A clinical study on “a breathing exercise for rehabilitation of patients with lung fibrosis” to improve lung function and quality of life in patients with idiopathic pulmonary fibrosis

Version 1.0
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Clinical study site: Shanghai Pulmonary Hospital of Tongji University
Principal investigator: Dr. Hui-Ping Li
Director of study implementation: Li Shen
Statistician: Aihong Zhang, Department of Medical Statistics, Tongji University, School of Medicine

Flow chart

Study phase	Screening	Treatment and follow-up		
Visit number	V1	V2	V3	V4
Number of months with the treatment (30 days per month)	-7-0d	3M	6M	12M
Number of days with the treatment The first day with the exercise is considered as day 1		91	181	361
Time window		±7d	±7d	±7d
Informed consent form	√			
Medical history	√			
Inclusion and exclusion criteria	√			
Physical examination and vital sign inspection	√	√	√	√
Smoking status	√	√	√	√
SGRQ score	√	√	√	√
6-minute walking test	√	√	√	√
Lung function examination [1]	√	√	√	√
HRCT[2]	√			√
Chest X-ray	√	√	√	√
Immunological examination[3]	√			√
Blood test, ESR, CRP[4]	√			√
Blood biochemistry[5]	√			√
Coagulation test[6]	√			√
Electrocardiography	√	√	√	√
Cardiac ultrasound	√			√
Pregnancy test	√			√
Adverse events		√	√	√
Concomitant drugs	√	√	√	√
Study diary	√	√	√	√
Randomization[7]	√			

1. Lung function examination includes: FEV1, FVC, DLCO, arterial blood gas, VRI-determined MEF, QLD, and EVP.
2. HRCT is submitted to the primary study site for review and verification. HRCT within one month is valid.
3. Immunological examination includes: complete rheumatology test (within 12 months before enrolment), peripheral blood flow cytometry for CD4 and CD8, and CRP.
4. Blood test includes: WBC, RBC, HB, PLT, lymphocyte percentage, and neutrophil percentage.

5. Blood biochemistry includes: ALT, AST, ALP, LDH, γ-GTP, TBIL, TP, Alb, BUN, Cr, K^+, Na^+, Cl^-, GLU, and test for liver fibrosis.
6. Coagulation test includes: PT, APTT, TT, and FIB.
7. Laboratory test results within 7 days before visit 1 are considered valid. Subjects that have older test results and enter randomization should re-take those tests.

Signature page

I have read this study protocol, version 1.0, date December 18, 2014, and agree to conduct the clinical study of "a breathing exercise for rehabilitation of patients with lung fibrosis" according to this study protocol and comply with the GCP principal and other relevant laws and regulations.

I will keep this study protocol and relevant contents confidential.

Sponsor: Shanghai Pulmonary Hospital of Tongji University

Principal investigator (Signature): Hui-Ping Li Date: Year Month Day

Statistician：

Principal statistician (Signature): Aihong Zhang Date: Year Month Day

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Synopsis

Title	A clinical study on "A breathing exercise for rehabilitation of patients with lung fibrosis" to improve lung function and quality of life in patients with idiopathic pulmonary fibrosis.
Indication	Idiopathic pulmonary fibrosis (IPF)
Objective	To evaluate the efficacy and safety of a breathing exercise on the improvement in lung function and quality of life in patients with IPF.
Design	Non-blinded, randomized control clinical study. Experimental group: with the breathing exercise Control group: without the breathing exercise Design: exploratory
Subjects	Patients with IPF
Inclusion criteria	1. Diagnosed with IPF according to the 2011 ATS/ERS/JRS/ALAT diagnostic guidelines. *The HRCT results are all submitted to the primary sponsor for confirmation. 2. Aged 50-80 years, man or non-pregnant woman. 3. Good compliance and willing to take the treatment following the study protocol and come to follow-up visits on time. 4. Agree and sign the informed consent form after the study objectives, methods, and possible discomfort associated with the treatment are explained to them sufficiently.
Exclusion criteria	1. Obvious pulmonary infection that requires anti-infection therapy (with respiratory or systemic infection within 4 weeks prior to screening visit). 2. Malignant tumor. 3. Severe disease in other system or severe dysfunction in other organs. 4. Participate in other clinical trials within 3 months prior to the screening visit. 5. Pregnant, breastfeeding, planning to become pregnant, or unable to use effective contraception. 6. Unable to tolerate the breathing exercise. 7. Conditions that investigators believe to cause the subjects become unsuitable for the study.
Withdrawal	1. After enrollment, subjects are found to fail to meet the inclusion criteria or meet the exclusion criteria. 2. Investigators decide to terminate the study based on the consideration of medical ethics. 3. Serious adverse events cause the subjects become unsuitable to continue the study. 4. Serious complications occur during the study.

	5. Violate the regulations relevant to this study protocol. 6. Subjects have poor compliance. After enrolment, subjects do not exercise or do not have any assessable record, stop the exercise before study completion, are unable to complete the exercise according to the instruction, including not exercising at the time specified by the study protocol, or have other possible factors that might affect efficacy observation. 7. Participate in other similar clinical studies. 8. Other conditions that investigators believe to cause necessary subject withdrawal.
Sample size	The indication of this study is IPF, which is a rare disease. Currently, the sample size is 120 cases.
Treatment	Experimental group: perform the breathing exercise for 9 minutes daily, which includes repetition of the exercise for 3 times consecutively with one-minute rest after each exercise. Other relevant treatments that exist prior to enrolment remain unchanged. Control group: Relevant treatments that exist prior to enrolment remain unchanged and do not perform the breathing exercise.
Efficacy endpoints	**Primary endpoints**: 1.Changes in FVC after versus before the breathing exercise. 2.Changes in oxygen saturation and walking distance in 6-minute walking test. **Secondary endpoints:** 1.Changes in lung function (FEV1, TLC, DLco, and PaO_2). 2.Quality of life: score of St. George's survey, reduction in the score is used for statistical analysis. 3.Changes in lung volume determined by chest X-ray. 4.Changes in lung lesions detected by HRCT scan **Time points for efficacy observation:** A complete study includes enrolment screening and a 360-day (12 months) period of efficacy observation for the breathing exercise. Subjects come to follow-up visit at day 90, 180, and 360 during the study. IPF exacerbation should be treated immediately.
Safety assessment	**1. Vital sign observation** Heart rate, respiration, and saturated oxygen are recorded daily before and after the exercise. **2. 12-lead electrocardiography (ECG)** ECG is performed before the exercise and 3, 6, and 12 months after starting the exercise. **3. Possible adverse reactions** During the study, the incidence of adverse reactions is usually 3-4%. The

