ELECTRONIC SUPPLEMENTARY MATERIAL

Study Protocol
This protocol has been provided by the authors to give readers additional information about their work.

Protocol for: An international randomised study of a home-based self-management program for severe COPD: the COPD Patient Management European Trial (COMET)

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on behalf of the C.O.M.E.T trial investigators

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AN INTERNATIONAL PHASE IV RANDOMISED TRIAL FOR MEDICAL AND MEDICO-ECONOMIC EVALUATIONS OF A HOME-BASED DISEASE MANAGEMENT PROGRAM IN PATIENTS WITH GOLD III/IV CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COMET: The COPD patient Management European Trial

Protocol Identification # ALMED-07-C4-008

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SUMMARY OF THE STUDY

TITLE OF THE STUDY	An International Phase IV Randomised Trial for Medical and Medico-Economic Evaluations of a Home-Based Disease Management Program in Patients with GOLD III/IV Chronic Obstructive Pulmonary Disease
COORDINATING INVESTIGATOR	Prof. Romain Kessler, MD Strasbourg University Hospital - France
STUDY CENTRES	Approximately 45 investigational centres located in 4 countries: France, Germany, Italy and Spain
STUDY PERIOD	Beginning of the study: September 2010 End of the enrolment: November 2013 *(38-month enrolment period)* End of the study: December 2014 *(14-month patient follow-up)*
PHASE OF DEVELOPMENT	Phase IV
METHODOLOGY	International, multicentre, open, randomised, prospective, controlled, parallel-group trial
OBJECTIVES	**Primary objective:** To evaluate a strategy of Chronic Obstructive Pulmonary Disease (COPD) management to reduce the number of hospital days in patients with GOLD III/IV COPD: a Home-Based COPD Management Program *versus* usual patient education and follow-up. **Secondary objectives:** - To assess the clinical outcome and the health-related quality of life, - To assess safety, - To evaluate medico-economic impact.
NUMBER OF PATIENTS	A total of 306 randomised patients, *i.e.,* 153 randomised patients in each of the 2 study groups
CRITERIA FOR INCLUSION AND EXCLUSION	**Inclusion criteria:** - Male or female patient aged ≥ 35 years old, - Current or ex-smoker with a smoking history ≥ 10 pack-years, - Patient having diagnosed COPD stage III or IV according to GOLD criteria: a post-bronchodilator FEV_1/FVC ratio ≤ 70% and FEV_1 < 50% of predicted value, - Patient who has had at least one COPD exacerbation leading to hospitalisation in the year before Selection, - Patient living within less than 2-hour transportation of the investigational centre, - Patient able to read and speak native language of his/her study country, - Patient having a touch tone telephone, - Patient willing and able to complete the requirements of the study including the signature of the Informed Consent. **Exclusion criteria:** - Patient previously randomised in the study,

	- Patient on LTOT for another reason than COPD, - Patient with a limited probability of survival *(< 6 months)* - Patient with a tracheostomy, - Patient receiving long term oral corticosteroids *(> 10 mg/day),* - Patient who has a condition which could limit compliance to study procedures *(alcohol, drug or solvent abuse, dementia, uncontrolled psychiatric illness, …),* - Patient not covered by a health insurance, - Patient living in a medicalised nursing home, - Patient who participated in another interventional clinical trial within 30 days before Selection.
INVESTIGATIONAL MANAGEMENT STRATEGIES AND INVESTIGATIONAL PLAN	**Investigational Management Strategy:** a home-based COPD management program combining: **1/** *An educational program*: adapted from the program "Living Well With COPD" from the McGill University and Health Centre, and provided to the patient by health counsellors through individual sessions, group sessions and telephone sessions. **2/** *A prospective telephone follow-up*: - Patient will be asked to transmit information about his/her health status to a dedicated vocal server at least once a week (*and at most once a day*) and to call each day his/her clinical status is worse than usual. - Automatic analysis of the data on the same day will lead to either a "well being status", a "worsening status" or an "alarm status", the latter being strictly defined by validated criteria. - Occurrence of a "worsening status" or of an "alarm status" will result in standardised interventions: a respiratory self-assessment by the patient at home and a phone call to the patient by a health counsellor to confirm the symptom changes and to provide support. - Only "alarm status" confirmed by the health counsellor will be transmitted to the investigator, who will in turn call the patient to give his/her medical decision. **Comparator:** Usual COPD education and patient follow-up as per investigational centre routine practice. **Study Periods:** **1/** *Selection Period*: period during which the patient eligibility is checked by the investigator and during which the patient is randomly assigned to one of the 2 study groups. **2/** *Run-In Period*: 5-week period during which medical evaluations are performed and during which the patient allocated to the home-based COPD management program receives the individual home education sessions. **3/** *Follow-Up Period*: 12-month period during which the patient receives his/her allocated management strategy. This period includes 4 evaluation visits at the investigational centre (every 3 months) and 4 standardised phone interviews with the centre between evaluation visits.

CRITERIA FOR EVALUATION	**Primary efficacy criterion:** Number of unscheduled hospital days whatever the reason, during the *Follow-Up Period* **Secondary efficacy criteria:** - Number of hospital days due to severe COPD exacerbations, - Number of moderate and severe COPD exacerbations, - Use of health care services due to COPD and to all causes, - Health-related quality of life, - Physiological parameters, - Functional impairment and disability index (BODE), - Anxiety and depression, - Compliance to oxygen therapy, - Changes in smoking status. **Safety parameters** **Medico-economic data**
STATISTICAL METHODS	All data collected will be tabulated descriptively by study group, on the Intention To Treat (ITT) data set. **Primary analysis of the primary efficacy criterion**: on the ITT data set, comparison of the normalised individual yearly number of unscheduled hospital days whatever the reason, during the *Follow-Up Period*, between both study groups, using the Wilcoxon's rank sum test in all countries pooled together **Supportive analyses of the primary efficacy criterion**: on the ITT data set, in each country where the number of randomised patients allows its performance, same separate descriptive exploratory analysis as the primary analysis of the primary efficacy criterion

LIST OF ABBREVIATIONS

6MWD	Six-Minute Walking Distance
6MWT	Six-Minute Walk Test
15D	Fifteen-Dimensional
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BMI	Body Mass Index
BODE	Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRP	C-Reactive Protein
DL_{CO}	Lung Diffusing capacity for carbon monoxide
DRG	Diagnosis Related Group
e-CRF	electronic Case Report Form
ECG	Electrocardiogram
EF	Ejection Fraction
ERS	European Respiratory Society
EVC	Endpoint Validation Committee
FAS	Full Analysis data Set
FEF_{25-75}	Forced Expiratory Flow between 25% and 75% of the vital capacity
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GMT	Greenwich Mean Time
GOLD	Global initiative for chronic Obstructive Lung Disease
GSM	Global System for Mobile communications
HADS	Hospital Anxiety and Depression Scale
IC	Inspiratory Capacity
ICD	International Classification of Diseases
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LTOT	Long Term Oxygen Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MMRC	Modified Medical Research Council
$PaCO_2$	Arterial Carbon dioxide partial Pressure
PaO_2	Arterial Oxygen partial Pressure
PASP	Pulmonary Artery Systolic Pressure
PIN	Personal Identification Number
PP	Per Protocol
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RV	Residual Volume
TE	Treatment Emergent
TLC	Total Lung Capacity
SAE	Serious Adverse Event
SE	Study Emergent
SGRQ-C	COPD-specific version of the Saint George's Respiratory Questionnaire
SpO_2	Arterial Oxygen Saturation measured by pulse oximetry
V_A	Alveolar Volume
WHO-DRUG	World Health Organisation-Drug reference list

1. INTRODUCTION

1.A STATE OF THE KNOWLEDGE

Chronic Obstructive Pulmonary Disease (COPD) represents a major medical and economic burden. It is common, affecting worldwide more than 10% of people aged 40 years and older, and severe, accounting for 4.8% of all deaths and 2.6% of all disability-adjusted life years. Due to both the epidemic of smoking and the ageing of populations, these numbers are predicted to increase over the next decade and, by 2020, COPD will rank seventh as a burden of disease and third as a cause of mortality [1].

COPD is defined as a non curable progressive lung disease characterised by an abnormal inflammatory response of the lungs to noxious particles or gases and an irreversible airflow limitation [2]. As this definition covers a large range of disease severity, the Global initiative for chronic Obstructive Lung Disease (GOLD) *(available from: http://www.goldcopd.org)* committee proposed to grade disease severity based on the level of lung function impairment into mild (GOLD Stage I), moderate (GOLD Stage II), severe (GOLD Stage III) and very severe disease (GOLD Stage IV). This staging is quite strongly associated with pathologic findings [3], global health status, and survival [4]. There is also a strong relationship between type/level of health care utilisation *(and related costs)* and disease severity [4;5]. Indeed, patients with GOLD Stages III and IV COPD are the highest consumers of acute care [6-9] and, because hospitalisations are a major cost driver, annual direct cost of a patient with severe COPD is about 3 times the cost of care for patients with moderate disease, and more than 10 times the cost of care for patients with mild disease [4;10].

A major problem for patients with COPD is the control of their disabling chronic respiratory symptoms *(mostly breathlessness, cough and sputum production)*. The intensity of these symptoms varies from day to day, and may increase acutely because of infections of the tracheobronchial tree or exposure to air pollutants [11]. Acute episodes, called *exacerbations*, require increased medication and are the main cause of hospital admission in COPD patients. Aside from being potentially life-threatening, exacerbations also significantly impact the course of the chronic disease, notably accelerating the rate of lung function decline [12], and reducing functional ability and quality of life [13-15]. Patients with COPD also frequently suffer from multiple comorbidities such as cardiovascular diseases, depression, malnutrition, muscle weakness and osteoporosis [16] that further contribute to their overall health impairment and their need for medical care and multiple hospitalisations.

To address this medical and medico-economic burden, several chronic illness management strategies have been applied to COPD. These approaches, initially developed for other common and disabling chronic diseases, aim to help patients have better day-to-day control of their chronic symptoms, thereby reducing the use and cost of acute health care services [17]. Core components of these management strategies include involvement of both the community and health system, employment of self-management plans, coordination of health care resources, decision supports, and clinical information systems [18]. All aim to foster efficient interactions between experienced health professionals and informed patients, who actively participate in their own care. Thus, main objectives of the programs evaluated in patients with COPD were to increase patient disease knowledge, enhance patient compliance to medication, encourage self-management, promote a healthier life style and facilitate communication with health carers. All these interventions have been shown to be lacking [19] and could substantially improve patient care while reducing risk factors for severe exacerbations [20;21]. However, the

means implemented to reach these goals were markedly different, including the distribution of printed materials, organisation of teaching sessions performed by hospital respiratory teams, specific trainings to develop patient self-management skills, and tele-assistance programs [18;22]. Major differences in the nature of the interventions resulted in an unclear assessment of the efficacy of disease management programs for COPD, further aggravated by the broad spectrum of illness severity, of intervention durations, and of efficacy criteria evaluated. Moreover, most studies were mainly local, including a relatively low number of patients, and only a few assessed cost data [23-25].

Several conclusions have however been drawn from these studies: ***first*, disease management interventions may be helpful and cost-effective**, mainly by reducing the need for acute care services and hospital use [20;24;26-28]. ***Second***, despite the insufficient standardisation of the interventions, it appears that **programs combining** the 3 elements of **self-management** *(education, behavioural changes, and motivation*) **and advanced access to medical care are the most effective** in improving patient outcome and reducing use of health services [18]. ***Third***, **disease management strategies need to be carefully targeted to the relevant level of disease severity to achieve success**.

1.B RATIONALE

The goal of the study is to evaluate a Home-Based Disease Management program specifically adapted for patients with GOLD III/IV COPD. Acute episodes requiring hospitalisation are more frequent in these patients with severely compromised lung function. Additionally, they are major contributors to health status decline and health costs. Therefore, the study primary objective is to show a significant reduction in the number of hospital days during the 12-month study follow-up in patients receiving the study program as compared to patients receiving usual care.

Key interventions of the study program combine four components of chronic care: *i)* patient education, *ii)* patient motivation *(to promote self-efficacy and self-management), iii)* closer patient follow-up to allow early detection of significant clinical worsening, and *iv)* coordination of health care to reduce time to treatment.

During the study, **patients of the Intervention group will receive an educational program provided by community-based health professionals** individually at home, in group sessions, and by telephone. The study educational program was adapted from the original 'Living Well With COPD' program, initiated, evaluated and implemented in Canada by the Montreal Chest Institute of the McGill University Health Centre since 1998. This program has been shown to have a sustained positive impact on patient's health, on health-related quality of life, and on the use of acute hospital care, resulting in significant cost of care savings [23;26;29]. The program contains disease knowledge education because it is essential for patients with COPD to understand their disease, risk factors for its progression, and objectives of their medication in order to promote compliance to therapeutics, including oxygen therapy [30], and to encourage "healthy behaviours" such as smoking cessation [31] and regular physical activity [32]. The program also contains a patient-tailored 'action plan' that includes teaching of techniques to self-perform home respiratory assessments, and specifying the steps to follow in particular situations, such as acute worsening of respiratory symptoms, so as to reinforce the patient's role in achieving better disease control.

Although early treatments of exacerbation result in lower hospitalisation rates and faster recovery times [33], many patients poorly recognise acute deterioration of their clinical state and/or do not have an adapted reaction when they recognise it [12;34;35]. To address this issue,

the study program combines patient education with a **telephone support in order to detect any significant clinical worsening early, and initiate an adapted treatment**. Significant clinical worsening will be defined on the basis of patient self-assessment of his/her respiratory symptoms, as commonly accepted and routinely used to diagnose an exacerbation *(available from: http://www.goldcopd.org)*, and as previously validated for the early detection of exacerbations [12-15;33].

While a relatively low number of **COPD patients are evaluated as having a severe GOLD stage** *(prevalence estimates of Stages III and IV COPD are about 2.4%, ranging 0.3 to 3.8, among people aged 40 years and older)* [1], these patients are the most disabled. Being on LTOT is usually associated with a marked limitation in activities of daily living [36], more frequent social isolation, anxiety and depression [37;38], and poor health-related quality of life [39]. End stage COPD patients are also more frequently exacerbated and are the greatest health consumers [40;41], mostly due to their high hospitalisation rate [42]. Thus, to be the most beneficial for patient health and the most cost-effective on a public health perspective, strategies directed at improving the control of chronic symptoms and at preventing severe exacerbations should primarily target patients with the most advanced stage**s** of COPD, and with the highest burden of assistance.

The study program is **community-based and home-based** primarily because patients with severe COPD have a low mobility, but also due to patient desire to be at home as much as possible [43], to a lack of hospital resources to provide education, and to the need to reduce the cost of health care for COPD.

Finally, patients will also be supported through a **telephone system,** which is widely accessible to a majority of people and easier to use than pocket computers for the targeted patient population. The telephone system has also proven to be effective in patients with severe COPD to provide education and support [20;21;44]. It will be used by patients to report at least once a week on their global health status and, if relevant, their symptom changes; and by health professionals to support patients in their education program and decision processes.

This study will be an international, prospective, randomised, "open label", comparative, parallel-group study. Randomisation will be used to reduce the potential bias in the allocation of patients to one or the other COPD management strategy and increase the probability to get comparable groups at study entry. For practical reasons, neither the patients nor the investigators will be blind to the study management strategy allocated. However, in order to limit the subjectivity of the assessment of efficacy, a hard endpoint *(i.e., number of hospital days during the patient follow-up, whatever the reason)* is defined as the primary efficacy criterion. Furthermore, an Endpoint Validation Committee will retrospectively review, in a blind manner, the medical reports of the patients who have been hospitalised during the study follow-up. Their review will be used by the sponsor as supportive information to discuss and interpret the study results.

1.C WORKING HYPOTHESES

This study is performed to demonstrate that a community-based, patient-centred disease management intervention combining several chronic care components *(patient education, clinical information system between patients and health professionals, and decision support)* can reduce acute hospitalisations and improve quality of life and other health-related parameters in patients with severe COPD.

It should be possible to achieve these goals through home support by more education, motivation, and monitoring of patients, leading to improved compliance to medications, including oxygen therapy. In addition, improved home support is expected to lead to healthier behaviours and earlier detection and treatment of significant clinical worsening, which in turn will help patients to better control their chronic symptoms and better react to acute clinical deterioration.

The primary hypothesis to be tested is that this Home-Based COPD Management Program will decrease the need for patients to be admitted to hospital, or the amount of time patients spent in the hospital for acute illness, as compared to a usual medical education and follow-up. Therefore, the **primary efficacy criterion** will be the number of unscheduled hospital days, whatever the reason, during the patient follow-up period. Rationale for this efficacy criterion is that hospitalisations reflect the most severe exacerbations, are associated with worsened health quality of life and increased mortality and account for the majority of health care costs in treating COPD. Additionally, they represent an objective measurable endpoint.

Additionally, **secondary criteria** will be evaluated including frequency of moderate and severe COPD exacerbations, use of health care services due to COPD and to all causes, compliance to oxygen therapy, if applicable, health-related quality of life, clinical outcome measurements and safety parameters. The education program is expected to reduce the frequency of severe COPD exacerbations and to increase patient health-related quality of life towards supporting independence and self-management and encouraging positive health behaviours. Particular attention will be paid to compliance to long term oxygen therapy (LTOT). Indeed, the benefit of LTOT on survival is strongly associated with the average daily treatment duration [45;46], and poor LTOT compliance is a predictor of hospital admissions in hypoxemic COPD patients [19;47;48]. Inconvenience, fear and overall misunderstanding of the role of supplemental oxygen result in daily usage which is generally less than prescribed [49], but that can be improved by proper patient education [50]. For study patients on oxygen therapy, compliance will be assessed using the medical device *NOWOX* which records daily hours of oxygen use and breathing frequency. Survival, rate of lung function decline, and functional ability will also be evaluated, but no significant benefit is expected from the program with regards to these parameters, as previously demonstrated [18;22].

In addition to benefits for individual patients, this COPD management program may also meet societal goals in decreasing the cost of COPD care by reducing hospital admissions and the hospital length of stay. Therefore, a **medico-economic evaluation** will also be performed based on intervention-specific cost of care, global cost of patient care, and patient utility. As the cost of medical services is highly dependent on local factors, and may vary substantially between countries, national medico-economic evaluations will be performed in each participating country.

Preventing the occurrence of severe acute events, and especially severe exacerbations, would be a major advance in COPD care. By improving disease knowledge, awareness of significant clinical deterioration and self-management skills for patients with GOLD III/IV COPD, this Home-Based COPD Management Program is expected to reduce the severity of exacerbations, the need for emergency hospitalisations, thus demonstrating the cost-effectiveness of such interventions.

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) guidelines and all applicable national laws, rules and regulations.

2. STUDY OBJECTIVES

2.A PRIMARY OBJECTIVE

The **primary objective** of the study is to evaluate a strategy of Chronic Obstructive Pulmonary Disease (COPD) management to reduce the number of hospital days in patients with GOLD III/IV COPD: a Home-Based COPD Management Program *versus* usual patient education and follow-up.

2.B SECONDARY OBJECTIVES

The **secondary objectives** of this study are:

- To assess the clinical outcome and the health-related quality of life,
- To assess safety,
- To evaluate medico-economic data, by estimating the costs of both management strategies and relating the cost difference to a difference in clinical outcome.

3. PATIENTS SELECTION

Eligible patients for this study are patients with GOLD III/IV COPD. Patients can be treated with all COPD relevant treatment, including home oxygen therapy and mechanical ventilation.

