FINAL RESEARCH PROJECT

BENEFITS OF EXERCISE TRAINING IN BRONCHIECTASIS: A RANDOMIZED CONTROLLED TRIAL DESIGN

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Als meus pares per ser-hi sempre. Gràcies per confiar en mi, recolzar-me i guiar-me.

To my practice tutor Ilias who showed me passion for what we do. I consider you more than a friend, but my mentor.

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ABBREVIATIONS

A

***ABPA**: allergic bronchopulmonary aspergil·losis*
***ATS:** American Thoracic Society*

B

***BMI**: Body index mass*
***BSI**: Bronchiectasis Severity Index*
***BTS**: British Thoracic Society*

C

***CEIm:** Comitè d'Ètica d'Investigació amb Medicaments*
***CF**: cystic fibrosis*
***CFTR-RD**: cystic fibrosis transmembrane regulator-related disease*
COPD: chronic obstructive pulmonary disease
***CT**: Computed tomography*

D

***DPB**: diffuse panbronchiolitis*

E

***ERS**: European Respiratory Society*

F

***FEV1:** Forced expiratory volume in the first second*
***FCV:** Forced vital capacity*

G

***GORD**: Gastro-oesophageal reflux disease*

H

***HIV**: Human immunodeficiency virus*
***HUJT**: Hospital Universitari Doctor Josep Trueta*

I

***ICS:** Inhaled corticosteroids*
***IID**: intestinal inflammatory disease*
***IPAQ-SF**: International physical activity questionnaire short-form*

L

***LFT:** lung function tests*

M

***MIP**: Maximal inspiratory pressure*

***MEP**: Maximal expiratory pressure*

METs: metabolic equivalent task

***mMRC:** Modified medical research council scale*

N

***NTM:** Non-Tuberculous mycobacteria*

***NTM-PD**: non-tuberculosis mycobacteria-pulmonary disease*

P

***PCD**: primary ciliary disease*

***PPD:** purified protein derivative*

Q

***Q'**: Pulmonary Perfusion*

***QoL-B**: Quality of Life-Bronchiectasis questionnaire*

R

***RM:** Maximum Repetition*

S

***SEPAR:** Sociedad Española de Pneumología y Cirugía Torácica*

***SPSS**: Statistical Package for Social Sciences*

T

***TB**: Tuberculosis*

V

***V':** Alveolar ventilation*

***V'O2**: Oxygen uptake / consumption*

***V'O2max:** Maximal oxygen uptake / consumption*

W

***WMA:** World Medical Association*

ABSTRACT

Background: Bronchiectasis is a chronic, progressive and persistent inflammatory lung disease which causes exercise intolerance and physical activity limitations, among others. Bronchiectasis patients experience worse dyspnoea perception and increased fatigue during exercise. Daily physical limitations are related to impaired health-related quality of life. Current treatment involves therapy for exacerbations and/or direct physiopathological factors of the disease but no treatment is targeting to improve peripheral symptoms. Some literature assessing effects of exercise training programmes in bronchiectasis reported beneficious outcomes regarding exercise capacity, although conclusions provided were low-quality evidence based.

Hypothesis and Objectives: We hypothesize that exercise training is effective in improving exercise tolerance. Therefore, the aim of this study is to evaluate the effect of an exercise training rehabilitation programme using an objective method to estimate the cardiorespiratory function in order to supply with rigorous data. Secondary objectives are to assess impact of exercise training in other relevant clinical variables such as respiratory muscle strength, number of exacerbations, dyspnoea perception, quality of life and pulmonary capacity.

Methods and Materials: This is a single institution, prospective, parallel controlled clinical trial. The study includes 114 patients with stable bronchiectasis and exercise intolerance from Hospital Josep Trueta's bronchiectasis-specialized unit. Patients will be randomly distributed into two groups: a control group (CG), which will receive usual care (ELTGOL technique), and the intervention group (IG), which will receive an 8-week exercise training rehabilitation programme and concomitant usual care (ELTGOL technique). Training sessions will be performed 3 times per week and will consist in interval endurance training, peripheral muscle strength training and respiratory muscle training. Data will be collected at the study onset and immediately after the end of the 8-week training sessions. Variables analysed will be maximum oxygen consumption, dyspnoea perception, quality of life, maximal respiratory pressures and pulmonary capacity. After intervention, there will be a 1-year period of follow-up to determine incidence of exacerbations of both groups.

__Key-words__: *non-cystic fibrosis bronchiectasis, peripheral symptoms, pulmonary rehabilitation, exercise capacity, physical activity, quality of life, exercise training, cardiopulmonary exercising tests.*

1. INTRODUCTION

Bronchiectasis is a chronic lung disease. It is defined as an abnormal and persistent dilation of the bronchi resulting from damage of the airway wall. It represents the final result of different underlying causes or diseases. Traditionally bronchiectasis has been classified in cystic fibrosis and non-cystic fibrosis related. Cystic Fibrosis has a well-defined homogeneous population, the most severe cases are identified at an early age and have faster rates of progression(1). It has attracted more commercial and scientific interest over the years. As a result, more studies have been conducted since then. However, it only accounts for a small percentage of bronchiectasis patients (1). On the other hand, non-cystic fibrosis bronchiectasis patients are a more heterogeneous population because of its etiological variability (1), who started to be managed in specialists units only few years ago, when research interest in the disease increased (1).

The present study will focus on non-cystic bronchiectasis.

1.1. EPIDEMIOLOGY

Historically, bronchiectasis was considered an orphan disease with little recognition of its importance. However, in the last decade a growth number of investigations began to demonstrate a marked rise in its prevalence and incidence, particularly in the elderly population (2) (3). These studies completely changed the medical community's perception of bronchiectasis and sparked new interest in it.

In 2012 the prevalence of bronchiectasis was 36.2 cases per 10 000 inhabitants in Catalonia *(Figure 2)* (2)*;* the mean age of patients was 68.3 years old and women represented 53.9% of all of them

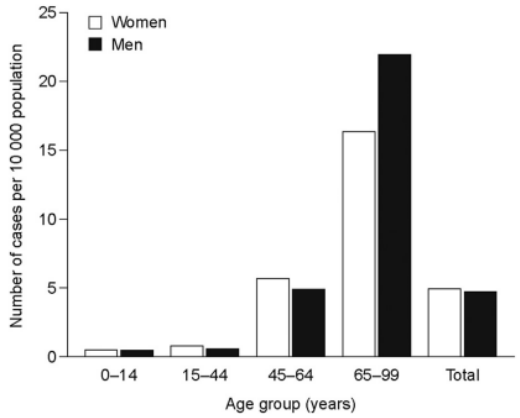

Figure 1. *Mean incidence of bronchiectasis by age and sex in Catalonia 2012* (9).

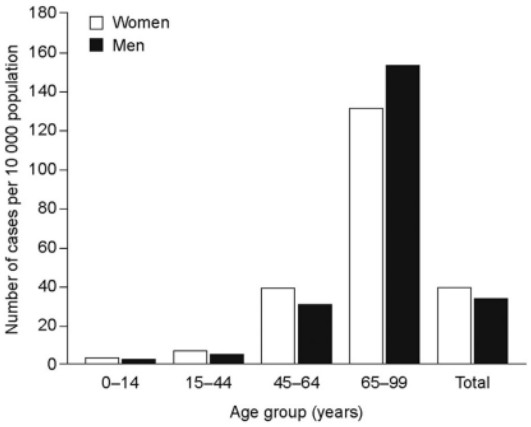

Figure 2. *Mean prevalence of bronchiectasis by age and sex in Catalonia 2012* (9).

Incidence rates were 4.81 cases per 10 000 inhabitants per year and again women showed higher results *(Figure 1).* Incidence and prevalence increased with age in both sexes. The group with higher incidence and prevalence were men between 65-99 years. This can be explained in part because of a higher proportion of men smoking between that age and high prevalence of COPD as a result (2). More than half of the patients were non-smokers (60.4%) (2).

Quint et. al. 2016 (3) showed similar data from a cohort study with a 10 year follow-up period in UK. From 2004 to 2013, women incidence increased from 21.2 per 100 000 person-year to 35.2 per 100 000 person-year; in men incidence grew from 18.2 per 100 000 person-year to 26.9 per 100 000 person-year (3). Prevalence also increased in both sex within 10 years (3). Over half the individuals (58.5%) were women, and the median age at diagnosis of adult bronchiectasis was 61.8 years (3).

According to estimates, the average annual cost of treatment in Spain is the mean cost is €4671.9 per patient, which increases significantly with severity (4).

1.2. PHISIOPATHOLOGY

Up until now, the physiopathology was described by the *Vicious Circle* hypothesis proposed by Cole et. al. (5), which postulated that a change in mucociliary clearance promoted persistent bronchial inflammation and bronchial infection (5). Ciliary epithelium changes cause mucociliary dysfunction and retention of secretions in the airway. There is also an increase mucus production and changes on its composition, such as greater viscosity and dehydration (1). Consequently, a disruption of the host defences happens which results in the establishment of persistent bacterial pathogens and chronic infection. Finally, chronic inflammation in the bronchial wall and abnormal remodelling of the airway leads to permanent dilation of the bronchi. In late stages of the disease, excessive inflammation of the airway causes rapid lung injury due to elastin degradation, causing an increased number of exacerbations and deterioration of respiratory function (5). Each element of the cycle potentiates the appearance of the others over time, resulting in a progressive and persistent process.

However, the most accepted hypothesis nowadays is the **"Vicious Vortex Concept**" *(Figure 1)* which offers a more holistic view of the disease and suggests interconnected components taking part on it physiopathology: infection, inflammation, epithelial-immune dysfunction, and lung destruction (6).

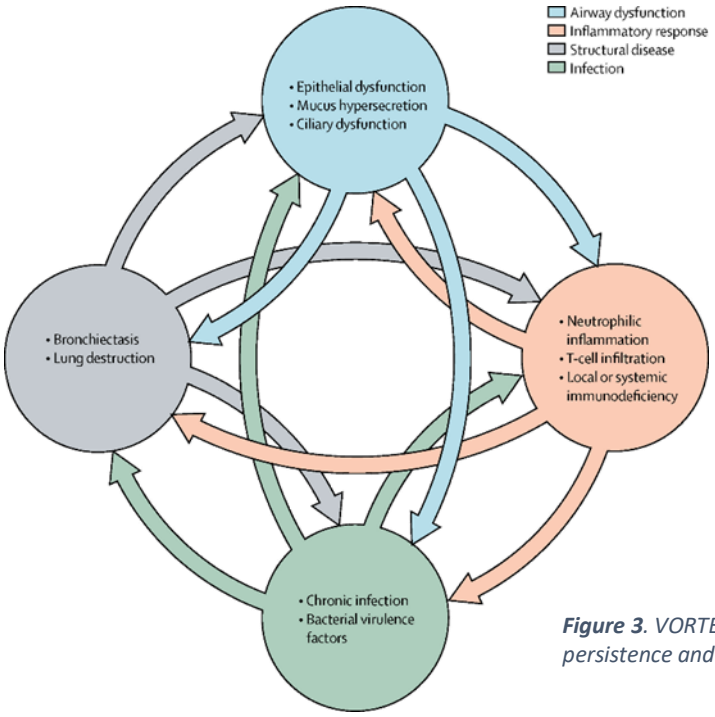

***Figure 3**. VORTEX VICIOUS CYCLE, a cycle of events that promote persistence and progression over time (6)*

Microorganisms that colonize respiratory mucosa are less virulent than those causing invasive disease (7). Nevertheless, they are capable of creating means to facilitate their survival, such as biofilm formation or hypermutability, and interfering with host defences (7). The bacterial load increases in time, leading to different clinical situations (7):

1. **Bronchial Colonization**: there is no inflammatory response other than sputum production. Three types may be distinguished:
    a. *Initial*: the patient is stable but there is an isolation of a microorganism not found before.
    b. *Intermittent*: there are positive and negative cultures for the microorganism during 1 month. The patient is under no antibiotic treatment.
    c. *Chronic*: there are three or more positive cultures for the same microorganism successively for a period time of 6 months.
2. **Chronic bronchial infection**: there is an inflammatory response This stage is characterized by persistent purulent sputum production (8)
3. **Bronchial Inflammation**: chronic inflammation due to persistence of the microorganism. There is a nonspecific bronchial response to infection with a large number of blood cells aimed to eliminate the microorganism. The response Is local with neutrophilic predominance, which can progress to systemic (7).

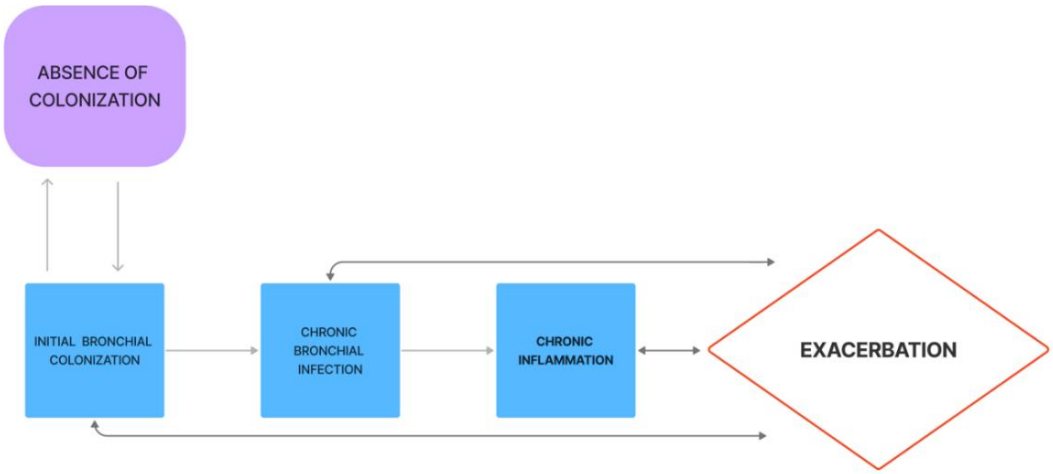

Figure 4. *Representation of the natural course of Bronchiectasis.*

1.3. AETIOLOGY AND RISK FACTORS

Bronchiectasis is the common final path of a wide range of diseases. In 38.1% of the cases the underlying cause cannot be identified and are classified as idiopathic (9). The most frequently identified cause is post-infective disease (9).

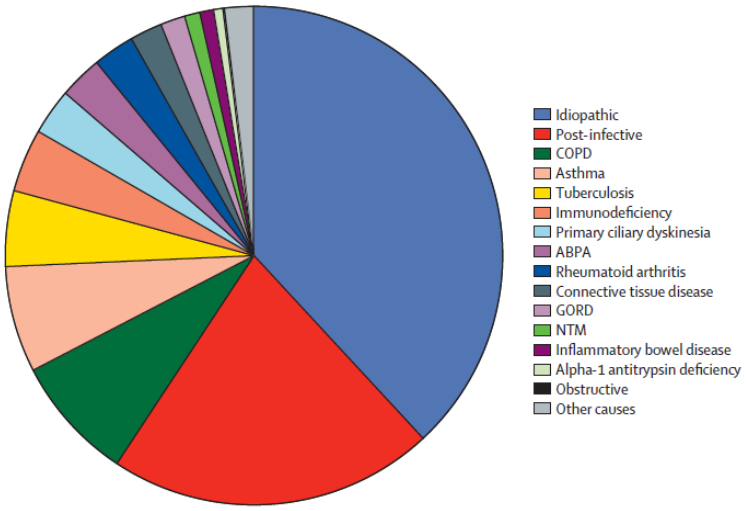

Figure 5. *Underlying causes of bronchiectasis in Europe* (10)

TABLE 1: IDENTIFIABLE CAUSES OF BRONCHIECTASIS (1)

Post-infection	Bacteria	*Pneumonia* The most frequent identified cause of bronchiectasis *Childhood respiratory Infections* *Pertussis* *Necrotizing Pulmonary infections*
	Mycobacteria	*Tuberculosis* (TB) *Non-Tuberculosis mycobacteria (NTM)*
	Fungi	*Allergic Bronchopulmonary Aspergillosis* (ABPA)
Bronchial Obstruction	Intrinsic	*Stenosis from scarring* *Bronchiolitis*

		Foreign body *Tumour*
	Extrinsic	*Diseased lymph nodes,* *Tumour* *Aneurysm*
Immune Deficiency	*Primary* *Secondary*	
Impaired mucociliary clearance	*Cystic Fibrosis* (CF)	Autosomal recessive disease caused by a mutation in CFTR gene (CF transmembrane conductance regulator) which encodes a chloride channel causing an altered ion epithelial transport. It affects ciliary cells of the whole body (1).
	Primary Ciliary Dyskinesia	Genetic disorder caused by a wide range of mutations which affect the ciliary structure (11).
	Young Syndrome	
Inflammatory pneumonitis	*Aspiration and gastroesophageal reflux disease* *Toxic inhalation (drugs, gases, etc)*	
Associated with other diseases	*Rheumatoid arthritis*	
	Inflammatory Bowel Disease	*Ulcerative colitis* *Crohn disease*
	Obstructive Chronic Lung disease (COPD) *and Asthma*	Bronchiectasis can be seen in both diseases and notably in the most advanced stages of them (13) (14).
	Other	*Systemic lupus Erythematosus* *Sjögren syndrome,* *Ankylosing spondylitis, sarcoidosis* Other respiratory diseases *Swyer-James syndrome* *a1-antitrypsin deficiency, Yellow nails syndrome*

1.4. DIAGNOSIS

Bronchiectasis diagnosis involves both clinical and radiological features, with or without associated disease. 20% of adults up to 65 years old can present radiological bronchiectasis with no symptoms associated (10).

1.4.1. Clinical Presentation

Bronchiectasis should be suspected in patients with recurrent respiratory infections with asymptomatic periods or persistent cough in between them and particularly, with no smoking history (1). Cough is commonly accompanied with purulent or mucopurulent sputum production (11).

An expert consensus group determined that the presence of two or more of the following criteria would confirm a clinical significant bronchiectasis: (1) a cough most days of the week; (2) sputum production most days of the week; (3) a history of exacerbations (12). Some patients may present history of recurrent haemoptysis (12).