	most common adverse reactions include fatigue and muscle pain. A small proportion of subjects with poor lung function or combined cardio-cerebral vascular diseases might develop an exacerbation of chest tightness and short of breath or cardiovascular and cerebrovascular ischemia, including angina, myocardial infarction, and cerebral infarction. **4. Cautions** The breathing exercise should be performed properly. If obvious short of breath occurs, subjects can use oxygen inhalation therapy simultaneously. The exercise should be performed step by step and subjects should not feel exhausted. The breathing exercise can be temporarily stopped on days when short of breath exacerbates.
Statistical analysis	All statistical analyses are performed with SPSS. All the statistical tests are 2-sided. $P \leq 0.05$ is considered statistically significant, and 95% confidential interval is used. Full analysis set is used for baseline data analysis. Full analysis set and per protocol set are used for efficacy endpoint analysis. Safety set is used for safety analysis. Continuous variables are described as mean ± standard deviation or median (minimum, maximum). Pairwise *t*-test is used for intra-group comparison of values after the treatment versus the baseline values. Analysis of variance (ANOVA) or rank sum test is used for inter-group comparison of values after versus before the treatment. Count variables are described as frequency (proportion). Chi-square test/Fisher's exact test or non-parametric test is used for inter-group comparison of values after versus before the treatment. Analysis of data loss: Data loss is described. Chi-square test or Fisher's exact test is used to compare the rate of total data loss and the rate of data loss due to adverse events between the 2 groups when necessary. Analysis of baseline balance: Student's t-test or chi-square test is used to compare demographic data and other baseline data so to test baseline balance. Efficacy analysis: For the primary endpoints, changes in FVC, VRI-determined MEF, QLD, and EVF, and lung volume determined by chest X-ray, analysis of covariance is used to analyze the continuous variables with baseline values as the covariance, and chi-square test/Fisher's exact test is used to analyze the count variables. For the secondary endpoints, changes in FEV1, TLC, DLco, PaO_2, oxygen

	saturation and walking distance in 6MWT, quality of life score, and chest HRCT, Student's *t*-test is used to analyze continuous variables with equal variance; rank sum test is used to analyze continuous variables with unequal variance; chi-square test/Fisher's exact test is used to analyze count variables. Safety analysis: Adverse events are described in tables. Fisher's exact test is used to compare the incidence of adverse events in the 2 groups when necessary. Laboratory test results are described, including results that are normal before the exercise but abnormal after the exercise and the association between the abnormal changes and the exercise.
Study duration	Start time: January 2015 End time: December 2018

List of abbreviations

6MWT	6-Minute Walking Test
AE	Adverse Event
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
BUN	Urea Nitrogen
CFDA	China Food and Drug Administration
Cl^-	Chloride
Cr	Creatine
CRO	Contract Research Organization
DLco	Diffusing capacity or transfer factor of the lung for carbon monoxide
ERS	European Respiratory Society
ESR	Erythrocyte Sedimentation Rate
EVP	Expiratory Vibration Energy Peak
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in one second
FIB	Fibrinogen
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLU	Glucose
HB	Hemoglobin
HRCT	High Resolution Computed Tomography
IEC	Institutional Ethics Committee
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
JRS	Japan Respiratory Society
K^+	Potassium

LDH	Lactate Dehydrogenase Enzyme
MD	Median
Mean	Mean
MEF	Maximum Energy Figure
Na^+	Sodium
PaO2	Partial Pressure of Oxygen
PLT	Platelet
PPS	Per Protocol Set
PRO	Protein
PT	Prothrombintime
QLD	Quantitative Lung Data
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SpO_2	Saturation of Peripheral Oxygen:
SS	Safety Set
TBIL	Total Bilirubin
TLC	Total Lung Capacity
TP	Total Protein
TT	Thrombin Time
UIP	Usual interstitial pneumonia
VRI	Vibration Response Imaging
WBC	White Blood Cell
γ-GTP	Glutamine Acyltransferase

1 Background

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease. The etiology of IPF remains unclear. The pathology of IPF progression is characterized by a slow progression of diffuse alveolitis and/or abnormal alveolar structure. IPF can ultimately lead to alveolar structural damage, pulmonary fibrosis, and honeycomb lung. The clinical presentation of IPF is characterized by irritating dry cough and a progressive exacerbation of breathing difficulty. The lung shows limited ventilation dysfunction at the early stage of IPF, and then gradually becomes diffuse dysfunction. Reduction in lung function not only adversely affects the quality of life but also is an early predictor for mortality of patients with IPF [1]. Thus, improvement in lung function can delay the exacerbation of breathing difficulty, and thus improve the quality of life and extend survival of patients with IPF.

Breathing exercise plays a key role in the management of IPF. Osamu [2] et al investigated the effects of a 10-week pulmonary rehabilitation program on lung function, blood gas, walking distance of 6-minute walking test (6MWT), severity of breathing difficulty, and quality of life in 30 patients with IPF. They found that lung function, blood gas, and the severity of breathing difficulty were not affected significantly whereas 6MWT and the quality of life were improved significantly by the rehabilitation program. Sabrina Bajwah [3] et al conducted a meta-analysis to investigate the efficacy of a series of pulmonary rehabilitation program as an intervention therapy on patients with ILD and found that the rehabilitation program improved the quality of life and 6MWD significantly. In China, Zeng et al [3] also tested a 2-month breathing exercise in 28 patients with IPF and showed that clinical symptoms, the quality of life, and blood gas parameters were all improved.