Definitions used for this study are those of the *Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease,* Global initiative for chronic Obstructive Lung Disease (GOLD) 2008 and 2011:

- **COPD**: 'Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. A clinical diagnosis of COPD should be considered in any patient who has dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. The diagnosis should be confirmed by spirometry. For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardised, and objective way of measuring airflow limitation. The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.'
- **COPD GOLD staging:**
  - Stage III: Severe COPD – Characterised by $FEV_1/FVC < 0.70$ and $30\% \leq FEV_1 < 50\%$ predicted.
  - Stage IV: Very Severe COPD – Characterised by $FEV_1/FVC < 0.70$ and $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus the presence of chronic respiratory failure. Respiratory failure is defined as an arterial pressure of oxygen (PaO_2) less than 8.0 kPa (*60 mmHg*), with or without arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 6.7 kPa (*50 mmHg*) while breathing air at sea level.
- **GOLD combined severity assessment** (*association between symptoms, spirometric classification and future risk for exacerbations*):

  'This approach, combined with an assessment of potential comorbidities, reflects the complexity of COPD better than the unidimensional analysis of airflow limitation previously used for staging the disease and forms the basis of the guide to individualised management.'

  As all patients included in the trial are GOLD III/IV, only Patient Groups C and D classes can occur:

  - **Patient Group C – High Risk, Less Symptoms:** typically GOLD III or IV and/or ≥ 2 exacerbations per year and mMRC grade 0-1.
  - **Patient Group D - High Risk, More Symptoms:** typically GOLD III or IV and/or ≥ 2 exacerbations per year and mMRC grade ≥ 2.

- **Criteria for Long Term Oxygen Therapy (LTOT):** 'Long term oxygen therapy is generally introduced in *Stage IV: Very Severe COPD* for patients who have:

- At rest on room air PaO_2^* ≤ 55 mmHg *(7.3 kPa)* with or without hypercapnia, or
- At rest on room air PaO_2^* between 55 mmHg *(7.3 kPa)* and 60 mmHg *(8.0 kPa)*, if there is evidence of pulmonary hypertension, peripheral oedema suggesting congestive cardiac failure, or polycythemia *(haematocrit > 55%)*.

* PaO_2 value having been assessed at rest and on room air and in stable state *(defined by a period of at least 3 weeks without exacerbation).*

A decision about the use of long term oxygen should be based on the waking PaO_2 values. The prescription should always include the source of supplemental oxygen *(gas or liquid)*, method of delivery, duration of use, and flow rate at rest, during exercise, and during sleep.'

- **LTOT:** 'The primary goal of oxygen therapy is to increase the baseline PaO_2 to at least 8.0 kPa *(60 mmHg)* at sea level and rest and/or to produce an SaO_2 at least 90%, which will preserve vital organ function by ensuring adequate delivery of oxygen. Treatment should be for at least 15 hours per day and preferably longer.'
- **Ventilatory support:** 'Non-Invasive Ventilation (*NIV*) is increasingly used in patients with stable very severe COPD. The combination of NIV with LTOT may be of some use in a selected subset of patients, particularly those with pronounced daytime hypercapnia.'
- **COPD exacerbation:** 'Event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.'

3.A NUMBER OF PATIENTS / ENROLMENT/ FOLLOW-UP PERIOD

This study will include a total of 306 patients *(153 in each group, see section 7.B.2),* randomly assigned to one of the two study groups detailed in section 4.A by centre, smoking status and need for respiratory assistance (*i.e., home oxygen therapy or Non-Invasive Ventilation)* for chronic respiratory failure at Selection**.**

The planned total study duration is 52 months, including a 38-month enrolment period and a 14-month follow-up for each randomised patient.

3.B INCLUSION CRITERIA

Patients who fulfil all the inclusion criteria are eligible for study participation. The criteria for inclusion are:

1) Male or female patient aged ≥ 35 years old,

2) Current or ex-smoker with a smoking history ≥ 10 pack-years,

3) Patient having diagnosed COPD stage III or IV according to GOLD criteria: a post-bronchodilator* FEV_1/FVC ratio ≤ 70% and a post-bronchodilator* FEV_1 < 50% of predicted value, assessed by pulmonary function tests performed less than 12 months prior to Selection. Patient can be treated with all relevant COPD treatment, including home oxygen therapy and mechanical ventilation,

   * measured 30 min after the inhalation of an adequate dose of a short-acting inhaled bronchodilator, e.g., 400 µg salbutamol or equivalent,

4) Patient who has had at least one COPD exacerbation leading to hospitalisation in the year before Selection,

5) Patient living within less than 2-hour transportation of the investigational centre,

6) Patient able to read and speak native language of his/her study country,

7) Patient having a touch tone telephone,

8) Patient willing and able to complete the requirements of the study including the signature of the Informed Consent after full explanation of the study by the investigator prior to participation.

3.C EXCLUSION CRITERIA

If any of the exclusion criteria are fulfilled, potential patients are not eligible for study participation. The criteria for exclusion are:

9) Patient previously randomised in the study,

10) Patient on LTOT for another reason than COPD, *e.g.,* for a concomitant significant chronic disease such as asthma, diffuse bronchiectasis including cystic fibrosis, sarcoidosis, lung fibrosis, kyphoskoliosis, neuromuscular disease, severe left chronic cardiac failure, …,

11) Patient with limited probability of survival *(< 6 months)*,

12) Patient with a tracheostomy,

13) Patient receiving long term oral corticosteroids therapy *(defined as continuous use of > 10 mg of prednisone or equivalent per day for more than 6 weeks. Successive courses of oral corticosteroids separated by a period of less than 7 days will be considered as continuous use)*,

14) Patient who has, in the knowledge of the investigator, a condition which could limit compliance to study procedures, such as:

    14.a) Alcohol abuse,

    14.b) Drug *(e.g., cannabis, cocaine, …)* abuse,

    14.c) Solvent abuse,

    14.d) Dementia,

    14.e) Uncontrolled psychiatric illness,

15) Patient not covered by a health insurance,

16) Patient living in a medicalised nursing home,

17) Patient who participated in another interventional clinical trial within 30 days before Selection.

3.D WITHDRAWAL CRITERIA

Reasons for **premature discontinuation of the allocated management strategy** include:

- Patient moving for long term stay in a medicalised nursing home,
- Any lack of compliance to the study procedures which can compromise the study progress, and, in particular, for the Intervention group only:
    a) Absence of phone call to the study vocal server to report clinical status for more than 1 month for another reason than being away from home,
    b) Refusal or inability to follow the four individual home education sessions before Visit 1 as detailed in section 4.B.3.1.

Whenever possible, in case of premature discontinuation of the allocated management strategy, patients will be followed up until Month 12 as initially planned *(by regular visits at the investigational centre and standardised phone interviews, as detailed in section 4.B.3.2)*.

Reasons for **study premature withdrawal** include:

- Patient moving away from the geographic area of the investigational centre resulting in the patient's inability to attend study visits,
- Withdrawn consent as described in the Patient Informed Consent,

- Death.

The reason, date and time for premature discontinuation of the allocated management strategy and/or study premature withdrawal will be recorded in the electronic Case Report Forms (e-CRF) of the patients concerned by their investigator. Survival data until Month 12 will be collected unless the patient disagrees.

The patient will be replaced only if premature discontinuation of the allocated management strategy or study premature withdrawal occurs before the end of Visit 1 *(see section 4.B.3.1).*

4. INVESTIGATIONAL PLAN

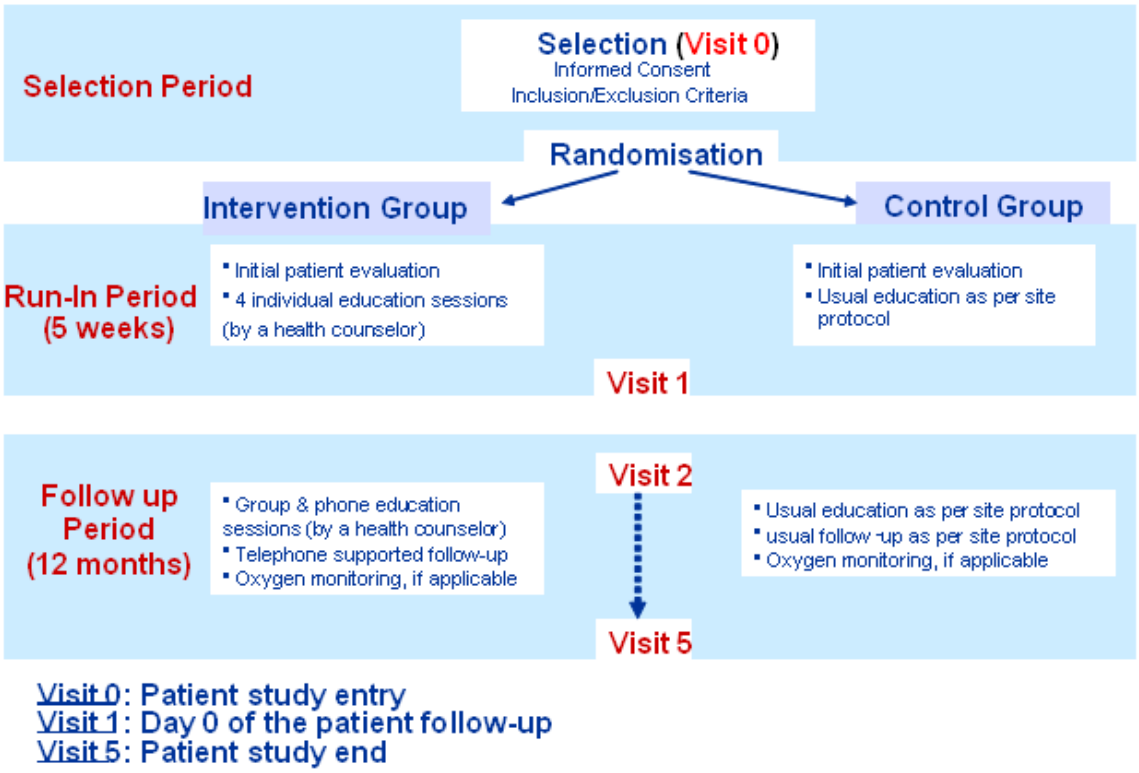
4.A STUDY DESIGN

This is an international, multicentre, open, randomised, prospective, controlled, parallel-group Phase IV study. It will be conducted in four (4) countries (France, Germany, Italy and Spain) and approximately forty-five (45) investigational centres.

Included patients will be randomly assigned by centre, smoking status and need for respiratory assistance (*i.e., home oxygen therapy or Non-Invasive Ventilation*) for chronic respiratory failure at Selection to one of the two (2) study groups:

- Either Home-Based COPD Management group *(Intervention group)*,
- Or the Usual COPD Education and Patient Follow-Up group *(Control group)*.

Figure 1: Schematic Study Design



4.B STUDY PLAN

The participants will follow the three (3) consecutive study periods as detailed below:

- *Selection Period*: period during which the patient is evaluated for inclusion/exclusion criteria and, if eligible, randomised in to one of the two (2) study groups *(Visit 0)*,
- *Run-In Period*: period from randomisation to Visit 1 *(visit at the investigational centre)*, during which all medical evaluations will be performed and, for patients randomised in the Intervention group, the four (4) individual home education sessions will be performed. This period will last 5 weeks *(± 5 days)* following randomisation.
- *Follow-Up Period*: 12-month period from the end of the *Run-In Period (end of Visit 1)* including 4 evaluation visits at the investigational centre *(every 3 months)* and 4 standardised phone interviews with the centre between evaluation visits. Moreover, for patients randomised in the Intervention group, the *Follow-Up Period* will include education sessions every month *(alternatively group and phone sessions)* and an at least weekly prospective telephone follow-up.

Patients randomised in the Control group will receive, during their *Run-In* and *Follow-Up Period*s, the usual COPD education and follow-up as per investigational centre routine practice.

4.B.1 *Selection of patients*

4.B.1.1. Recruitment

After receiving local ethics committees and national competent authority approvals *(see section 9.A)*, patients will be recruited by the investigators of the participating investigational centres among their patients with GOLD III/IV COPD. After full explanation of the study by the investigator, signed and dated Informed Consent will be obtained from patients who accept to participate to the study *(see section 9.B)*, before the onset of any study specific procedures.

4.B.1.2. Selection *(Visit 0)*

Patients who meet all inclusion criteria and none of the exclusion criteria *(see sections 3.B and 3.C), i.e.,* all eligible patients, will be included. A 3-digit patient number *(selection number)* will be assigned in sequential order *(001, 002,)*, in each investigational centre separately, to each patient having signed and dated his/her Informed Consent.

During Visit 0, the investigator will:

- Perform a physical examination including vital signs, pulse oximetry, height and weight,
- Randomise the patient (*see section 4.B.2*),
- Schedule an appointment for Visit 1, five (5) weeks *(± 5 days)* after Visit 0,
- Schedule all medical evaluations and laboratory samplings to be performed between Visit 0 and Visit 1,
- Provide the patient with the "Patient's Study Diary"*,

- Send a standardised education request form to the health counsellor and provide the patient with a fulfilled written action plan *(for patients randomised to the Intervention group only).*

* "Patient's Study Diary" contains the following: schedule of planned contacts *(visits at the investigational centre, phone interviews, and for patients in the Intervention group, education sessions)*; investigator's name and telephone number, and all useful contacts; weekly forms for the patient to record any use of health care services *(medical and paramedical consultations, attendances at emergency departments, hospitalisations)*; and, for patients of the Intervention group only, space to report the date and results of their home respiratory self-assessments *(SpO_2, pulse rate, FEV_1 and body temperature as detailed in sections 5.A.1.2 and 5.A.4).*

During Visit 0, for each eligible patient, the investigator will record the following data in the e-CRF:

- Date of Visit 0 and date of signature of Patient Informed Consent,
- Date of birth, sex, height and weight,
- Results of the physical examination including vital signs *(i.e., systolic and diastolic blood pressures)* and pulse oximetry *(pulse rate and SpO_2)* on room air and also, only for patients on oxygen therapy, on oxygen,
- Social conditions *(civil status, area of residence and type of residence),*
- COPD history including:
  - ✓ Date of diagnosis and suspected cause of COPD,
  - ✓ Smoking status and history *(i.e., current or ex-smoker, the later being defined as patients who have stopped smoking for at least 6 months prior to Visit 0, current number of cigarettes smoked per day, estimated number of pack-years, smoking start and stop dates, if applicable),*
  - ✓ Results and date of the most recent pulmonary function tests available *(including Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC), as both raw values and percentages of predicted values, as well as FEV_1/FVC ratio),* performed in stable state less than one year prior to Visit 0,
  - ✓ Patient-reported number of previous moderate and severe COPD exacerbations *(as defined in section 6.A.2.2)* having occurred in the year prior to Visit 0,
- Medical and surgical history not related to COPD and concomitant diseases,
- COPD and non-COPD medication, including oxygen therapy, CPAP, Non-Invasive Ventilation and vaccines performed in the year prior to Visit 0 *(see section 5.D),* and contraception method used, if applicable,
- Start date and criteria for oxygen prescription, if applicable:
  - ✓ Results and date of the most recent resting arterial or capillary blood gases on room air available, performed in stable state *(defined by a period of at least 3 weeks without exacerbation),* within 12 months prior to Visit 0 *(including pH, PaO_2, $PaCO_2$, HCO_3^- and SaO_2),*

- ✓ Presence/absence of the following *(including dates of measurement or assessment, when present)*: pulmonary hypertension, peripheral oedema and haematocrit > 55%.

4.B.2 *Method of assigning patients to study groups*

According to their smoking status, their need for respiratory assistance *(i.e., home oxygen therapy or Non-Invasive Ventilation)* for chronic respiratory failure at Selection and their investigational centre, included patients will be randomly assigned to either the Intervention group or the Control group, according to a computer generated randomisation list pre-specified prior to the study start. The randomly allocated study group to a given included patient and the corresponding 4-digit randomisation number will be attributed in sequential numerical order by the study dedicated telephone Interactive Voice Response System (IVRS). This randomisation number will be used throughout the study as the identification number for all randomised patients.

The randomly allocated study group and the corresponding 4-digit randomisation number will be notified to the investigator through the IVRS and they will be confirmed automatically *via* an e-mail and/or fax sent to the investigator. The investigator will print the randomisation confirmation e-mail/fax and file it in the investigator binder.

Neither the patient nor the study personnel of the investigational centre will be blinded as to the study group allocated, after randomisation.

4.B.3 *Study implementation*

4.B.3.1. Run-In Period

At the end of the *Selection Period*, randomised patients will start the *Run-In Period*. During the *Run-In Period*, patients will undergo medical evaluations and laboratory sampling to evaluate their COPD at study entry. Patients will receive COPD education according to their randomly allocated study group, i.e., either the Intervention group or the Control group. The *Run-In Period* will last 5 weeks *(± 5 days)* and will finish when Visit 1 is completed.

Exceptionally, the duration of the *Run-In Period* may be prolonged by 4 supplemental weeks *i)* in the occurrence of a medical event which is expected to be resolved within 4 weeks *(for example, a COPD exacerbation starting during the Run-In Period)*, or *ii)* to allow patients included at hospital discharge to reach sufficient clinical stability to perform the medical tests required and, for patients of the Intervention group, to receive the education sessions in optimal conditions.

INITIAL PATIENT EVALUATION

The following medical evaluations and laboratory samplings will be performed for patients of both study groups at the investigational centre, and while the patient is in stable state *(defined by a period of at least 3 weeks without exacerbation)*:

- Medical evaluations *(as detailed in sections 6.A.2.5 and 6.B.1)*
  - ✓ Post-bronchodilator pulmonary function tests *(spirometry)*,
  - ✓ Six-minute walk test on room air or on oxygen for patients on oxygen therapy,
  - ✓ Transthoracic Doppler echocardiography,
  - ✓ 12-lead supine resting electrocardiogram.

- Laboratory samplings *(as detailed in section 6.B.2)*
    - ✓ Resting arterial or capillary blood gases on room air,
    - ✓ Venous blood sampling for measurements of haemoglobin, haematocrit and C-Reactive Protein (CRP).

Medical tests and laboratory samplings that were routinely performed before Selection and signature of the Informed Consent can be used for initial patient evaluation: they will not have to be repeated if performed within 3 months before randomisation, in stable clinical conditions, and if all parameters to be reported in the eCRF had been collected.

Initial patient evaluation should be completed before Visit 1 and all results will be recorded by the investigator in the e-CRF at Visit 1.

COPD EDUCATION

Patients randomised in the Control group will receive the usual COPD education as per investigational centre routine practice. The content and modalities of each centre will be collected before study initiation, as well as any modifications throughout the study period, if applicable.

Patients randomised in the Intervention group will undergo four (4) individual home education sessions, performed on a weekly basis by a community-based health professional *(called for the study 'health counsellor' and detailed in section 5.A.1)*:

- The four sessions will be performed before Visit 1, in a minimum of 3 weeks and a maximum of 5 weeks after randomisation.
- Each individual session is planned to last 60 to 90 minutes during which the health counsellor will use specific teaching material in local study language and will give the patient the printed education documents *(handbooks and brochure, as detailed in section 5.A.1.1)* and the study medical devices *(portable pulse oximeter, spirometer and thermometer, as detailed in section 5.A.4).* The patient will also be trained to perform phone call**s** to the study dedicated vocal server. After each education session, the understanding and skills of the patient will be assessed and a report will be sent by the health counsellor to the investigator concerned.

VISIT AT THE INVESTIGATIONAL CENTRE *(VISIT 1)*

Before seeing the investigator, patients will complete on their own **the three (3) following questionnaires** *(as detailed in section 6.A.2.4 and 6.A.2.7 and provided in Appendix 3)*:

- The COPD-specific version of the St George's Respiratory Questionnaire *(SGRQ-C)*[51],
- The 15D health-related quality of life instrument *(available from: http://www.15d-instrument.net),*
- The Hospital Anxiety and Depression Scale (HADS) [52].

Validated versions of these three (3) questionnaires in the four (4) study languages *(German, French, Italian and Spanish)* will be used.