Other symptoms may include bronchial hyperresponsiveness and breathlessness depending on the lung function involvement, musculoskeletal or pleuritic chest pain, whenever pleura is affected, weakness and loss muscle mass and weight (1). In clinical examination airway may appear normal or some pathological respiratory sounds can be detected such as crackles, rhonchi and/ or wheeze. (1). Predominantly, patients present an obstructive respiratory pattern. In very severe stages patients can present clubbing, cachexia, respiratory failure or *cor pulmonale* (1).

1.4.1.1. Exacerbations

During the disease exacerbations may occur, which are defined as a deterioration in three or more of the following key symptoms for at least 48 h: *cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis and a clinician determines that a change in bronchiectasis treatment is required* (13). Reducing exacerbations is crucial since they increase bronchial inflammation, cause disease's progression, worsen quality of life and increase hospital and treatment expenses.

1.4.1.2. Microbiology

Most common microorganisms isolated in sputum cultures of patients with bronchiectasis are *Pseudomonas aeruginosa* and *Haemophilus Influenza* (9). *Pseudomonas* has been related with more severe disease and faster progression, more frequent exacerbations and reduced quality of life, compared with other microorganisms (11).

Gram-positive microorganisms are less common. They are mostly represented by *Streptococcus pneumoniae* (7%) and *Staphylococcus aureus* (12). On the other hand, NTM are also common in bronchiectasis patients with an increasing prevalence, particularly in the United States (13), as they are difficult to eradicate due to their tenacity and pervasiveness in the environment.

1.4.1.3. Peripheral symptoms and Exercise Intolerance

Respiratory and peripheral muscles impairment are present in chronic inflammatory pulmonary diseases such as bronchiectasis (14). Initially it was thought to be consequence of ventilatory factors. However, over the last 20 years it has been proved to be result of a multifactorial process.

During exercise it is required a major ventilation load in order to remove increased production of CO2 and keep Ph. Ventilation is also extra-stimulated by hypoxemia due to lung disease during exercise and lactate production. In chronic lung diseases there is an increased inspiratory and expiratory resistance and/or reduced compliance which leads to a major pressure required for airflow (in order to give movement or displacement of sarcomeres). Consequently, respiratory muscles need to do extra work to permit breathing causing respiratory muscle fatigue. Thus, ventilatory function is impaired and less O2 is delivered resulting in muscle dysfunction (15). This process is represented in *Figure 6*.

Muscle dysfunction causes weakness and respiratory insufficiency which leads to inactivity and chronic under-loading of the muscles (16). In order to avoid dyspnoea and fatigue, most bronchiectasis patients adopt sedentary behaviours causing loss of

physical capacity (17) due to muscle mass loss and reduced strength. This leads to sarcopenia which is associated with less oxidative capacity of muscles that affects negatively to fatigue perception (15).

Main determinants of muscle dysfunction are inactivity and nutritional disorders associated to these patients who are mostly malnourished, although other causes may be systemic inflammatory mediators due to the inflammatory state of lungs, reduced oxygen, chronic respiratory acidosis, use of corticoids and other comorbidities (16). Moreover, a study cohort showed a progressive affection of lung diffusion in bronchiectasis patients which can cause gas exchange limitation during exercise resulting in exercise intolerance (18). With under-loading of the muscles there is also a reduction of capillary density that causes reduced regional blood flow delivery, reduced nutrient delivery and waste removal (16).

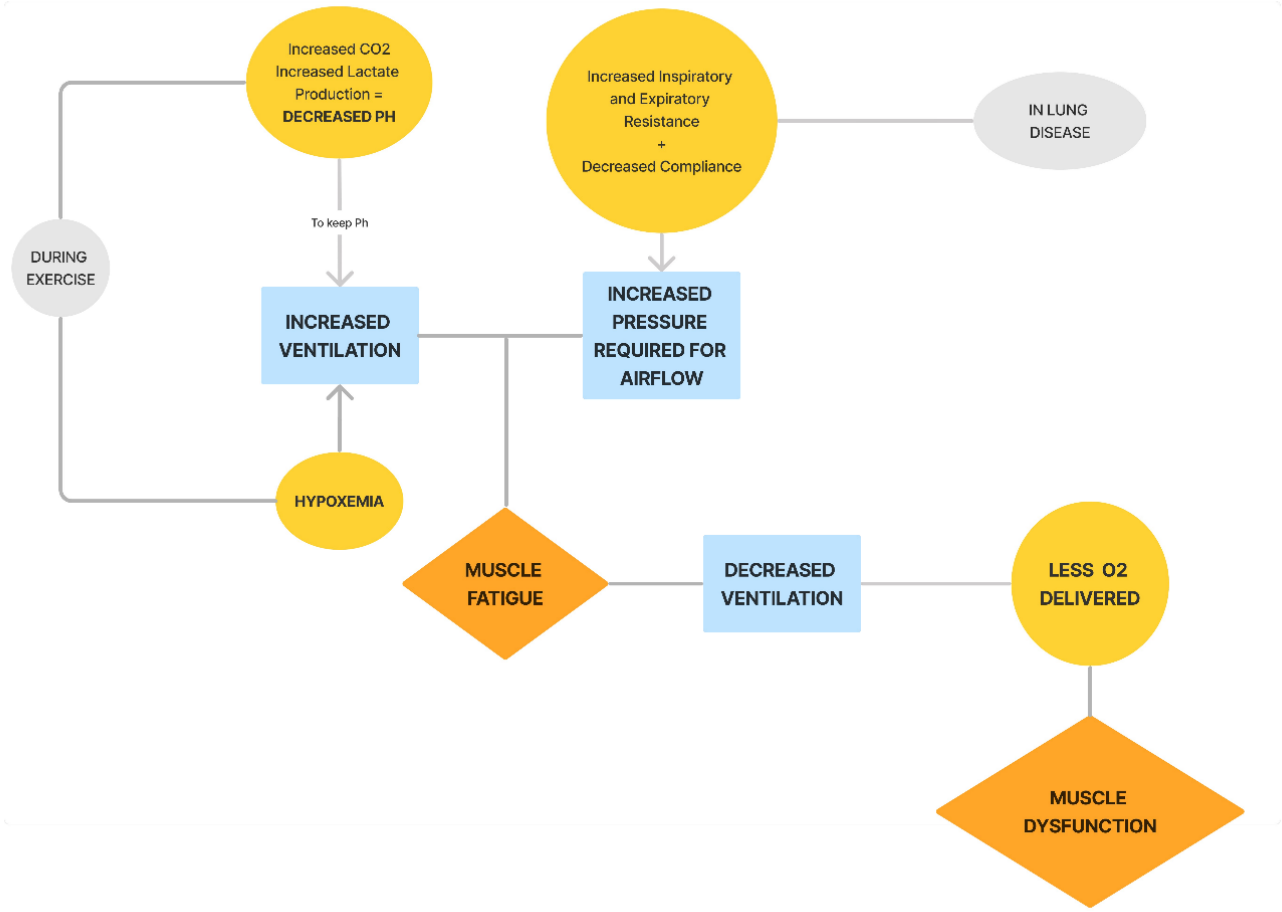

Figure 6: *Physiopatholgical process of peripheral symptoms in bronchiectasis.*

Skeletal muscle deconditioning plays an important role in functional loss in bronchiectasis. Patients following an exercise training program experience improved exercise tolerance, less limitation in daily activities and improved health-related quality of life due to reconditioning (19).

Dyspnoea is considered another determinant in exercise intolerance among these patients, which is present in 60% of them (15).

1.4.2. Radiological findings

Computed tomography (CT) is currently the gold standard to make a diagnosis and determine extension and progression of the disease (20). A national consensus has suggested definitions according to chest CT findings. This group of experts rate the following 4 criteria with a score of more than the mean value of all scores together for establishment of radiological bronchiectasis (12):

- → Inner airway-artery diameter ratio of ≥1.5
- → Outer airway –artery diameter ratio of ≥1.5
- → Lack of tapering of the airway
- → Visibility of airway in the periphery

Morphologically bronchiectasis can be classified in 3 subgroups:

1. **Cylindrical bronchiectasis**: is presented with the railway sign. Is the most common form of bronchiectasis and it results in uniform enlargement of the bronchi and absence of the normal distal tapering of the airway.
2. **Varicose bronchiectasis**: there is a combination of narrowed and dilated segments to the affected bronchus. In this case, the string of pearls sign can be seen.
3. **Cystic Bronchiectasis**: is the most severe form and happens when there is a saccular dilation and extension to the pleural surface. It can give a “bunch of grapes” appearance.

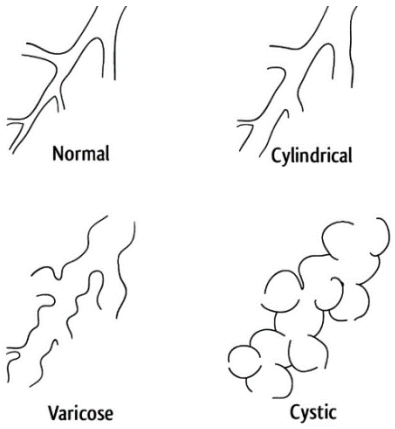

Image 1. *Representation of different structural types of bronchiectasis (40).*

Bronchiectasis can also be detected by visualizing indirect signs. The following table shows the most common direct and indirect signs present in bronchiectasis CT (20):

TABLE 2: DIRECT AND INDIRECT OF RADIOLOGICAL DIAGNOSIS

Direct Signs	**Indirect Signs**

- **Bronchial dilation (airway-artery diameter ratio ≥1)**
  o Abnormal bronchial contour
  o Signet ring sign (in transverse slice in cylindrical bronchiectasis)
  o Tram-Track sign (in horizontal slice in cylindrical bronchiectasis)
  o String of pearls sign (in horizontal slice in varicose bronchiectasis)
  o Bunch of grapes sign (in cystic bronchiectasis)
- **Lack of bronchial tapering** *(Image 2)*
- **Visualization of peripheral bronchi** (in contact with the mediastinal pleura or within 1cm of the costal pleura) *(Image 3)*
	- **Peri-bronchial thickening**
	- **Mucoid impaction**
	  o Tubular or Y-shaped structures
	  o Rounded or branching opacities (in transverse slice)
	  o Air-fuid levels
	- **Mosaic pattern**
	- **Centrilobular nodules**
	- **Tree-in-bud nodules**
	- **Focal areas of air tapping**
	- **Atelectasis**

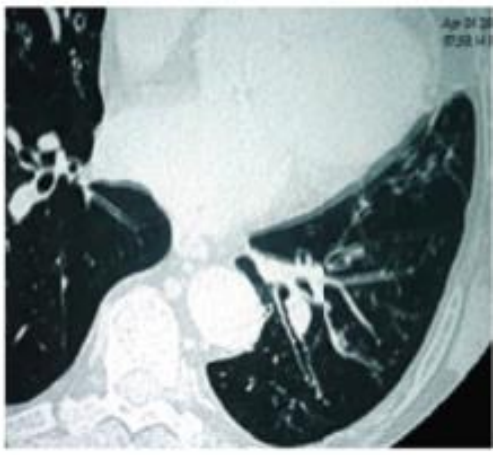

Image 2: *Lack of tapering of the bronchi (39)*

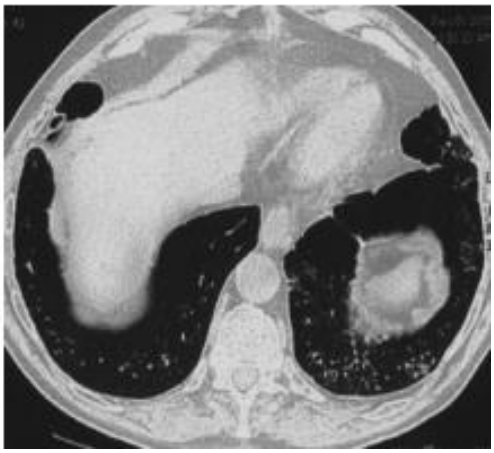

Image 3: *Visualization of peripheral bronchi (39)*

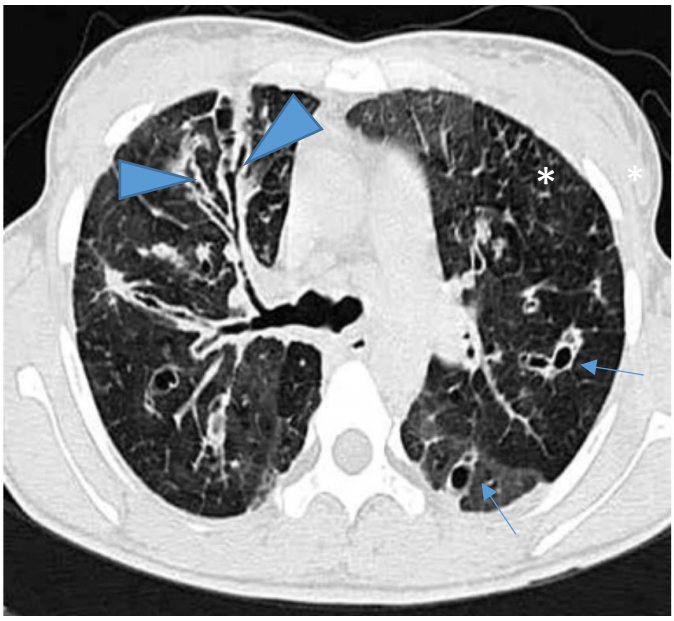

Image 4*: Bronchiectasis CT with peripheral bronchial visualization (*), signet ring sing (arrow) and lack of tappering of the bronchii (arrow head)*

1.4.3. Etiological Diagnosis

It is important to conduct an etiological diagnosis in order to establish the underlying cause and treat correctly in the case a specific treatment is available (21). To identify the most plausible causes, an initial evaluation must be made, consisting in a complete clinical history and physical examination (1) (22).

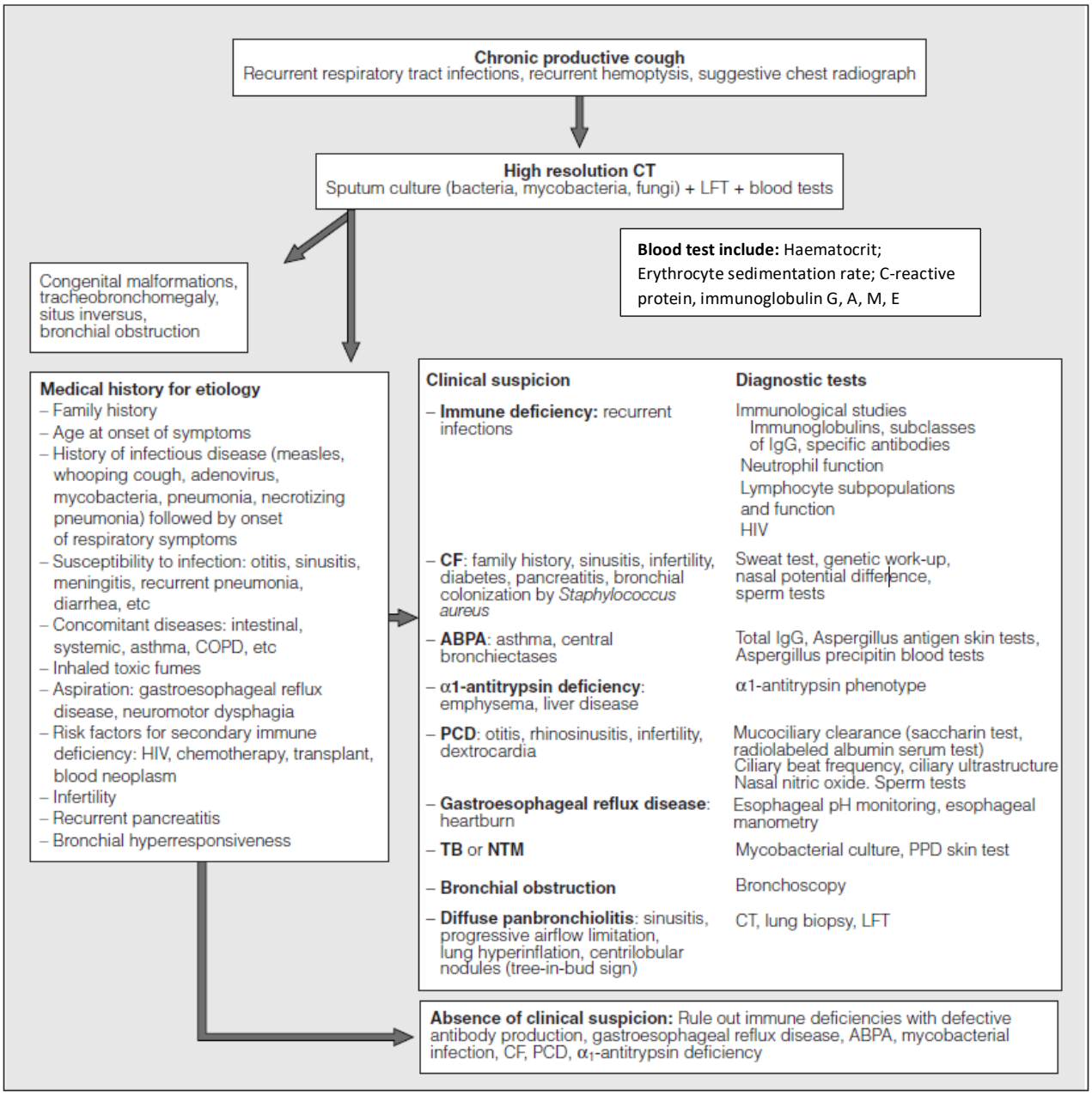

Figure 7: *Bronchiectasis aetiological diagnostic algorithm (1).*

1.5. GRADING AND CLASSIFICATION

We dispose of two clinical scales used to assess severity and the prognosis of bronchiectasis: FACED and Bronchiectasis Severity Index (BSI). Both provide likelihood of mortality (23).

BSI objective is to predict relevant clinical outcomes (24) and is used to evaluate severity and prognosis in clinical practice (25). It is based in 9 variables including several values for each one (25): age, body mass index, FEV1% predicted, previous hospitalizations and exacerbations, dyspnoea perception, colonization by *Pseudomonas aeruginosa* and other microorganisms and radiological extension of the disease *(Annex 2).* BSI classifies bronchiectasis patients in 3 subgroups: *Low severity* (from 0 to 4 points); *Intermediate severity* (from 5 to 8 points); *High severity* (up to 9 points). Each severity class have a predicted mortality and morbidity associated, shown in *Figure 7* (24).