Breathing exercise includes abdominal breathing, pursed-lip breathing, resistance breathing, sectional breathing (or partial breathing), end-inspiratory pause breathing, and whole body breathing. Whole body breathing exercise can increase lung ventilation, enhance the work capacity of respiratory muscles, reduce residual gas in alveoli after deep exhalation, and decrease alveolar expansion. Whole body exercise can also improve breathing efficiency, increase limb muscle force, and attenuate chronic respiratory disease-induced muscle dysfunction. Furthermore, exercise alleviates patient’s fear and anxiety toward physical activity and builds self-confidence. In addition to improving pulmonary ventilation and gas exchange, alleviating the symptoms of short of breath and hypoxia, enhancing the force and endurance of breathing muscles, whole body breathing exercise can also enhance the overall strength and activity of patients so to further improve lung function and quality of life, thus ultimately restore normal daily life [4]. Previous studies demonstrated that whole body breathing exercise improved immune function and lung

function indexes, including pulmonary vital capacity, FEV1, maximum voluntary ventilation, and peak expiratory flow [5,6]。

Breathing activity is completed through the coordinated movement of the diaphragm, intercostal, abdominal, and pelvic floor muscles. Scalene, sternocleidomastoid, serratus, pectorals, trapezius, latissimus dorsi, and erector spinae muscles also play critical roles in assisting breathing activity. During deep inhalation, the contraction of the diaphragm and intercostal muscles is enhanced, and other auxiliary inspiratory muscle, such as sternocleidomastoid muscle and pectoral and back muscles, also contract to further expand the chest cavity. During deep exhalation, inspiratory muscles relax, and auxiliary expiratory muscles, such as muscles of abdominal wall, intercostal muscle, contract actively to further shrink the chest cavity.

Based on the unique clinical feature, endurance deterioration, in patients with IPF [7], Dr. Huiping Li from Shanghai Pulmonary Hospital of Tongji University developed a breathing exercise for rehabilitation of patients with lung fibrosis. This breathing exercise is a whole body breathing exercise and includes the following 3 movements: deep breathing using the whole lung, deep breathing using unilateral lower lung, and deep breathing using the upper lung. The 3 movements mainly exercise the neck, chest, waste, and upper limbs. During the exercise, patients perform deep inhalation and exhalation. The breathing exercise aims to improve lung function and quality of life.

The breathing exercise is currently used by patients with interstitial lung fibrosis. After approval by the institutional ethics committee (IEC), this clinical study with Shanghai Pulmonary Hospital of Tongji University as the primary sponsor, is conducted to test the efficacy of the breathing exercise to improve lung function and quality of life in patients with IPF.

2 Objective

To evaluate the efficacy and safety of “a breathing exercise for rehabilitation of patients with lung fibrosis” to improve lung function and quality of life in patients with IPF.

3 Design

3.1 Overall design

This single center, non-blinded, randomized control clinical study aims to evaluate the safety and efficacy of performing a breathing exercise daily for one year on the improvement in lung function and quality of life in patients with IPF. A total of 120 eligible patients with IPF, man or woman, are randomized into 2 groups, control and experimental groups, with 60 patients per group. Patients in the experimental group

perform the breathing exercise for 9 minutes daily following the instruction. The 9-minutes exercise includes repetition of the breathing exercise for 3 times consecutively with one-minute rest after each exercise. The duration of the study is 12 months (one year).

3.2 Sample size calculation

According to the changes after versus before the breathing exercise in the primary efficacy endpoints, such as FVC and lung volume determined by chest X-ray, this study hypothesizes that patients in the experimental group may have improved FVC. The assumption for sample size calculation is $\alpha = 0.05$ and Power = 80%. Patient ratio of experimental to control groups is 1:1. Previous publication showed that breathing exercise for 12 months improved lung function by 5% compared with the control. Thus, sample size in the experimental and control group is estimated to be 20.8 patients, respectively. The sample size calculation is based on the equation of 2-mean comparison. The statistical analysis software, PASS, is used for sample size calculation. With the assumption of 10% data loss and consideration of relevant national guidelines, thus, 22 patients for each group are required for this study. This study enrolls 60 patients in the experimental and control groups, respectively.

3.3 Randomization

Stratified block randomization is used. Random number is generated by a certified statistician using SAS software. CDs containing the instruction and demonstration of the breathing exercise is numbered consecutively. Patients were randomly assigned to the LHP's RRPF exercise (exercise group) or control group using sealed envelopes with randomized results by SAS analysis software. The total number of the CDs equals to the sample size. Investigators distribute the CDs in the consecutive order to subjects according to the randomization scheme. The CD number remains unchanged during the study.

4 Study subjects

4.1 Inclusion criteria (Subjects are included when meeting all of the 4 criteria):

1) Subjects were diagnosed with IPF according to the 2011 ATS/ERS/JRS/ALAT guidelines. *HRCT results are all submitted to the primary sponsor for confirmation.
    a) Subjects do not have other ILDs with known causes, including family history, occupational exposure, connective tissue disease, and drug-related toxic side effects.
    b) HRCT presents usual interstitial pneumonia (UIP) when subjects do not have surgical biopsy.
    c) If subjects have surgical biopsy, both HRCT and biopsy results are reviewed for diagnosis. HRCT presents typical UIP or meet the criteria for UIP:
        - Typical UIP meets the following 4 criteria: a) lesions are mainly at the base of the lung and under the pleura; b) with grid opacity; c) honeycomb changes with or without traction bronchiectasis; d) no

other features that are not related with UIP.

- UIP meets the following 3 criteria: a) lesions are mainly at the base of the lung and under the pleura; b) with grid opacity; c) no other features that are not related with UIP.
- Features of non-UIP: the lesions are mainly at the upper and middle lobe and surround the bronchial vessels, and subjects present excessive ground glass changes, diffuse micro-nodule, multiple cystic lesions (far away from the honeycomb lesions), diffuse ground-glass changes or gas trap, and pulmonary bronchial changes.