During Visit 1, the investigator will record the following data in the e-CRF:

- Date of Visit 1,

- Results of the physical examination including vital signs *(i.e., systolic and diastolic blood pressures)*, weight and pulse oximetry *(pulse rate and SpO_2)* on room air and also on oxygen for patients on oxygen therapy,
- Changes in social conditions, if applicable,
- Changes in smoking status, if applicable,
- Recovery from concomitant diseases since Visit 0, if applicable,
- Assessment of the severity of dyspnoea using the modified Medical Research Council Dyspnoea Scale [53],
- Comorbidities to allow the calculation of the Charlson Comorbidity Index [54],
- Changes in COPD and non-COPD medication, including oxygen therapy, CPAP, Non-Invasive Ventilation and vaccines *(as detailed in section 5.D)*, since Visit 0, if applicable,
- Occurrence of COPD exacerbations *(as defined in section 6.A.2.2)* since Visit 0,
- Occurrence of other Adverse Events *(see section 6.B)* since Visit 0,
- Results and dates of the medical evaluations and laboratory samplings performed during the *Run-In Period*,
- Serial number of the *NOWOX* device assigned to the patient, if applicable.

At the end of the visit, if the patient is on oxygen therapy**,** the investigator will give to the patient the *NOWOX* medical device, after having initialised it and having explained to the patient its correct use *(see section 5.A.4.1)*. All patients on oxygen therapy will receive the *NOWOX* user manual and simplified user sheet in their native language and they will be instructed to wear the *NOWOX* each time they use oxygen therapy and to bring it at each of their study visits at the investigational centre.

4.B.3.2. Follow-Up Period

The *Follow-Up Period* starts at the end of Visit 1 and will last 12 months for each patient.

Patients will undergo during this period:

- **Visits** at the investigational centre every 3 months *(Visits 2 to 5)*,
- **Standardised phone interviews** performed by an investigational centre staff member every 3 months between the patient visits at the investigational centre *(Centre phone contacts 1 to 4)*,
- And, **for patients randomised in the Intervention group**, education sessions given by a health counsellor every month *(alternatively group and phone sessions)*, and an at least weekly prospective telephone follow-up while **for patients randomised in the Control group**, the usual COPD education and follow-up as per investigational centre routine practice.

VISITS AT THE INVESTIGATIONAL CENTRE *(VISITS 2 TO 5)*

Visits 2 to 5 are scheduled at Month 3, Month 6, Month 9 and Month 12 from Visit 1, respectively. These visits may vary from their planned timelines starting at Visit 1 by ± 30 days, without modifying the initially planned timelines of the following visits if a given visit needs to be advanced or postponed.

During Visits 2 to 5, the investigator will record the following data in the e-CRF:

- Date of Visit,
- Results of the physical examination including vital signs *(i.e., systolic and diastolic blood pressures)*, weight and pulse oximetry *(pulse rate and SpO_2)* on room air and also on oxygen for patients on oxygen therapy,
- Changes in social conditions, if applicable,
- Changes in smoking status, if applicable,
- Recovery from concomitant diseases since the last visit, if applicable,
- Changes in COPD and non-COPD medication, including oxygen therapy, CPAP, Non-Invasive Ventilation and vaccines *(as detailed in section 5.D)*, since the last visit, if applicable,
- Occurrence of COPD exacerbations *(as defined in section 6.A.2.2)* since the last visit,
- Occurrence of other Adverse Events *(see section 6.B)* since the last visit,
- For patients on oxygen therapy, checking of the *NOWOX* device *(to detect the need for an exchange or return of the device at study end)*, and, if applicable, the reason for exchanging or returning the *NOWOX* device and the serial number of the new *NOWOX* device assigned, whenever necessary; of note, patients starting oxygen therapy during their study participation will be given a NOWOX following the procedure described in section 4.B.3.1 and their start date and criteria for oxygen prescription will be collected, as described in section 4.B.1.2.
- Use of health care services *(see section 6.A.2.3)* since the last visit.

At Visit 3 *(Month 6)* and **Visit 5** *(Month 12 or study end in case of premature withdrawal)*, additional questionnaires and examinations will be performed as follows:

- The SGRQ-C, 15D and HADS questionnaires *(as detailed in sections 6.A.2.4 and 6.A.2.7 and provided in Appendix 3)*, self-administered before the consultation with the investigator at **Visit 3** (M6) and **Visit 5** (M12),
- Assessment of the severity of dyspnoea using the modified Medical Research Council Dyspnoea Scale at **Visit 5** (M12),
- Comorbidities to allow the calculation of the Charlson Comorbidity Index at **Visit 5** (M12),

Medical evaluations (pulmonary function tests, six-minute walk test on room air or on oxygen if the patient is on oxygen therapy, transthoracic Doppler echocardiography and ECG, as detailed in sections 6.A.2.5 and 6.B.1) performed while the patient is in stable state (defined by a period of at least 3 weeks without exacerbation) performed between **Visit 4** (M9) and **Visit 5** (M12), and recorded by the investigator in the e-CRF at **Visit 5**,

- Laboratory samplings *(as detailed in section 6.B.2)*: resting arterial or capillary blood gases on room air and venous blood sampling *(for measurements of haemoglobin, haematocrit and CRP)* performed between **Visit 4** (M9) and **Visit 5** (M12), and recorded by the investigator in the e-CRF at **Visit 5,**
- Collection at **Visit 5** (M12) by the investigator of the *NOWOX* device, if applicable, and all other study medical devices provided to the patient of the Intervention group (*i.e, the portable pulse oximeter, spirometer and thermometer*).

STANDARDISED PHONE INTERVIEWS BY AN INVESTIGATIONAL CENTRE STAFF MEMBER

Standardised phone contacts will be scheduled every 3 months between the patient and a staff member of the investigational centre to collect information regarding the patient use of health care services *(medical and paramedical consultations, attendances at emergency departments, hospitalisations, …).* Four (4) phone interviews *(Centre phone contacts 1 to 4)* will be scheduled respectively at Month 1.5, Month 4.5, Month 7.5 and Month 10.5 from Visit 1 *(each phone contact may vary from its planned timeline by ± 15 days, without modifying the initially planned timelines of the following phone contacts, nor the planned schedule of the patient visits at the investigational centre).*

During the standardised phone interviews, the patient will be asked to read his/her notes in the "Patient's Study Diary" *(see section 4.B.1.2)* since the last visit at the investigational centre. The information collected through a standardised questionnaire in local language will be recorded in the e-CRF by the investigational centre staff member in charge of the interview and validated by the investigator. At the end of each phone interview, the patient will be reminded of the date and time of his/her next visit at the investigational centre and, if applicable**,** to bring back the *NOWOX* device.

EDUCATION AND FOLLOW-UP

Patients randomised in the Control group will receive the usual COPD education and follow-up as per investigational centre routine practice.

Patients randomised in the Intervention group will attend education sessions *(alternatively group and phone sessions)* dispensed by the health counsellor and will undergo a prospective telephone follow-up:

- *Group education sessions*

The first group education session will be scheduled 2 months after Visit 1, and thereafter every 4 months until Month 12. Each group education session will last about two hours and will be animated by two (2) health counsellors who will use specific teaching material in local language *(described in section 5.A.1.1).* The main aim of these group education sessions is to reinforce the patients' knowledge and skills regarding their action plan.

- *Phone education sessions*

The first phone education session will be scheduled 1 month after Visit 1 and thereafter every month (*except months when a group session is performed*) until Month 12. Supplemental phone education sessions will be scheduled if a COPD exacerbation occurs or on patient's request. Each phone education session will last about half an hour and aims to assess/reinforce the specific skills and behaviours that the patient needs to acquire and to maintain over time, *i.e.*, in particular the importance of self-evaluation and regular symptoms reporting, and the procedures that will be implemented in case of a clinical deterioration.

- *Prospective telephone follow-up*

Patients will be instructed to phone to the study dedicated vocal server to report their clinical status *(as detailed in section 5.A.1.2 and Appendix 2)* at least once a week *(and at most once a day)*, and each day their clinical status is worse than usual.

In case they report a deterioration of their overall clinical status, patients will be asked to perform a home respiratory self-assessment *(pulse oximetry, spirometry, and temperature)* and to report the results of their measurements in their study diary. They will be called back by a health counsellor within 2 hours following their telephone report *(or on the first following working day if the report occurs during week-end or public holiday)*. The health counsellor will review the questionnaire with the patient, validate it, collect additional parameters via a second questionnaire including the results of the patient's respiratory self-assessment and provide the patient with adequate reinforcement and counselling. If a significant deterioration of the patient's clinical status is confirmed *(scoring methodology is provided in Appendix 2*), the investigator in charge of the patient follow-up will be informed, so as to take the appropriate medical decision and communicate it to the patient on the same day.

4.B.4 *Evaluation of protocol compliance*

Any deviations of protocol procedures described in section 4.B.3 will be reported in the e-CRF of the patients concerned, together with any other abnormalities or incidents occurring during the study.

Protocol deviations correspond to non-compliance with the protocol *(e.g., non-compliance with the study procedures, the follow-up duration, the attendance to the education sessions or the prospective telephone follow-up, etc...)*. Such deviations do not require the patients concerned to be withdrawn from the study but the corresponding data must be recorded in the e-CRF. The impact of all encountered deviations on the evaluation criteria will be assessed by the sponsor study personnel, prior to the database lock. The sponsor study personnel will also decide whether a Per Protocol data set needs to be defined prior to the start of the statistical analysis *(see section 7.B.3.1)*.

4.B.5 *Study premature withdrawals*

If at any time the study procedures are considered compromised, the concerned patient may be withdrawn from the study at the investigator's discretion. Moreover, patients are free to discontinue their participation in the study at any time as described in their Informed Consent.

The reason and date of study premature withdrawal will be recorded in the e-CRF of the patients concerned *(e.g., consent withdrawn, death, etc...)* by the investigator. As mentioned in section 3.D, patients who are prematurely withdrawn from the study during the *Follow-Up Period* will not be replaced.

5. COPD MANAGEMENT STRATEGIES AND MEDICAL DEVICES

5.A DESCRIPTION OF COPD MANAGEMENT STRATEGIES AND OF MEDICAL DEVICES

The study will compare a Home-Based COPD Management Program *(Intervention group) versus* a usual patient education and follow-up *(Control group)*. Patients of both study groups will be equipped with the *NOWOX* device to monitor oxygen therapy if they are on oxygen therapy at Selection or during their study participation.

5.A.1 *Home-Based COPD Management Program*

The study Home-Based COPD Management Program consists in:

- A specific COPD educational program,
- A specific COPD prospective telephone follow-up.

5.A.1.1. Study specific COPD educational program

The educational program used in this study is adapted from the validated program "Living well with COPD" [23;26;29]. The original program was developed to be delivered by trained health professionals to patients with COPD and includes patient education materials *(handbooks, brochure and written action plan)* and supportive teaching materials for the trainers *(guides and flipchart)*. Original materials were developed in two languages *(Canadian French and Canadian English)* and are available on the "www.livingwellwithcopd.com" website.

Adaptation of the original program for the needs of study was performed by a team composed of Dr Jean Bourbeau, the owner of the program, health professionals of the McGill University *(Montreal, Canada)* and health professionals specialised in respiratory diseases of the 4 study countries.

The education materials that will be used in the study *(Table 1)* were adapted from the originals for the purpose of this study to account for:

- The severity of the study disease. Content of the program has been adapted to the severity of the patients who will be enrolled as patients with GOLD III/IV COPD and especially those with chronic respiratory failure have different capabilities compared to a general COPD population for which the original education program was developed,
- The number, modalities and content of the patient educational sessions. Content of the training and related patient and trainers materials were adapted to the planned study individual/group/phone education sessions *(content and materials are summarised in Table 1)*,
- The study countries. Education documentation for patients and trainers have been translated in the four (4) study languages and adapted for cultural differences from the Canadian French version of the original program.

Table 1: Content of the Study Specific COPD Educational Program

Session	Duration (min)	Topics	Living well with COPD materials for patients	Living well with COPD materials for health counsellors
Individual # 1	60-90	**- Knowledge assessment** **- Disease knowledge:** defining COPD, risk factors and symptoms; COPD medication, including oxygen therapy **- Behaviour change:** compliance to medication **- Self-management skills:** correct use of COPD medications	**- Handbook** *"Understanding COPD and taking your medication"* **- Handbook** *"Long term oxygen therapy"* **- Brochure** *"Summary guide"*	**- Trainer guide** *"Understanding COPD and taking your medication"* **- Flipchart**
Individual # 2	60-90	**- Knowledge assessment** **- Disease knowledge:** dyspnoea; stress and anxiety factors **- Behaviour change:** manage breathing and stress and save energy **- Self-management skills:** techniques for breathing, coughing, managing stress and anxiety; energy conserving techniques	**- Handbook** *"Breathing and stress management, and energy conservation"* **- Brochure** *"Summary guide"*	**- Trainer guide** *"Breathing and stress management, and energy conservation"* **- Flipchart**
Individual # 3	60-90	**- Knowledge assessment** **- Disease knowledge:** evaluate chronic symptoms; identify and avoid triggers **- Behaviour change:** prevent and manage symptoms aggravation **- Self-management skills:** symptoms monitoring; avoidance of aggravating factors; respiratory self-assessment; managing symptoms worsening	**- Handbook** *"Integrating an action plan into your life"* **- Written action plan**	**- Trainer guide** *"Integrating an action plan into your life"* **- Flipchart**
Individual # 4	60-90	**- Knowledge assessment** **- Disease knowledge:** importance of nutrition, sleep and physical activity **- Behaviour change:** smoking cessation; compliance to medication; maintain an active life; integrate healthy habits in everyday life **- Self-management skills:** methods to increase physical and leisure activities, while adhering to oxygen therapy; keep healthy sleep and nutrition habits	**- Handbook** *"Adopt and maintain a healthy lifestyle"* **- Module** *" Long term oxygen therapy"* **- Brochure** *"Summary guide"*	**- Trainer guide** *"Adopt and maintain a healthy lifestyle"* **- Flipchart**
Group	90-120	**- Needs assessment** **- Behaviour change:** maintenance of healthy habits and integration of self-management skills for life **- Self-management skills:** brief review of all self-management techniques; focus on action plan: symptoms monitoring, respiratory self-assessment; managing symptoms worsening	**- Handbook** *"Integrating an action plan into your life"* **- Written action plan**	**- Trainer guide** *"Group session"* **- Flipchart**
Phone	30	**- Assessment of behaviour change:** integrated behaviours, barriers to change and reasons *(knowledge, beliefs, etc...)* **- Self-efficacy reinforcement** on various self-management skills		**- Standardised educational phone interview**

The program will be administered to the patient by health professionals *(nurses, physiotherapists, …)*, called for the study purpose "health counsellors", especially trained to educate COPD patients and to the education program. Duration of each session, content and related materials are listed in Table 1.

5.A.1.2. Study specific COPD prospective telephone follow-up

Patients will have to report their clinical status by telephone to a dedicated, full free, vocal server at least once a week (*and at most once a day*) and each day their clinical status is worse than usual. During the phone call, the patients will enter their study identification number and will answer a questionnaire in their native language by pressing numbers on their touch-tone phone. Patient's answers will lead to an automatic scoring of their clinical status *(a sample of the script of the questionnaire and methodology to assess the clinical status score is provided in Appendix 2).*

Results of the scoring will determine the actions to be taken by the patient, the health counsellor and the investigator *(as detailed in Appendix 2).* In brief, in case of significant clinical status deterioration, the patient will perform at home a respiratory self-assessment *(measurements of FEV_1, SpO_2 on room air and also on oxygen for patients on oxygen therapy, pulse rate and temperature)*; the health counsellor will provide support and reinforcement, and the investigator will call the patient to provide his/her medical decision.

5.A.2 *Usual COPD education and patient follow-up*

The usual COPD education and patient follow-up will be defined as the ones in force during the study in the investigational centres.

The current routine of each centre will be collected before study initiation, as well as any modifications afterwards.

5.A.3 *Oxygen sources*

Oxygen prescriptions to the study patients will follow the standard protocols of the investigational centres, and they will be at the investigator's discretion throughout the study period.

5.A.4 *Medical devices*

5.A.4.1. NOWOX

The medical device *NOWOX (Figure 2)* is small *(dimensions are 58 * 28 * 60 mm)*, light *(total weight of 30 g)*, wireless, and maintenance free. It is made of RADEL R and CE-marked.

Figure 2: *NOWOX* Device

The *NOWOX* is connected in line between the oxygen source and the patient nasal cannula as shown in Figure 3. The device is compatible with standard nasal cannulae and standard oxygen tubing.

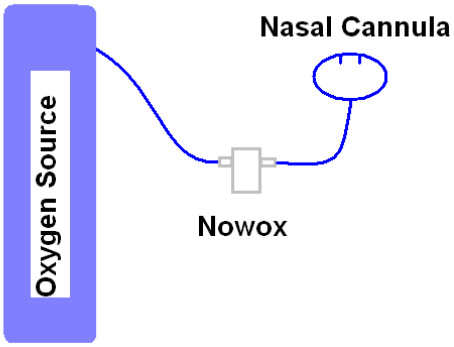


Figure 3: *NOWOX* Connection Between the Nasal Cannula and the Oxygen Source

The *NOWOX* is compatible with the following types of oxygen sources:

- Oxygen concentrators,
- Oxygen cylinders *(gaseous oxygen)*,
- Stationary and mobile oxygen tanks *(liquid oxygen)*.

Of note, NOWOX is not to be connected to the oxygen source when the patient is on a CPAP device or a home ventilator.

The device makes measurements every five minutes and stores the summarised data every hour. A data record contains the following fields:

- A unique numeric index to identify the record,
- The GMT date and time of the record,
- The percentage of time during which oxygen flow was detected during the past hour *(in percentage of one hour)*,
- The percentage of time of oxygen use during the past hour *(in percentage of one hour)*, defined by detection of simultaneous oxygen flow and patient's breathing,
- The average respiration rate recorded during the past hour *(in breaths per minute)*,
- The peak respiration rate recorded during the past hour *(in breaths per minute)*.

The data stored by the *NOWOX* will be downloaded by the manufacturer when the device is returned by the patient to the investigational centre *(i.e., at the end of the patient's participation in the study, or in case the device has to be replaced for any reason)* using a Personal Computer equipped with a radio frequency communication port and the dedicated software *(NOWOX monitor v1.0)*. The data will be identified only with the device serial number, and will be saved on a CD-Rom, which will be sent to LINCOLN, in charge of the study data management. Then, they will be transferred electronically into the trial database *(see section 7.A)*.

Ten percent of the *NOWOX* devices will be equipped with a GSM gateway, allowing the automatic sending of the data to a sponsor central server. GSM-equipped *NOWOX* data will be downloaded by the manufacturer as previously described after the return of the device to the investigational centre. Data sent through the GSM gateway will only be used by the sponsor to check major dysfunctions throughout the study conduct. These data sent through the GSM gateway will be identified only with the device serial number. They will not be recorded in the study database and will not be associated with the patient selection or randomisation numbers.

More information are provided in the current versions of the *NOWOX* and *NOWOX* gateway user manuals, both available in the 4 study languages.

5.A.4.2. Oximeter

The medical device Onyx® 9500 *(Nonin Medical)* is a self-contained digital fingertip pulse oximeter, incorporating the electronics and sensor in one unit. It measures instantaneous SpO_2 and pulse rate. This product complies with current ISO references, current Medical Devices Directive and is CE marked. User manuals are available in the 4 study languages.

5.A.4.3. Spirometer

The Vitalograph® asma-1 *(Vitalograph)* is a portable medical device measuring lung function *(FEV_1 and peak expiratory flow)*. The device allows the setting of personal best or predicted *(reference)* values. It complies with current ISO references, current Medical Devices Directive, and is CE marked. User manuals are available in the 4 study languages.

5.A.4.4. Thermometer

The electronic ear and forehead thermometer *(ref. 13673-56, Orgalys)* is a medical device measuring temperature instantly and accurately. Measuring range is 32.0°C - 42.9°C with an accuracy of ± 0.2°C from 36.0°C to 39.0°C. The device complies with the current Medical Devices Directive and is CE marked. User manuals are available in the 4 study languages.

