STATISTICAL ANALYSIS PLAN

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.

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.

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 Fishers 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.

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 regression) 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.

2.3. Management of modifications to the Statistical Analysis Plan

Section 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.
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.

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.

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).

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.

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).

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.