchial device, with a low morbidity, allowing us to consider the lung volume reduction with coils technique as low risk technique.

The results of the studies and the data currently available demonstrate a clinically significant effectiveness in terms of improvement of dyspnea, exercise capacity and lung function, which allows considering that the lung volume reduction with coils has a high probability of clinical benefit.

### 12.3. Information brochure and Informed consent form

See annex 1.

### 13. DATA MANAGEMENT, STUDY DATA AND DOCUMENTS RETENTION

#### 13.1. Data collection

Case Report Forms will be designed specifically for this study by a team consisting of clinicians, methodologists, data manager and statisticians. The data will be reported on the CRFs with duplicate pages. The original page of the CRF will be sent to the coordinating site (CHU of Reims) and the duplicate will remain at the participating site. The records (originals of the CRFs) will be centralized in the office of the coordinating site (Pulmonology department, Maison Blanche Hospital, CHU of Reims, Professor Lebargy), will be kept in a locked, metal wardrobe in an office that will be locked when the coordinator is not in the office.

#### 13.2. Data entry

The creation of the database (using Access 2000 software) will be done by the Methodological Assistance Unit at the CHU of Reims. Double data entry will be done manually by the Research and Clinical Study Department at the CHU of Reims and an automated comparison of the data will be performed. All missing or inconsistent data will be handled by checking back the original paper form. The database will be submitted CNIL (*Commission Nationale de l'Informatique et des Libertés*). Quality control of the data will be done randomly on 10% of the files. A data manager will verify the coherence of the data and the operational state of the databases. All inconsistent data will be confirmed by reviewing the original paper document and will be corrected. The databases will then be transferred to SAS and locked.
13.3. Data analysis

The data analysis will be performed by the Methodological Assistance Unit at the CHU of Reims according to the pre-defined analysis plan. The software used will be SAS.

13.4. Data and documents retention

The paper record will be centralized in the Pneumology department at CHU of Reims (Professor Lebargy), stored in a locked, metal file wardrobe in an office that will be locked when the coordinator is not present. Because the study is conducted in compliance with the law of biomedical research and in compliance with the applicable laws and regulations, the documents will be archived by the sponsor and by the principal investigator for 15 years from the date the research is completed.

14. FINANCING AND INSURANCE

The study was accepted by the Ministry of Health in the context of the STIC program, except of cancer, 2012. The budget was accepted and approved by the Minister of Health. A budget of 1,3 Million (euros) has been allocated by the General Administration of the Offer of Care for the conduct of this study.
PneumRx is co-financing this study for 500,000 Euros. The completed budget is described in Part 17.

An agreement will be concluded between PneumRx and the CHU of Reims. Clinical trial agreements will be concluded between the sponsoring site (CHU of Reims) and the other participating sites.
The insurance is provided by the sponsor, in compliance with the legal requirements, through the Hospital and Mutual Insurance Company (policy number 138.834 – Société Hospitalière des Assurances Mutuelles).

15. STRATEGIES FOR STUDY SUCCESS

The potential challenges associated with the study, and the proposed solutions are described in the table below.
<table>
<thead>
<tr>
<th>Potential Challenges</th>
<th>Proposed solutions</th>
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| Insufficient Enrolment                                   | • Publication of the clinical trial in the Respiratory Disease Journal (*Revue des Maladies Respiratoires*).  
• Publication of the clinical trial in the Info-Respiration letter (*Lettre Info-Respiration*).  
• Internet website dedicated to patients and doctors (after approval of regular authorities).  
• Creation of a telephone hotline.  
• Publications of the clinical trial in the press.  
• Diffusion of the clinical trial via the push-list the French Pulmonary Federation (*Fédération Française de Pneumologie*).  
• Diffusion via the national association of patients with alpha-1 antitrypsin deficiency (*association nationale des patients présentant un déficit en alpha-1 anti-trypsine*). |
| Investigator inexperienced with the lung volume reduction with coils technique | • Initial training of all investigators on the technique by PneumRx, prior to the inclusion of the first patient.  
• Hiring by PneumRx of a full-time expert to support the investigators.  
• 3 « experts » investigators who participated in the feasibility trial and who have performed at least 10 interventions (Prof Marquette, Professor Deslée and Professor Deslée) will assist as expert the other teams that have not yet performed a procedure.  
• The systematic attendance of one of the three expert for the first three procedures performed by each team. |
| Heavy workload (12 months follow-up, visits, treatments)  | • Full time coordinator CRA.  
• Part time use (0.15 full time equivalence - 0.15 ETP) in each participating site.  
• Multiples visits by the coordinator CRA on site for team support. |
| Difficulty of the medico-economic analysis               | • Collaboration with the team with recognized expertise in STIC medico-economic evaluations. |
| Difficulty of the Statistical analysis                   | • Collaboration with an expert methodological team.  
• Budgeted statistical analysis time. |
| Valuation in terms of publication                         | • Multidisciplinary collaboration (clinical, methodological, medico-economic) allowing the possibility of publications in high impact journals. |
16. PUBLICATION POLICY

The results of this research will be published, whether they are positive or negative. For each publication, the respective position of the various co-authors will depend upon the contribution of each to the accomplishment of the study and to the redaction of the article.