5.B PACKAGING AND LABELLING OF THE MEDICAL DEVICES

5.B.1 *NOWOX*

The *NOWOX* devices will be supplied with the user manual in a box according to European regulations. The trial protocol number "ALMED-07-C4-008" will be stuck on each packaging and each device will have an individual serial number.

Each time a *NOWOX* device is assigned to a patient, the investigator will report the *NOWOX* serial number in the patient's e-CRF as detailed in section 4.B.3.

5.B.2 *Oximeter, spirometer and thermometer*

The oximeter, spirometer and thermometer devices will be supplied with their user manuals, according to European regulations. The trial protocol number "ALMED-07-C4-008" will be stuck on each packaging and on each device.

5.C STORAGE, ACTIVATION, USE AND RETURN OF THE MEDICAL DEVICES

5.C.1 *NOWOX*

The *NOWOX* devices are shut down after manufacturing to preserve their battery. They can be stored for one year away from a heat source, without shortening their useful life. After a device has been activated, the battery life time is 2 years. In any case, if the battery runs out, the data stored by the *NOWOX* devices are saved and can be downloaded.

The *NOWOX* device has to be activated once prior to its use, before its connection to the nasal cannula and the oxygen source, by inserting a paperclip twice in the reset pinhole *(detailed procedure is described in the NOWOX user manual).* A blinking optical control *(several blue flashings)* indicates that the device has gone through a self-test and is functional. The device is then connected to the patient nasal cannula and to the oxygen source.

The recommendations for use of the *NOWOX* and the specific Material Safety Data Sheet are detailed in the *NOWOX* user manual. A risk analysis has been performed by the sponsor and the manufacturer of the *NOWOX* in accordance with the standard ISO 14971 *(application of risk management to medical devices).*

Used and unused devices and their related materials *(NOWOX devices, NOWOX GSM gateways, and documentation)* will be returned to the sponsor at the end of the trial.

5.C.2 *Oximeter, spirometer and thermometer*

Used and unused devices and their related materials and documentations will be returned to the sponsor at the end of the trial.

5.D CONCOMITANT TREATMENTS

All concomitant treatments administered to the patient *(including vaccines, oxygen therapy, home ventilation and CPAP)* will be recorded by the investigators in the e-CRF, with the following information:

- **For the pharmaceutical therapies**: treatment names and dosage, route of administration, dose per administration and posology, start and end dates or ongoing medication, and the reason for their prescription,
- **For the vaccines**: names and date of administration,
- **For oxygen therapy**: start and, if applicable, end dates, daily prescribed hours of use, prescribed flow rates *(at rest, during exercise and during sleep)*, type of oxygen source(s) including the name of the device(s) used,
- **For home ventilation and CPAP**: start and end dates, if applicable.

5.D.1 *Allowed medications*

All COPD and non-COPD medications which are deemed necessary by the investigator for the patient's welfare may be administered at any time at the investigator's discretion. They will be recorded accordingly in the e-CRF.

5.D.2 *Not permitted medications*

Long term oral corticosteroids therapy is not permitted at Selection. Long term use is defined as continuous use of > 10 mg of prednisone or equivalent per day for more than 6 weeks. Successive courses of oral corticosteroids separated by a period of less than 7 days will be considered as continuous use.

However, if during the study *Follow-Up Period*, a patient requires such a therapy, he/she will not be withdrawn from the trial but the corresponding data must be recorded by the investigator in the e-CRF.

The patients will not be allowed to participate to any other interventional study during their participation to this trial.

6. STUDY EVALUATIONS

6.A EFFICACY EVALUATIONS

6.A.1 *Primary efficacy criterion*

The primary efficacy criterion is the **number of unscheduled hospital days, whatever the reason, during the *Follow-Up Period*** for each randomised patient.

Hospitalisations are defined as stays in the following facilities:

- Emergency room, if duration of stay is > 24 hours,
- Intensive care unit, intermediate care unit, surgical or medical wards,
- Nursing facilities following an acute hospital stay.

Scheduled inpatient rehabilitation will not be considered as hospitalisations.

The number of unscheduled hospital days will be calculated for each randomised patient based on the following information recorded by the investigators in the e-CRF for each hospitalisation separately during the *Follow-Up Period*:

- Reason for admission,
- Type of facility,
- Dates of admission and discharge for each facility.

These data will be normalised by total number of days that the patient will have participated in the *Follow-Up Period* to yield the duration of hospitalisations per year, as detailed in section 7.B.3.5.

Each hospitalisation will also be reported as a Serious Adverse Event as defined in section 8.A.

6.A.2 *Secondary efficacy criteria*

6.A.2.1. Number of hospital days due to severe COPD exacerbation

On the basis of the reasons for admission of each hospitalisation during the *Follow-Up Period*, as reported by the investigators in the e-CRF, the number of hospital days due to severe COPD exacerbation will also be calculated for each randomised patient.

6.A.2.2. Number of moderate and severe COPD exacerbations

Each time the patients experiment a COPD exacerbation throughout the study, the investigators will record the following information in the e-CRF:

- Date of diagnosis,
- Medication prescribed for treating the exacerbation *(name, dosage and duration),*
- Dates of admission and discharge from hospital, if applicable.

Moderate COPD exacerbations will be defined as exacerbation of symptoms not requiring hospitalisation but ending with a prescription of antibiotics and/or systemic corticosteroids.

Severe COPD exacerbations will be defined as exacerbation of symptoms requiring hospitalisation and/or leading to death [55]. In the subgroup of patients experiencing at least one severe COPD exacerbation during their *Follow-Up Period*, the time elapsed between Visit 1 and the date of the first severe COPD exacerbation *(defined by either the date of hospital admission or the date of death)* will be described as the time to first severe COPD exacerbation *(expressed in number of days elapsed since Visit 1).*

A new episode of moderate/severe COPD exacerbation will be counted when patients have been off systemic corticosteroids and/or antibiotics for at least 14 days following their previous exacerbation [56].

6.A.2.3. Use of health care services due to COPD and to all causes

The investigators will record the following information about use of health care services during the *Follow-Up Period:*

- For each medical or paramedical consultation: date, type of visit *(home versus out-patient visit)*, category of health care provider consulted *(specialist physician, primary care physician, nurse, respiratory therapist, …)* and the reason for consulting,
- Home hospitalisation: start and end dates.

The health counsellors will record the following information about use of health care services during the *Follow-Up Period (for the Intervention group only):*

- For each unscheduled phone call *(on patient's request or because of the symptom scoring)*: date, duration of the phone call and the reason for calling.

If any of the use of health care services recorded are the results of an AE or SAE, then the appropriate e-CRF should also be completed by the investigator.

6.A.2.4. Health-related quality of life

Quality of life will be assessed for each randomised patient every 6 months *(corresponding to Visits 1, 3 and 5)* using the self-administered COPD-specific version of the St George's Respiratory Questionnaire *(SGRQ-C)* [51] and the 15D health-related quality of life instrument *(http://www.15d-instrument.net)*, in their linguistically validated versions for the 4 study countries. Time to complete each questionnaire is about 10 minutes for SGRQ-C and 5-10 minutes for 15D.

- The SGRQ-C *(sample provided in Appendix 3)* is a disease-specific questionnaire designed to measure the impact of respiratory disease on overall health, daily life, and perceived well-being. It has been developed for use by patients with asthma and COPD. The questionnaire is composed of 14 questions grouped in 2 sections: 'Symptoms' *(questions 1 to 7, which address the frequency of respiratory symptoms)* and 'Activity and Impacts' *(questions 8 to 14, which address the patient's current state in terms of disturbances to daily physical activity and psycho-social function).* Each questionnaire response has a unique empirically derived weight, ranging from 0 to 100, the highest scores indicating poorer health status. The total score and the three (3) component subscores will be calculated *(symptoms, activity and impacts)* by using the scoring algorithm manual provided by the SGRQ-C owner. A mean change score of 4 units is associated with a slightly efficacious treatment, 8 units with a moderately efficacious treatment and 12 units with a very efficacious treatment [57].

- The 15D *(sample provided in Appendix 3)* is a generic, comprehensive *(15-dimensional)*, self-administered instrument for measuring present health status in adults and for estimating cost-effectiveness of interventions. It is composed of 15 questions *(mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity)* with 5 alternative responses to each question. A set of utility weights will be used to score the patient's responses and to generate the 15D score *(single index number)* on a 0-1 scale, where a score of 1 represents a perfect state. The 15D has been already used as a utility measure in COPD [58].

6.A.2.5. Physiological parameters

Results of the following medical evaluations will be recorded for each randomised patient at Visits 1 and 5:

- Pulmonary function tests, performed according to ATS/ERS guidelines [59-61], and including:
    - Spirometry: for measurements of Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC), Forced Expiratory Flow between 25% and 75% of the vital capacity (FEF_{25-75}), Inspiratory Capacity (IC), and the FEV_1/FVC ratio.

  The values reported by the investigator will be post-bronchodilator values in absolute values and percentage of predicted values in force in the investigational centre.
- Six-Minute Walk Test (6MWT) on room air or on oxygen for patients on oxygen therapy, performed according to ATS/ERS guidelines [62]. The investigator will report *i)* the six-minute walking distance *(in meters) (the percentage of predicted value based on age, height, weight and sex [63] will be calculated by the e-CRF), ii)* the SpO_2 value at rest before starting the 6MWT, *iii)* the minimum SpO_2 value recorded during the 6MWT, *iv)* the pulse rate value at rest before starting the 6MWT, *v)* the maximum pulse rate value recorded during the 6MWT *(the percentage of maximum theoretical heart rate will be calculated by the e-CRF) [64], vi)* the reason for premature ending of the 6MWT, and the number of minutes walked before discontinuation, if applicable, and *vii)* the oxygen flow rate(s) delivered during the 6MWT, if applicable.

- Transthoracic Doppler echocardiography. The investigator will report *i)* the estimated Pulmonary Artery Systolic Pressure (PASP), derived from tricuspid regurgitation and expressed in mmHg *(a PASP of 35 mmHg and above will be considered as the cut-off value for pulmonary hypertension)* [65], *ii)* the left ventricular Ejection Fraction (EF), as a parameter of systolic left heart function, expressed in percentage *(a EF of 50% and below will be considered as the cut-off value for systolic left heart dysfunction)* and *iii)* parameters to estimate and quantify diastolic left heart function, derived from the transmitral flow: deceleration time of the early transmitral flow *(expressed in milliseconds)*, peak velocity of the early transmitral flow *(E-wave, representing the early filling phase, expressed in cm/sec)*, peak velocity of the late transmitral flow *(A-wave, representing the atrial contraction, expressed in cm/sec)*. Ratio of the peak velocity of the E-wave to the A-wave will be calculated by the e-CRF. It is expected that these measurements will not be possible in a number of patients, approximately estimated to one third, because of technical limitations due to chest wall configuration [66;67].

6.A.2.6. Functional impairment and disability index (BODE index)

The Body mass index, airflow Obstruction, Dyspnoea and Exercise (BODE) capacity index has been shown to predict mortality in patients with COPD. It ranges from 0 to 10 with highest scores indicating higher risks of death [68].

The BODE index will be calculated for each randomised patient using the following physiological parameters reported by the investigators at Visits 1 and 5 *(see section 6.A.2.5)*:

- Forced Expiratory Volume in one second *(FEV_1)*, assessed by spirometry and recorded in percentage of predicted values in force in the investigational centre [60].
- Six-minute walking distance assessed during a six-minute walk test on room air or on oxygen for patients on oxygen therapy and reported in meters [62].
- Dyspnoea score, assessed by the Modified Medical Research Council (MMRC) dyspnoea scale.
- Weight at each visit and height at Selection, allowing the calculation of the Body Mass Index (BMI).

From these variables, the BODE index will be calculated for each patient at Visits 1 and 5 as follow:

Parameters	Points on BODE Index			
	0	1	2	3
FEV_1 *(% of predicted values)*	≥ 65	50–64	36–49	≤ 35
6-min walking distance (m)	≥ 350	250–349	150–249	≤ 149
MMRC dyspnoea scale	0–1	2	3	4
BMI (kg/m^2)	> 21	≤ 21		

Table 2: Variables and Point Values Used for the Calculation of the BODE Index

Then, the calculated BODE index will be categorised in 4 quartiles as previously defined [68]: quartile 1 will be defined as a score of 0 to 2, quartile 2 as a score of 3 or 4, quartile 3 as a score of 5 or 6 and quartile 4 as a score of 7 to 10.

6.A.2.7. Anxiety and depression

Anxiety and depression will be assessed for each randomised patient every 6 months *(corresponding to Visits 1, 3 and 5)* using the linguistically validated versions of the Hospital Anxiety and Depression Scale *(HADS provided in Appendix 3)* [52] for the 4 study countries. The questionnaire consists of seven items for depression (HAD-D) and seven items for anxiety (HAD-A). Each item is scored on a 4-point scale, ranging from 0 to 3. One anxiety and one depression scale are scored by summing patient's answers: a score ≥ 8 on either part will be used as the cut-off point for the presence of symptoms suggestive of anxiety or depression. The questionnaire has previously been used to screen depression and anxiety in out-patients with COPD [69] and patients with COPD requiring oxygen therapy [70].

6.A.2.8. Compliance to oxygen therapy

Compliance to oxygen therapy will be assessed for each randomised patient being on oxygen therapy at Selection or during his/her study participation using the data stored and downloaded from the *NOWOX* device.

These data will be used to estimate the average daily use of oxygen therapy of each randomised patient being on oxygen therapy during the time period he/she is on oxygen therapy during the *Follow-Up Period*, in hours per day.

Average daily use of oxygen therapy will be calculated from all cumulated percentages of oxygen use per hour recorded by the *NOWOX* device throughout the *Follow-Up Period*, converted to hours and normalised by using the total number of days of the patient's effective follow-up at home *(days during which patient is hospitalised will not be taken into account for the calculation).*

6.A.2.9. Smoking status

Smoking status will be reported by the investigators at Visits 0 to 5, as any changes *(e.g., stopping or re-starting smoking)* may impact the outcome measurements. Results of HbCO measurements performed from the arterial or capillary blood gas sample at Visits 1 and 5 will also be considered.

6.B SAFETY EVALUATIONS

All Adverse Events (AEs) occurring during the whole study period will be recorded as detailed in section 8. Their reports in the e-CRF will include:

- The nature of the events, their start and end dates, their severity,
- The corrective treatment(s) started if applicable,
- The required adjustment of COPD medication, including oxygen therapy, home ventilation, if applicable,
- The outcome of the events and their relationship to the allocated study intervention as assessed by the investigator.

AEs will include all hospitalisations, whatever their associated diagnoses afterwards, and deaths throughout the study period.

6.B.1 *Clinical parameters*

A physical examination including vital signs *(i.e., systolic and diastolic blood pressures*), weight and pulse oximetry *(for the measurement of pulse rate and SpO_2)* on room air and also on oxygen for patients on oxygen therapy will be recorded at each of the **six (6)** visits at the investigational centre.

A 12-lead supine resting electrocardiogram (ECG) will be performed prior to Visits 1 and 5 and potential significant abnormalities will be recorded by the investigators in the e-CRF.

The Charlson Comorbidity Index [54;71] will be used to assess the importance of comorbidities. It will be calculated by the e-CRF for each randomised patient based on the comorbidities reported by the investigator at Visits 1 and 5. The Charlson Index contains 19 conditions. Each comorbid condition is assigned to a score of 1 to 6, proportional to the disease-related risk of death. Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, COPD, connective tissue disease, peptic ulcer disease, mild liver disease and diabetes are assigned a score of 1. A score of 2 is assigned to diabetes with end-organ damage, hemiplegia, renal disease and malignancies, including leukaemia and lymphoma. A score of 3 is assigned to moderate or severe liver disease, whereas AIDS and metastatic malignancies are assigned a score of 6. The global score ranges from 0 to 33, the highest scores indicating more comorbidities, and it was shown to be predictive of mortality in COPD [68].

6.B.2 *Laboratory parameters*

Prior to Visits 1 and 5, the following blood samples will be assayed by the laboratory of each investigational centre for each randomised patient:

- Resting arterial or capillary blood gases on room air, *i.e.*, pH, PaO_2, $PaCO_2$, HCO_3^-, HbCO and SaO_2.
- Venous blood sampling: haemoglobin *(anaemia will be defined as a haemoglobin level below 13 g/dL and polycythemia as a haemoglobin level ≥ 17g/dL for males and ≥ 15g/dL for females [72])*, haematocrit and CRP [73;74].

Additional blood samples may be collected at the investigator's discretion, in the patient's interest, in case of technical problems during the initial assays performed and/or clinically significant abnormalities evidenced requiring specific additional checks and follow-up until stabilisation or normalisation.

6.C MEDICO-ECONOMIC EVALUATIONS

6.C.1 *Costs estimation*

Overall costs will be estimated for each randomised patient from the perspective of the health care payer *(i.e., the National Health System in force in the country, with the latest version of the corresponding national tariffs system and reimbursement schedule available at the end of the study)*. The unit will be the patient. Only health care direct costs will be considered, neither the costs to the family nor the costs to the society will be estimated.

Overall resources used for the patient's medical management *(collected in volume, i.e., by type and/or unit of time, before being priced according to the national tarifs system in force)* will be recorded prospectively alongside the study by the study personnel, as the data used to estimate the overall costs from the perspective of the health care payer for each randomised patient have four (4) components which are part of the clinical parameters recorded, including:

- For each unscheduled hospitalisation *(including home hospitalisations)*: the dates of admission and discharge, the type of facility, the primary and secondary diagnoses *(as mentioned in section 6.A.1)*, as well as the additional expensive medical procedures and acts performed during hospitalisation, if relevant *(including laboratory and other diagnosis examinations)*, and the specific expensive treatments administered or technical devices and equipments used during hospitalisation, whenever possible,
- For each health care consultation: the date, the location, the category of health care provider consulted and the reason for consulting *(as detailed in section 6.A.2.3)*,
- For the patients in the Intervention group and for each unscheduled phone call to the health counsellor *(on patient's request or because of symptom scoring)*: the date, the reason for calling, as well as the duration of the phone call and associated procedures set up by the health counsellor, and duration of the investigator actions in case of confirmed alarm status *(as mentioned in section 6.A.2.3)*,
- For the patients in the Intervention group and for each scheduled education session: the date and duration of the education session performed, its type and location.

Moreover, the fixed costs of the study specific COPD educational program *(including flipcharts, guides, handbooks and brochures listed in section 5.A.1.1)* and the fixed costs of the patient's monitoring *(including the set-up and maintenance of the dedicated vocal server in its latest version in use at the end of the study)* will be recorded by the sponsor.

From the perspective of the health care payer, billing data will be the monetary parameters used in the cost-of-care overall evaluation. To estimate them, for each unscheduled hospitalisation separately, the Diagnosis Related Groups (DRGs) prospective payment system in force in each participating country will be used. Depending on the national tariffs system, all diagnoses *(either primary or secondary)*, additional expensive medical procedures and acts, specific expensive treatments administered and technical devices and equipments used will first be coded for each hospitalisation separately, and then, they will be converted in DRG, by the national grouping software in use, taking into account the number of days of hospitalisation in each ward. At the end of the study, in each participating country, the last available annual valorisation scheme in force, for the DRGs will be used, as provided by the official national administrative documents, and corresponding electronic version.

All diagnoses *(either primary or secondary)* will first be coded using the World Health Organisation (WHO) International Classification of Diseases (ICD) dictionary, versions 9 or 10, depending on the country, in their local language. Lists of codes for medical procedures, acts, specific expensive treatments and technical devices and equipments are country-specific. They will be recorded with their algorithmic conversion in DRG and additional cost items, as well as the version of the dictionary in use for each hospitalisation, separately, whenever possible.