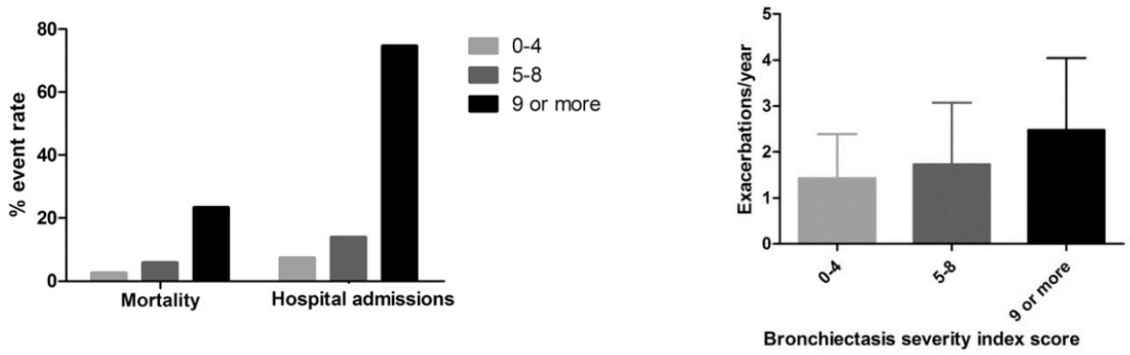

***Figure 8**: Potency of Bronchiectasis Severity Index in predicting mortality, hospital admissions and exacerbations (45)*

FACED score is mainly used to predict mortality in a 5-year follow up. Moreover, in long term predicted mortality, it has been proved to have superior predictive capacity than BSI (44). It includes 5 dichotomous variables easy to obtain, which suppose less complexity in calculating and interpreting its results **(FACED)**: **F**EV1%, **A**ge, **C**hronic colonization by *Pseudomonas aeruginosa*, **E**xtension (number of lobes affected in the CT) and **D**egree of Dyspnoea *(Annex 2).* Results obtained range from 0 to 7 points and classify patients in 3 subgroups: *mild bronchiectasis* (from 0 to 2 points); *moderate bronchiectasis* (from 3 to 4 points); *severe bronchiectasis* (from 5 to 7 points).

Although FACED score has shown excellent ability to predict prognosis and mortality, it does not account for the number and severity of exacerbations (26). Consequently, a new assessment tool was developed: E-FACED score (26). It preserves the FACED score's

exceptional capacity to predict respiratory and all-cause mortality while including exacerbations as a predictable parameter to assess mortality, lung function deterioration and severity of the disease (26).

1.6. STANDARD TREATMENT

Treatment is based in primary in treating aetiology whenever is possible, improving impaired mucociliary clearance, treating and controlling exacerbations, and finally preventing or suppressing acute and chronic bronchial infection.

1.6.1. Etiological treatment

Some of bronchiectasis aetiologies have treatment which targets specific factors involved in their physiopathology. Those aetiologies must be checked and identified as soon as possible In order to provide properly treatment.

TABLE 3: CAUSES OF BRONCHIECTASIS WITH SPECIFIC TREATMENT (1).

- Defective antibody production
- ABPA
- Gastroesophageal reflux disease
- Bronchial obstruction
- Mycobacteria infection
- α1-Antitrypsin deficiency
- Cystic Fibrosis
- Concomitant diseases (COPD, asthma, inflammatory bowel disease, autoimmune disease, panbronchiolitis)

1.6.2. Mucociliary clearance impairment

All techniques aimed to improve removal of airway secretions will impact positively on bronchiectasis course since bronchiectasis patients suffer from impaired mucociliary clearance and sputum retention. These techniques include breathing strategies, directed coughing, positive expiratory pressure devices, airway oscillating devices and mechanical tools applied to the external chest wall (27). They are recommended 1-2

times per day in those patients with productive cough or sputum difficult to expectorate (22), although different techniques used will depend on patient's age and ability to perform the manoeuvres, as well as quality-evidence of effectiveness (1).

ELTGOL technique *(L'Expiration Lente Totale Glotte Ouverte en décubitus Latéral)* is an airway clearance technique consisting in slow expiration with the glottis opened in a lateral posture. Its objective is to control expiratory flow and prevent airway closure, facilitating mucus clearance. Mucus removal from airways depend on 2 mechanisms: ciliary activity and expiratory airflow (28). ELTGOL is based in the two-phase gas-liquid flow model. According to this model, the shear force produced by airflow moving across mucus can outweigh the resistive forces present in the mucus layer and cause mucus removal (29). A peak expiratory rate of 30-60L/min is capable of breaking adhesive bonds between mucus layer and the airway epithelial surface (30). We place the patient in lateral decubitus position as airflow velocity is inversely proportional to airway diameter. In a lateral position we reduce total cross-sectional area of peripheral airways (29), increasing airway flow (31). By slowly exhaling through an open glottis while raising intraluminal pressure, airway patency is maintained (32) favouring mucus clearance from peripheral airway. ELTGOL technique has been demonstrate to be effective in increasing the sputum removal and reduce impact of cough (33). It is indicated for patients that have hypersecretive mucus production and willing to collaborate (34)

The elimination of secretions can also be aided by hypertonic saline solution, mannitol or bromhexine (35), which can enhance clearance by reducing mucus viscosity. Moreover, the use of mannitol improves symptoms' severity (36). Staying hydrated and using a nebulizer with a hypertonic saline solution can be helpful in all type-causes of bronchiectasis (37).

1.6.3. Bronchial Colonization and Infection

The aim is to identify as soon as possible the first *Pseudomonas aeruginosa* colonization in order to give adequate oral and inhaled antibiotic treatment. In chronic bronchial infections antibiotic treatment is based on the clinical presentation, microorganism isolated and the antibiogram results (1).

1.6.4. Exacerbations

Treatment of exacerbations is based in increasing secretions removal, treat infection associated and prevent from bronchospasm. Initially an empiric antibiotic will be provided. In the case a microorganism had been isolated before (due to past colonisations or bronchial infections), a specific antibiotic will be of choice (1). Duration must be at least 10 days and until there is no purulent sputum. In case of *Pseudomonas* infection treatment will be provided for 14 to 21 days (16).

TABLE 4: ANTIBIOTIC ROUTES OF ADMINISTRATION IN EXACERBATION (38).

Oral Antibiotic Therapy	Intravenous Antibiotic Therapy
• Mild exacerbations.	• Severe exacerbations. • Microorganisms resistant to oral antibiotics. • Patients with CF and *Pseudomonas* species not previously isolated. • No response to oral antibiotic therapy.

1.6.5. Bronchial inflammation

In addition to having an antimicrobial effect, macrolides have immunomodulatory benefits (39) and interfere in microorganism's biofilm formation (1). They are indicated in chronic bronchial infection by *Pseudomonas* and other microorganisms difficult to control with adequate treatment (1), as they have been seen to reduce number of exacerbations (40).

Inhaled corticosteroids (ICS) are not a routine treatment. They are used to reduce bronchial hyperactivity (41) and sputum volume (37). Recommendations for using ICS focus on bronchiectasis patients with underlying asthma or COPD (22).

1.6.6. Education and nutritional treatment

It is crucial to provide patients with advice on lifestyle decisions and how they can affect their condition (42) to minimize effect of modifiable factors.

Commonly, bronchiectasis patients present nutritional disorders and low index mass is a risk factor for mortality (24). Diet supplements have to be advisable in patients with BMI <20 kg/m2 or people losing weight rapidly (1). Although prevalence of smokers among bronchiectasis patients is low, tobacco consists an another independent risk factor for mortality and cessation has to be a must advice between them (43). In restricted fluids situations we must provide high-energy, polymeric enteral diets. In the same way, if there is a high metabolic stress situation (albumin <3g/dL) protein supplements have to be prescribed (1).

1.6.7. Surgery

Surgery is reserved in localized bronchiectasis difficult to treat when causes that can cause re-apparition have been excluded. Another indication may be palliative purposes (1).

1.7. PROGNOSIS AND FOLLOW-UP

1.7.1. Prognosis

Bronchiectasis course is progressive without treatment and irreversible. Prognosis is mostly influenced by the underlying cause, the degree of tissue damage and the consequences over the respiratory function (1,33). *Pseudomonas* has been considered a critical and adverse agent for prognosis of bronchiectasis and its management (44).

Mortality in Spanish bronchiectasis patients is mostly related to respiratory diseases (42.9%), followed by neoplasia (9.1%) and cardiovascular disease (9.1%) respectively (45). In both men and women, mortality rates were reported to be more than twice higher than in the general population in a cohort study based in UK population (3). However, life expectancy can be similar to general population if a proper treatment and management is established (23).

Most frequent complications related to bronchiectasis include haemoptysis, respiratory failure (46), malnutrition and osteoporosis (47). Furthermore, patients present increased risk of cardiovascular events such as stroke and coronary heart disease (48).

1.7.2. Follow-up

In order to slow progression and improve survival it is important to provide adequate treatment, implant preventive measures and check patients frequently to detect early complications or exacerbations (1). Protocol consists in a multi-disciplinary management aimed to assess the following parameters related to bronchiectasis progression (1):

1. **Aetiology:** it is crucial to perform check-ups to patients with a specific-treatment cause so as to determine whether if the cause is still present or if it has been adequate treated (1).

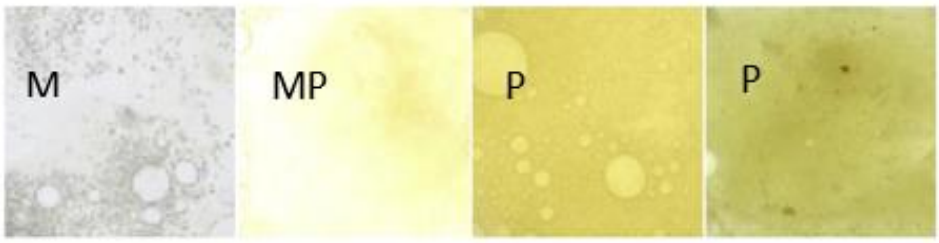

Image 5. *Table to assess the colour of sputum from least to most purulent.* M: mucous; MP: mucopurulent; P: purulent. (76)

2. **Clinical picture:** visits should be arranged every 1 to 6 months in order to assess severity stage of the disease, comorbidities and progression. Therefore, new symptoms and exacerbations have to be reported, as well as mucoid sputum colour and volume, to determine level of inflammation in the airways (1) *(Image 4).*
3. **Bronchial colonization-infection**: during an exacerbation, it is imperative to recollect a sputum sample for culture in order to determine pathogens related to patient's worsening and its sensibility to different antibiotics (1).
4. **Respiratory function**: it is recommended to undergo a spirometry at least once a year, depending on severity of the disease. FEV1 is the most important

predictor of mortality because of the relation between airflow limitation and to thickening of the bronchial wall. Arterial blood gases and exercise tests are also proposed once a year if necessary (1).

5. **Systemic inflammation**: to detect systemic inflammatory markers an annual blood test should be performed, including the following parameters (1): Haematocrit; Erythrocyte sedimentation rate; C-reactive protein, immunoglobulin.

   Nutritional parameters should also be assessed, and more specific tests depending on clinical suspicious (1)
6. **Structural damage:** it is recommended to perform a CT scan every 2 years and whenever chest x-ray suggest new lesions (49). Chest x-ray is indicated when a complication occurs (1).
7. **Nutrition:** Bronchiectasis is strongly related to malnutrition. Thus, it is important to asses nutritional status in these patients by assessing BMI (1).
8. **Quality of life** using validated questionnaires (1)
9. Determine **level of treatment compliance** and **rehabilitation performance.**

1.8. EXERCISE TRAINING IN BRONCHIECTASIS

Pulmonary function decline with age (50), mostly because of a loss of lung elastic recoil, greater chest wall compliance and less strength of respiratory muscles (57). In elderly, pulmonary arterial pressure tends to be higher due to pulmonary vessel stiffness and decreased left ventricle compliance (50). As consequence, older people present lower cardiac output during exercise (50). In addition, within years there is a grow of alveolar dead-space. Exercise produces an increased alveolar ventilation (V') causing pulmonary perfusion (V'/Q') mismatch which contribute to exercise-induced hypoxaemia in elderly subjects (10). These patients can show a decrease in capillary-arterial density, resulting in less pulmonary capacity for gas exchange (50). Pulmonary mechanics and respiratory muscle function are also impaired in old people. Elderly suffer from lung structural changes such as less bronchial diameter and distal duct ectasia (50). Diaphragm and intercostal muscles present higher stiffness with age due to calcification (50). All this factors contribute in decline vital capacity and relative limitation in tidal volume (50), causing airflow limitation during exercise.

Bronchiectasis affects mostly elderly population (3). Therefore, these patients will suffer consequences of exercise limitation because of age and the physiopathology of the disease itself. Although impaired function of lungs does not respond to exercise training, evidence suggests that continuing physical activity in old age is related to a better ability of exercising, since it improves central (cardiac output) and peripheral (muscle O2 extraction) function (50), ameliorating exercise capacity.

1.8.1. Physical Condition in Bronchiectasis

Many bronchiectasis patients have a largely inactive lifestyle and sedentary behaviour (defined a ≤1.5 METs) (17). A cross-sectional study considered 42% of these patients to be inactive and 29% low active by using a graduated step-based physical activity index (17). Only 11% of patients met the recommended physical activity guidelines (17). Independent factors related to reduced physical activity involve pulmonary function, dyspnoea and functional capacity (18). In bronchiectasis, sedentary behaviour alone consists in an independent predictor of hospitalization since low physical activity

contributes to an increased risk of hospitalization by 5.91 times in these patients (17). Low physical activity levels and increased sedentary behaviour have been related to a higher number of exacerbations over one year (51). Consequently, it negatively impacts on their quality of life and prognosis of the disease.

Few studies aimed to describe bronchiectasis patients towards physical activity and exercise capacity. Patients show low muscle strength, especially in lower limbs (*biceps bacchii* and *quadriceps femoris*) and reduce functional capacity compared with their healthy peers (52). They also present worse dyspnoea perceptions which was considered one of the main limiting factors for exercise tolerance (15). Muscle strength is also directly associated with exercise tolerance. However, there was no evidence of relation between exercise capacity and extension of bronchiectasis (14). Peripheral symptoms are more prevalent within severity of the disease (14). Quality of life is also impaired among these patients, mostly due to daily life activities limitation because of exercise intolerance (51).

1.8.2. Evidence of Exercise Training

Exercise training is a new key under development for bronchiectasis management. Studies that have examined effects of exercise in bronchiectasis patients have demonstrated short-term benefits such as improved capacity to undo physical activity, less dyspnoea and fatigue perception (67) (68) (69). These improvements were sustained in time, but different results were observed, ranging from 3 months (70) to 12 months (71). Also, physical activity has been related to delaying lung function deterioration within years (53).

Results regarding Quality of life are also favourable (72). Moreover, a long-term follow-up study reported lower incidence of exacerbations in participants included in full pulmonary rehabilitation programs (68).

Although the known multiple benefits of physical activity in health status, reviews demonstrate low evidence of improvements of exercise training in stable bronchiectasis patients (54). Long-term benefits are lack-evidenced, as well as effects on cough-related quality of life, psychological symptoms and muscle strength (54). Impact of exercise

training in acute exacerbations was proved to be low (54). The main reason of disfavourable results is the absence of large studies with greater number of participants. Accordingly, authors suggest that additional randomized controlled trials are required to reduce imprecision of effects observed in exercise training use (54).

1.8.3. Guidelines

All guidelines recommend participating in rehabilitation programmes and taking regular exercise to those patients with impaired exercise capacity (22) despite of low evidence its benefits.

European Respiratory Society (ERS) (22) recommend that adult patients with exercise intolerance should take part in rehabilitation programmes tailored to patient's symptoms, physical capacity and disease characteristics as a strong recommendation and high quality evidence (22). They consider rehabilitation as a comprehensive intervention based on different therapies such as exercise training, education and behaviour change (55).

On the other hand, the *Spanish Society of Pulmonology and Thoracic Surgery* (SEPAR) recommend undergoing rehabilitation programmes to stable patients diagnosed with bronchiectasis and mMRC>1 as a high recommendation with moderate-quality evidence (56). Considerations of SEPAR are as follows (56):

- Three supervised rehabilitation sessions per week for at least 8 weeks have demonstrated effectiveness.
- Aerobic exercise consists in moderate-high intensity work (walking, running, cycling or swimming). It can include muscle strength potentiation of lower and upper limb with progressive load. These interventions have been proved to enhance exercise tolerance and quality of life.
- Effects sustained in time for a period of 12 months' post-exercise.
- Respiratory rehabilitation decreases number of exacerbations significantly, although duration of antibiotic therapy is the same.

The *British Thoracic Society* (BTS) guidelines for management of bronchiectasis include pulmonary rehabilitation as a high recommended practice to individuals who are

functionally limited by shortness of breath (mMRC score≥1) (57). They suggest consideration of both inspiratory muscle training together with pulmonary rehabilitation to enhance the maintenance of training effects (57).

1.8.4. Exercise Training in other Respiratory Diseases

Chronic Obstructive Pulmonary Disease (COPD)

1/3 of COPD patients present muscle weakness and respiratory muscle dysfunction (14). It has been distinctly demonstrated that pulmonary rehabilitation lowers dyspnoea, boosts exercise tolerance, and enhances quality of life in these patients (58). Reviews also support evidence of exercise training benefits in COPD patients (59). Recommendations of Respiratory Societies are addressed to all COPD symptomatic stages and include strength training, endurance training and aerobic exercise(60).

Cystic Fibrosis (CF)

Cystic Fibrosis patients with higher levels of physical fitness present better survival rates (58). A Cochrane review demonstrates gains in exercise capacity, strength, and quality of life, with some indication of a slower deterioration in lung function (61). An overview of five systematic reviews suggests patients should take moderate to intense exercise for 30 minutes 3 to 4 days per week with strong recommendation but moderate quality evidence (62). Currently, recommendations approach to increase or maintain aerobic and strength activity as part of basis in management of cystic fibrosis (63).

1.8.5. Training Modalities in Pulmonary Rehabilitation

Training modalities that have been proved to improve exercise capacity in obstructive lung disease are:

Endurance training

Endurance training is used to improve aerobic capacity. Higher intensity of the test is associated with major physiological benefits (64), although some patients are not able to perform it due to severe symptoms related to the disease.