2) Aged 50-80 years, man or woman.
3) Subjects show good compliance, are able to cooperate with investigators for efficacy observation, and are willing to do the exercise according to the instruction described in this study protocol and come back follow-up visits on time.
4) Subjects agree and sign the informed consent form after the study objective, method, and possible discomforts are explained to them sufficiently.

4.2 Exclusion criteria (Subjects are excluded when meeting any one of the criteria):

Subjects that have any one of the following conditions are exclude:

1) Obvious lung infection that requires anti-infection therapy (with respiratory infection and/or systemic infection within 4 weeks prior to the screening visit).
2) Malignant tumor.
3) Severe disease and dysfunction in other organ.
4) Participate in other clinical studies within 3 months prior to the screening visit.
5) Pregnant, breastfeeding, planning to become pregnancy, or unable to use effective contraception.
6) Unable to tolerate the breathing exercise.
7) Other conditions that investigator believe to cause the subjects become unsuitable for the study.

4.3 Subject withdrawal

4.3.1 Investigators decide to withdraw subjects

1) After enrolment, subjects are found to fail to meet the inclusion criteria or meet the exclusion criteria.
2) Investigators decide to withdraw subject based on the consideration of medical ethics.
3) Subjects develop serious adverse events (SAEs) and become unsuitable to continue the study.
4) Subjects develop other serious complications during the study.
5) Subjects violate the regulations that are relevant to this study protocol.
6) Subjects have poor compliance. After enrolment, subjects do not exercise or do not have any assessable record. Subjects stop the exercise before study completion. Subjects are unable to complete the exercise following the instruction described in

this study protocol. For instance, subjects do not exercise at the required time. Subjects have other conditions that may affect the efficacy evaluation.
7) Subjects participate in other similar clinical studies during the study.
8) Subjects have other conditions that investigator believe to cause the withdrawal of the subjects.

4.3.2 Subjects withdraw voluntarily

Subjects withdraw the informed consent and decide to withdraw the study. According to the rules in the informed consent, subjects have the right to withdraw the study or stop the exercise or follow-up visits (consider as data loss) without explicit announcement of the withdrawal. Reasons for voluntary withdrawal should be collected and recorded. For instance, subjects might withdraw the study because they are unable to tolerate some adverse events (AEs).

4.3.3 Procedure of withdrawal

Eligible subjects that withdraw the study for any reason at any time are considered data loss as long as they do not complete the efficacy observation or the follow-up visits specified in this protocol.

For subjects that withdraw the study, investigators should record the time and reasons for the withdrawal and evaluate the subjects according to the withdrawal procedure specified in this protocol. Subjects that withdraw the study because of AEs or abnormal laboratory test results should be followed up till the AEs are resolved or the abnormal laboratory test results restore to normal/baseline values. Data of subjects that withdraw the study should be kept and included in the full analysis set (FAS).

4.4 Removal of subjects

When any one of the following conditions occurs in subjects during the study, investigators should determine whether the subjects should be removed from the study bases on the consideration of the extent of study completion and reasons for removal. Investigators should record the subject removal.

1) Subjects voluntarily withdraw the study.
2) Subjects fail to meet the inclusion criteria.
3) Subjects cannot complete the study because of AEs.
4) Subjects do not comply with the procedure. For instance, subjects do not exercise or do not have any exercise record.
5) Subjects take medications because of AEs, and the medications interfere in the study endpoints.
6) Investigators believe subjects have other conditions that make them become unsuitable to continue the study, and the investigators decide to end the study for the subjects.
7) After study completion, subjects require removing all of their data and do not

want their data to be included in the study results.

4.5 Study termination

Study termination is defined as ending the study for subjects before study completion. The purpose of study termination is to protect subjects' benefits, ensure the quality of the study, and avoid unnecessary financial loss. Early study termination should be reported to all the parties involved in the study timely. The study should be terminated for subjects when any of the following conditions occurs:

1) Serious safety issue occurs.
2) The testing treatment has no clinical significance.
3) Serious flaws are found in the study protocol during the study and seriously interfere in efficacy evaluation. Serious deviation from the study protocol occurs during study implementation and causes impossible efficacy evaluation. For instance, the blinded information is exposed.
4) The study sponsor terminates the study because of funding shortage and administration issue.
5) CFAD or IEC terminates the study for some reasons.

Study termination can be temporary or permanent, and all the records should be properly stored for future review when the study is ended.

5 Breathing exercise for rehabilitation of patients with lung fibrosis

5.1 Introduction

Dr. Huiping Li from Shanghai Pulmonary Hospital of Tongji University designed the breathing exercise and prepared the CDs containing the instruction and demonstration of the breathing exercise. Subjects perform the breathing exercise for 9 minutes daily according to the instruction, which includes repetition of the breathing exercise for 3 times consecutively with one-minute rest after each exercise. The following is the procedure of the breathing exercise in details:

The first movement: Deep breathing using the whole lung (repeat this movement for 4-6 times within one minute).

Key points: Subjects stand straight. The distance between the 2 feet should be similar to the width of the shoulder. Both arms contact the thighs closely, and then subjects raise both arms outward slowly until both hands meet on top of the head and inhale deeply simultaneously. Subsequently, subjects lower both arms slowly and exhale deeply simultaneously.

The Second movement: Deep breathing using unilateral lower lung (repeat this movement for 4-6 times within one minute).

Key points: Subjects stand straight. The distance between the 2 feet should be similar

to the width of the shoulder. Both arms contact the thighs closely, and then subjects raise the right arm outward slowly until it is vertical to the horizon line and inhale deeply simultaneously. Subsequently, subjects bend the body leftward with 30-60 degrees slowly and exhale deeply. Subjects then return to the straight standing position slowly. Next, subjects raise the left arm outward slowly until it is vertical to the horizon line and inhale deeply simultaneously. Subsequently, subjects should bend the body rightward with 30-60 degrees slowly and exhale deeply simultaneously. Subjects then return to the straight standing position slowly.