The total costs of other health care consultations will be estimated for each randomised patient and each category of health care service, by multiplying the number of categories of consultations *(from the date of Visit 1 (included) onwards)*, by their individual national unit cost, from the perspective of the National Health System tariffs in force, at the end of the study.

For the patients in the Intervention group, the total individual duration spent by the health counsellor and the investigator, for scheduled and unscheduled actions, separately, will be multiplied by the hourly national health care professional income, as fixed by the National Health System tariffs in force, at the end of the study.

6.C.2 *Cost-effectiveness*

The cost-effectiveness evaluation performed will relate the estimated difference in costs between both COPD management programs in the perspective of the health care payer to a difference in medical outcome over the 12-month *Follow-Up Period*. The medical outcomes which will be taken into account in this evaluation will be:

- the number of unscheduled hospital days whatever the reason for hospitalisation *(i.e., the primary efficacy criterion defined in section 6.A.1),*
- the number of deaths.

6.C.3 *Cost-utility*

An incremental cost per Quality-Adjusted Life Year (QALY) gained will be estimated by calculating the ratio between the incremental cost of the Intervention group *(receiving the Home-Based Disease Management Program)* and the Control group *(receiving the usual COPD education and follow-up of their investigational centre)* and the incremental utility.

The incremental cost will be estimated by calculating the difference between the average total costs per patient *(from the date of Visit 1 (included) onwards)* in both study groups.

Incremental utility will be estimated by using the self-evaluations of the 15D health-related quality of life instrument and the Finnish scoring algorithm. QALY weights will be calculated for each six-month study period, and they will be applied to the time period lived throughout the 12-month *Follow-Up Period*.

QALYs per patient in both study groups will be compared and, if relevant, related to the additional incremental cost required to produce one additional QALY *(incremental cost-utility analysis, as detailed in section 7.B.3.6).*

6.D ENDPOINT VALIDATION COMMITTEE

An Endpoint Validation Committee (EVC) will be established to review in a blind manner all hospitalisations having been reported for each randomised patient during the *Follow-Up Period.* The major reason is that hospitalisation may be considered as a potentially biased outcome measure, because somewhat subjective, and physician- or centre-dependent, as health care availability, each physician's routine practice and social considerations can markedly influence the decision to hospitalise a patient.

The EVC will be composed of three (3) independent physicians with clinical and research expertise in COPD. The 3 members will be appointed by the sponsor (AIR LIQUIDE *Santé* INTERNATIONAL) but will not be involved in the study conduct.

The role of the EVC members will be to adjudicate the reason and appropriateness of all hospital admissions and, for hospitalisations due to COPD exacerbation, to check for the presence of recognised criteria for hospital admission as published in the GOLD 2008 guidelines. Adjudication rules will be defined by the EVC members and sponsor representatives before starting adjudication of cases.

To adjudicate all hospitalisations recorded, the EVC members will review all individual medical reports *(anonymous reports, blinded for study group allocation, and translated in English by the study Clinical Research Associates (CRAs))* related to hospitalisations having occurred in randomised patients during the *Follow-Up Period*. The following will be adjudicated:

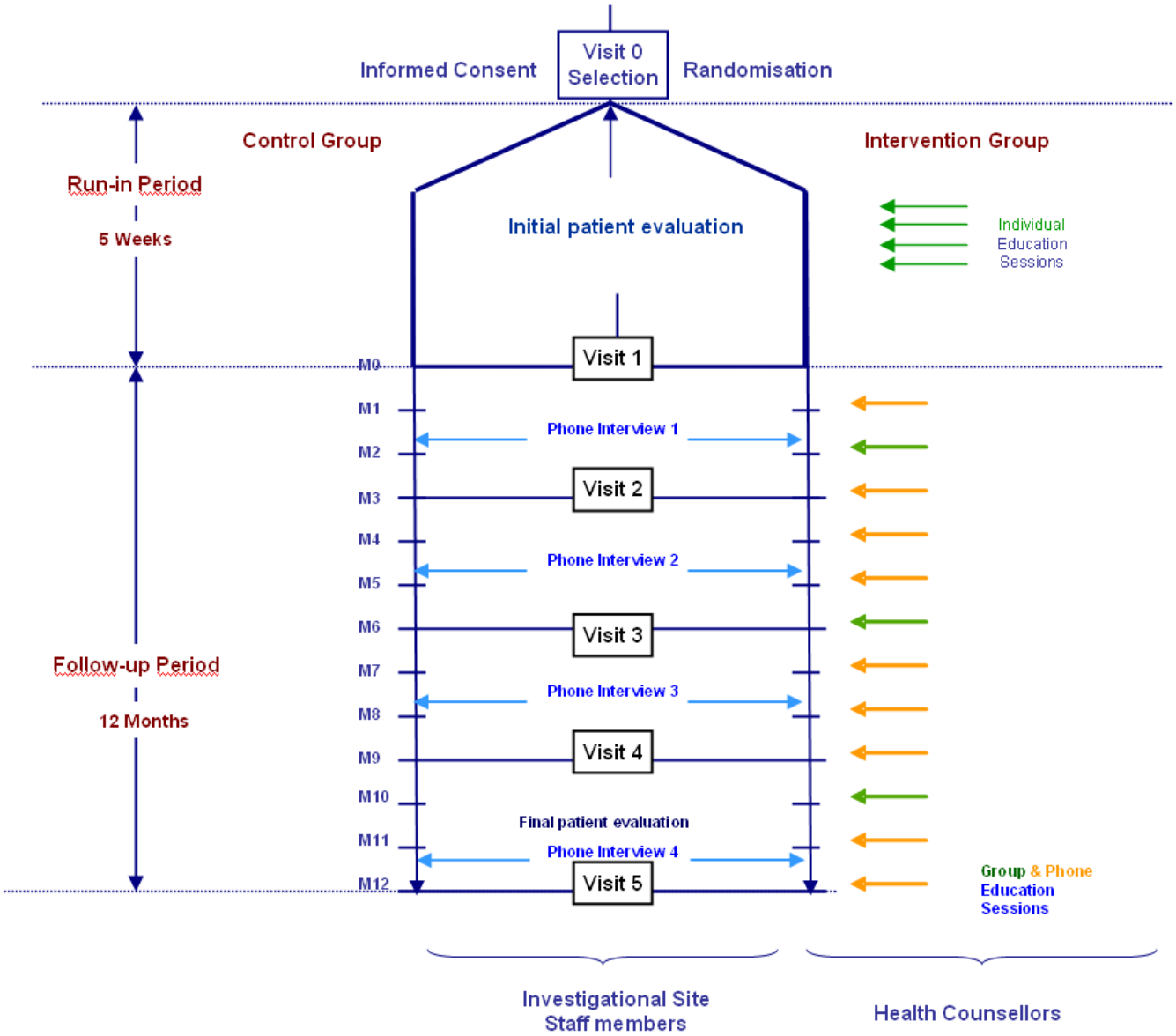
- Criteria for hospitalisation,
- Reason for hospitalisation: first attributing the hospitalisation to a specific cause, then distinguishing hospitalisations directly related to COPD and to other causes, then grouping them into general pathophysiological categories *(respiratory, cardiovascular, cancer or other),*
- Cause of prolonged hospitalisation *(defined by an overall duration of hospitalisation > 30 days).*

Each EVC member will independently analyse, by batches of 50 cases, all hospitalisation reports and will provide the sponsor with a written signed adjudication form for each of them. Cases will be considered as resolved if the 3 members agreed on adjudication parameters. Regular telephone meetings will take place during the study and will be organised to discuss only the reports not unanimously adjudicated in order to further review *(additional medical information could be requested to the investigational centre)* and discuss the case until complete consensus is achieved. Consensus will be written into a final dated and signed adjudication form. All forms and subsequent analyses will be used by the sponsor as supportive information to discuss and interpret the study results. Indeed, whatever the conclusions of the EVC members on the definition of the primary efficacy criterion, the information recorded by the investigators will be used for the primary analysis of the primary efficacy criterion.

6.E STUDY FLOW CHART OF EXAMINATIONS AND EVALUATIONS

Examinations and Evaluations	Selection	Run-In	Follow-Up			
	Visit 0	Visit 1*	Visit 2	Visit 3	Visit 4	Visit **5**
	Minus 5 weeks	Day 0	Month 3	Month 6	Month 9	Month **12**
Informed consent	X					
Demographics – child-bearing potential	X					
Medical and surgical history	X					
Physical examination, vital signs and pulse oximetry, weight *(and height at Selection)*	X	X	X	X	X	X
Smoking status assessment	X	X	X	X	X	X
Concomitant medication, including vaccines, **oxygen therapy**, home ventilation and CPAP, if applicable	X	X	X	X	X	X
Social conditions assessment	X	X	X	X	X	X
Inclusion and Exclusion criteria including *(but not limited to)*: - Quantification of airflow obstruction - **At least 1 hospitalisation for exacerbation in the year before selection**	X X(a) X					
Randomisation	X					
Medical evaluations: Post-bronchodilator pulmonary function tests, six minute-walk test, transthoracic Doppler echocardiography and 12-lead supine resting ECG		X(**b**)				X(**c**)
Laboratory tests: Arterial/capillary blood gases on room air (including HbCO), haemoglobin, haematocrit and CRP		X(**b**)				X(**c**)
Questionnaires SGRQ-C, 15D and HADS		X(**d**)		X(**d**)		X(**d**)
Train and dispense the *NOWOX* device, **if applicable**		X	X	X	X	
Assessment of dyspnoea *(MMRC dyspnoea scale)* and of comorbidities *(Charlson comorbidity index)*		X				X
Report COPD exacerbations and use of health care services		X	X	X	X	X
Adverse events		X	X	X	X	X
Collect the *NOWOX* and other study medical devices, **if applicable**						X

* Exceptionally, in the event of a medical problem which is expected to be resolved within 4 weeks *(e.g., a COPD exacerbation)* **or in case clinical stability is not reached after hospital discharge**, the time interval between Visit 0 and Visit 1 may be prolonged by a maximum of 4 supplemental weeks.
(a) Assessed by pulmonary function tests performed less than 12 months prior to Visit 0.
(b) Tests performed within 3 months before selection can be reported.
(c) To be performed in the timeframe between this visit and the previous Visit.
(d) To be sel**f**-administered before the consultation with the investigator.


Informed Consent
Visit 0
Selection
Randomisation
Control Group
Intervention Group
Run-in Period
5 Weeks
Initial patient evaluation
Individual
Education
Sessions
Visit 1
M0
M1
Phone Interview 1
M2
Visit 2
M3
M4
Phone Interview 2
M5
M6
Visit 3
M7
Phone Interview 3
M8
M9
Visit 4
M10
Final patient evaluation
M11
Phone Interview 4
M12
Visit 5
Follow-up Period
12 Months
Group & Phone
Education
Sessions
Investigational Site
Staff members
Health Counsellors

7. STATISTICAL ANALYSIS

7.A DATA COLLECTION

An electronic data capture system will be used for this study. The electronic Case Report Forms (e-CRF) used will be designed to record all data related to the study which are to be recorded by the investigators and the health counsellors. Laboratory results and their normal ranges will be entered into the e-CRF by the investigators.

Patients' self-evaluations will be collected in paper format and double-entered into the trial database by data entry operators. Electronic data exported from the *NOWOX* device and from the dedicated vocal server which are not transcribed in the e-CRF will be transferred electronically into the trial database.

During the study, the electronic Case Report Forms (e-CRF) for all participating patients will be filled in by the health counsellors and the investigators *via* Internet and they will be reviewed by the Clinical Research Associates (CRA) on a regular basis. Each investigator and health counsellor will receive a Personal Identification Number and password to connect personally to the e-CRF. The investigators, health counsellors, CRA, data manager and authorised persons will all have individual documented personal access to the e-CRF data, with specific restricted rights depending on their function in the study conduct *(for example, read access only for CRA, medical signature only dispensed to investigators, …)*. The e-CRF will be designed by Lincoln in compliance with the protocol specifications, under the supervision of AIR LIQUIDE Santé INTERNATIONAL.

Data entry at the investigational centre will be performed for each patients visit by the investigator or the designated person from his/her team, using the e-CRF screens specifically designed for the study.

Upon their entry, data will be transmitted *via* Internet from the investigational centre to the trial database. A computerised data review will be performed. Checks for missing data, out of ranges data and consistency will be carried out, according to a pre-specified consistency checks book. Whenever required, electronic queries with deferred corrections will be issued in the e-CRF to the investigator for resolution and electronic signature, and they will be tracked until corrections are entered in the trial database and validated.

All data corrections in the e-CRF must be made by the investigator or the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded in chronological order using the audit trail feature of the e-CRF, including the identity of their author, date and reason for modification.

After the last visit of each patient, when the last queries have been answered, the investigator must attest by entering his/her Personal Identification Number and password, both:

- the authenticity of the data collected in the e-CRF of the given patient,
- and the consistency between the data entered in the e-CRF and those recorded in the corresponding source documents, with the exception of data directly reported in the e-CRF which are considered source data.

Adverse events, concomitant diseases, as well as medical and surgical histories will be coded using the current MedDRA version, while concomitant medication will be coded using the current WHO-DRUG dictionary version.

AIR LIQUIDE *Santé* INTERNATIONAL or any company appointed by the latter will be responsible for the storage of data.

A copy of the original e-CRF data will be kept by the investigator at the end of the study to store them as the current GCP guidelines recommend it.

At the end of the study, the validated database will be locked upon request of AIR LIQUIDE *Santé* INTERNATIONAL following the completion of all steps required, *i.e.*, resolution of all queries, Clinical and Pharmacovigilance databases reconciliation *(for all Serious Adverse Events entered in the Pharmacovigilance database),* and medical and statistical review by the sponsor study personnel *(see section 4.B.4).*

Moreover, once all patients have performed their *Run-In Period* and their data recorded at Visit 0 and Visit 1 have been validated, a preliminary partial database lock will be performed and the description at Selection and during the *Run-In Period* as detailed in section 7.B.3.2 will be performed globally, whatever the study group allocated on the Intention To Treat (ITT) data set defined in section 7.B.3.1.

7.B STATISTICAL METHODS

The primary analysis of the primary efficacy criterion is detailed in section 7.B.3.5. All other efficacy, safety and medico-economic statistical results provided will be exploratory and exclusively descriptive. They may not lead to any causal interpretation. As a consequence, the statistical significance level of the various two-sided tests performed will be 5.0%. No adjustment for multiplicity will be made.

At the end of the study, after the database lock, the statistical analysis will be performed by ITEC Services under the supervision of AIR LIQUIDE *Santé* INTERNATIONAL using the current version of the SAS® software, according to the statistical analysis plan approved after the medical and statistical review performed by the sponsor study personnel *(see section 4.B.4).*

Thorough description of all parameters reported will be presented separately by study group *(defined by the education program allocated to the patient at random, i.e., either the Intervention group or the Control group),* using the observed case approach. Summary tabulated results will be provided by study group and assessment time, if relevant or they will be replaced by the corresponding individual data listings if too few patients are concerned.

Quantitative parameters will be described using the following statistics: number of patients, mean, standard deviation, minimum, median and maximum values. Qualitative parameters will be described using frequencies and percentages and for binary variables, by their two-sided 95.0% confidence intervals of the observed rates *(assumed to be binomially distributed in both study groups).*

7.B.1 *Evaluation parameters*

The efficacy criteria will be recorded by the investigators as described in section 6.A. Their analysis is described in section 7.B.3.5.

The primary efficacy criterion will be the number of unscheduled hospital days whatever the reason for hospitalisation as defined in section 6.A.1.

The secondary efficacy criteria defined in section 6.A.2 include the number of hospital days due to severe COPD exacerbations, the number of moderate and severe COPD exacerbations, the use of health care services due to COPD and to all causes, the health-related quality of life, physiological parameters, the BODE index, the Hospital Anxiety and Depression Scale (HADS), the evaluation of compliance to oxygen therapy and respiration rate as recorded by the *NOWOX* device *(in the subgroup of patients on oxygen therapy at Selection and/or during their study participation)*, as well as changes in smoking status.

The safety criteria detailed in section 6.B include clinical and laboratory parameters, as well as Adverse Events. Their evaluation throughout the study period is described in section 7.B.3.7.

The medico-economic criteria defined in section 6.C include the estimates of the overall costs from the perspective of the health care payer, as well as cost-effectiveness and cost-utility. Their evaluation is described in section 7.B.3.6.

7.B.2 *Determination of sample size*

The primary objective of this phase IV study is to show that the set-up of the Home-Based Disease Management Program in patients with GOLD III/IV COPD reduces the individual yearly duration of unscheduled hospitalisations whatever their reason. Based on published results [24] and assuming:

- an expected difference of 10 days of hospitalisation between the average individual yearly duration of unscheduled hospitalisation whatever their reason observed in the Intervention group and in the Control group,
- an estimated common standard deviation of 25 days,
- a type I error set to $\alpha = 0.05$ *(two-sided conditions)*,
- and $(1-\beta)$ power equal to 0.90,

and using the nQuery Advisor® software Version 6.01 and the estimation provided for the Wilcoxon *(Mann-Whitney)* rank-sum test for a continuous outcome, the number of patients required is estimated to be 143 per study group.

With an expected 25.0% dropout rate per year over the *Follow-Up Period (i.e., at most 6.25% over the first 3 months (between Visit 1 and Visit 2) with no available individual data allowing the estimation of the primary efficacy criterion (as detailed in section 7.B.3.5) for the concerned patients)*, this sample size estimation results in randomising around 306 patients, *i.e.*, approximately 153 patients in the Intervention group and 153 patients in the Control group.

7.B.3 *Statistical methodology*

7.B.3.1. Data sets analysed

Two (2) different analysis data sets are foreseen. They will be exhaustively defined prior to the database lock *(see section 4.B.4)*:

- Full Analysis data Set *(FAS or extended safety data set)*, composed of all randomised patients having entered the *Run-In Period (starting at Visit 0, as defined in section 4.B.3.1)*. This FAS will be used for description of dropouts, and extended evaluation of safety,
- Intention To Treat (ITT) data set, which will be the subset of the FAS, composed of all randomised patients having entered the *Follow-Up Period (starting at the end of Visit 1, as defined in section 4.B.3.2)*. This ITT data set will be used for description at Selection, and evaluation of efficacy, safety and medico-economic parameters.

If prior to the database lock *(see section 7.A)*, it appears necessary to define a secondary Per Protocol (PP) data set, which would be a subset of the ITT data set, composed of all randomised patients who have no major protocol deviations throughout their study period, this PP data set would be used for the secondary supportive analysis of the primary efficacy criterion and check of its robustness. For example, if it appears that 25.0% or more of the patients from the ITT data set have prematurely discontinued their allocated COPD management strategy and completed the study as initially planned *(as described in section 3.D)*, a secondary supportive analysis of the primary efficacy criterion would be added comparing the recorded average yearly duration of unscheduled hospitalisations whatever their reason, between three (3) groups: *i)* patients from the Intervention group having completed the study as planned, *ii)* patients from the Intervention group having prematurely discontinued the evaluated Home-Based Disease Management Program without being prematurely withdrawn from the study and *iii)* patients from the Control group.

7.B.3.2. Description at Selection and during the Run-In Period

At Selection *(Visit 0)* and during the *Run-In Period (up to the end of Visit 1)*,

- patients' background, demographic data, social conditions,
- characteristics of the study disease, *(including GOLD stages classification and combined severity assessment classes as defined in section 3. separately)*,
- need for oxygen therapy at Selection *(whatever its duration prescribed)* with its criteria for prescription and average daily duration prescribed,
- need for continuous Long Term Oxygen Therapy *(i.e., with daily oxygen duration prescribed of 15 hours or more)* at Selection,
- need for home Non-Invasive Ventilation (NIV) at Selection with its average daily duration prescribed,
- need for Continuous Positive Airway Pressure (CPAP) at Selection,
- smoking status and history,
- results of arterial or capillary blood gases,
- vital signs and pulse oximetry *(split by conditions of measurement: either on room air or on oxygen)* measurements,
- as well as the 6-minute walking distance and related parameters *(split by conditions of assessment: either on room air or on oxygen)*,
- the patient's self-evaluations, the severity of dyspnoea,
- the Charlson Comorbidity Index score,
- the transthoracic Doppler echocardiography measurements,

- the clinical interpretation of a 12-lead ECG tracing,
- and the modalities of oxygen prescription, if applicable,

will be described by study group *(and globally)*, on the Intention To Treat (ITT) data set *(defined in section 7.B.3.1)*.