Continuous training and Interval training

Continuous and interval training have been demonstrated to improve significantly exercise capacity and health-related quality of life. They also contribute to increase capillary-to-fibre ratio and cause a change in fibre-type distribution, increasing aerobic slow-twitch muscle fibres (type I) and decreasing anaerobic fast-twitch muscle fibres (type IIb) (65). Interval training is a modification of endurance training in which high-intensity exercise is regularly interspersed with periods of rest or lower intensity exercise (58). Interval training is evidenced to be associated with fewer symptoms during exercise, as it supposes lower metabolic and ventilation stress and lower rates of dynamic hyperinflation compared to continuous training (66). As consequence, it has been seen to present better tolerability rates when talking about perceived respiratory and peripheral muscle discomfort (67).

To sum up, interval training may be feasible to perform by patients with severe airflow obstruction. Moreover, it can help to avoid frustration during exercise training and improve patients' motivation and adherence to the programme.

Cycling and walking tests

Cycle training needs less equipment, space and costs. They minimize dyspnoea sensation and the potential of oxygen desaturation (68). These are the main reasons why cycle endurance training is mostly used in training programmes testing patients with obstructive disease of the airway. However, walking is the most important daily activity of these patients. Hence, patients' walking skills should be exercised too as they will be more useful in everyday life of the patient. In addition, it has been found that walking-based endurance is very effective in improving exercise capacity and quality of life in these patients (69).

Resistance and strength training

Resistance training is capable of reducing peripheral muscle dysfunction. On the other hand, strength can lead to gain muscle mass and strength (70). Furthermore, it is more tolerable as it causes fewer dyspnoea (71). A combination of these two techniques is highly recommended in those patients with limited ability to perform resistance tests due to marked ventilator restriction (60). A systematic review found out that benefits of

strength training do not depend on the mechanism or method itself. Therefore, the ideal strength programme is still unknown (72).

Inspiratory muscle training

Inspiratory muscle training can enhance inspiratory muscle strength and endurance, and contributes in reducing dyspnoea. In consequence, there is an improvement in hypercapnia and walking capacity. Even though there is no evidence that it has effects on quality of life or functional exercise capacity, in patients with inspiratory muscle weakness (defined as max inspiratory pressure <60cmH20) it increases max inspiratory pressure and improves exercise performance (73).

2. JUSTIFICATION

Bronchiectasis is a common chronic bronchial inflammatory disorder. In the last decades, an increasing number of cases have been seen, particularly in people older than 60 and supposes high health costs since its course is progressive, especially in more severe stages. However, there is no standardized treatment licensed by regulatory authorities in Europe or USA, probably due to the difficulty in showing benefits because of high heterogeneity of the disease. Therefore, cost-effectiveness studies of treatments for bronchiectasis are needed.

Bronchiectasis patients present decreased muscle strength, reduced endurance, fatigue and dyspnoea that cause several limitations in their daily life. Most of them avoid performing physical activity because of exercise intolerance, which in second term, causes deconditioning and an impaired quality of life. Moreover, patients with more sedentary behaviour have an increased risk to be hospitalized due to an exacerbation.

Endurance and strength training have been reported to improve peripheral muscle strength and aerobic capacity in COPD patients. Although similar effects are expected to occur in bronchiectasis patients, the evidence is low. Current guidelines recommend exercise training as part of its management in those patients with more exercise intolerance, although evidence provided is low-qualified. Some studies have shown that exercise training improves some clinical variables in bronchiectasis patients such as number of exacerbations, exercise capacity, dyspnoea perception, quality of life and respiratory symptoms. Therefore, training programmes could become an essential tool in management of bronchiectasis and be implemented as part of its treatment in near future.

However, we just have few literature assessing training in bronchiectasis and these studies are way far for homogeneous in design, population, type of exercise, duration, intensity and frequency. Furthermore, only one study assesses effects of exercise training by measuring oxygen uptake (V'O2), which consists in the most objective parameter to determine exercise tolerance. Nevertheless, in the mentioned study, intervention was a home-based programme.

Given the present clinical situation of bronchiectasis, new studies are desirable to investigate effects of exercise training in bronchiectasis with high-quality evidence support, in order to guide a specific approach in clinical practice.

This study will provide quality information about effects and benefits of exercise training in patients with bronchiectasis. We will use a complete standardised protocol of exercise training in terms of type of exercise, quantity and intensity of effort performed, and we will measure maximal oxygen consumption (max V'O2) as the main variable to determine exercise tolerance.

To our knowledge, this research will be the first study to report high quality data of exercise training effects in bronchiectasis, as well as a clear and standardized guidance on the crucial elements and best practices for carrying out particular training programs for these patients in clinical practice. If our hypothesis is confirmed, patients will be able to benefit from exercise effects on symptoms, progression and quality of life.

3. HYPOTHESIS

3.1. Primary hypothesis

Exercise training improves exercise capacity in patients with bronchiectasis in a stable state and exercise intolerance.

3.2. Secondary hypothesis

In patients with bronchiectasis in a stable state and exercise intolerance, **exercise training:**

- Improves **respiratory muscle strength.**
- Improves **quality of life**.
- Reduces the number of **exacerbations per year**.
- Improves **dyspnoea perception.**
- **I**mproves **pulmonary capacity**.

4. OBJECTIVES

4.1. Primary objective

To assess the **effectiveness of exercise training in improving exercise capacity** in patients with bronchiectasis in a stable state and exercise intolerance compared to usual care (ELTGOL technique)

4.2. Secondary objectives

To determine in patients with bronchiectasis in a stable state and exercise intolerance compared to usual care (ELTGOL technique) the **effectiveness of exercise training in**:

- Improving **Respiratory muscle strength**, measured by Maximal Inspiratory and Expiratory pressure.
- Improving **quality of life**, measured by *The Quality of Life-Bronchiectasis* questionnaire (QoL-B).
- Reducing **frequency of exacerbations** per year.
- Improving **dyspnoea perception,** measured by *mMRC score* questionnaire.
- Improving **pulmonary capacity**, assessed by FEV1 and FVC .

5. METODHOLOGY

5.1. Study design

This is a **parallel randomised group**, **single institution**, **prospective**, **controlled** clinical trial.

All patients who meet the inclusion criteria will be allocated randomly 1:1 in one of the two groups:

1. **Control group** will receive standard management (ELTGOL technique).
2. **Intervention group** will receive standard management (ELTGOL technique) and exercise training, which includes interval endurance training, strength muscle training and respiratory muscles training.

The effects of exercise training on the described variables will be assessed and compared between the two groups after 8 weeks of intervention. All participants will then be prospectively followed for a year to assess changes in the frequency of exacerbations.

The current study will be submitted to the Doctor Josep Trueta Hospital's Medication Research Ethics Committee (CEIm), and it will not be carried out until it receives its approval. Additionally, it will be submitted to the Clinical Trial Registry (clinicaltrials.gov) for publication of the results and subsequent disclosure authorization.

5.2. Study Population

Adult patients (≥18 years of age) with clinically significant bronchiectasis (12) confirmed by chest CT in stable state (no exacerbations in the previous month), controlled in the Hospital Universitari Josep Trueta's specialized bronchiectasis unit will be enrolled.
The Hospital Universitari Josep Trueta (HUJT) outpatient clinic registry will serve as our sample frame, from where participants will be chosen. Individuals who match the population characteristics will be invited to participate in the research.

5.2.1. Inclusion Criteria

Inclusion criteria will be as follows:

1) Exercise capacity reduce to disease (mMRC ≥2)

2) An impaired lung capacity (FEV1 <50%).
3) At least 1 exacerbation in the previous year (57).
4) No changes medication in the last 4 weeks.
5) Sedentary behaviour (sitting down ≥540minutes/weekday by IPAQ-SF)
6) Individuals who commit attend all of the measurement appointments and at least 80% of the intervention sessions.
7) Willing to give informed consent.

5.2.2. Exclusion Criteria

If any individual accomplish the following exclusion criteria will be automatically rejected from participating:

1) Any physical or cognitive disorder that might interfere with protocol performance.
2) Significant comorbidity that would limit the ability to undertake exercise training (cardiovascular, cerebrovascular or musculoskeletal disorder).
3) Diagnosis of Cystic Fibrosis.
4) A primary diagnosis of COPD.
5) Diagnosis of active tuberculosis (TB), non-TB mycobacterial (specially *Mycobacterium abscessus*) or any other pulmonary multi-resistance infection.
6) Participation in pulmonary rehabilitation programme in the last year.
7) Active smoker.
8) Pregnant women.
9) Haemoptysis as a current symptom.

5.2.3. Withdrawal Criteria

All patients selected and who agree to participate in the study must follow all the instructions given and accomplish the follow-up appointments. Just the reasons below exempt them from continuing with the protocol:

1. Patients who do not perform the 80% of the study programme.
2. Exacerbations and/ or hospitalizations during the study programme for any reason.

3. Patients lost to follow-up: when patient does not attend scheduled visits and/or training sessions. In that case the investigator will call the patient. After 2 no-responded calls, patient will be considered lost to follow up.
4. Revocation of informed consent requested by patient or voluntary decision to leave.

It is crucial to thoroughly explain the entire process, any side effects, and the anticipated outcomes for them to minimize possibilities for a patient to abandon. Any participant loss will be declared and recorded, together with the data and the reason for withdrawal from the study.

5.3. Study setting

Population will proceed from the specialized- bronchiectasis unit of Hospital Josep Trueta which is in charge of doing the follow up and management of patients with bronchiectasis that come from the health region of Girona.

The study will be regarded as a single institution. Nonetheless, the cooperation of two facilities is required: Hospital Santa Caterina in Salt and Hospital Josep Trueta in Girona.Hospital Josep Trueta will be the coordinator centre and will provide the sample frame. The initial visit, the gathering of sociodemographic data, the completion of questionnaires, and the administration of functional tests (spirometry, MIP and MEP determination) will also take place there.Exercise training sessions and oxygen uptake measurements will be executed in the rehabilitation gymnasium of Santa Caterina Hospital.

5.4. Sample

5.4.1. Sample Size

In a two-sided test, assuming a risk of an α-error of 0.05 and a β-error of 0.20, i.e., statistical power equal to 80%, and a drop-out rate of 15%, we will need **114 subjects** to detect a minimal difference of 40%.

Minimum variations in V'O2max that we want to detect will be assumed from results observed in other studies assessing exercise training effects in COPD patients, that reported V'O2max values improve from 10% to 40% (74) (75). Moreover, the only study published assessing V'O2max in bronchiectasis patients undergoing exercise training reported a mean difference of 1.96 +/- 5.2561 ml/ min/kg in V'O2max values, which is equivalent to 37% (54).

This minimal difference value and its standard derivation associated will allow for the identification of a large impact size that is equal to or more than 1. Computations were carried out with the Prof. Dr. Marc Saez' software based on 'pwr' package of the free statistical environment R (version 4.3.1).

5.4.2. Sample selection and Enrolment

A probabilistic random sampling method will be used to select participants for the study. All individuals from the sample frame who fit the population characteristics will be issued a number. We will obtain 114 random numbers by utilizing **a random number generator tool**. Patients assigned with the numbers generated will be asked to participate in the clinical trial.

Eligible patients will be invited to take part of the research throughout a phone call. If they have a scheduled routine visit with the pulmonologist in the coming days, they will extend an invitation in person. Following a clear explanation of the study to the patients, those who will be interested in taking part will be arranged for a first visit to verify they meet all inclusion and none of exclusion criteria, and give informed consent.

When the complete number of patients needed to create the sample group will be reached, the procedure will come to a conclusion.

5.4.3. Time of Recruitment

Since only 32 patients can participate in the exercise program at once (we need 32 more for the control group), we anticipate a recruiting time of 6 months in order to acquire a minimum of 64 initial patients.

This takes into consideration all unforeseeable circumstances that may happen. Prior to their acceptance of participating, we must first get in touch with these patients, either over the phone or on the day of the consultation, and make sure they meet all inclusion criteria and none of the exclusion ones. They will receive a thorough explanation of the intervention and be given time to consider their options and clear up any questions before providing informed consent.

5.5. Study Variables and Measuring Instruments

5.5.1. Independent variables

The independent variable for this study will be the **type of rehabilitation performed**: exercise training (consisting in interval endurance training, peripheral muscle strength training and respiratory muscle training) or ELTGOL airway clearance technique.

They will be assessed as a **nominal dichotomous qualitative variable** and will be expressed by the type of intervention undergone (*Exercise training* / *ELTGOL technique*).

5.5.2. Dependent variables

Primary dependent variable: **Maximum Oxygen Uptake** *(V'O2max)*

It is defined as the maximum rate at which oxygen can be consumed. Hence, it is obtained during maximum exercise effort. V'O2max is commonly used to assess aerobic capacity and function of the systems involved (respiratory, cardiovascular and musculoskeletal system) (76).

V'O2max will be interpreted in millilitres of O2 uptake per minute and kg of weight. Therefore, we will evaluate it as a **continuous quantitative variable**.

To determine V'O2max values an ergometry will be conducted, which is an effort exercise test (cycling), and the non-invasive analysis of gas exchange during breathing. V'O2max values will be obtained by calculating the amount of oxygen exhaled compared to oxygen from environment. Ergometry mask is placed tightly covering the mouth and the nose to properly control concentration of gas inhaled and exhaled.

Oxygen uptake (V'O2) increases with increased effort (approximately 10 mL/min/watt)(77), until it reaches a plateau, this will be indicative for V'O2 max to be reached. Reference values on health individuals will be taken from ERS Statement on cardiorespiratory testing (78).

Secondary dependent variables

- **Inspiratory and expiratory muscle strength**: maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are described as the preferable parameters to evaluate respiratory muscle strength since both MIP and MEP reflex the synergistic action of inspiratory and expiratory muscles (79).
  To estimate MIP and MEP values we will determine the maximum pressure that a subject can generate at the mouth by using a digital manometer connected to a flanged mouthpiece.
  Results will be presented in H20 cm, and analysed as a **quantitative continuous variable**.

- **Quality of life**: *The Quality of Life –Bronchiectasis* (QoL-B) questionnaire will be used to evaluate quality of life, which consist in a self-administrated patient-reported outcome bronchiectasis-specific test based in 37 items distributed in 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden) (80). It collects symptoms and health-related quality of life information.
  Quality of Life, a score, will be measured as a **discrete quantitative variable.**

- **Number of exacerbations**: exacerbation will be considered as "*A deterioration in three or more of the following key symptoms for at least 48 h*: *cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis and a clinician determines that a change in bronchiectasis treatment is required"* (13).
  Whenever this clinical situation will occur, the patient will stop undergoing intervention. We will report exacerbation incidence in the participants who will

be able to finish the intervention from the study onset to 1 year after the study end.

Exacerbation incidence will be described as the number of exacerbation per patient over 1 year, a **discrete quantitative variable.**

- **Dyspnoea**: in order to assess the degree of baseline functional disability due to dyspnoea we will use the modified Medical Research Council (mMRC) scale, a questionnaire based in 4 clinical options depending on the patients' degree of dyspnoea perceived during daily life activities (*Annex 3).* Scale results range from 0 to 4, being 0 physiological breathlessness and 4 dyspnoea as a limiting factor for basic activities.

  This variable will be categorized in a dichotomous qualitative variable (No Severe: 0,1,2 and Severe: 3,4).

- **Pulmonary capacity**: the following parameters will be obtained under spirometry performance.
  - **Forced Vital Capacity** (FVC): represents the lung size in litters and is obtained by measuring the total volume of the air that can be exhaled after a deep inhalation. FVC outcomes will be measured in litters (L) and in proportion (%) of FVC results compared to reference values. Therefore, it will be evaluated as a **continuous quantitative variable** (L and %).
  - **Forced Expiratory Volume in 1 second** (FEV1): measures the amount of air that a person can move out of the lungs in the first second of a forced exhalation. It gives information about airflow limitation. FEV1 outcomes will be measured in litters per second (L/s) and in proportion (%) of FEV1 outcomes compared to reference values. It will be evaluated as a **continuous quantitative variable** (L/s and %).

TABLE 5: STUDY DEPENDENT VARIABLES

VARIABLE	DESCRIPTION	MEASUREMENT	WHAT IS ASSESSED	UNITS
Maximum Oxygen Uptake (V'O2max)	Continuous quantitative	Ergometry	Cardiorespiratory capacity	Ml/min/kg
Maximal inspiratory and expiratory pressure	Continuous quantitative	Pressure in the mouth calculated by a manometer	Respiratory muscle strength	H2O cm
Dyspnoea Perception	Ordinal qualitative	mMRC questionnaire	Degree of functional disability due to dyspnoea	Score points
Quality of Life	Ordinal qualitative	Quality of Life-Bronchiectasis Questionnaire	Health-related quality of life in bronchiectasis patients	Score points
Exacerbations	Discrete quantitative	Incidence of exacerbations during 1 year follow-up		Nº
FVC	Continuous quantitative	Spirometry	Lung capacity	Litters and %
FEV1	Continuous quantitative	Spirometry	Airflow state	Litters per second and %

5.5.3. Co-variables

Co-variables will be determined in order to describe characteristics of both groups and analyse possible confusion / interaction factors.

- **Sex**: it will be described as a dichotomous nominal qualitative variable and will include the categories: men/women. Results will be expressed by proportion (%) of men and women for each group. It will be obtained from the patient's ID card or any other official document and registered in the data collection document.

- **Age**: it will be described as a continuous quantitative variable. Results will be expressed in years. It will be obtained from the patient's ID card or any other official document and registered in the data collection document.
  Birth day will also be recorded.

- **Bronchiectasis aetiology**: it will be analysed as a categorical nominal qualitative variable. It will be obtained from the patients' clinic history.

- **Severity of the disease:** it will be described as an ordinal qualitative variable. Results will be obtained using BSI score (*Annex 2*).

- **Body Index Mass (BMI):** it will be described as a continuous quantitative variable in kg/m^2. Results will be obtained using the equation: weight in kilograms divided by height in meters squared.

- ***Pseudomonas chronic infection*:** It will be analysed as a non-dichotomous qualitative variable, including the categories: Yes / No. Data will be obtained through microbiological cultures of sputum samples**.**

- **Peripheral oxygen saturation**: it will be analysed as a continuous quantitative variable. Results will be determined by pulsed or transcutaneous oximetry and expressed in %.