The third movement: Deep breathing using the upper lung (repeat this movement for 4-6 times within one minute).
Key points: Subjects stand straight. The distance between the 2 feet should be similar to the width of the shoulder. Two arms are crossed and placed at the back of the neck. Subjects bend the neck forward and exhale deeply simultaneously. Subjects then extend both arms (maintain the crossed position) backward, straight the neck, and inhale deeply simultaneously.

5.2 Management of CDs containing exercise instruction and demonstration
To safely manage the CDs containing the instruction and demonstration of the breathing exercise, investigators assign a special drug manager to manage the CDs and to record the acceptance, distribution, use, and return of the CDs.

According to the rules specified in this protocol, investigators should only distribute the CDs to the subjects included in this study. Each subject only receives the CD that is assigned to her or him. In each follow-up visit, investigators collect subjects' diary book and record exercise time and other parameters representing physical condition and vital signs.

After study completion, all the CDs are collected by the study sponsor if local disposal is not authorized by the sponsor.

5.3 Prohibited and permissive concomitant drugs
1) During the study, subjects are allowed to use antifibrotic agents, such as acetyl-l-cysteine and pirfenidone. Antitussive, antiasthmatic, and anti-infection drugs, which are necessary to relieve symptoms for subjects, are also allowed.
2) Drugs that may induce fibrosis, such as amiodarone, are prohibited.

Concomitant drugs are documented in details and analyzed. When AEs occur, the correlation between the AEs and the concomitant drugs should be particularly

analyzed.

5.4 Cautions

Subjects should follow the instruction strictly when performing the breathing exercise but should not over exercise. If obvious short of breath occurs, subjects can use oxygen inhalation therapy simultaneously. Subjects should perform the breathing exercise step by step and should not feel exhausted.

The breathing exercise can be temporarily paused on days when short of breath exacerbates. However, the number of days with the exercise should ≥80% of the total number of days in a follow-up cycle.

6 Efficacy evaluation and safety assessment

6.1 Efficacy endpoints

1) **Primary endpoints:**
   a) Changes in FVC after versus before the exercise.
   b) Changes in oxygen saturation and walking distance during 6MWT.
2) **Secondary endpoints:**
   a) Changes in indexes representing lung function, including FEV1, TLC, DLco, and PaO_2.
   b) Quality of life score in the St. George's Respiratory Questionnaire (SGRQ). The reduction in the score is used for statistical analysis.
   c) Changes in lung volume measured by chest X-ray after versus before the exercise.
   d) Changes in lesions determined by HRCT.

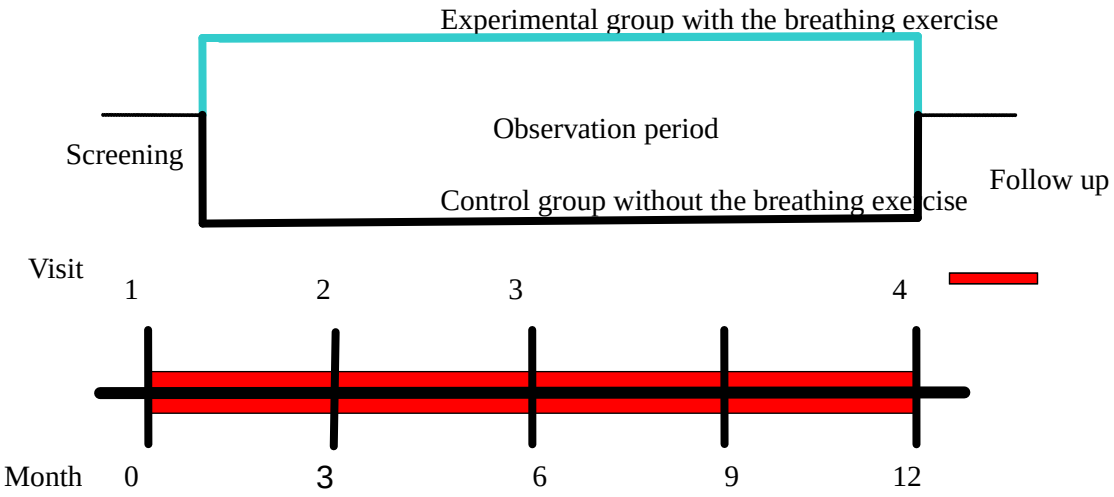
6.2 Safety assessment

AEs and changes in physical examination, vital signs, laboratory tests, and 12-lead ECG compared with the baseline values are described.

7 Study process and patient visits

The complete study process include enrolment screening and a 360-day (12 months) efficacy observation. Subjects come to follow-up visits on day 90 (3 months), 180 (6 months), and 360 (12 months) after starting the exercise.

IPF exacerbation should be treated immediately. If the number of days with exercise is ≥80% of the total number of days in each follow-up cycle, subjects can continue the study.



7.1 Screening period:

Day 0 to day 7 (visit 1)

- Informed consent.
- Medical and medication history, physical examination, vital signs, and smoking status.
- Lung function examination (within the recent 7 days): FVC, FEV_1, TLC, DL_{CO}, and blood oxygen analysis, FEV_1 and FVC are measured following the ATS guidelines for lung function test. Drugs for relieving pulmonary symptoms should not be used within 4 hours prior to the lung function test.
- 6MWT: maximum walking distance and SpO2 before and after the test.
- SGRQ.
- HRCT within the recent one month.
- Chest X-ray with the recent 7 days.
- Routine laboratory tests (within the recent 7 days): blood test, ESR, CRP, blood biochemistry, pregnancy test, coagulation test, immunological tests (peripheral blood flow cytometry and CRP).
- ECG (within the recent 7 days).
- Rheumatology test (within the recent 3 months).
- Cardiac ultrasound (Estimation of pulmonary artery pressure within the recent 3 months).
- Inclusion and exclusion criteria.
- Randomization, distribution of the CDs of the breathing exercise, and the first exercise under the instruction and supervision of investigators.
- Distribution of the diary books and pulse oximeter. Investigators provide instructions on recording exercise details and proper use of the pulse oximeter.