If a secondary PP data set is defined *(see section 7.B.3.1)* and if 10.0% or more of patients from the ITT data set are excluded from the PP data set, the description of patients by study group *(and globally)* at Selection and during the *Run-In Period (up to the end of Visit 1)* will be repeated on the PP data set, for all parameters apart from standard safety evaluation criteria.

At Visit 1, CRP, as well as haematology results will be tabulated by study group *(and globally)* as both quantitative parameters *(raw values converted in international units, if necessary)* and qualitative parameters *(relative positions regarding normal ranges in use in each laboratory involved)*.

Results of the most recent pulmonary function tests performed in stable state prior to Selection, and results of the pulmonary function tests performed during the *Run-In Period* will be tabulated descriptively *(as both raw values and percentages of predicted values, when applicable)*, by study group *(and globally)*, together with the ratios FEV_1/FVC and RV/TLC *(in the subgroup of patients for whom body plethysmography measurements at Visit 1 were collected)* as reported by the investigators in the electronic Case Report Forms.

No systematic statistical test will be performed to compare both groups of patients at Selection and during the *Run-In Period (up to the end of Visit 1)* on any data sets analysed. They will only be performed if any clinically significant imbalances between study groups appear to be of major importance for the interpretation of the primary efficacy criterion results and need to be cautiously examined in order to determine whether the randomisation has failed or not. If this descriptive analysis provides any clues on potential imbalances, further statistical investigations will be carried out using homogeneity tests and if necessary, the factor adjusting strategy will be redefined and the corresponding potentially predictive factor will be added to the ones pre-listed in section 7.B.3.5.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by study group *(and globally)* using the MedDRA codes of System Organ Classes and preferred terms.

All concomitant treatments with start date at the latest on the day preceding the patient's randomisation will be tabulated descriptively by study group *(and globally)* using the WHO-DRUG dictionary and the Anatomical Therapeutic Chemical (ATC) classification. Three (3) tables will be provided:

- one table showing the number and percentage of patients with at least one concomitant treatment with start date at the latest on the day preceding randomisation, by therapeutic area *(ATC1 code corresponding to ATC system main group)*,
- one table by both ATC1 code and ATC system subgroup *(ATC2 code)*,
- and one table showing the number and percentage of patients with at least one respiratory system concomitant treatment with start date at the latest on the day preceding randomisation, by ATC system subgroups *(ATC2, ATC3 and ATC4 codes)*.

7.B.3.3. Handling of dropouts and missing data

The number and percentage of patients prematurely withdrawn from the study after their randomisation will be provided by study group *(and globally)* for all randomised patients *(i.e., on the FAS defined in section 7.B.3.1),* as well as for the subgroup of randomised patients having entered the *Follow-Up Period (i.e., on the ITT data set defined in section 7.B.3.1).* All withdrawn patients after randomisation will be further described by study group *(and globally)* regarding their time to dropout and reason for premature withdrawal. Particular attention will be paid to the description of Adverse Events *(either serious or not serious, according to their regulatory definition provided in section 8.A)* leading to study premature withdrawal, as detailed in section 7.B.3.7.

Time to dropout for any reason *(expressed in number of days)* throughout the *Follow-Up Period* will be described by study group, on the ITT data set, using Kaplan-Meier's estimates. It will be compared between both study groups with the Log rank test.

Moreover, time to death whatever its associated diagnosis *(expressed in number of days)* throughout the *Follow-Up Period* will be described by study group, on the ITT data set, using Kaplan-Meier's estimates. If relevant, it will be compared between both study groups with the Log rank test.

If relevant, the handling of missing data and/or mistimed evaluations will be described in the statistical analysis plan approved prior to the database lock. Whenever needed, the most pragmatic approach will be used to extrapolate missing information according to the Intention To Treat principles.

7.B.3.4. Evaluation of protocol deviations

Prior to the database lock, all protocol deviations encountered throughout the study will be reviewed *(see section 4.B.4)* and their consequences on the efficacy evaluations performed will be evaluated. A deviation will be considered major when it is likely to bias significantly the interpretation of the efficacy results, especially the primary efficacy criterion *(i.e., the individual yearly duration of unscheduled hospitalisations whatever their reason).* All other protocol deviations will be considered minor.

A listing of all protocol deviations will be provided for all randomised patients *(i.e., on the FAS defined in section 7.B.3.1),* including the type *(major/minor)* of protocol deviations according to the decisions made. The number and percentage of patients with protocol deviations will be tabulated by study group *(and globally)* and type of protocol deviations on the Intention To Treat (ITT) data set *(defined in section 7.B.3.1).*

Protocol deviations which will be evaluated will include:

- deviations in inclusion and exclusion criteria,
- deviations in dates of visits and assessments times, including the cases of study premature withdrawals,
- deviations in the allocation and/or the performance of the study educational program.

7.B.3.5. Evaluation of efficacy

The evaluation of efficacy will be performed by study group, on the Intention To Treat (ITT) data set *(defined in section 7.B.3.1)*.

If it appears necessary to define a secondary Per Protocol (PP) data set *(as mentioned in section 7.B.3.1)*, a listing highlighting all patients excluded from the PP data set and the reason(s) for their exclusion will be provided by study group, according to the decisions made prior to the database lock.

PRIMARY ANALYSIS OF THE PRIMARY EFFICACY CRITERION

The primary analysis of the primary efficacy criterion will correspond to the primary objective of the study, which is to evaluate a strategy of COPD management to reduce the average yearly duration of unscheduled hospitalisations whatever their reason, in patients with GOLD III/IV COPD.

In order to deal with patients followed-up over different duration, their individual recorded cumulated number of unscheduled hospital days whatever their reason *(D_i expressed in days, as recorded by the investigators)* will be normalised on a yearly basis, by multiplying D_i by the ratio [365 days / total number of days of the patient's *Follow-Up Period*] and rounding it at the nearest integer. Thus, a patient for whom 18 unscheduled hospital days have been recorded over a 6-month *(182 days)* follow-up prior to study premature withdrawal will be analysed as having experienced a yearly estimated duration of hospitalisation of [18 x (365/182)] ~ 36 days. In the same manner, a patient for whom 18 unscheduled hospital days have been recorded over a 2-year *(731 days)* follow-up will be analysed as having experienced a yearly estimated duration of hospitalisation of [18 x (365/731)] ~ 9 days.

On the ITT data set *(defined in section 7.B.3.1)*, the normalised individual yearly duration of unscheduled hospitalisations whatever their reason will be considered as categorical data (*0, 1, 2, 3, 4, ... days*) and compared between the 2 study groups using the Wilcoxon's rank sum test, in all investigational centres and countries pooled together.

This non-parametric test is commonly used to test that the multinomial distributions of an ordinal categorical parameter are the same across 2 independent samples.

The null hypothesis of interest H_0 is that the distribution of the normalised individual yearly duration of unscheduled hospitalisations whatever their reason in the Intervention group is equal to the one observed in the Control group. The alternative 2-sided hypothesis H_1 is that the distribution of the normalised individual yearly duration of unscheduled hospitalisations whatever their reason in the Intervention group is different from the one observed in the Control group.

If $F_{Intervention}$ denotes the multinomial distribution of the normalised individual yearly duration of unscheduled hospitalisations whatever their reason in the Intervention group and $F_{Control}$ the multinomial distribution of this primary efficacy criterion in the Control group, the Wilcoxon's rank sum statistic tests:

H_0: $F_{Intervention} = F_{Control}$

against H_1: $F_{Intervention} \neq F_{Control}$.

SUPPORTIVE ANALYSES OF THE PRIMARY EFFICACY CRITERION

The primary analysis of the primary efficacy criterion will be repeated in a descriptive and exploratory manner in each of the 4 participating countries where the number of randomised patients allows the performance of this analysis separately.

Moreover, if it appears necessary to define a secondary PP data set *(defined in section 7.B.3.1)*, the robustness of the results of the primary analysis of the primary efficacy criterion will be checked by repeating it on the PP data set, first, globally with all countries pooled together and in a second step, in each of the 4 participating countries where the number of randomised patients allows the performance of this analysis separately.

ADDITIONAL ANALYSES OF THE PRIMARY EFFICACY CRITERION

To further explore the primary criterion, a parametric analysis of variance of the primary efficacy criterion will be performed on the ITT data set including three (3) factors: study group and country effects, as well as their interaction.

The primary analysis of the primary efficacy criterion and its supportive analyses will be repeated on the duration of unscheduled hospitalisations whatever their reason, confirmed in a blind manner by the members of the EVC *(see section 6.D)*.

An exploratory multiple-factor regression analysis will also be performed to identify the independent predictors of the primary efficacy criterion. The statistical model building will follow the principle of seeking the most parsimonious model which still explains the data. The clinically relevant factors which will be investigated will be:

- study group,
- gender,
- age classified in the six (6) categories pre-defined in the Charlson Comorbidity Index *(i.e., < 50, [50 ; 60[, [60 ; 70[, [70 ; 80[, [80 ; 90[and [90 ; 100[years old)*,
- smoking status at Visit 1,
- need for respiratory assistance (*i.e. oxygen and/or home Non-Invasive Ventilation (NIV) at Selection (Visit 0),*
- need for Continuous Positive Airway Pressure (*CPAP*) at Selection *(Visit 0))*,
- need for respiratory assistance *(i.e., oxygen therapy and/or home Non-Invasive Ventilation (NIV))* at Selection *(Visit 0)* and/or during the study participation,
- need for Continuous Positive Airway Pressure (*CPAP*) at Selection *(Visit 0)* and/or during the study participation,
- need for continuous Long Tem Oxygen Therapy *(i.e., daily oxygen duration prescribed of 15 hours or more)* at Selection *(Visit 0)* and/or during the study participation,
- experience of at least 2 moderate or severe COPD exacerbations during the *Follow-Up Period* as recorded by the investigators,
- baseline FEV_1 value *(expressed as percentage of predicted value)* classified in the four (4) categories pre-defined in the BODE index *(i.e., ≤ 35,]35 ; 50[, [50 ; 65[and ≥ 65%)*,
- Body Mass Index (BMI) at Selection classified in the two (2) categories pre-defined in the BODE index *(i.e., ≤ 21 and > 21 kg/m²)*,
- baseline BODE index classified in the four (4) categories mentioned in section 6.A.2.6 *(i.e., [0 ; 2], [3 ; 4], [5 ; 6] and [7 ; 10])*,

- baseline Charlson Comorbidity Index *(which may be separated in a few appropriate categories prior to the exploratory research of its potential predictive role on the primary efficacy criterion).*

If the descriptive analysis of the comparability of study groups at Selection and/or during the *Run-In Period* reveals any random imbalance of clinical significance between both study groups *(as specified in section 7.B.3.2),* this list of a priori identified potentially predictive factors will be implemented accordingly.

To carry out the exploratory multiple-factor regression planned, the following analyses will be performed successively:

- in a first step, a two-factor regression analysis involving the study group and each of the investigated factor listed above separately, as well as their interaction will be performed. If some factors or their interaction appear to be predictive *(i.e., statistically significant at level* α *= 0.10)* of the primary efficacy criterion, they will be gathered into a multiple-factor model in addition to the study group factor. Backward elimination at level $\alpha = 0.10$ will then be applied for the model determination. Any factor remaining in the model will be considered an independent predictor,
- in a second step, an exploratory multiple-factor regression analysis involving the study group and all factors selected in the first step described above, including their interaction, if relevant, will be performed to identify the independent predictors of the primary efficacy criterion. Conclusions regarding the study group effect will be generalised if they apply to all subgroups based on other factors.

Goodness-of-fit *(i.e., predicted values are an accurate representation of the observed values)* of the final selected model will be investigated by providing summary measurements of the distance between observed and fitted values. Moreover, an analysis of the residuals of the final selected model will be performed *(using both Pearson's and deviance residuals).*

ANALYSES OF THE SECONDARY EFFICACY CRITERIA

All analyses of the secondary efficacy criteria will be performed on the ITT data set *(defined in section 7.B.3.1).*

The number of hospital days due to severe COPD exacerbations will be analysed in exactly the same way as the primary efficacy criterion, including its primary, supportive and additional analyses previously described.

The number of moderate and severe COPD exacerbations separately as recorded by the investigators will be compared between both study groups with the Wilcoxon's rank sum test, in all countries pooled together.

Time to first severe COPD exacerbation *(expressed in number of days)* throughout the *Follow-Up Period* will be tabulated by study group, as quantitative data, in the subgroup of patients from the ITT data set experiencing at least one severe COPD exacerbation during their *Follow-Up Period*, as reported by the investigators, in all countries pooled together.
Moreover, time to first severe COPD exacerbation throughout the *Follow-Up Period* will be described globally by study group, on the ITT data set, using Kaplan-Meier's estimates to display the probability of survival and of experiencing severe COPD exacerbation. Survival times will be censored at the earliest time of occurrence of the following events:

- the patients' last contact *(this will apply to the subgroup of patients who never experience any severe COPD exacerbation and who are never hospitalised for any reason during their Follow-Up Period),*
- the time to first severe COPD exacerbation *(for the subgroup of patients experiencing at least one severe COPD exacerbation during their Follow-Up Period),*
- the time to first hospital admission for another reason than COPD exacerbation *(for the subgroup of patients hospitalised at least once during their Follow-Up Period),*
- the time to death for another reason than COPD exacerbation, if applicable.

If relevant, time to first severe COPD exacerbation will be compared between both study groups with the Log rank test.

The use of health care services due to COPD and to all causes separately will be tabulated by study group and type or unit of time *(i.e., qualitatively in terms of volume without being priced).* Each category separately will be compared between both study groups using either the Student's t test or the Wilcoxon's rank sum test depending on their distribution.

SGRQ-C total score and component subscores: quantitative descriptive statistics of the SGRQ-C total score and of each of its three (3) component subscores *(symptoms, activity and impacts)* will be tabulated by study group and visit, using the observed case approach. The absolute variations *"*post-*Run-In Period* – baseline *(self-evaluated prior to Visit 1)"* will also be tabulated by study group and visit, for each score and subscore separately.

Moreover, to visualise the evolution of each score and subscore separately, arithmetic means of each score and their 95.0% confidence intervals will be represented graphically *(the x-axis being the assessment time-axis and the y-axis being the arithmetic mean-axis)* with both study groups being represented separately on the same graph, using the observed case approach.

An analysis over time of the mean profile of the SGRQ-C total score and of each of its subscores separately will be performed within a mixed model to deal with patients followed-up over different duration, using the MIXED procedure of the current version of the SAS® software and type III sums of squares. The global parametric analysis of covariance model on repeated measurements used will include the following factors:

- score assessed during the *Run-In Period* as covariate,
- study group and visit as fixed factors,
- interaction between study group and visit and interaction between study group and score assessed during the *Run-In Period (i.e., the covariate)* as fixed factors,
- patient as random factor.

In a first step, the best structure of the variance-covariance matrix will be identified using the Akaike's Information Criterion (AIC), which is based on the Restricted Maximum Likelihood (REML) and the number of covariance parameters. The model with the AIC lowest value will be considered as the best one. In a second step, inference will be drawn about fixed effects in the frame of the model with the best structure of the variance-covariance matrix selected in the first step.

When relevant, appropriate contrasts will be calculated and the associated confidence intervals will be displayed. In case of a statistically significant interaction evidenced at level $\alpha = 0.10$, further separate parametric analyses of variance may be carried out, if appropriate and potentially relevant from a clinical point of view.

15D health-related quality of life instrument: the 15D score will be tabulated over time, analysed and represented graphically in exactly the same way as the SGRQ-C total score.

Pulmonary function tests parameters: for each spirometry parameter recorded by the investigators *(as listed in section 6.A.2.5)*, separately, quantitative descriptive statistics will be tabulated by study group and visit, using the observed case approach.

For each spirometry parameter assessed, separate global parametric analyses of covariance on Visit 5 *(Month 12 or study end in case of premature withdrawal)* measurements will also be performed using a mixed model, including the following factors:

- the corresponding spirometry parameter measured during the *Run-In Period* as covariate,
- study group as fixed factor,
- interaction between study group and corresponding spirometry parameter measured during the *Run-In Period (i.e., the covariate)* as fixed factor,
- patient as random factor.

Six-Minute Walking Distance (6MWD) and related parameters: the 6MWD will be tabulated using quantitative descriptive statistics, by study group, visit and conditions of assessment *(i.e., either on room air or on oxygen)*, using the observed case approach.

Moreover, in the subgroup of patients having performed their 6MWTs in the same conditions at Visits 1 and 5, a global parametric analysis of covariance of the 6MWD assessed on Visit 5 will be performed using a mixed model including the following factors:

- the 6MWD assessed during the *Run-In Period* as covariate,
- study group and conditions of assessment as fixed factors,
- interaction between study group and 6MWD assessed during the *Run-In Period (i.e., the covariate)* and interaction between study group and conditions of assessment as fixed factors,
- patient as random factor.

The other parameters recorded during each 6MWT performed *(as listed in section 6.A.2.5)* will only be tabulated using descriptive statistics, by study group, visit and conditions of assessment, using the observed case approach.

Transthoracic Doppler echocardiography parameters: for each transthoracic Doppler echocardiography parameter recorded by the investigators or calculated by the e-CRF *(as listed in section 6.A.2.5)*, separately, quantitative descriptive statistics will be tabulated by study group and visit, using the observed case approach.

For each parameter, separate global parametric analyses of covariance on Visit 5 measurements will also be performed using the same model as the one described for the pulmonary function tests, the corresponding transthoracic Doppler echocardiography parameter measured during the *Run-In Period* being the covariate of the analysis model.

BODE index: the BODE index will be tabulated by study group and visit, using the observed case approach, as both quantitative and categorical data *(using the four (4) categories mentioned in section 6.A.2.6, i.e., [0 ; 2], [3 ; 4], [5 ; 6] and [7 ; 10]).*

Moreover, a global parametric analysis of covariance on Visit 5 measurements will be performed using the same model as the one described for the pulmonary function tests, the BODE index assessed during the *Run-In Period* being the covariate of the analysis model.

Hospital Anxiety and Depression Scale (HADS) scores: the HAD-D and HAD-A scores calculated by using the algorithm provided by their owner will be tabulated separately over time, analysed and represented graphically in exactly the same way as the SGRQ-C total score.

Moreover, at each visit separately, the number and percentage of patients presenting a HAD-D score ≥ 8, as well the number and percentage of patients presenting a HAD-A score ≥ 8 will be tabulated separately, by study group.

Prescription of oxygen therapy: over the *Follow-Up Period*, the number and percentage of patients for whom oxygen therapy is implemented *(while the patient was not on oxygen therapy at Selection)* will be tabulated descriptively by study group. The concerned patients will be further described by study group regarding their time to onset of oxygen therapy and criteria for prescription. If relevant, time to onset of oxygen therapy *(expressed in number of days)* throughout the *Follow-Up Period* will be described by study group, using Kaplan-Meier's estimates, and it will be compared between both groups with the Log rank test.

If relevant, these descriptions will be repeated to highlight the onset of the prescriptions of continuous Long Term Oxygen Therapy *(LTOT, i.e., the start of daily oxygen duration prescribed of 15 hours or more)* over the *Follow-Up Period*.