- **Sedentary Behaviour**: it will be assessed by the International Physical Activity Questionnaire –Short form (IPAQ-SF) which consists in 7 questions assessing physical activity in daily life during the last 7 days. Patients have to indicate time of physical activity undertaken in different domestic situations (*Annex 5*) (81). Results are expressed in MET-minute/week. Each type of physical activity has a MET value associated (82):
  - Walking MET= 3.3
  - Moderate MET = 4.0

- Vigorous MET = 8.0

Walking + Moderate + Vigorous MET-min/week scores add up to a combined total physical activity MET-min/week.

Because of its non-normal distribution, results are presented as the median MET-minutes of physical activity in the last week. In this case, physical activity is analysed as a **discrete quantitative variable**.

- **Comorbidities**: it will be analysed as a categorical nominal qualitative variable. Information will be obtained from the patients' clinic history.

- **Current medication**: it will be analysed as a categorical nominal qualitative variable. It will be obtained from the patients' clinic history.

TABLE 6: STUDY CO-VARIABLES

VARIABLE	DESCRIPTION	MEASUREMENT	UNITS/CATEGORY
Sex	Dichotomous nominal qualitative	Patient's clinical history and/or anamnesis	Male / Female
Age	Continuous quantitative	Patient's clinical Histoy and/or anamnesis	Years
Bronchiectasis Aetiology	Categorical nominal qualitative	Patient's clinical history	See *Aetiology (section 1.3)*
Severity of Bronchiectasis	Ordinal qualitative	BSI score	Score points
Body Index Mass	Continuous quantitative	Height and weigh determination	Kg/ m2
***Pseudomona* colonization**	Dichotomous qualitative	Microbiological sputum culture	Yes / No

Peripheral Oxygen saturation	Continuous quantitative	Pulsioxymeter device	%
Sedentary Behaviour	Discrete quantitative	IPAQ-SF	MET-minute / week
Comorbidities	Categorical nominal qualitative	Patient's clinical history	
Current Medication	Categorical nominal qualitative	Patient's clinical history	

Other information that will be reported during the whole study programme will be:

- Number of deaths and cause.
- Number of withdraw patients, cause and time of abandoning.
- Side effects experienced because of intervention.

5.5.4. Measurements

All performances will be supervised by a pulmonologist and a physiotherapist. They will give an explanation of how to perform test correctly and main objectives to achieve. Contraindications for every test will be checked before every measurement.

V'O2max and Ergospirometry

Maximum oxygen uptake will be determined while performing an ergometry in a *ergoline 100* bicycle. The cycle-ergometer will be calibrated once a day.

Test will be performed following a stepped incremental protocol: the initial resistance will be 0 watts (w) and it will increase progressively at a rate of 10-15w/min (depending on the patient mMRC score). The speed will be constant at 60 r.p.m. The test will be considered finished when the patient experiences volitional fatigue. Patient will be asked not to talk and communicate with hand signals. 4 signals will be taught before starting:

- OK signal (everything is okay; patient can continue doing the test)
- So-so signal (patient is starting to feel limitation symptoms and/or fatigue)
- 1-minute signal (patient feels that in less than a minute he/she will have to stop)
- Stop signal (patient cannot continue performing the test)

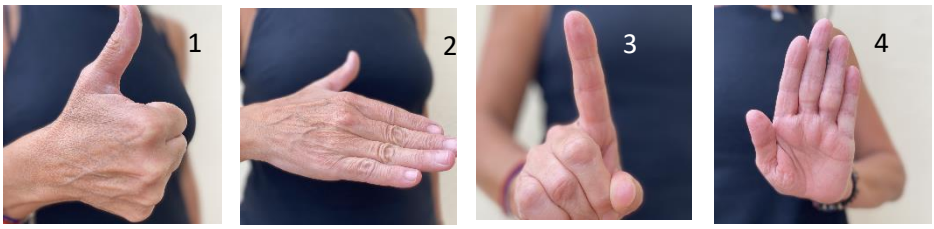

Image 6: *Signals to communicate during ergometry. In order: 1 OK signal; 2 so-so signal; 3 one-minute signal; 4 stop signal*

The ergometry incorporates a mask with CO2 and O2 analyser called *pneumotogrph* which will be calibrated before every attempt. V'O2max will be determined as the highest value over 30s during the test (when the plateau will be achieved). VO'2 values and duration time will be recorded automatically by the ergometer sensor. Next, it will be stored in a database for further analysis and interpretation of differences.

In every attempt, we will monitor blood pressure (BP), heart rate (HR), cardiac function (ECG) and oxygen saturation monitoring (Sat O2).

Image 7: *Pneumotograph*

Image 8: *Gas analyser mask*

Results will not be valid if the patient has to stop the test for a non-pulmonary reason (e.g., chest pain, muscle pain). Therefore, we will determinate the cause of exercise limitation and exclude all test results that do not end because of respiratory dysfunction.

TABLE 7: CAUSE OF EXERCISE LIMITATION

	RESPIRATORY LIMITATION	**CARDIOVASCULAR LIMITATION**	**PERIPHERAL MUSCLE LIMITATION**	**PERIPHERAL DECONDITIONING**
V'O2 peak	↓	↓	↓	↓
V'O2 at anaerobic thereshold	NORMAL	NORMAL o ↓	LIKELY ↓	↓
Peak HR	↓	LIKELY NORMAL	↓	NORMAL
Sat 02	NORMAL o ↓	NORMAL	NORMAL	NORMAL

TABLE 8: ERGOMETRY CONTRA-INDICATIONS (83)

Acute or severe chronic cardiorespiratory disease causing functional impairment:

- Severe congestive heart failure
- High-grade congenital heart defects
- Cardiomyopathy
- Severe arrhythmias
- Thromboses
- Malignant hypertension or pulmonary hypertension

Acute or severe disease of other organ systems:

- Nephritis
- Poorly controlled diabetes mellitus
- Electrolyte disturbances

***Image 9**: Ergometry used to determine V'O2 in Santa Caterina Hospital*

Maximal inspiratory and expiratory pressure (MIP and MEP)

MIP and MEP determinations will be obtained by following the ATS statement on Respiratory Muscle Testing (58). The digital manometer will be calibrated before every measurement.

Patients will be carefully informed about the procedure. They will be seated and ordered to breath normally for 1 minute. The flanged mouthpiece will be placed between upper and lower teeth and held firmly in order to avoid air leakage. Nose will be closed using a nose clip. A valve system allows to breath normally until the manoeuvre will be performed.

1. MIP: After 3 cycles of normal breathing we will instruct the patient to expire to residual volume and hold breath for 3 seconds (*Mueller Maneuver*). We will ask the patient to rise his/her hand to indicate when all air has been expired.

2. MEP: after 3 cycles of normal breathing we will instruct the patient to inspire the total lung capacity and hold breath for 3 seconds *(Valsalva Maneuver).*

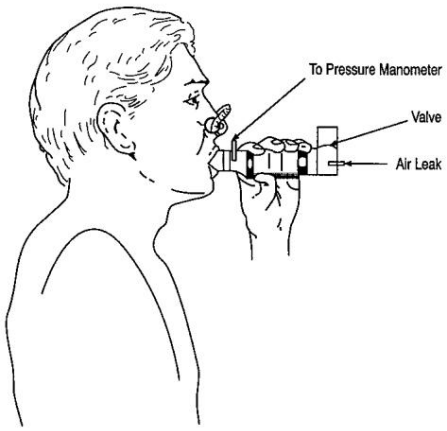

Image 10: Measurements of maximal respiratory pressures (59)

We will repeat this performance until 3 acceptable tests will be achieved (no air leakage, holding breath for 3 seconds) and 2 of them will be repeatable (maximum difference between attempts <20% the mean value). The selected value will be the highest one among the 3 accepted. Measurements will be performed a maximum of 8 times. Reference values in healthy people are (84): Females MIP (63.1 ± 20cm H20) and MEP (78 ± 24 cmH20): males MIP (86.8 ± 28 cmH20) and MEP (115 ± 37 cmH20).

Basal dyspnoea perception

Patients will be asked to self-respond the *mMRC scale* questionnaire *(Annex 4).*

Physical Activity Condition

Patients will be asked to self-respond the *IPAQ- SF* questionnaire *(Annex 5).*

Quality of Life

Patients will be asked to self-respond *The Quality of Life-Bronchiectasis* questionnaire *(Annex 6).*

Number of exacerbations

Exacerbations will be considered as described in *variables (see 5.5.2)*. We will train patients to identify whenever an exacerbation will occur and ask them to attend the clinic for further examination. If an exacerbation occurs during the intervention programme period, the participant will be excluded from the study, as we assume he or she will not be able to attend 80% of the sessions.

During the follow-up period, exacerbations for every patient will be recorded specifying the following information: duration of exacerbation, treatment undertaken, severity of symptoms and need of hospitalization. In the case a patient is hospitalized due to an exacerbation, we will determine if the reasons for hospital admission match our definition of an exacerbation by asking to the emergency doctor or checking clinical history of the patient. Otherwise it will not be taken into account as an exacerbation. Data collection period will be 12 months since the end of the intervention programme.

Pulmonary Capacity

Spirometry will be performed using the ATS *(American Thoracic Society)* Standardization of Spirometry (85).

Regarding test setting, all spirometry attempts will be performed in same ambient temperature, barometric pressure and time of the day. This information will be recorded.

A spirometer will be used. All equipment will be calibrated every day with 3 different fluxes, and technicians will confirm spirometers meet the standards. Patients will be carefully informed about the procedure and able to ask. Technicians will give them instructions and encouragement throughout the performance. Patients will be required not to take bronchodilators 6-24h before the test. They will be seated in a correct posture (shoulders a little back and chin a slightly elevated). For the different manoeuvres determination, a mouth piece and nose-clip will be used.

For FEV1 and FVC determination patients will be asked to perform a maximal inspiration followed by a maximal expiration without hesitating. We will encourage to keep until a plateau will be reached or the forced expiratory time hits fifteen seconds.

Results will be accepted if they meet the following criteria (based on adults population) (68):

- A good start of exhalation with extrapolated volume <5% of FVC or 0.150 L, whichever is greater
- Free from artifacts
- No cough during first second of exhalation (for FEV1)
- No glottis closure or abrupt termination (for FVC)
- No early termination or cutoff (for FVC). Timed expiratory volumes can be reported in maneuvers with early termination, but FVC should be reported only with qualification.
- Maximal effort provided throughout the maneuver
- No obstructed mouthpiece

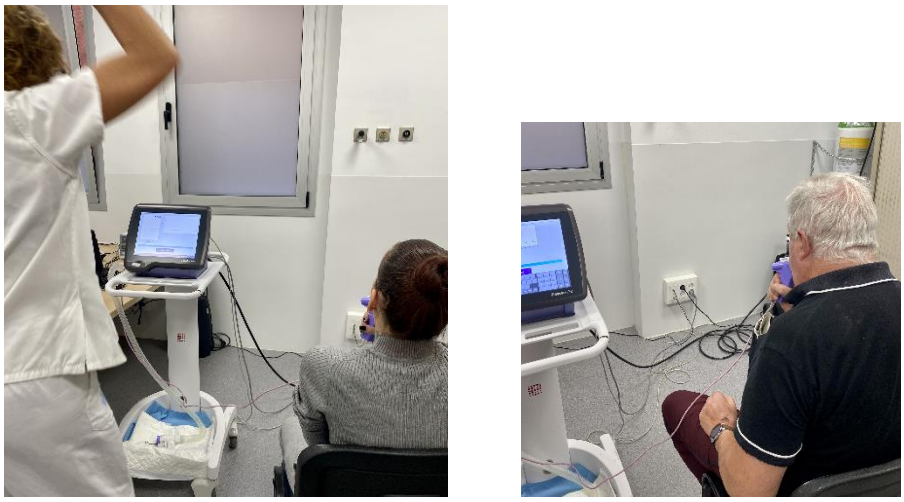

Image 11: Spirometry performance in the Josep Trueta Hospital.

We will report results if there will be minimum 3 acceptable manoeuvres with a maximum of 8 attempts. The differences between the 2 best manoeuvres must be <5% or 150mL. We will take the best result.

Reference values are based on the Global Lung Function Initiative (GLI) equations, which considers different phenotypes depending on the ethnical origin applicable across all ages (from 3 to 95 years old), as well as biological sex, height and weight.

TABLE 9: SPIROMETRY CONTRA-INDICATIONS (85)
Due to increases in myocardial demand or changes in blood pressure: acute myocardial infarction <1 week; systemic hypotension or severe hypertension; significant atrial/ventricular arrhythmia; non-compensated heart failure; uncontrolled pulmonary hypertension; acute *cor pulmonale*; clinically unstable pulmonary embolism; history of syncope related to forced expiration/cough
Due to increases in intracranial/intraocular pressure: cerebral aneurysm; brain surgery <4 weeks; recent concussion with continuing symptoms; eye surgery <1 week
Due to increases in sinus and middle ear pressures: sinus surgery or middle ear surgery or infection <1 week
Due to increases in intrathoracic and intraabdominal pressure: presence of pneumothorax; thoracic surgery <4 weeks; abdominal surgery <4 weeks: late-term pregnancy; infection control issues; active or suspected transmissible respiratory or systemic infection: physical conditions predisposing to transmission of infections

5.6. Study Intervention

5.6.1. Randomization

Subjects will be randomly placed in one of both groups at a rate of 1:1. In order to minimize bias, a simple computerized randomisation will be applied by using *SPSS software*

- Intervention Group: 57 patients will undertake the Exercise training, as well as receive usual care (ELTGOL technique).
- Control Group: 57 patients will be treated with usual care (ELTGOL technique).

After giving informed consent, patients' data will be stored in a database under a number of identification generated automatically by the software. This will ensure protection of participants' confidentiality.

5.6.2. Blinding

It is not possible to apply masking techniques since both interventions involve subjects' participation and they will be carried out in very different conditions. Consequently, the present study will be un-blinded as both participants and investigators will be aware of the intervention applied for every patient. This will be discussed as a limitation below.

However, statisticians responsible of analysing outcomes will be deprived of knowing further information, which will preserve them to commit subjective bias in the data study.

5.6.3. Intervention

Participants will be randomly placed in 2 homogeneous groups in terms of and baseline characteristics as well as age and sex.

After baseline measurements and before intervention will start, both groups will receive an hospital session in order to receive an educational workshop, explanation of different aspects of their condition, dietary recommendations and self-management of the disease. In addition, all participants will be encouraged to follow an active and healthy life style to ensure similarities in physical and nutritional condition. They will also be taught how to perform ELTGOL technique properly by professional physiotherapists and to identify exacerbation's symptoms. The intervention will be carried out as follows.

5.6.3.1. Control Group

Patients included in the Control Groups will be trained by the physiotherapist and required to perform the ELTGOL exercises at home twice-daily for 15 min if only one lung affected, and 30 min when both lungs are affected (15 min each side).

To ensure protocol compliance, patients will be responsible of reporting in a diary with the following information: time of the day when ELTGOL was performed, frequency and duration. If they are not able to perform ELTGOL, it will be imperative to report the reason and the day. They will also be asked to bring the diary at the end of the intervention. The diary's contents will be gathered and kept in a database.

5.6.3.2. Intervention Group

Patients of intervention group will conduct

- 3 exercise training sessions per week, which will consist in endurance training, strength training and inspiratory muscle training.
- Airway clearance technique ELTGOL (same protocol as control group)

Prior to starting the study, all patients will attend the rehabilitation gym to familiarize themselves with the equipment and minimize the effects of test habituation. All patients will be trained by a physiotherapist to perform intervention exercises property. All sessions will be supervised by one physiotherapist, and interventions will be embedded in a multidisciplinary approach, including medical supervision, nutritional and psychosocial management. Modifications will be done adapting every patient's ability.

Before starting:

- Recommendations: they should wear comfortable clothing and appropriate shoes to undergone exercise. Neither heavy meals nor vigorous exercise are recommended within 2h of starting the training. Alcohol, other drugs, and stimulants like coffee should not be consumed 2h prior to the intervention.
- Warm up: patients will be addressed to warm-up for 10 minutes in the ergocycle with no load resistance.

ENDURANCE TRAINING

Endurance training will be performed on an **ergometer static bicycle** *(Ergoline 100)* following an interval modality.

Intensity of exercise will be established for all patients at 80% of their maximal work rate, determined as the maximum work load achieved in the ergocycle exercise in the first session. Borg scale *(Annex 6)* will be used to detect perceived exertion (Annex 6). When Borg scale rated perceived dyspnoea as moderate during exercise, training work load will be increased progressively 5% to 10% of peak capacity. We will try to reach 150% of the baseline maximum work peak for each patient at the end of the intervention programme.

Image 12: *ergo cycle ergoline 100 from the Santa Caterina Hospital's rehabilitation gymnasium*

Image 13: *Rehabilitation gymnasium of Santa Caterina Hospital*

Interval protocols:

1. INTERVENTION: 30 seconds exercise at 80%-150% of maximum work load followed by 30 seconds of rest. Repeated cycles until session time is finished.
2. 2 minutes of active recovery at 20% of maximum work load.
3. 3 minutes of passive recovery seated on a chair

Total exercise time will be 15-20 minutes of ergometry per session (including rest periods). Progressively duration will increase to 45-60 minutes per session until the end of the study intervention.

RESISTANCE/ STRENGTH TRAINING

Resistance (or strength) will be trained by repetitive weights exercise of relatively heavy loads in local muscle groups. Sessions will be conducted 3 times per week:

- Upper limb muscles: *triceps brachialis, biceps brachialis, deltoids, latimissimus dorsi* and *pectoralis major.*
- Lower limb: *quadriceps femoris*.