7.2 Treatment period:

1) Day 90 (3 months) ±7 days (visit 2)

The following tests are performed on day 90 after starting the exercise:

- Physical examination, vital signs, and smoking status
- Chest X-ray
- Lung function test (FVC, FEV_1, TLC, DL_{CO}, blood gas)
- SGRQ
- 6MWT
- ECG
- Review the diary books
- AEs and concomitant drugs

2) **Day 180 (6 months) ± 7 days (visit 3)**

The following tests are performed on day 180 after starting the exercise:

- Physical examination, vital signs, and smoking status
- Chest x-ray
- Lung function test (FVC, FEV_1, TLC, DL_{CO}, blood gas)
- SGRQ
- 6MWT
- ECG
- Review the diary books
- AEs and concomitant drugs

3) **Day 360 (12 months) ± 7 days (visit 4)**

The following tests are performed on day 360 after starting the exercise:

- Medical and medication history
- Physical examination, vital signs, and smoking status
- Lung function test (FVC, FEV1, TLC, DLCO, blood gas)
- SGRQ
- 6MWT
- HRCT
- Chest X-ray
- Routine laboratory tests: blood test, ESR, CRP, blood biochemistry, coagulation test, immune index (peripheral blood flow cytometry, CRP)
- ECG
- Cardiac ultrasound
- Review the diary books
- AEs and concomitant drugs

8 Adverse events and evaluation

8.1 Definition of adverse event

An AE is any abnormal physical characteristic, symptom, or medical condition that occurs or exacerbates after subjects start the breathing exercise. The AEs may or may not be associated with the exercise. Preexisting medical conditions or diseases prior to the initiation of this study are considered as AEs only when they exacerbate after starting the exercise. Abnormal laboratory test results are considered clinically significant only when they cause clinical symptoms or signs, and are considered as

AEs only when clinical intervention is required.

8.2 Observation and recording of adverse events

Investigators should instruct subjects clearly and sufficiently to faithfully report any change in medical conditions after starting the exercise. Investigators should avoid suggestive questions to subjects. When evaluating efficacy, investigators should closely monitor the occurrence of AEs, estimate the severity of the AEs, analyze the reasons for the AEs, manage the AEs properly, and follow up the AEs. AEs should be reported in the specific AE tables in the case report forms.

8.3 Classification of adverse events according to severity

1) Mild: Subjects mention the AEs without being asked suggestively. Subjects are able to tolerate the AEs easily. The AEs only cause mild discomforts, do not affect daily activities, and do not need clinical intervention.
2) Moderate: Subjects report the AEs voluntarily. The AEs affect daily activities, are bearable to subjects, and require routine clinical intervention.
3) Severe: Subjects show AE-associated clinical presentation. The AEs significantly affect daily activities, are unbearable to the subjects, and require bed rest and active clinical intervention.

8.4 Determination of the association between adverse events and the breathing exercise

The association between AEs and the breathing exercise is classified into the following 5 categories: 1) absolutely associated; 2) very possibly associated; 3) possibly associated; 4) possible not associated; 5) absolutely not associated. The 1-3 categories are considered as breathing exercise-associated AEs.

The following criteria should be used when the association between AEs and the breathing exercise is determined: 1) the time sequence of the initiation of the breathing exercise and the occurrence of suspected adverse reactions; 2) whether the suspected adverse reactions match the already known breathing exercise-associated adverse reactions; 3) whether the suspected adverse reactions disappear or are relieved after the subjects stop the exercise; 4) whether the suspected adverse reactions re-occur after subjects resume the exercise. 5) the suspected adverse reactions occur when exercise, disappear when exercise stopped. According to the criteria, the association of AEs and the breathing exercise can be determined using the following table:

Evaluation Results	Evaluation criteria				
	1	2	3	4	5
absolutely associated	＋	＋	－	＋	＋
very possibly associated	＋	＋	－	＋	?
possibly associated	＋	＋	±	±	?

possible not associated	＋	—	±	±	?
absolutely not associated	—	—	+	—	—

Notes: ＋: Yes; -: No; ±: yes or no; ?: Unknown.

8.5 Period of reporting adverse events

The period of reporting AEs in this study is from starting the breathing exercise to the end of the last follow-up visit. AEs, which occur during this period, should be recorded in the case report forms regardless their association with the breathing exercise. AEs that occur beyond this period should also be reported as AEs if investigators believe the AEs may be possibly associated with the breathing exercise.

8.6 Serious adverse events

Serious AEs (SAEs) are serious medical conditions that occur during the study. These serious medical conditions may by life-threatening, require hospitalization, extend the duration of hospitalization, cause sustained or severe disability, functional loss, or death, or cause congenital malformations or birth defects. Investigators believe those serious medical conditions may injure the subjects severely and require medication or surgical treatment to avoid bad patient outcomes.

If SAEs occur during the study, the parties that are responsible for the study must take immediate measures to protect subjects' safety. Investigators should fill the SAE report with details, sign, and date the report. Investigators should report the SAEs to the IEC of Shanghai Pulmonary Hospital of Tongji University, CFDA, and administrative departments of public health within 24 hours. The report should include the following information: the source of the report, subjects' general information, the name of the breathing exercise in this study, the name, duration, severity, and the association with the breathing exercise of the SAEs, treatment, and the outcomes of the SAEs.

Sponsor: Shanghai Pulmonary Hospital of Tongji University Contact person: Dr. Huiping Li	Tel: +86 021-65115006-1055 Fax: +86 021-65115006-1055
IEC of participating hospital Contact person: Jiaying Wu	Tel:021-65115006-1055 Fax:021-65115006-1055

8.7 Follow-up of adverse events

All AEs are followed up till the AEs are resolved properly or till the final reports of the subjects with the AEs are completed after study completion. Subjects with SAEs should be followed up till the SAEs are resolved properly even after study completion.