In the subgroup of patients on oxygen therapy at Selection and/or during their study participation and on the period of their oxygen prescription overlapping their holding of the *NOWOX* device, the average daily duration prescribed will be tabulated by study group. For each patient for whom a change in the daily duration of oxygen prescription is recorded throughout the *Follow-Up Period*, the individual daily duration of oxygen prescription will be estimated by using the sum of all recorded daily durations prescribed multiplied by the number of days of the corresponding prescription, divided by the total number of days on oxygen therapy. In case of missing or incomplete information necessitating monthly approximation in this average calculation, it will be considered that each month lasts 30.5 days.

Compliance to oxygen therapy: in the subgroup of patients on oxygen therapy at Selection and/or during their study participation and on the period of their oxygen prescription overlapping their holding of the *NOWOX* device, the average daily use of oxygen therapy over 24 hours, as well as the average use of oxygen therapy at night *(i.e., over the time interval [22:00 ; 6:00]*) and the average use of oxygen therapy during the day *(i.e., over the time interval]06:00 ; 22:00[*) will be calculated separately over at most eight (8) successive periods *(for the first patients included in the study who have been followed up 24 months)* defined by the scheduled visits of the patients at the investigational centre, without taking into account the recordings collected by the *NOWOX* device on the day of each actual visit, *i.e.,* when applicable, over the successive periods:

- between the day following the actual date of Visit 1 and the day preceding the actual date of Visit 2 *(both included) (period 1),*
- between the day following the actual date of Visit 2 and the day preceding the actual date of Visit 3 *(both included) (period 2),*
- … and so on, up to the last period between the day following the actual date of Visit 8 and the day preceding the actual date of Visit 9 *(both included) (period 8, if applicable).*

The average daily use of oxygen therapy and its two (2) components at night and during the day separately, will be tabulated by study group, over each period separately, using quantitative descriptive statistics. These tabulations, as well as their graphical representations and analyses over time described below will be performed twice in the subgroup of patients on oxygen therapy at any time throughout their study participation and on the period of their oxygen prescription overlapping their holding of the *NOWOX* device: first, on all recordings collected by the *NOWOX* device for all patients constituting the ITT data set, and second, on the recordings collected on the days when patients from the ITT data set are not on any concomitant respiratory assistance *(i.e. Continuous Positive Airway Pressure (CPAP) therapy and/or home Non-Invasive Ventilation (NIV))* as reported by the investigators. They will be repeated in a second step in the subgroup of patients on continuous LTOT *(i.e., with daily oxygen duration prescribed of 15 hours or more)* at any time throughout their study participation and on the period of their LTOT prescription overlapping their holding of the *NOWOX* device.

Moreover, to visualise the evolution of the recordings, arithmetic means of each average daily use of oxygen therapy calculated separately and their 95.0% confidence intervals will be represented graphically *(the x-axis being the period-axis and the y-axis being the arithmetic mean-axis)* with both study groups being represented separately on the same graph.

An analysis over time of the mean profile of the average daily use of oxygen therapy and its two (2) components separately will be performed within a mixed model to deal with patients followed-up over different duration, using the MIXED procedure of the current version of the SAS® software and type III sums of squares. The global parametric analysis of variance model on repeated measurements used will include the following factors:

- study group and period of evaluation as fixed factors,
- interaction between the study group and the period of evaluation as fixed factor,
- patient as random factor.

In a first step, the best structure of the variance-covariance matrix will be identified using the Akaike's Information Criterion (AIC), which is based on the Restricted Maximum Likelihood (REML) and the number of variance parameters. The model with the AIC lowest value will be considered as the best one. In a second step, inference will be drawn about fixed effects in the frame of the model with the best structure of the variance-covariance matrix selected in the first step.

When relevant, appropriate contrasts will be calculated and the associated confidence intervals will be displayed. In case of a statistically significant interaction evidenced at level $\alpha = 0.10$, further separate parametric analyses of variance may be carried out, if appropriate and potentially relevant from a clinical point of view.

Moreover, to explore further the collected data, the average daily use of oxygen therapy and its two (2) components separately will be calculated separately over the first week *(i.e., the first 7 days)* following each patient's visit at the investigational centre *(from the day following the actual date of Visit 1 onwards)* and over the last week *(i.e., the last 7 days)* preceding each patient's visit at the investigational centre *(from the last 7 days preceding the actual date of Visit 2 onwards)*, without taking into account the recordings collected by the *NOWOX* device on the day of each actual visit. These weekly means will be tabulated by study group, over each 7-day period separately, using quantitative descriptive statistics. The pre-investigational centre visit weekly means and the post-investigational centre visit weekly means separately will be represented graphically and analysed in the same way as the quarterly means of the daily use of oxygen therapy previously described.

Additionally, for each unscheduled hospitalisation separately, the average daily use of oxygen therapy and its two (2) components separately will be calculated separately over the week *(i.e., the 7 days)* preceding each unscheduled hospital admission and over the week *(i.e., the 7 days)* following each unscheduled hospital discharge, without taking into account the recordings collected by the *NOWOX* device on the days of hospital admission and discharge. These weekly means will be tabulated by study group and sequential number of hospitalisation, over each 7-day period separately, using quantitative descriptive statistics. No statistical test will be performed.

In the subgroup of patients on oxygen therapy at Selection and/or during their study participation and on the period of their oxygen prescription overlapping their holding of the *NOWOX* device, for each patient and each day on oxygen prescription, the relative difference '100 x *(daily use of oxygen therapy over 24 hours as estimated by the NOWOX device – corresponding individual daily duration of oxygen prescription ($D_{O2\ prescribed}$))* / $D_{O2\ prescribed}$' will be calculated, as well as the absolute difference 'daily use of oxygen therapy over 24 hours as estimated by the *NOWOX* device – corresponding individual daily duration of oxygen prescription ($D_{O2\ prescribed}$)'.

Both differences will be tabulated by study group, over the successive periods between the scheduled visits of the patient at the investigational centre previously defined, separately and globally, using quantitative descriptive statistics. These tabulations, as well as their graphical representations and analyses over time described below will be performed twice in the subgroup of patients on oxygen therapy at any time throughout their study participation and on the period of their oxygen prescription overlapping their holding of the *NOWOX* device: first, on all recordings collected by the *NOWOX* device for all patients constituting the ITT data set, and second, on the recordings collected on the days when patients from the ITT data set are not on any concomitant respiratory assistance *(i.e., Continuous Positive Airway Pressure (CPAP) therapy and/or home Non-Invasive Ventilation (NIV))* as reported by the investigators. They will be repeated in a second step in the subgroup of patients on continuous LTOT *(i.e., with daily oxygen duration prescribed of 15 hours or more)* at any time throughout their study participation and on the period of their LTOT prescription overlapping their holding of the *NOWOX* device.

Arithmetic means of both average differences separately and their 95.0% confidence intervals will be represented graphically *(the x-axis being the period-axis and the y-axis being the arithmetic mean-axis)* with both study groups being represented separately on the same graph. Moreover, in each study group separately, individual average relative differences will be plotted by corresponding individual daily duration of oxygen prescribed. The same graph will be produced for individual average absolute differences. If a linear or a quadratic trend can be foreseen in any study group, appropriate regression models may be evaluated to assess statistically the trend observed.

Moreover, for each average difference, separate global parametric analyses of variance on repeated measurements will be performed using the same model as the one previously described for the average daily use of oxygen therapy.

Respiration rate evaluated by the *NOWOX* device: the average daily respiration rate and the average daily peak respiration rate will be calculated separately over the same periods and in the same way as the average daily use of oxygen therapy. Both estimations of the respiration rate will then be tabulated, analysed and represented graphically in exactly the same way as the average daily use of oxygen therapy previously described *(except its last part related to the relative and absolute individual differences between the NOWOX estimations and the actual prescriptions of oxygen therapy)*.

Changes in smoking status: from Visit 1 onwards, the number and percentage of patients who are current smokers and the number and percentage of patients who are ex-smokers will be tabulated by study group and visit. The corresponding histogram will also be produced.

Moreover, from Visit 1 onwards, a shift table will be provided by study group and visit to depict the number and percentage of patients with the four (4) possible categories of smoking status evolution since their Selection *(Visit 0)*:

- number and percentage of patients ex-smokers at Visit 0 and ex-smokers at the post-Run-In tabulated visit,
- number and percentage of patients current smokers at Visit 0 and current smokers at the post-Run-In tabulated visit,
- number and percentage of patients ex-smokers at Visit 0 and current smokers at the post-Run-In tabulated visit,
- number and percentage of patients current smokers at Visit 0 and ex-smokers at the post-Run-In tabulated visit.

At each visit separately, the smoking status evolution since Visit 0 will be compared between both study groups using either the Pearson's Chi-Square test or the Fisher's exact test depending on their distribution.

7.B.3.6. Medico-economic evaluation

The medico-economic evaluation in terms of costs will be performed in each country separately by the medico-economics consultants. It will be carried out on the ITT data set *(defined in section 7.B.3.1)*, using the observed case approach, without any extrapolation of missing data on all data recorded throughout the *Follow-Up Period*.

MAIN EVALUATION OF OVERALL COSTS

Average overall individual costs per month will be tabulated in each country, as quantitative data, by study group, from the perspective of the health care payer *(as defined in section 6.C.1)*.

The main medico-economic evaluation performed will be the comparison of these average overall monthly costs between both study groups, in each country where the number of randomised patients allows the performance of this analysis, separately, using the Student's t test or the Wilcoxon's rank sum test, depending on the shape and type of the distribution of the national overall individual costs per month recorded.

If the number of randomised patients in a given country does not allow the performance of this country-based analysis, the overall resources used for the patient's medical management collected in volume in all participating countries pooled together will be priced globally with the national tariffs system in force in the given country, before being compared between both study groups, using either the Student's t test or the Wilcoxon's rank sum test.

COST-EFFECTIVENESS

If this main medico-economic evaluation reveals a statistically significant study group difference, at level $\alpha = 0.05$, in a given country, in a second step, the overall costs per patient, from the perspective of the health care payer will be related to the primary efficacy criterion, by estimating a cost per unscheduled hospital day avoided whatever its reason in each study group, separately.

Average overall costs and benefits will be estimated with Kaplan-Meier's sample averages and bootstrap replications, before calculating the 95.0% confidence intervals of Incremental Cost-Effectiveness Ratios *(ICERs, i.e., the overall net costs (defined as the difference in overall costs on the Home-Based Disease Management Program – those on the usual program) divided by the corresponding net benefits (i.e., the difference in both numbers of unscheduled hospital days whatever their reason))*.

If performed, this cost-effectiveness evaluation will be repeated, by relating the overall costs per patient, from the perspective of the health care payer, to the number of deaths, in each study group separately, by replacing the previous denominator of the calculated ICERs by the difference in the numbers of deaths in both study groups.

COST-UTILITY

In the same manner, if the main medico-economic evaluation reveals a statistically significant study group difference, in a given country, a cost-utility evaluation will be performed, in the same way as the cost-effectiveness evaluation, the denominator of the calculated ICERs being in that case, the difference in QALYs *(as defined in section 6.C.3)*.

7.B.3.7. Evaluation of safety

Safety data will be tabulated descriptively by study group *(and globally)* and assessment time, when relevant. Whenever applicable, they will be tabulated twice: first, during the *Run-In Period* on the FAS *(defined in section 7.B.3.1)* and second, during the *Follow-Up Period* on the ITT data set *(defined in section 7.B.3.1)*. No statistical test will be performed.

EXTENT OF EXPOSURE

Duration of the *Run-In Period*, duration of the *Follow-Up Period* and overall study duration will be tabulated *(expressed in months, rounded at one digit)* by study group *(and globally)*, as both quantitative and categorical data.

Overall study duration is defined as the time interval between the actual date of Selection *(included)* and the actual date of the last visit *(or phone contact)* performed by the investigator *(visit planned to be performed at the time of premature withdrawal or on theoretical visit date corresponding to Month 24 (for the first patients included in the study) or Month 12 (for the patients included afterwards)) (excluded), i.e.*, as the quantity "date of last visit performed by the investigator - date of Selection".

Cumulative individual number of days on oxygen therapy will be tabulated *(expressed in months, rounded at one digit)* by study group *(and globally)*, as both quantitative and categorical data. It will be calculated taking into account the individual start date of each oxygen prescription and its corresponding end date, if applicable, for each oxygen prescription overlapping the overall study duration previously defined. If a given patient starts his/her oxygen therapy after his/her date of Selection in the study and if he/she ends it definitively before his/her last study visit, his/her individual number of days on oxygen therapy will be calculated as "end date of the oxygen prescription – start date of the oxygen prescription + 1 day". For patients who were never prescribed oxygen therapy throughout their whole study participation, the individual number of days on oxygen therapy will be described as equal to 0 days.

ADVERSE EVENTS

Any adverse event *(either serious or not serious, according to their regulatory definition provided in section 8.A)* having been reported throughout the study for a given patient will be classified by preferred term and corresponding System Organ Class, using the MedDRA terminology, prior to the database lock.

Any Adverse Event (AE) reported after Visit 1 will be considered Study Emergent (SE):
i) if it begins after Visit 1 date,
or *ii)* if its start date is unknown,
or *iii)*if it begins before Visit 1 and worsens at any time during the *Follow-Up Period*.

If applicable, any AE starting before Visit 1 and going on afterwards will be considered study emergent if its severity is missing or partially filled in. In the same manner, any AE starting before Visit 1 with missing or incomplete end date will be considered study emergent. If the same AE occurs twice in a given patient, once with onset and end dates during the *Run-In Period* and once during the *Follow-Up Period*, it will be described twice, as both an AE occurring before Visit 1 and a SE AE.

The time period for the assessments of AEs is the time interval between Selection *(Visit 0)* and Study End *(Visit 9 for the first patients included in the study or Visit 5 for the patients included afterwards)*, divided in two (2) successive periods: the *Run-In Period* and the *Follow-Up Period*.

All reported AEs will be classified in these two (2) periods, according to their start date. AEs reported during the *Run-In Period* will be tabulated on the FAS and on the ITT data set separately, as described below, if relevant or they will only be listed if too few patients are concerned.

The number and percentage of patients having experienced at least once a given SE AE during the *Follow-Up Period* will be tabulated by study group *(and globally)*, System Organ Class and preferred term. Tabulations will include:

- the number and percentage of patients having experienced at least once a given SE AE,
- the number and percentage of patients having experienced at least once most common SE AEs *(defined as those occurring in at least 5.0% of the patients from the ITT data set)*, if it appears to be relevant,
- the number and percentage of patients having experienced at least once a given SE AE, by most severe intensity,
- the number and percentage of patients having experienced at least once a given SE AE, by most severe relationship to the allocated study intervention.

The number and percentage of patients having experienced at least once a given SE AE during the *Follow-Up Period* will also be tabulated by study group *(and globally)* and System Organ Class only.

Over both study periods, separately and globally, an additional summary table will be provided by study group *(and globally)*, including:

- the number and percentage of patients having experienced at least one SE AE,
- the number and percentage of patients having experienced at least one study intervention associated SE AE *(study intervention associated SE AEs being defined as SE AEs for which the investigator has reported at least once relationship to the allocated study intervention, either not excluded or unassessable)*,
- the number and percentage of patients having experienced at least one AE leading to premature discontinuation of the allocated management strategy,
- the number and percentage of patients having experienced at least one AE leading to study premature withdrawal.

Moreover, over both study periods, separately and globally, a summary table will be provided by study group *(and globally)*, including:

- the total number of SE AEs reported,
- and the distribution of the number of SE AEs reported by patient *(by 5-event categories: [1 ; 5], [6 ; 10], [11 ; 15], …)*.

Both summary tables will also be provided for Serious Adverse Events (SAEs), over both study periods, separately and globally. If relevant, the number and percentage of patients having experienced at least once a given SAE will also be tabulated by study group *(and globally)*, System Organ Class and preferred term, separately from all AEs, in a second step, to retrieve them more easily.

For the whole evaluation of AEs *(including the counting of the number of AEs reported)*, recurring AEs *(i.e., AEs classified with the same preferred term)* for a given patient in a given period will only be counted once for the concerned patient in the concerned period.

All SAEs reported throughout the study, from the date of Selection onwards, will be listed and exhaustively described on an individual basis, by study group, including all reported information on the AEs specific e-CRF, as well as their start date *(i.e., the time interval between the date of Visit 0 and the occurrence of SAEs)*, period of occurrence and duration.

All AEs leading to premature discontinuation of the allocated management strategy, as well as all AEs leading to study premature withdrawal *(both of these AEs constituting significant AEs)* will be listed and exhaustively described, on an individual basis, by study group, in exactly the same way as SAEs, throughout the study.

Results of ECG and physical examination will not be tabulated or listed, as any new abnormal findings diagnosed after the *Run-In Period* should be reported as AEs *(if clinically significant)*.

CLINICAL PARAMETERS

For each measurement of vital signs *(i.e., systolic and diastolic blood pressures)*, weight, pulse rate and SpO_2 split by conditions of measurement *(either on room air or on oxygen*), quantitative descriptive statistics will be tabulated by study group *(and globally)* and visit, using the observed case approach.

For each parameter separately *(i.e., systolic and diastolic blood pressures, weight, pulse rate and SpO_2 on room air)*, the absolute variations "post-*Run-In Period* – baseline *(measured at Selection)*" will also be tabulated by study group *(and globally)* and visit throughout the *Follow-Up Period*.

In the subgroup of patients on oxygen therapy at Selection for whom pulse rate and/or SpO_2 are measured at least once on oxygen from Visit 1 onwards, the absolute variations "post-*Run-In Period* – baseline *(measured at Selection)*" on oxygen will also be tabulated by study group *(and globally)* and visit throughout the *Follow-Up Period* for all collected measurements on oxygen.

Moreover, to visualise the evolution of the data collected separately, arithmetic means of each parameter *(i.e., systolic and diastolic blood pressures, weight, pulse rate and SpO_2 on room air)* and their 95.0% confidence intervals will be represented graphically *(the x-axis being the assessment time-axis and the y-axis being the arithmetic mean-axis)* with both study groups being represented separately on the same graph, using the observed case approach.

CHARLSON COMORBIDITY INDEX

The Charlson Comorbidity Index scores recorded by the investigators will be summarised descriptively by study group *(and globally)* and visit, using the following statistics: number of patients, mean, standard deviation, minimum, median and maximum raw values. The absolute variations "post-*Run-In Period* – baseline *(evaluated at Visit 1)*" will also be tabulated by study group *(and globally)* and visit throughout the *Follow-Up Period*.

ARTERIAL OR CAPILLARY BLOOD GASES

For each arterial blood gas assayed *(i.e., pH, PaO_2, $PaCO_2$, HCO_3^-, HbCO and SaO_2)*, separately, quantitative descriptive statistics of recorded values will be tabulated by study group *(and globally)* and visit, using the observed case approach.

Moreover, to visualise the evolution of each arterial blood gas assayed, arithmetic means of the recorded values of pH, PaO_2, $PaCO_2$, HCO_3^-, HbCO and SaO_2, separately and their 95.0% confidence intervals will be represented graphically *(the x-axis being the assessment time-axis and the y-axis being the arithmetic mean-axis)* with both study groups being represented separately on the same graph, using the observed case approach.

HAEMOGLOBIN, HAEMATOCRIT AND C-REACTIVE PROTEIN (CRP)

For haematology and CRP results, separately, the following descriptive statistics will be tabulated by study group *(and globally)* and visit, using the observed case approach:

- number of patients, mean, standard deviation, minimum, median and maximum raw values *(converted in international units, if necessary)*,
- number and percentage of patients above, below or within normal ranges in use in each laboratory involved.

The absolute variations ″post-*Run-In Period* – baseline *(measured prior to Visit 1)*″ will also be tabulated by study group *(and globally)* and visit throughout the *Follow-Up Period*.