Technique:

- Exercise 'hanger' (that exercise the *latissimus dorsi muscle*)
- Exercise "double bicep curl" (*bíceps brachii*)
- Exercise 'butterfly' (*pectoralis major muscle*)
- Exercise 'neck press' (*triceps brachii and deltoids*)
- Exercise 'leg extension' (*quadriceps femoris*)

Exercise will include primarily dynamic repetitions of both concentric (muscle shortening) and eccentric (muscle lengthening) muscle actions. Sequence will be the same for all participants during all sessions: *latimisimus dorsi > biceps brachialis > pectoralis major > triceps brachialis and deltoids > quadriceps femoris.*

Protocol (86):

1. 6-12 repetitions x 2-4 times at ranging intensities from 50% to 85% of the one repetition maximum (1RM) (the maximal load that can be moved only once over the full range of motion without compensatory movements (87))
2. Intensity will be increased progressively by 2% to 10% of 1RM if one to two repetitions over the desired number are possible on two consecutive training sessions.
3. Speed of exercise will be required to be moderate: 1-2 seconds concentric and 1-2 seconds eccentric

Image 14: *Hanger exercise*

Image 15: *Double Biceps Curl exercise*

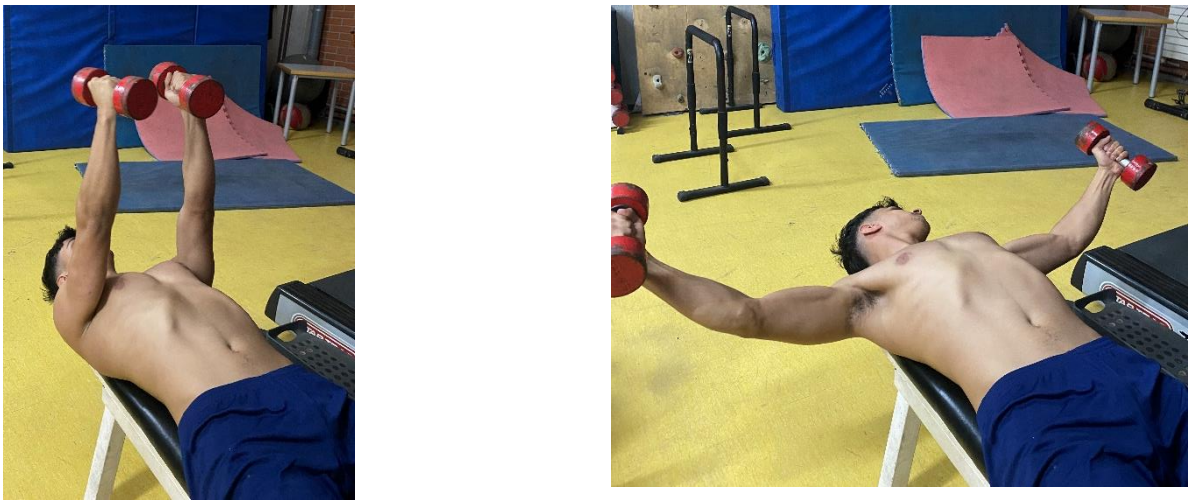

Image 16: *Butterfly exercise*

Image 17*: Neck press exercise*

Image 18: *Leg extension exercise*

INSPIRATORY MUSCLE TRAINING

To exercise inspiratory muscles a resistance device called "threshold loading" will be used. The patient will have to inhale strongly to open a spring-loaded valve against an individualized load (60). Inspiratory training will be performed 3 times per week.

Initially, intensity will be established to be >30% of maximal inspiratory pressure and it will be increased stepwise as tolerated (73). Protocol:

- 2 minutes of inspiratory muscle training.
- 1-minute resting.
- Repeat this cycle 7 times per session.

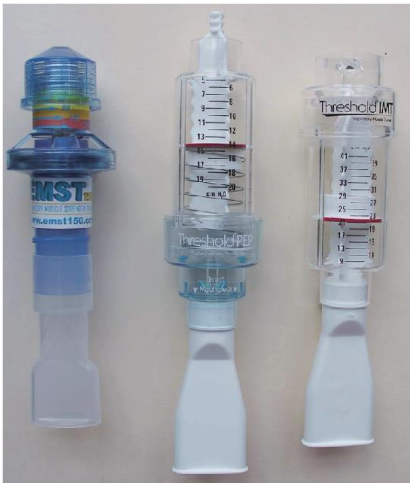

Image 19: *Threshold Device (88)*

TABLE 10: SUMMARY OF THE EXERCISE TRAINING

	INTERVAL TRAINING	STRENGTH TRAINING	INSPIRATORY MUSCLE TRAINING
FREQUENCY	3 days per week	3 days per week	5 days per week
MODE	30 s exercise – 30 s rest	2-4 sets of 6-12 repetitions	Threshold loading
INTENSITY	80-100% of Maximum Work rate the first 3-4 sessions, and increase by 5-10% until achieved 150%	Initially 50-85% of 1RM, and increased by 2-10% of 1RM if 1-2 are possible on two consecutive training sessions.	Initially >30% MIP and increasing as tolerated
DURATION	Initially 15-20 minutes / session, and increase until 45-60 minutes / session	1-2 seconds concentric and 1-2 seconds eccentric alternately	7 x 2 minutes of IMT and 1 minute of rest between each interval

5.7. Follow-up and Data Collection

A data manager will be designated as the person responsible of creating a computer-based database where all information collected will be stored.

After enrolment of participants, those who agreed to take part of the present study programme will be scheduled for a first visit in the external clinic with the main investigator. First visit will consist in:

- Confirm inclusion criteria and rule out exclusion criteria
- Explanation of the study: patients will receive oral and written (*Annex 6*) information about the study justification, main objectives and procedure of the intervention.
- Participants will give informed consent *(Annex 7).*
- Responsible physicians will collect socio-demographic and clinical data and other non-physical measures. Information will be obtained mainly from clinical history, questionnaires and/or anamnesis.

- Pulmonologists will fill the "case report form" (see *Annex 8*) to collect all data referent to co-variables assessed in the study.

Patients will then be required to come in for a follow-up appointment where baseline measurements will be taken. V'O2max measurement will take place in the Santa Caterina Hospital's rehabilitation gymnasium, while functional tests measuring MIP, MEP and lung capacity (FEV1, FVC, FEV1/FVC, VE, VT) will take place in the Josep Trueta Hospital. In the outpatient clinic, patients will also be required to complete questionnaires on their quality of life, level of physical activity, and perception of their basal dyspnoea. All information collected will be stored in a database for further analysis. All baseline measures and data collection will be preferable done less than a week before starting the training programme. Additionally, all participants will receive a common educational first session.

After, individuals will be randomized in 2 groups. From this start point intervention for both groups will begin and will last **8 weeks**. Information collected from both groups during this period of time will be the following:

- Exacerbations whenever occur.
- Hospitalizations due to any reason whenever occur.
- Drop-outs: reason of quitting and date.
- Side effects of intervention.
- Deaths, reason and time.

Within a week of the intervention's completion, post-intervention measures will be carried out in the hospital that has the appropriate equipment for determining each variable. Diary information about ELTGOL performance will also be collected from both groups.

Follow-up will continue for 1 year in order to report prospectively number of exacerbation of participants from both groups. Clinical coordinator will be the one in charge of the follow-up procedure. Each patient will be responsible of informing the clinical coordinator (by calling to a given phone number) whenever an exacerbation will occur. Clinical coordinator will confirm that exacerbations meet the consensus definition and will report information. Every two months, patients will receive a call from the

clinical coordinator to provide updates on their follow-up appointments. After 1-year period, the study follow-up will be concluded.

Figure 9: *Data collection process*

5.7.1. Patient Journey

	1-6 months pre-intervention	**<1 week pre-intervention**	**INTERVENTION PERIOD (8 weeks)**	**<1 week post-intervention**	**1-year Follow-up post-intervention**
STUDY INVITATION	X				
1st VISIT Informed consent and co-variables collection	X				
2nd VISIT Pre-intervention dependent variables collection		X			
EDUCATION SESSION		X			
Collection of ELTGOL information in the diary			X		
TRAINING SESSIONS (Intervention Group)			X		
4th VISIT Post-intervention dependent variables collection				X	
EXACERBATION COMMUNICATION					X

5.7.2. Flow Chart

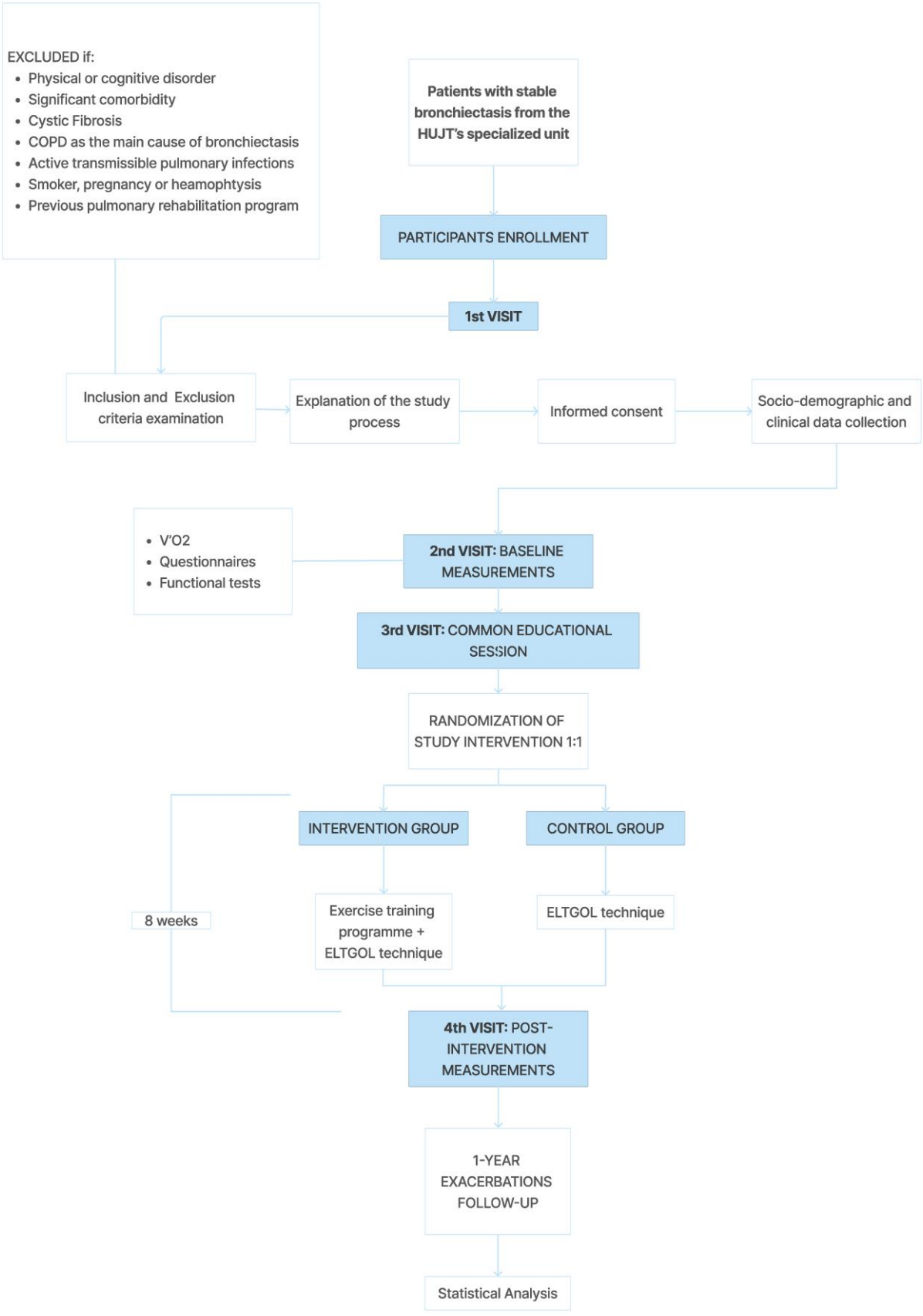

***Figure 10**: Patient's flow chart*

5.8. Safety

Patients may experience dyspnoea, productive cough and fatigue during exercise and report it as adverse reactions. However, this may be consequence of their intrinsic exercise limitation (89). Indeed, intervention goal is to reduce symptoms with adaptive responses with regular training. Moreover, exercise training will be performed using an interval mode, which will minimize limitation symptoms perception.

Cross-contamination between patients training together could also become a risk. Therefore, we will give hygiene education and provide a clean environment where to train.

Other adverse reactions associated with exercise training that have been identified are:

- *Bronchoconstriction*.
- *Hypoxaemia:* reduction in oxygen saturation of less than ninety percent, which is more common in patients with impaired lung function (89).
- *Pneumothorax:* it can occur from high intrathoracic pressure combined with pressure breath hold during weight training (90). In that case, patient will be excluded for participating anymore.
- *Haemoptysis:* can be triggered by sport (89). Mild or moderate haemoptysis will be indicative to stop exercising.
- *Cardiac Arrhythmia:* it is observed to happen to 5-10% of people with bronchiectasis during exercise (91). Risk factors are hypoxaemia and chronic therapy with macrolides (89), so patients under these circumstances will be specially monitored.
- *Musculoskeletal lesions* (fractures, sprains, and strains): because of high prevalence of osteoporosis in bronchiectasis, these kind of exercise-induced injuries are more common than in general population (89).
- *Fluid and electrolyte losses* due to sweating.
- *Spleen injury and haemorrhage:* it is a rare side effect that occurs in patients with portal hypertension (89).
- *Aneurism:* is related to high blood pressure rates when performing cardiorespiratory efforts (92).

To ensure patient safety, the following requirements will be applied:

- Prior to program participation we will perform a pre-test assessment in order to ascertain the right degree of activity for each patient.
- It will be determined whether patients require additional cardiac examinations to guarantee the prescription of safe exercise training. Severe cardiovascular comorbidities will be ruled out before starting intervention.
- Exercise training sessions will be supervised by specialized physiotherapists, who will be trained to enable and ensure recognition of comorbidities symptoms and adverse reactions.
- Contraindications of every test will be checked before starting.
- Vital function will be monitored during variable measurements.
- In the case oxygen therapy is required to undertake exercise it will be provided and flow rate will be adapted to maintain adequate oxygenation.
- Patients will continue their usual medication regimen for any condition concurrently with the study treatment.
- Gym equipment will be confirmed to meet safety standards.
- Every between training sessions the gymnasium will be carefully decontaminated and patients will be educated to keep with hygiene measures. Patients with a multi-resistant chronic infection will train isolated.
- Patients who will suffer an exacerbation and/or hospitalization for any cause during the study will be asked to abandon the programme.

6. STATISTICAL ANALYSIS

A qualified statistician will do the statistical analysis. Version 29.0.1 of the Statistical Package for Social Sciences (SPSS) software will be used to perform it.

For every analysis, a 95% confidence interval will be established. Accordingly, statistically significant results will be defined whenever a p value appears <0.05. P value for every result will be reported to determine significance.

6.1. Descriptive Analysis

Descriptive analysis will provide information about characteristics of both groups. Baseline features between groups are expected to be similar in order to compare exercise training outcomes property. On the other hand, socio-demographic and clinical data should be distributed symmetrically in both groups in order to control possible confusion factors (mating) by using randomization techniques. Outcomes of every variable with will be assessed and presented independently.

Continuous quantitative variable outcomes (V'O2, FEV1, FVC, FEV1/FVC, VE, VT, MIP and MEP) will be presented as the mean value +/- standard derivation for each group (intervention and control group) in every measurement time. The primary dependent variable (V'O2) will be assessed in this group.

Discrete quantitative (number of exacerbations, quality of life and MET-minutes per week) as well as continuous quantitative variables not following a normal distribution will be presented as the median of results obtained associated to its interquartile range (1^{st} and 3^{rd} percentile) for each group in every measurement time. The assumption of normality was checked by means of Shapiro–Wilk tests.

Finally, qualitative variables outcomes (basal dyspnoea perception) will be presented as proportions (%) and absolute values (n) of individuals corresponding to every category of the variable for each group in every measurement time.

6.2. Bivariate Inference

To analyse impact of exercise training by comparing V'O2max of both groups over time, we will use a **Student's t test**. The other continuous quantitative dependent variables assessed (MIP and MEP, MET-minutes per week, number of exacerbations, FVC, FEV1) will be also analysed using a Student's test.

In discrete quantitative variables (number of exacerbations and MET-minutes per week, exacerbations), median outcomes will be compared using a **Mann-Whitney's U.**

A **Chi-square test** will be used to determine differences of qualitative dependent variables (basal dyspnoea perception and quality of life) in both groups after

intervention. In case that the expected number of cases in a cell will be lower than 5, the **Fisher's exact test** will be used

Additionally, all results will be stratified by co-variables. BMI will be categorized in low weight (<18 kg/m^2), normoweight (18-25 kg/m^2), overweigth (25-30 kg/m^2), obese (>30 kg/m^2). The other quantitative co-variables will be categorized in quartiles.

6.3. Multivariate Analysis

Since this is a randomized clinical trial, it would not be necessary to adjust for possible confounders. However, we will adjust for covariates in order to control unmeasured confounders that could be associated with any of them.

To assess the association between exercise training and V'O2max, MIP and MEP, and pulmonary capacity (FVC, FEV1) we will use **linear regression,** as they will appear described as continuous quantitative variables. All measurements will be controlled for all co-variables.

Number of exacerbations and quality of life (discrete quantitative variables) association with exercise training will be evaluated by using a **Poisson regression**. Again, we will control for all covariables.

In the case of basal dyspnoea perception, which corresponds to a dicothomous qualitative variable, a **logistic regression** will be used. Comparison will be done again adjusting by the covariables.

7. WORK PLAN AND CHRONOGRAM

The study research team will be composed by the following members:

- MAIN INVESTIGATOR (MI): the person who will be in charge of elaborating the study protocol based on an exhaustive bibliographic research, organizing the project and join the research team. MI will be responsible for resolving any doubt and consider advises, as well as to present the study to the CEIC for its ethical evaluation and approval.

- DATA ENTRY (DE): the person responsible for collecting data measurements from the clinical chart and report them in the database, along with providing the statistician with the results. CC will be an independent observer who will notify unexpected interim analysis results or other matters to the MI.

- CLINICAL COORDINATOR (CC): the individual in charge of overseeing the study procedure, scheduling appointments, organize the professional training sessions, and patient monitoring during the year after the intervention.

- HEALTH CARE PROFESSIONALS (HP): will include primarily pulmonologists (P), nurses (N) and physiotherapists (PH).

- OTHER PERSONNEL: Statistical analyst (S), Laboratory personnel (LP), Training personnel (TP), and Nutritionists (Nu). The statistician will be responsible for carrying out the statistical analysis of the results obtained, interpreting and providing conclusive results.

7.1. PHASE 0: Study Design

Before the study is initiated, the main investigator must determine whether the existing protocol applied in clinical practice is effective. In our given study problem, the change of protocol to include exercise training in standard management of bronchiectasis generates the need to carry out studies with higher statistical power to test the hypothesis.