9 Data management and statistical analysis

9.1 Data management

9.1.1 Data entry and revision

Data entry and management are handled by data managers from the Department of Public Health and Statistics of The Second Military Medical University. The data managers use the software Epidata 3.0 for data entry and management. To ensure the accuracy of data entry, 2 data managers enter the data independently in duplicate, and then the data entry by the 2 data managers is compared and verified.

For questions in case report forms, the data managers prepare a data request queue (DRQ), which is then forwarded to investigators by clinical inspectors. The investigators should verify the data entry according to the original records and answer the DRQ timely. Based on the answers, the data managers then revise, confirm, and enter the data.

9.1.2 Database lock

After the DRQ is completely resolved and the accuracy of the established database is confirmed, the data managers prepare a data management audit report. The analysis data set is confirmed. The audited database is then locked. Data files are not allow for revision after database lock.

9.2 Statistical analysis

9.2.1 Selection of data for statistical analysis

According to intention-to-treat (ITT) principal, full analysis set (FAS) includes all of the subjects that are randomized and exercise at least once during the study. FAS is used for efficacy analysis. For subjects that do not have complete records for the study, the principal of last observation carried forward (LOCF) is used.

Per protocol set (PPS) includes all the subjects that comply with the study protocol, do not receive prohibited drugs during the study, and complete the required contents in the case report forms. Imputation is not performed on missing data. For efficacy evaluation, both FAS and PPS are used for statistical analysis.

Safety set (SS) includes all of the enrolled subjects that exercise at least once and have records of post-exercise safety assessment. SS is used for safety analysis.

9.2.2 Statistical analysis plan

Statistical analysis plan is prepared by statisticians. Final version of the plan should be completed before database lock. The statistical analysis software SPSS is used. The statistical analyses include:

Subject distribution: The sample size, subject distribution, and proportion of subject withdrawal and subject removal in each center are compared. Reasons for study termination are displayed in tables.

Data balance analysis: Demographic data and baseline values are compared to estimate baseline balance. Chi-square test or Fisher's exact test is used to compare count variables, such as sex. Student's *t*-test or Wilcoxon rank sum test is used to analyze continuous variables, including age, respiratory parameters, and blood pressure. Disaggregated data/categorical data are analyzed by Cochran-Mantel-Haenszel (CMH) test.

Compliance analysis: Subject compliance in the 2 groups, for instance, whether subjects exercise at the protocol-specified time and intensity or whether subjects receive prohibited drugs during the study, are compared.

Efficacy analysis:
Primary endpoints: FVC; oxygen saturation and walking distance in 6MWT. Covariance analysis is used for the primary endpoints. Dependent variables are changes in the primary endpoints after versus before the exercise, and baseline values are covariates. Intergroup interaction is taken into account in the analysis. Student's *t*-test is used to compare the primary endpoints before the exercise between the 2 groups and compare the changes in the primary endpoints after versus before the exercise between the 2 groups, if the data are normally distributed and have equal variance. The statistic is *t*. If the data are not normally distributed or have unequal variance, Wilcoxon rank sum test is used. The statistic is *z*. Pairwise *t*-test is used for intra-group comparison of the values after versus before the exercise, if the data are normally distributed. The statistic is *t*. If the data are not normally distributed, signed rank test is used. The statistic is *S*.

Secondary endpoints: TLC, FEV_1, DLco, SpO2, SGRQ score, lung volume determined by chest X-ray, and HRCT score. Student's *t*-test is used to compare the secondary endpoint values before the exercise between the 2 groups and compare the changes in the secondary endpoints after versus before the exercise between the 2 groups, if the data are normally distributed and have equal variance. The statistic is *t*. If the data are not normally distributed or have unequal variance, Wilcoxon rank sum test is used. The statistic is *z*. Pairwise *t*-test is used for intra-group comparison of the values after versus before the exercise, if the data are normally distributed. The statistic is *t*. If the data are not normally distributed, signed rank test is used. The statistic is *S*.

Safety analysis: AEs, adverse reactions, SAEs, and severe AEs in the 2 groups are described. Chi-square test or Fisher's exact test is used to compare the incidence of those events between the 2 groups. The name, onset time, severity, and the association with the exercise of AEs, adverse reactions, SAEs, and severe AEs are listed and described in tables.

Concomitant drug distribution: The distribution of concomitant drugs in the 2 groups are described. Chi-square test or Fisher's exact test is used to compare the

incidence of concomitant drugs between the 2 groups. The name, dose, administration method, starting time, and ending time of the concomitant drugs are listed and described in tables.

Changes in vital signs, laboratory test, and ECG after versus before the exercise are described. Subjects with normal vital signs, laboratory test, and ECG before the exercise and abnormal values after the exercise and subjects with abnormal values before and after the exercise are described in details in tables.

9.2.3 Questions related with statistical analysis

1) Statistical analysis software: The software SPSS is used for all the statistical analyses.
2) Significant level: The significant level is 0.05. $P \leq 0.05$ is considered statistically significantly different. *P* value is 2-sided, and 95% confidential interval is used.
3) Estimation of missing items: Missing primary endpoints are filled using the LOCF principal.

10 Record and storage of case report form

Case report forms (CRF) are printed on carbonless paper in triplicate. Participating investigators fill the CRF clearly and neatly during the clinical observation of the study (black or dark blue ink should be used to fill the CRF). All of the fields in CRF should be filled, and missing and empty fields are not acceptable (fields without appropriate answers should be filled with straight lines). The filled content may not be altered unless revision is confirmed to be necessary. The old contents in a field are crossed with a straight line and the correction is written next to the straight line. Signature and date of the revision are placed near the correction. All of the data in CRF should be error free and the consistency of data in CRF and the data in subjects' original medical record should be verified. Values that are unusually high or beyond the clinically acceptable range should be verified. Photocopies of test result sheets are attached to CRF. CRF are review, verified, and signed by the principal investigator.

All of the participating centers should store the original records properly, including all of the subjects' medical records, signed informed consent, photocopies of CRF, and the record of distribution of CDs containing the instruction and demonstration of the breathing exercise, so that CFDA and the sponsor can review, evaluate, and examine the original records. The participating centers should store the data of the study for 5 years after study completion.