A shift table will also be provided for haemoglobin, haematocrit and CRP separately to depict the number and percentage of patients with post-*Run-In Period* decreased laboratory values *(from Within Normal Ranges to Below, from Above normal ranges to Within Normal Ranges or from Above normal ranges to Below)*, the number and percentage of patients without changes *(either always Within Normal Ranges or Above or Below)* and the number and percentage of patients with post-*Run-In Period* increased laboratory values *(from Below to Within Normal Ranges, from Within Normal Ranges to Above or from Below normal ranges to Above)* by study group *(and globally)*, as compared to their baseline values *(measured prior to Visit 1)*.

Moreover, the number and percentage of patients with post-*Run-In Period* anaemia or polycythemia *(as defined in section 6.B.2)* at each visit separately will be tabulated by study group *(and globally)*.

DESCRIPTION OF CONCOMITANT TREATMENTS

All concomitant treatments with start date at the earliest on the day of the patient's randomisation will be tabulated descriptively by study group *(and globally)*, on the ITT data set *(defined in section 7.B.3.1)*, using the WHO-DRUG dictionary and the Anatomical Therapeutic Chemical (ATC) classification. All reported concomitant treatments will be classified in two (2) successive periods: the *Run-In Period* and the *Follow-Up Period*, according to their start date.

Over these two (2) periods, separately and globally, three (3) summary tables will be provided by study group *(and globally)*:

- one table showing the number and percentage of patients with at least one concomitant treatment with start date at the earliest on the day of the patient's randomisation, by therapeutic area *(ATC1 code corresponding to ATC system main group)*,
- one table by both ATC1 code and ATC system subgroup *(ATC2 code)*,
- and one table showing the number and percentage of patients with at least one respiratory system concomitant treatment with start date at the earliest on the day of the patient's randomisation, by ATC system subgroups *(ATC2, ATC3 and ATC4 codes)*.

Additionally, over the *Run-In Period* and the *Follow-Up Period*, separately and globally the number and percentage of patients for whom either Continuous Positive Airway Pressure (CPAP) or home Non-Invasive Ventilation (NIV) separately is implemented (*while the patient was free of both of them at Selection*) will be tabulated descriptively by study group (*and globally*), on the ITT data set, with their average daily duration prescribed.

8. ADVERSE EVENTS

8.A DEFINITION

An adverse event is defined as any undesirable and unintended sign or symptom *(that could include a clinically significant abnormal laboratory finding)* occurring in a patient participating to a clinical trial and which does not necessarily have a causal relationship with the study intervention.

Adverse events are classified by the investigator according to their severity *(mild, moderate or severe)*.

A **Serious Adverse Event (SAE**) is any adverse event which:

- Results in death*,
- Is life-threatening *(actually places the patient at risk of death at the time of the event),*
- Requires patient hospitalisation or prolongation of existing hospitalisation,
- Results in disability or incapacity *(e.g., any temporary or permanent clinically significant handicap),*
- Is a congenital anomaly/birth defect,
- Or is considered serious by the investigator.

* Death is an outcome and usually not the reported term of the SAE. For example, if "*death due to myocardial infarction*" occurs, myocardial infarction should be reported as the SAE and death should be reported as its outcome.

All adverse events not corresponding to these definitions will be considered not serious Adverse Events (**AEs**).

8.B COLLECTION AND REPORTING OF SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. In order to fulfil the safety reporting obligations, the investigator should report all Serious Adverse Events occurring during the study, whether related to the study intervention or not, within 24 hours in the dedicated screen of the e-CRF, or when the e-CRF is not available, by fax or telephone to ITEC Services, for the attention of:

1. Dr Jack AUZERIE, ITEC Services
2. Nathalie CIENCIEWIEZ, ITEC Services
3. Nathalie DUBON, ITEC Services

Tel: +33 (0) 5 57 77 85 00
Fax: +33 (0) 5 57 77 85 01

A copy of the document to be filled in and faxed in case the e-CRF is not available will be provided in the investigator binder.

If ITEC Services cannot be reached, AIR LIQUIDE *Santé* INTERNATIONAL Pharmacovigilance department should be contacted:

Tel: + 33 (0) 1 40 62 85 72
Fax: +33 (0) 1 40 62 85 40
Email : vigilance.alsi@airliquide.com

If the Pharmacovigilance Department cannot be reached, AIR LIQUIDE *Santé* INTERNATIONAL COMET study team at the Research and Development Centre Claude Delorme could be contacted:

Tel: + 33 (0) 1 39 07 65 18
Fax: +33 (0) 1 39 07 61 99

The initial SAE declaration should include the following information: patient selection number, brief description of the event, its start date, and the reason(s) why the investigator considers the event serious.

The time period for the consideration and reporting of AEs *(either serious or not, according to their regulatory definition provided in section 8.A)* starts at the patient Selection *(i.e., at Visit 0)* and continues up to the last study visit *(i.e., up to Visit 5).*

The medical devices provided by AIR LIQUIDE *Santé* INTERNATIONAL for the study conduct are all CE marked and they are not under evaluation during the study. The investigators should thus follow the regular process for reporting any incidents and near-incidents related to those medical devices, whenever they occur throughout the study period.

9. ADMINISTRATIVE AND REGULATORY ASPECTS

9.A ETHICS COMMITTEES AND NATIONAL COMPETENT AUTHORITIES

The study will be conducted in compliance with Good Clinical Practice guidelines, the most recent revised version of the Declaration of Helsinki *(Seoul, October 2008 attached in Appendix 1)* and the European Directive 2001/20/EC on 4th April 2001 *(on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).*

The protocol and subsequent substantial amendments *(if applicable, see section* 9.D) are to be submitted to the local ethics committee and national competent authority for approvals in each participating country.

The enrolment of patients in the study could be started in a given participating country only after the written approvals of the corresponding local ethics committee and national competent authority.

9.B PATIENT INFORMATION AND CONSENT

The investigator must provide the patient with a verbal explanation of the study in which the patient is invited to take part, particularly, concerning the study intervention, the expected benefits and potential risks faced during the study. The investigator must also answer any questions the patient may have regarding the study. The patient must be given an information sheet which is easy to understand in their native language. A blank copy of the patient information sheet in each local study language will be submitted to the ethics committees for approvals, together with the protocol.

Informed Consents forms signed by the patient prior to his/her study participation will be provided in three (3) copies:

- One signed copy to be given to the patient,
- One signed copy to be kept by the investigator,
- One signed copy to be placed by the investigator in an envelope for the sponsor. This envelope will be sealed with the CRA during one monitoring visit (*see section 9.C*).

9.C STUDY MONITORING, AUDIT AND INSPECTION

The study will be monitored regularly *(visits and telephone monitoring)* by AIR LIQUIDE *Santé* INTERNATIONAL personnel or any company appointed by the latter. During the monitoring visits, the Clinical Research Associate (CRA) will verify the consistency of the data recorded in the e-CRF with the source data *(patient's medical file, nurse's chart, etc...)*. The CRA will also verify the presence and completeness of the investigator file and general study compliance with Good Clinical Practice (GCP) guidelines.

An on-site audit may be performed by the sponsor or designee personnel.

Participation in the study implies agreement with regard to all inspections by the regulatory authorities.

9.D PROTOCOL AMENDMENT

Any changes to the protocol influencing the study conduct or which may affect patient safety, particularly modifying the study objectives, study design or population, must be the subject of an amendment to the current protocol.

The amendment must be accepted by the sponsor, the national coordinators, each local ethics committee and national competent authority before it is brought into application.

Administrative modifications or minor corrections which would not affect the study conduct are to be approved by the sponsor and the investigator, and communicated to each local ethics committee for information.

The sponsor reserves the right to stop the study at any time further to specific information giving rise to concern for patient safety.

9.E INSURANCE AND LIABILITY

AIR LIQUIDE *Santé* INTERNATIONAL is protected by an insurance policy *(AXA CORPORATE SOLUTIONS Assurances)* taken out with the Cabinet DIOT *(4 rue Jules Lefebvre - F-75426 Paris Cedex 09 - France)*, concerning the civil liability of the investigators taking part in this study.

The insurance certificates are to be provided to the local ethics committee and national competent authority in each participating country at the submission for clinical trial approvals.

9.F CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the sponsor's responsibility.

At the end of the study, upon the completion of the data analysis, a final report, including a review of the study objectives and methods, and a presentation and discussion of the study results will be drawn up according to ICH Guidelines *(Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95)*. This report will be a clinical and statistical integrated report which will be signed by the sponsor representatives and the coordinating investigator.

9.G FILING OF THE STUDY DOCUMENTS

All documents related to the study must be kept by the investigator for a period of 15 years.

9.H USE OF THE INFORMATION AND THE PUBLICATION

The study results are the sole and exclusive property of AIR LIQUIDE *Santé* INTERNATIONAL. Nevertheless, the sponsor is aware that its property rights over the data must not prevent the investigator from communicating the study results to the scientific community.

Provided any such presentations do not prevent recognition of its industrial property rights, AIR LIQUIDE *Santé* INTERNATIONAL therefore authorises the investigator to draw up and present any scientific papers concerning the study as defined into the signed agreement between AIR LIQUIDE *Santé* INTERNATIONAL and the investigator.

10. INVESTIGATOR'S APPROVAL (SIGNATURES PAGE)

I have read the protocol with the following title:

"An International Phase IV Randomised Trial for Medical and Medico-Economic Evaluations of a Home-Based Disease Management Program in Patients with GOLD III/IV Chronic Obstructive Pulmonary Disease"

Sponsor number: ALMED-07-C4-008 **- ID RCB number:** 2009-A00807-50

I agree with the content and the way in which this study is to be conducted.

I will attempt to complete the enrolments into the study over the study period.

I will provide copies of the protocol and all information furnished to me by the sponsor, to all relevant staff members. I will discuss this material with them to assure that they are fully informed regarding the study conduct.

I agree to archive the study documents *(copy of the Informed Consent for each patient, back-up of electronic Case Report Forms on an appropriate support to archive data, correspondence, paper source documentation, etc…)* for a period of 15 years.

I agree to refrain from publishing all or part of the information concerning this study as defined into the signed agreement between AIR LIQUIDE *Santé* INTERNATIONAL and I.

INVESTIGATOR

NAME *(IN CAPITAL LETTERS)*

INVESTIGATOR'S SIGNATURE

DATE OF SIGNATURE

FOR AIR LIQUIDE *SANTE* INTERNATIONAL

MRS LINDA MYRICK
MEDICAL GASES GROUP MANAGER

SIGNATURE

DATE OF SIGNATURE

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12. APPENDICES

APPENDIX 1: DECLARATION OF HELSINKI

APPENDIX 2: PATIENT SYMPTOM MONITORING AND HEALTH CARER'S ACTIONS

APPENDIX 3: PATIENT QUESTIONNAIRES

APPENDIX 1: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this

population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be

included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

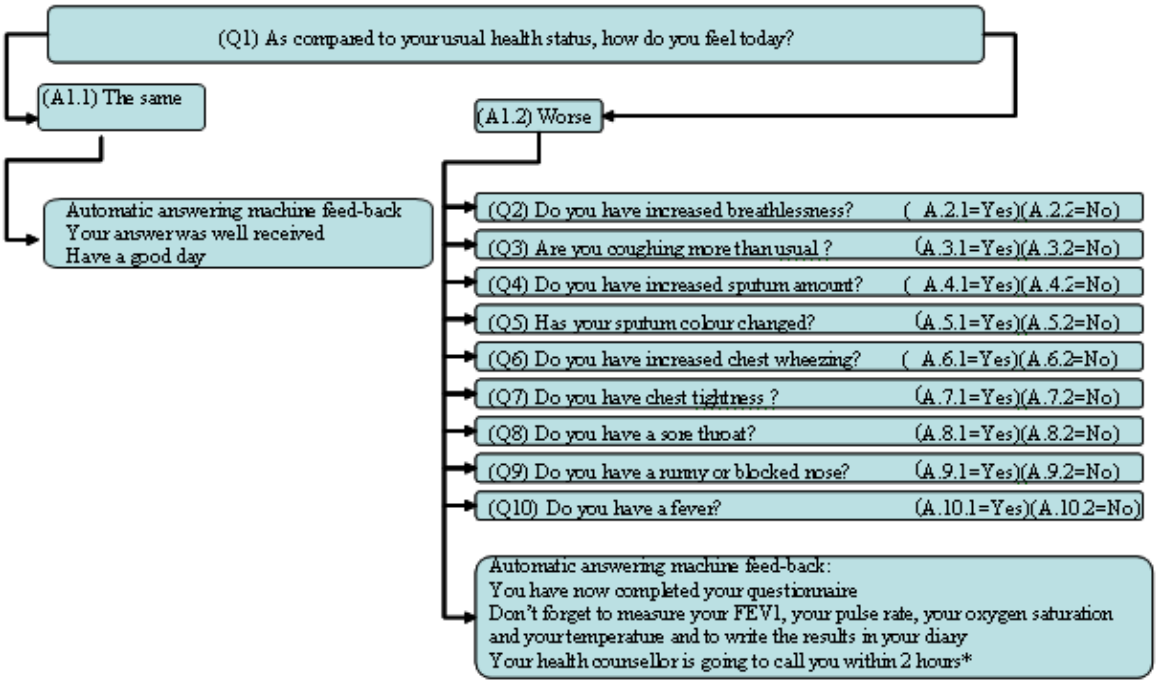
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX 2: PATIENT SYMPTOM MONITORING AND HEALTH CARER'S ACTIONS

Patient self-reporting of clinical status

The patients randomised to the Intervention group will have to contact the free of charge telephone number of the vocal server after the usual morning deterioration is stabilised, *i.e.* between 9 and 12 AM, to report their clinical status. They will be instructed to contact the server at least once a week *(and at most once a day)* and each day their clinical status is worse than usual.
After identification, the patients will be questioned in their native language *(Suppl. Figure 1)* and will be asked to answer each question by pressing one touch on their phone. Each answer will be automatically stored in a centralised database and will result in an automatic immediate scoring to allow an appropriate feedback message to the patient by the answering machine.

Suppl. Figure 1. Sample of patient's questionnaire



Scoring methodology

Calculation of the score will be automatically performed at the time of patient phone call. All patient answers are mandatory to calculate the score. Result of the score will be stored in the study centralised database.

Scoring will result in one of 3 potential clinical statuses: a "*Well Being status*", a "*Worsening status*" or an '*Alarm status*'.

The '*Well Being status*' is defined by answer A.1.1.

The *'Alarm status'* is defined by answer A.1.2 AND at least two (2) positive answers to questions Q2, Q4 or Q5, OR answer A1.2 AND one (1) positive answer to questions Q2, Q4 or Q5 AND at least one (1) positive answer to questions Q3, Q6-10 for two (2) consecutive days. If the patient reports only one (1) positive answer to questions Q3 or Q6-10 *(with negative answer to Q2, Q4 and Q5)* during ≥ 5 consecutive days, this question will be excluded from scoring calculation until the patient answers negatively to the question.

The "*Worsening status*" is defined by all other combinations.

Health counsellor actions in case of 'Worsening' or 'Alarm' status

In case of '*Alarm status'* or '*Worsening status'*, the vocal server will immediately generate an automatic message to the health counsellor.

Following reception of this automatic message, the health counsellor will call back the patient within two (2) hours during working days, and on the next working day if the message is received during weekend or public holidays.

During the phone call to the patient, the health counsellor will

- **Check with the patient the answers to questions Q2 to Q10**; if the patient changes one answer to the questionnaire, the health counsellor will change it accordingly through his/her web interface *(but both answers will be stored)* and a updated scoring calculation will be immediately performed according to the same rules as detailed in previous section.
- **Record additional parameters** *(listed in Suppl. Table 1)* that will be immediately reported in the study database through his/her individual web portal to be accessible at any time by the investigator.
- **Provide appropriate counselling** by repeating the usual recommendations of the education program regarding inhaler use, compliance to oxygen therapy, use of techniques and strategies. The phone call will end by repeating emergency number, hospital physician number and family physician number and by the importance for the patient to evaluate himself/herself the next morning and do his/her self-reporting.
- **In case of confirmed 'Alarm status',** inform the patient that his/her investigator will contact him on the same day for medical decision application.

Suppl. Table 1. Additional parameters recorded by phone by the health counsellor

Yes/No questionnaire
Are you alone at home?
Do you have new or increase in fatigue?
Do you have new or worse difficulty with sleep?
Do you have sudden development of resting dyspnea?
Do you have a decrease in daily activities because of worsening dyspnea or increased breathlessness with daily activities?
Do you have new or increase in peripheral oedema?
Do you have headaches today?
Are you using your inhaler(s) more than usual?
Are you using your oxygen more than usual?*
Have you started taking steroid tablets today?
Have you started taking antibiotics today?
Have you started taking other medications today?
Results of the self-testing
Body temperature (°C)
Pulse rate (beats per minute)
SpO_2 (%) at rest **
FEV_1 *(absolute value and percentage of predicted)*

* applicable only for patients on oxygen therapy
** on room air, or on oxygen *(with the flow rate prescribed at rest)* for patients on oxygen therapy

Investigator actions in case of alarm status

Any '*Alarm*' status validated by the health counsellor will generate an immediate automatic message via 2 different means *(among E-mail, phone call, SMS, Fax)* to the investigator to notify that one of his/her patient has reached the '*Alarm*' status. The message will contain the following: patient identification number and the phone number of the corresponding health counsellor.

The investigator will have a personal dedicated access to web portal allowing him/her to examine patient report including *i)* history of patient clinical status reporting; *ii)* answers to the additional questionnaire and paraclinical data entered by the health counsellor.

The investigator must inform the patient of his/her medical decision within 3 hours following reception of the '*Alarm*' status notification, by phone. Decision can be the following:

- Nothing to implement,
- Therapeutic adjustment,
- Visit to a physician *(community or hospital, general practitioner or specialist),*
- Emergency room visit, hospitalisation.

The investigator will also report on the same day the date/time and nature of his/her decision through his/her dedicated web portal. Medical decision will be automatically and immediately transmitted to the health counsellor, and will end the alarm management from the point of view of the health counsellor.

Technical and functional specifications of the web-based application and of the vocal server

The study vocal server is a patient-dedicated interactive voice response system (IVRS) allowing patients to report in their native language their clinical status. The IVRS is coupled with a web-based application allowing the following:

- Check that the patient has called at least once during the preceding 7 days:

In case the patient has not called, the IVRS generates the seventh day 3 automatic phone calls *(1:30 PM; 2:00 PM; 2:30 PM)* to the patient, then an automatic phone call at 2:30 PM to the health counsellor *(on working days)* if the patient has not called the vocal server despite the 3 automatically generated phone calls.

- Check that the patient has answered to all questions to allow the clinical status scoring.
- Perform immediately the scoring to allow an immediate automatic feed-back to the patient in his/her native language at the end of the phone call.
- Store the patient's answers received via IVRS and the result of the score in the study database.
- Generate immediate automatic messages to the patient's health counsellor in his/her native language in case of 'Worsening status' or 'Alarm status', via 2 different means *(among E-mail, phone call, SMS, Fax).*
- Check that the appropriate actions were made by the patient's health counsellor following the reception of a 'Worsening status' or an 'Alarm status':

During the phone call to the patient, the health counsellor will be connected through his/her personal web portal allowing the instant reporting of the phone call. In case the report is not performed within the allocated time frame *(within 2 hours on working days; otherwise, on the next working day)* following the reception of the 'Worsening status' or 'Alarm status' message by the health counsellor, the IVRS will generate an automatic phone call to the patient's health counsellor.

- Generate immediate automatic messages to the patient's investigator in case of confirmed 'Alarm status', via 2 different means *(among E-mail, phone call, SMS, Fax).*
- Check that the appropriate action was made by the patient's investigator following the reception of a confirmed 'Alarm status':

In case the investigator has not reported the medical decision within 3 hours following the reception of the confirmed 'Alarm status' message by the investigator, the IVRS generates an automatic phone call to the patient's health counsellor, who will, in turn, be in charge to contact the investigator.

APPENDIX 3: PATIENT QUESTIONNAIRES