After the study objectives are established and clearly defined, bibliographic research is done to ascertain the most recent and high-quality evidence of the topic. The most current data and research on the subject have been gathered.

Next, protocol is elaborated by the main investigator. This step lasts for around 2 months (September and October 2023). The principal investigator is responsible for creating a database to report all information collected (November 2023). In order to guarantee participants' confidentiality, each of them will be assigned a number of identification so

information will be registered anonymously. The database will be filled simultaneously as results of each patient are obtained.

Following step will be personal research recruitment, which will be done in December 2024. MI will invite all health care professionals needed in the study to participate, including pulmonologists, physiotherapists and nurses from Hospital Josep Trueta and Hospital Santa Caterina. There will be an explanation of main objectives and procedures of the protocol, question resolutions and consideration of advices.

Protocol will be presented to the Ethics Committee for its ethical evaluation and approval (December 2023- January 2024). In order to permit results publication and guarantee information disclosure in the future, it will also be registered with the Clinical Trial Registry (January 2024-February 2024).

7.2. PHASE 1: Professional Preparation

In February 2024, professionals who agreed to participate will receive an information session about details of the study and role of each collaborator. There will be an explanation of the work chronogram, which includes regular meetings to guarantee proper study advancement.

During the following 2 months (March and April of 2024) 3 more sessions will be conducted tailored for each professional and conducted by Training Personnel:

a) Pulmonologists and nurses: they will receive training sessions to guarantee that the sample selection is carried out correctly, emphasizing the inclusion and exclusion criteria. If carried out properly, it will enable accurate population representation. They will be taught how to perform tests adequately to obtain acceptable and reproducible measurement outcomes. This training will standardise the way data is collected. ERS statement of cardiorespiratory test performance will be used as reference (78).

b) Physiotherapists: training will be provided to unify the method of airway clearance technique information given to all participants. They will also be given instructions

of how to perform the exercise training sessions correctly during exercise training sessions. It will be based on the Global Training programme applied in COPD patients, explained in Intervention group (*see 5.6.3.2*) (93).

7.3. PHASE 2: Field Work

Recruitment and intervention phase will happen between May 2024 and November 2024. During these months, sample selection, enrolment and intervention programme will be carried out.

Briefly, after selecting the study sample and confirm presence of inclusion criteria and none exclusion criteria, participants will be explained the procedure and asked to sign the informed consent if they agree to participate. Then, baseline data will be collected as well as sociodemographic and clinical information (reported in case report form; see *Annex 8*)

Participants will be randomly located in one of the two groups: Intervention control (who will undergo the intervention programme) and Control group (who will receive current management). Intervention for both groups will start in November 2024.

Training sessions will be conducted from Monday to Saturday. The gymnasium will be available from 4 pm to 9 pm and sessions will last 1h. It has a 4 people capacity to train at the same time which means everyday 16 people will be able to train (4 hours 4 people per hour). Every patient will attend the rehabilitation gym 3 times per week so there will be two rounds of patients per week:

- 16 patients dong training sessions on Monday, Wednesday and Friday.
- 16 patients doing training sessions on Tuesday, Thursday, Saturday.

Therefore, over eight weeks, 32 patients will complete the training sessions simultaneously. With 57 people in the intervention group, it will take a total of 16 weeks to finish the intervention for all participants. However, because unanticipated events can happen and taking into account some patients will have to train isolated due to multi-resistant infections, we project a total period of 24 weeks. Intervention will be finished in May 2025.

Finally, post-intervention data will be collected within 1 week after the end of the intervention for each participant. Patients will be followed by a period of 12 months to report exacerbations incidence over 1-year post-intervention. Follow up will be concluded in May 2026. Information will be stored until this time before giving it to the Statistical analyst.

7.4. PHASE 3: Data Analysis and Conclusions

A Statistical analyst will be contracted to perform statistical analysis of the results using a descriptive, bivariate and multivariate method. This will take place during May-June 2026.

After statistical conclusions of the study will be obtained, the research team will discuss the findings and elaborate a final report.

7.5. PHASE 4: Publication of the Results

Between July and August of 2026, the MI will redact a final article including background, introduction and justification of the study, methods and materials, results and analysis of them, discussion and final conclusion. The article will be presented to the main journals on this topic to be published in order to make information arrive to all professionals of the field.

TABLE 11: STUDY CHRONOGRAM

	2023						2024												2025												2026											
	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
PHASE 0: Study Design																																										
Bibliography research																																									
Protocol Elaboration																																									
Database Creation																																									
Team Recruitment																																									
CEIC approval																																									
Clinical Trial Registration																																									
PHASE 1: Professional Preparation																																									
Informative meeting																																									
Training sessions																																									
PHASE 2: Field Work																																									
Sample Recruitment																																									
Baseline measures																																									
Intervention																																									
Post-test measures																																									
Exacerbation Follow-up																																									
PHASE 3: Data Analysis and Conclusions																																									
Statistical analysis																																									
Research team discussion																																									
PHASE 4: Publication of Results																																									
Article's redaction																																									
Publication																																									
Info dissemination																																									

8. STRENGTHS AND LIMITATIONS

Taking into consideration that this is a clinical trial, it will offer high quality evidence. Furthermore, our study's single institution condition makes sample recruitment easier and will ensure that the diagnosis and treatment are uniform since same pulmonologists will have diagnosed patients using the same criteria. We will also be able to guarantee they receive appropriate treatment and follow-up care. As consequence, Cofounding factors will be more under control.

The main limitation of this study is the impossibility of being blinded. However, this limitation is not expected to alter outcomes since most of the dependent variables of the study (including the main) are determined using objective parameters. Nevertheless, individuals from intervention group could experience Hawthorne effect and this could influence in the self-questionnaire responses. To minimize the impact of un-blinded effects, statistic analyst will not be able to know which study group (control or intervention) the information comes from. Consequently, the analysis of the results will be as objective as possible.

Additionally, since participants will come from the health region of the province of Girona, the study sample will be more representative of the population, increasing external validity. However, some participants will be required to mobilize from their hometown/city to Girona three times a week, which will increase the study economical expenses due to patient transportation and may suppose selection bias. Although our study would require the participation of two hospitals, the distance between them is minimal, so we do not anticipate this to cause any further limitation.

We will use a probabilistic random sampling method, giving to the study higher representativeness of the population. All patients will have same probabilities of being elected for participating, which ensure equal distribution of cofounders and interaction factors and minimize selection bias committing.

When talking about the intervention we have to assume it needs the patient contribution. Implementing exercise habits in these kind of patients may be difficult as they present high baseline sedentary rates. Therefore, adherence to it will suppose a

challenge and drop-outs are expected to be higher than in other studies. This limitation has been taking into consideration when calculating the sample size needed, assuming an abandoning rate of 15%.

Outcome tests may prose variability in terms of procedures and other factors that can influence results. Consequently, all measurements will be done with equipment that meet standards of quality and which will be properly calibrated before every attempt to avoid non-differential missclassification bias. Moreover, to minimise inter-personal variability, all pulmonologists will receive training sessions in order to homogenize measurement procedures. Repeated measures will be done in the same time of the day to avoid inter-day variability.

Diagnosis of exacerbations may be a subjective determination. To reduce heterogeneity, we will use a reference definition and we will check in all cases if the clinical situation matches our definition of an exacerbation. Otherwise it will not be taken into account as an exacerbation. This way of proceeding will improve internal validity of the study.

9. FEASIBILITY

We firmly believe that this clinical trial is possible to be carried out due to several reasons.

Firstly, the research team will be composed by a multidisciplinary group of professionals with numerous years of experience and expertise in the field of pulmonary rehabilitation and who have been recently enrolled in similar clinical trials. Given their background in research and pulmonary procedures, our department will be ready to take on this clinical trial.

We will use the rehabilitation gymnasium in Santa Caterina Hospital which is already totally equipped. Other test employed will be those which are part of daily routine measurements so there will be no need to purchase any extra equipment or devices. No special authorization is needed to utilize the facilities because the gymnasium is specifically reserved in the afternoon to conduct rehabilitation therapies for lung disorders. For that reason, this research will not result in higher labour or material

expenses in interventional rooms. In addition, since exercise training may improve the severity of the condition and lower the frequency of exacerbations, we anticipate a further decrease in the expenditures associated with bronchiectasis resulting in an intervention that is more economically viable.

Total number of participants needed to provide sufficient power to the present study is 114 and recruitment time is estimated to last 6 months, which is logistically reasonable. Appointments will take place in just two different centres located in the same metropolitan area which will facilitate the transport of patients. Study sample comes from patients controlled in the same specialized unit so we will ensure all participants present homogeneous characteristics in terms of bronchiectasis diagnosis and adequate management. Moreover, they are current patients of the clinic which will make it easier to enrol them given established confidence and closer relation.

The intervention itself is simple to carry out, does not require invasive procedures, and may be done simultaneously on more than one person. Since all groups will receive usual treatment and the intervention program has minimal side effects associated, we will ask for low intervention clinical trial qualifying. In the event that the request is granted, we will not have to pay realization taxes and the hospital's clinical insurance will cover the patients included in this study.

10. BUDGET

10.1. Personnel Costs

Research team members taking part of the study (MI, CC, DE, N, P and PH) will not be paid as their participation will be done during current workday. Other personnel currently working in the hospital who will perform the study's activities during their normal clinical practice (nutritionists, laboratory personnel) will not cause additional costs too.

To analyse the collected data and produce a statistical conclusion, a statistician will be employed. With an estimated 40 hours of work necessary in total and an hourly wage of 75 euros, the total cost will come to 3000€.

To ensure that physiotherapists have the knowledge necessary to conduct training sessions effectively, a training technician will also be hired. Pulmonologists will also learn how to do measuring tests from his/her. We calculate that the total cost of the three training sessions they will provide will be 1000€.

10.2. Services Expenses

Randomization software tool *SPSS* as well as other informatics services such as the database storage will be provided by the statistic analyst so their price is included in the final cost of the analyst.

Transportation of patients who need to be transported from their basic health area to Girona city/ Salt city will be provided. We anticipate a total of 4000€ for transportation expenses.

10.3. Insurance Expenses and Taxes Costs

Since both groups will receive current care and the intervention does not entail a significant increase in risk, we will ask for minimal intervention clinical trial qualification. Should the CEIC grant our appeal, the hospital insurance will provide coverage for all participants. However, we should consider that clinical trial insurances typically cost 100€ per participant.

10.4. Material Expenses

Exercise training sessions will be conducted in the rehabilitation gymnasium in Santa Caterina Hospital in Salt, which already have all material needed. However, some tests performances require additional costs. Based on the prices established by the *ORDER SLT/63/2020*, of March 8, which approves the public prices of the Catalan Health Service, still in force, costs will be:

- Spirometry: 41 €
- MIP and MET: 43€
- Ergometry: 226 €

- Thereshold device: 60€ per person (each patient from intervention group will receive one for the entire trial period)

All patients will undergo two of each test and patients from the intervention group will acquire one therefore per person.

Questionnaires will be provided as free.

We will also have to print some documents:

- Informed consent: 1 pages
- Explanation sheet: 5 pages
- Case report form: 2 page
- The Quality of life questionnaire: 3 pages
- IPAQS: 1 page
- mMRC: 1 page
- BSI: 1 page

We assume cost to print per page will be 0.05 €. A total of 20 pages will be printed per participant (1 time the informed consent, explanation sheet, case report form and 2 times the QoL-B, IPAQ-SF, mMRC and BSI per patient), so we estimate the total cost of printed documents will be approximately 114€.

10.5. Publication and Divulgation Costs

We aimed to publish in the best respiratory journals which to our knowledge are *New England Journal of Medicine* and *The Lancet Respiratory*. A total of 4000 € will be set aside for publication.

Aditionally, we plan to present our study results at the SEPAR Conference, as well as the *Catalan Pulmonology Society* and the *European Respiratory Society* Congresses. To cover the cost of the inscription as well as travel and lodging, we will budget a total of 6000 €.

TABLE 12: TOTAL ESTIMATED BUDGET

	Quantity	Price per Unit	TOTAL price
PERSONNEL SERVICES			
Statistic analyst	40 hours	75€/ hour	3,000€
Training technicians	3 sessions		1,000€
SERVICES EXPENSES			
Insurance Expenses and Taxes Costs	1 contraction	100€ / patient	0 € (if we are considered low intervention)
Transportation expenses	1 contraction		4000 €
MATERIAL			
Spirometry	2 per patient	41€ each	9,348€ total (82€/ person)
MIP and MEP determination	2 per patient	43 € each	9,804€ total (86 €/ person)
Ergometry	2 per patient	226€ each	51,528 € total (452 €/ person)
Thereshold device	57	60€ each	3,420€
Printed documents	20 pages / patient	0.05€/ page	114€
PUBLICATION AND DIVULGATION COSTS			
Publication to Journals	1 contraction	4,000€	4,000€
Conference presentation (inscription + travel/accommodation expenses)	1-2 people		6000 €
			TOTAL 92,214€

11. LEGAL AND ETHICAL CONSIDERATIONS

Fundamentals of the study will be established based on the ethical principles of the Declaration of Helsinki (1964) and the statements of The Principles of Biomedical Ethics (1979).

- **The Declaration of Helsinki**: it was redacted in June 1964 by the World Medical Association (WMA) with the purpose of creating universal statements of ethical principles for medical research involving human subjects. Last review was released in October 2013.
- **The Principles of Biomedical Ethics**: first edition was published in 1979 by Beauchamp and Childress. They postulated that for any medical practice to be ethical, it must respect all four of the following principles: Autonomy, Non-Maleficence, Beneficence and Justice.

To guarantee the study meet the ethical requirements expressed by the Medical Community it will be presented to the Medication Research Ethics Committee (CEIm) of Hospital Universitari Josep Trueta. For its approval we will ensure to accomplish the following:

Autonomy will be preserved since all individuals invited to participate will be carefully informed about the procedure of the study. They will be given oral and written explanation in an understandable and clear language. They will be explained that the offer can be accepted or rejected without any prejudice or detriment. In the case they accept to take part of the study, they will sign an informed consent to guarantee totally comprehension of the procedure and autonomic desire to participate. People not capable of understanding the process and objectives of the study or not willing to give informed consent will be rejected to join us. Throughout the study, each participant's values and personal preferences will be respected and they will be free to withdraw from the study under any circumstance.

The exercise training programme consists in a non-invasive procedure with few potential risks associated. To minimise adverse effects, we will apply some security measures explained in *Safety Section (see 6.1)*. Risks are related to exercise

performance. Therefore, safety will be provided during the intervention and the outcome measurements to both groups. Contraindications will be checked before every training or measurement attempt, and people in risk of getting harm will be excluded from participating. To avoid maleficence, all participants will receive approved standard treatment.

Sport and physical activity has been widely evidenced to provide health benefits in all clinical conditions. Our expectations are to see similar effects in bronchiectasis and supply them with their benefits. All procedures will be tailored for every patient's needs. At any case, the study will generate new knowledge about bronchiectasis management possibilities, taking into account that advantages exceed any possible risks. Population selection has been design according to the study needs. Procedure has been carried out following an equitable distribution without any positive or negative discrimination.

The development of this study will adhere to the most recent Spanish and European laws, guaranteeing to accomplish with:

- "Ley 14/2007, de 3 de julio, de Investigación Biomédica".
- "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".
- "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".
- "Regulation (EU) 2016/679 of 27 April 2016: Protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)"

We will also follow European guidelines of "International Conference on Harmonization E6 (R2) on Good clinical practice".

PRIVACY AND CONFIDENCIALITY

Legal accomplishment of Data protection and confidentiality of participants will be verified. Data and information collected will be stored in a database under a number of

identification for each patient to keep anonymity. In addition, only the Research Team and the Statistic analysts will have access to this information.

TRANSPARENCY

Results of the present study will be published regardless of unfavourable data or events. All study members will declare no conflicts of interest. Participants will be informed clearly throughout every step of the work plan in the case any unforeseen happen.

12. IMPACT

Bronchiectasis is a chronic disorder that produces physical limitations and an impairment of quality of life. Despite inactivity has been associated to negative outcomes for individuals with bronchiectasis, it has not been well studied.

On the other hand, in other chronic lung diseases exercise therapies' benefits have been widely proven. There is some evidence that exercise training in bronchiectasis could provide similar effects and improve patients' health-related quality of life. This is supported by physiopathology of the disease which explains why during exercise they experience limitation symptoms. However, studies published provide low-quality evidence because of methodological limitations and do not purpose any standardised protocol.

The present clinical trial is expected to provide high-quality evidence of effects of exercise training in the bronchiectasis population with higher exercise intolerance rates. It has been methodologically designed to supply with rigorous information about exercise capacity, respiratory muscle strength, dyspnoea perception, quality of life and pulmonary capacity before and after training sessions to generate an evidence-based conclusion of real impact of exercise training in these patients. Sample size is adequate to support evidence of results obtained and representativeness of the study population guarantees enough external validity to extrapolate conclusions. Exercise tolerance will be assessed by using the maximum oxygen uptake which is considered the gold standard to determine exercise capacity and will ensure objective and reproducible results. Moreover, it will be the first bronchiectasis-based study which establishes a standardized protocol to be implemented as part of current management of the disease.

Indeed, if we confirm our hypothesis, exercise training rehabilitation could be implemented as part of current management of bronchiectasis which would mean a big step in how medical professionals deal with the disease as well as how patients live with it.

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14. ANNEXES

15.1. ANNEX 1: BSI score

Age	• <50 years (0 points) • 50-60 years (2 points • 70-70 years (4 points) • ≥80 years (6 points) POINTS:
Body Mass Index (BMI)	• ≥ 18.5 (0 points) • <18.5 (2 points) POINTS:
FEV1% predicted	• >80% (0 points) • 50-80% (1 point) • 30-49% (2 points) • <30% (3 points) POINTS:
Hospital admission in the preceding 2 years	• No (0 points) • Yes (5 points) POINTS:
Exacerbations in the previous year	• 0-2 (0 points) • ≥3 (2 points) POINTS:
Medical Research Council Dyspnoea Scale (MRC)	• 1-3 (0 points) • 4 (2 points) • 5 (3 points) POINTS:
Pseudomonas Aeruginosa colonization	• No (0 points) • Yes (3 points) POINTS:
Colonization with other microorganisms	• No (0 points) • Yes (1 point) POINTS:

Radiological extension (≥ involved loves or cystic bronchiectasis)	• No (0 points) • Yes (1 point) POINTS:
	TOTAL POINTS:

15.2. ANNEX 2: Modified Medical Research Council score (mMRC)

DESCRIPTION	**GRADE**
I only get breathless with strenuous exercise	0
I get short of breath when hurrying on level ground or walking up a slight hill	1
On level ground, I walk slower than people of my age because of breathlessness, or I have to stop for breath when walking at my own pace on the level	2
I stop for breath after walking about 100 meters or after a few minutes on level ground	3
I am too breathless to leave the house or I am breathless when dressing/undressing	4

15.3. ANNEX 3: International Physical Activity Questionnaire –Short Form (IPAQ-SF)

During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?	a) _____ days per week b) No vigorous physical activities Skip to question 3
How much time did you usually spend doing vigorous physical activities on one of those days? **Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.**	a) _____ hours per day b) _____ minutes per day c) _____ Don't know/Not sure
During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.	a) _____ days per week b) No moderate physical activities Skip to question 5
How much time did you usually spend doing moderate physical activities on one of those days? **Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure**	a) _____ hours per day b) _____ minutes per day c) _____ Don't know/Not sure

During the last 7 days, on how many days did you walk for at least 10 minutes at a time?	a) _____ days per week b) No walking Skip to question 7
How much time did you usually spend walking on one of those days?	a) _____ hours per day b) _____ minutes per day c) _____ Don't know/Not sure
During the last 7 days, how much time did you spend sitting on a week day? Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television	a) _____ hours per day b) _____ minutes per day c) _____ Don't know/Not sure

15.4. ANNEX 4: The Quality of Life-Bronchiectasis questionnaire

During the last 7 days, to what extent have you had difficulty with:				
	SEVERE DIFFICULTY	MODERATE DIFICULTY	LOW DIFFICULTY	NONE DIFICULTY
1. To perform effort activities, for example garden activities or physical activities				
2. To walk at the same pace as other people				
3. To transport heavy objects such as books or shopping bags				
4. To climb stairs				
During the last 7 days, indicate how often:				
	ALWAYS	OFTEN	SOMETIMES	NEVER
5. You have felt good				
6. You have felt tired				
7. You have felt restless				
8. You have felt energized				
9. You have felt exhausted				
10. You have felt sad				
11. You have felt depressive				
Are you currently under bronchiectasis treatment?			YES	NO
			(Continue)	(Go to question 15)
	ABSOLUTELY NOTHING	A LITTLE	MODERATELY	A LOT
12. In which extent do bronchiectasis treatments your daily life more difficult?				
13. Currently, how much time do you daily spend in bronchiectasis treatments?				
14. How much does it cost to reconcile your daily				

life with bronchiectasis treatment?				
	EXCELENT	GOOD	REGULAR	BAD
15. Which one do you think is your present health status?				
Taking into consideration your health status in the last 7 days, indicate in which extent the following affirmations are true to you				
	TOTALLY	IN PART	A LITTLE	NOTHING
16. I have to limit effort activities such as walking or physical activities				
17. I have to stay at home more than I would like				
18. I worry about expose myself to other ill people				
19. It is difficult for me to intimate with my partner (kiss, hugs)				
20. I live a normal life				
21. I am worried that my health status will worsen				
22. I think my cough bothers others				
23. I usually feel alone				
24. I feel healthy				
25. It is difficult for me to plan future planes (holidays, reunions,…)				
26. I feel embarrassed when I cough				
	I DON'T HAD ANY PROBLEM	I MANAGED TO KEEP WITH THEM WITH A LITTLE DIFICCULTY	I DELAYED DOING THESE ACTIVITIES	I COULDN'T DO THESE ACTIVITIES
27. In the last 7 days, in which extent you had problems to keep with				

your job work, home chores or other daily?				
	ALWAYS	OFTEN	SOMETIMES	NEVER
28. How often do bronchiectasis condition interfere in achieving your home, job, family and personal goals?				
In which frequency during the last 7 days:				
29. Have you felt breathless when doing a greater effort activity such as garden activities or chores?				
30. Have you experienced lung sound such as wheezled?				
31. have you felt chest pain?				
32. Have you felt breathless when talking?				
33. Have you waken up in the night because of cough?				
Indicate how have you felt during the last 7 days				
	A LOT	MODERALELY	A LITTLE	ABSOLUTELY NOTHING
34. Have you felt congestion in the chest?				
35. Have you cough during the day?				
36. Have you expulsed mucus when coughing?				

15.5. ANNEX 5: Modified Borg Scale

SCORE	LEVEL OF DYSPNOEA
0	NONE
0.5	EXTREMELY MILD
1	VERY MILD
2	MILD
3	MODERATE
4	INTENSE
5	RATHER INTENSE
6	
7	VERY INTENSE
8	
9	ALMOST UNBEARABLE
10	UNBAREABLE

15.6. ANNEX 6: Patient's informative sheet (Catalan Version)

FULL D'INFORMACIÓ AL PACIENT

Nom de l'estudi: ***Benefits of Exercise training in Bronchiectasis***
Centre coordinador: **Hospital Universitari Doctor Josep Trueta** (HUJT)
Investigador/a principal: **Dra Montserrat Vendrell i Dr Gerard Muñoz**

Benvolgut/da Sr/Sra:

Aquest és un full informatiu sobre els aspectes més rellevants de l'estudi al qual ha sigut convidat a participar. És important que llegeixi amb atenció i pregunti qualsevol dubte que li pugui sorgir.

DESCRIPCIÓ I OBJECTIUS DE L'ESTUDI

Definició

Les bronquièctasis són una malaltia crònica de la via aèria que poden apareixen com a conseqüència de moltes causes diferents. Es caracteritzen per provocar una dilatació dels bronquis permanent (augmenta el seu diàmetre) que predisposa a patir infeccions bronquials amb augment de la producció i acumulació de moc. Finalment s'acaba produint una inflamació excessiva que malmet les parets dels bronquis.

Símptomes

Entre els símptomes més freqüents trobem la dispnea (falta d'aire), la tos productiva i la expectoració de moc. Altres símptomes que poden aparèixer són la limitació de l'activitat física com augment de la fatiga al practicar esport o debilitat muscular. Per tot, suposa una malaltia amb gran limitació per a la realització de les activitats de la vida diària.

Tractament

Actualment el tractament no és curatiu, sinó que es basa en controlar els símptomes i evitar la progressió de la malaltia. Els tractaments tenen com a objectiu reduir els efectes de la pròpia malaltia com l'acumulació de moc, mitjançant tècniques de drenatge de les secrecions, així com la infecció o la inflamació, amb fàrmacs dirigits a reduir-les. No obstant, avui en dia encara no disposem de tractaments efectius per a la reducció dels símptomes relacionats amb l'activitat física, ja que la recerca que s'ha realitzat fins a dia d'avui és escassa.

Objectius

El nostre objectiu principal és determinar quin és l'efecte de seguir un programa de re-entrenament a l'esforç en el subgrup de pacients amb bronquièctasis amb més limitació a l'esforç. Volem demostrar que introduir programes de rehabilitació física pot millorar la capacitat física i com a resultat, la qualitat de vida relacionada amb la salut.

A més, també valorarem l'efecte de l'exercici físic sobre la capacitat pulmonar, la sensació de dispnea, la qualitat de vida, la força dels músculs respiratoris i el nombre d'aguditzacions.

COM HO FAREM?

Els pacients seleccionats que compleixin amb les característiques que demanem per formar part de l'estudi es distribuiran de forma aleatòria en dos grups equitatius:

- GRUP A: Rebrà les sessions d'exercici físic
- GRUP B: No rebrà les sessions d'exercici físic

D'aquesta manera podrem comprovar els efectes de l'exercici físic mitjançant la comparació dels dos grups.

Mesures generals

Els dos grups seguiran rebent el tractament estàndard durant tota la intervenció i a més, els dos realitzaran tècniques de drenatge de secrecions autògen des de casa (tècnica ELTGOL), que consisteix en exercicis respiratoris per afavorir la sortida de moc de la via aèria.

Abans de començar, tots els participants rebran sessions dirigides per la bona realització dels exercicis de drenatge de secrecions i consells dietètiques i nutricionals així com maneig bàsic de la pròpia malaltia.

Les mesures dels paràmetres que ens interessa conèixer s'efectuaran durant la setmana abans de l'inici de la intervenció i la setmana després del final de la intervenció. Així doncs, tots els participants seran cridats a assistir al gimnàs de l'Hospital Santa Caterina i al departament de pneumologia de l'Hospital Josep Trueta 2 cops durant tot l'estudi.

Pel que fa a la intervenció

La intervenció NOMES serà realitzada per aquells participants que de forma aleatòria hagin sigut assignats al grup d'intervenció

La intervenció es durà a terme al gimnàs de l'Hospital Santa Caterina (Salt) i consistirà en 3 sessions d'aproximadament 1h, 3 dies a la setmana durant 8 setmanes. L'horari serà de 4 a 8 de la tarda i cada pacient haurà d'assistir a la franja que li pertoqui (en cas que alguna persona tingui predisposició per una hora concreta s'haurà d'informar a l'equip coordinador).

Durant cada sessió es practicaran els següents exercicis

- Ergometria (bicicleta estàtica): serà un exercici de 15-30 al 80% de l'esforç màxim.
- Entrenament de la força muscular: serà un exercici amb peses per entrenar diferents grups musculars (bíceps, tríceps, dorsal, deltoides, pectoral i quàdriceps)
- Entrenament dels músculs inspiratoris: mitjançant un aparell que s'entregarà a l'inici de la intervenció.

POSSIBLES RISCOS

Els possibles riscos que poden sorgir estan relacionats amb la pràctica de l'exercici físic durant la intervenció i/o el mesurament dels paràmetres d'interès. Engloben els següents efectes adversos:

- **Broncoconstricció**: espasme / contracció de la via aèria que pot arribar a ocloure-la.
- **Hipoxèmia**: disminució de la quantitat d'oxigen que circula a la sang.
- **Pneumotòrax**: fuga d'aire a l'espai entre els pulmons i la paret toràcica.
- **Hemoptisis**: emissió de sang del tracte respiratori per la boca.
- **Arítmies cardíaques**
- **Fractures i/o esquinços**
- **Alteracions hidroelectrolítiques**
- **Lesions de la melsa**
- **Aneurismes**: protuberància o abombament anormal dels vasos sanguinis.

Per tal de minimitzar els riscos associats a la intervenció es prendran les següents mesures de seguretat:

- Es realitzaran tests pre-entrenament per assegurar que cada pacient realitza l'exercici en el grau d'intensitat que pot assolir.
- S'exclourà qualsevol tipus de malaltia o alteració cardio-vascular abans d'iniciar la intervenció
- Abans de cada sessió es farà una revisió de les contra-indicacions de cada prova.
- Totes les sessions seran supervisades per fisioterapeutes entrenats per a identificar i tractar correctament les complicacions que puguin sorgir.
- Durant el mesurament de variables els pacients seran monitoritzats.
- Es suplementarà oxigen a aquells pacients que ho necessitin durant la l'exercici físic
- Tots els pacients continuaran amb la seva medicació habitual.
- L'equipament serà comprovat de complir amb els estàndards de seguretat
- Davant una agudització i/o hospitalització el pacient haurà d'aturar la seva participació a l'estudi.

BENEFICIS

Tot i que tenim poca evidència dels efectes de l'exercici físic en pacients amb bronquièctasis, en altres malalties com l'MPOC o la fibrosi quística aquest aspecte de la malaltia ha sigut àmpliament estudiat. Les teràpies de rehabilitació a l'esforç han demostrat ser beneficioses en la reducció de la dispnea i la fatiga, millora de la tolerància a l'exercici i de la qualitat de vida.

Actualment, la teràpia de re-entrenament a l'esforç en aquestes malalties apareix en les guies de pràctica clínica oficials.

CONFIDENCIALITAT

Totes les dades recollides seran emmagatzemades a una base de dades sota un numero d'identificació confidencial per garantir l'anonimat de tots els pacients.

La gestió i anàlisi de les mateixes es realitzarà tal com s'estipula a la normativa espanyola i europea: *"Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos"*; "*Ley orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales"*

Només els investigadors que composen l'equip d'estudi juntament amb el comitè d'Ètica d'investigació amb Medicaments de l'Hospital Josep Trueta (CEIm). Els participants tindran dret a revisar la informació recollida sobre ells i així com de rebre una còpia d'aquesta.

DIFUSIÓ DE RESULTATS

El protocol serà registrat al Registre Espanyol d'Assaigs clínics abans del seu inici. Un cop finalitzat l'estudi els resultats i conclusions es publicaran a diverses revistes científiques d'interès. També serà presentat al congres que organitza *la Societat Espanyola de Pneumologia i Cirurgia Toràcica (SEPAR).*

Totes les dades seran publicades de forma anònima i cap informació referent a la seva identitat serà exposada.

PARTICIPACIÓ

La participació a aquest estudi és totalment voluntària i pot revocar la seva decisió en qualsevol moment del curs sense cap prejudici ni detriment.

Les següents situacions l'exempten de seguir amb la participació: exacerbació i/o hospitalització durant el període de intervenció, efectes secundaris severs.

La participació no implica cap compensació econòmica ni per part dels participants ni per part de l'equip de recerca.

S'assegura el compliment dels estaments d'ètica en investigació així com el compliment de dret dels pacients. Tots els participants tenen dret a rebre informació detallada de tots els processos i a satisfer tots els dubtes que puguin sorgir.

Per assegurar la voluntat dels participants i confirmar que han compres la informació rebuda a través d'aquest full, els pacients hauran de firmar un full de consentiment informat on es compromet a assistir al **80% de les sessions** i a **totes les cites de mesures de paràmetres**.

ASSEGURADORA

Com que es tracta d'un estudi de baix nivell de intervenció, qualsevol prejudici sobre la seva salut derivat de la intervenció serà cobert per l'assegurança del nostre centre sobre responsabilitat civil. Així doncs davant de qualsevol dany causat serà adequadament tractat i recompensat econòmicament.

Així ho empara la normativa europea i la legislació espanyola actual.

CONTACTE

Davant qualsevol dubte o inconvenient que pugui sorgir abans, durant i després de l'estudi podrà posar-se en contacte amb el següent numero de telèfon que ofereix servei gratuït i les 24h del dia: _____

Durant el període posterior a la intervenció també haurà de comunicar qualsevol símptoma d'agudització al numero anterior.

Li recomanem que guardi el full per si el vol consultar més endavant.

15.7. ANNEX 7: Informed Consent (Catalan Version)

DOCUMENT DE CONSENTIMENT INFORMAT

Jo, _____ *(nom i cognoms*), amb document d'identificació personal _____ *(DNI/ NIE),* declaro que:

- He llegit i he comprés correctament tota la informació que apareix al *Full d'Informació al Pacient.*
- He rebut tota la informació necessària.
- He pogut exposar i satisfer qualsevol dubte.
- He disposat del temps necessari per a prendre una decisió.
- Entenc els possibles riscos associats a l'estudi així com els beneficis que en poden derivar.
- No he ocultat cap informació essencial clínica o personal que puguin ser rellevants per la correcta efectuació de l'estudi.
- Comprenc que la meva participació és totalment voluntària.
- Comprenc que no seré compensat econòmicament per la meva participació.
- Comprenc que la realització de l'estudi no resultarà en beneficis econòmics per l'equip investigador.
- Comprenc que les meves dades personals i mediques seran confidencials i utilitzats exclusivament amb finalitats d'investigació.
- Entenc que puc revocar aquest document en qualsevol moment i sota qualsevol circumstancia sense rebre prejudicis ni detriments.

En conseqüència:

- Dono lliurement el meu consentiment per la participació del present assaig clínic i autoritzo l'ús de les meves dades per al seu anàlisi, en el present estudi i futures investigacions.
- Em comprometo a assistir al 80% de les sessions de rehabilitació i a totes les cites concertades per l'equip investigador
- Em comprometo a comunicar qualsevol signe / símptoma d0agudització en l'any posterior a la realització de la intervenció.
- Accepto que l'equip investigador em pugui contactar en el futur si es necessari

Signatura del pacient Signatura de l'Investigador responsable

☐ ACCEPTO

☐ NO ACCEPTO

Lloc i data: _____, _____ de _____ de l'any _____

15.8. ANNEX 8: Case report form

FULL DE RECOLLIDA DE DADES SOBRE CO-VARIABLES

Nom de l'estudi: ***Benefits of Exercise training in Bronchiectasis***

Centre coordinador: **Hospital Universitari Doctor Josep Trueta** (HUJT)

Investigador/a principal: **Dra Montserrat Vendrell i Dr Gerard Muñoz**

Codi d'identificació del/la pacient: _____

Lloc i data: _____, _____ de_____ de l'any _____

1. DATA DE NAIXAMENT (dia/mes/any): ____ / ____ / _____
2. EDAT (anys): _____
3. SEXE BIOLÒGIC: Femení ____ Masculí ____
4. ÍNDEX DE MASSA CORPORAL (IMC= kg/m2): Pes _____ kg; Alçada _____ cm
    a. Baix pes: IMC < 18.5 ___
    b. Pes normal: IMC 18.5 – 24.9 ___
    c. Sobrepes: IMC 25-29.9 ___
    d. Obesitat: IMC ≥ 30 ___
5. ETIOLOGIA DE LES BRONQUIECTASIS: _____
6. ÍNDEX BSI: _____ punts
    a. Lleu (0-2 punts) ____
    b. Moderat (3-4 punts) ____
    c. Sever (5-7 punts) ____
7. COLONITZACIÓ DE PSEUDOMONA: SI____ NO____
8. SATURACIÓ D'OXIGEN PERIFERICA: ____ %
9. IPAQ-SF (Sedentarisme): _____ MET-minuts / setmana
10. COMORBIDITATS
    a. Cardiovasculars: ____
        Quines:_____
    b. Respiratòries: _____
        Quines: _____
    c. Cerebro-vasculars: ____
        Quines: _____

b. Neoplàsies: ____

Quines: _____

c. Altres: ____

i. _____

ii. _____

iii. _____

iv. _____

v. _____

vi. _____

11. MEDICACIÓ HABITUAL :

_____

_____

_____

_____

_____