11 Ethics requirement

The study implementation should follow the Declaration of Helsinki and Good Clinical Practice (GCP) strictly. The study should be conducted in accordance with this study protocol.

11.1 Ethics committee

Before the study starts, the study protocol, informed consent form, and other materials that are to be distributed to subjects should be reviewed and approved by the IEC of the primary sponsor. The approval documents should be kept by the study sponsor. During the study, major revision of the study protocol should be approved by IEC before implementation.

11.2 Informed consent form

Investigators must explain to subjects that participation in the study is completely voluntary; subjects have the rights to withdraw the study freely at any stage of the study without being discriminated; the treatment and medical benefits of subjects are not affected by the withdrawal; the subjects can continuously receive effective treatments. Investigators must ensure that subjects understand that participation in the study and all the personal data collected during the study are confidential. In addition, the nature, aims, possible predicted benefits, and possible potential risk and inconvenience of the study should be explained to subjects. Subjects should be informed that they might be allocated into different study groups; they have other available therapies; they have rights and obligations according to the Declaration of Helsinki. Subjects should be provided with sufficient time to consider whether to participate in the study. Subjects should sign the informed consent form if they agree to participate in the study.

12 Quality control and assurance

12.1 Clinical inspection

Clinical inspectors from Shanghai inCROM Clinical Research Organization for Medicines visit and inspect the participating centers regularly to ensure the strict compliance with the study protocol. The clinical inspectors also audit the data in CRF to ensure the consistency of the data in CRF and the original data.

12.2 Training

Before the study starts, study managers of each participating center should train investigators regarding the study protocol. Investigators should read and understand the study protocol, understand GCP principal, consistent documentation, and evaluation criteria, and conduct the study in strict accordance with the study protocol.

12.3 Operation compliance

The sponsor complies with GCP and Drug Registration Regulation. The testing drug is manufactured under GMP condition and undergoes strict quality inspection. Laboratory tests are performed according to SOP in each participating center. The clinical examination lab in each participating center should have internal quality control and should have the therapeutic evaluation certificate issued by the Clinical Trial Center of the Minister of Health.

12.4 Data verification

Conclusions of this study should be based on the original data. Data management

measures should be implemented during the study and at the stage of data processing to ensure data reliability.

12.5 Control of data loss

Active measures to prevent data loss should be implemented.

13 Summary

Statistical analysis results of each participating center should be submitted to the study sponsor for preparation of the clinical study report (CSR). The CSR is then reviewed, verified, and approved by each participating center, and then is submitted to the sponsor. The study sponsor and participating centers should achieve the CSR.

14 Predicted study progression

October 2014: complete the first draft of study protocol design and the associated documents.
January 2015: Initiate the study
December 2015: Complete subject enrolment
December 2016: Complete the treatment
February 2017: Complete CSR

Attachment 1

The St. George's Hospital Respiratory Questionnaire

This questionnaire is designed to help us learn more about how your breathing is troubling youand how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are. Please read the instructions carefully and ask if you do not understand anything. Do not spend a long time deciding on your answers.

PART 1 -- Four Week Description

Please describe how often your lung/respiratory problems have affected you over the last four weeks. Please fill in one circle for each question.

	almost every day	several days a week	a few days a month	only with lung/respiratory infections	not at all
1) Over the last 4 weeks, I have coughed	O	O	O	O	O
2) Over the 4 weeks, I have brought up phlegm (sputum)	O	O	O	O	O
3) Over the last 4 weeks, I have had shortness of breath	O	O	O	O	O
4) Over the last 4 weeks, I have had episodes of wheezing	O	O	O	O	O

5) During the last 4 weeks, how many severe or very unpleasant episodes of lung/respiratory problems have you had?

more than 3 pisodes... O
3 episodes..... O
2 episodes..... O
1 episode..... O
No episodes ..... O

6) How long did the worst episode of lung/respiratory problem last?
Go to Question 7 if you didn't have a severe episode.

a week or more ..... O
3 or more days ..... O
1 or 2 days ..... O
less than a day ..... O

7) Over the last 4 weeks, in an average week, how many good days (with few lung/respiratory problems) have you had?

none ..... O
1 or 2 ..... O
3 or 4 ..... O
nearly every day ..... O
every day ..... O

8) If you wheeze, is it worse in the morning?
If you don't wheeze, go to the next page.

No. ..... O
Yes ..... O

Part 2

Section 1:

How would you describe your lung/respiratory condition? Please fill in one circle only.

The most important problem I have ..... O
Causes me a lot of problems ..... O
Causes me a few problems ..... O
Causes me no problem ..... O

If you have ever held a job, please fill in one of the circles.

My lung/respiratory problem made me stop my job ..... O

My lung/respiratory problem interferes with my job or made me change my job.....O

My lung/respiratory problem does not affect my job ..... O

Section 2:

These are questions about what activities usually make you feel short of breath.

Please fill in each circle that applies to you now.

	True	False
Sitting or lying still	O	O
Washing yourself or dressing	O	O
Walking in the house	O	O
Walking outside on level ground.....	O	O
Walking up a flight of stairs	O	O
Walking up hills	O	O
Playing sports or active games (baseball, tennis, etc).....	O	O

Section 3:

These are more questions about your cough and shortness of breath.

Please fill in each circle that applies to you now.

	True	False
Coughing hurts	O	O
Coughing makes me tired	O	O
I am short of breath when I talk	O	O
I am short of breath when I bend over	O	O
My coughing or breathing disturbs my sleep	O	O
I become exhausted easily	O	O

Section 4:

These are questions about other effects that your lung/respiratory problem may have on you. Please fill in each circle that applies to you now.

	True	False
My coughing or breathing is embarrassing in public	O	O
My lung/respiratory problem is a nuisance to my family, friends, or neighbors	O	O
I panic or get afraid when I cannot catch my breath	O	O
I feel that I am not in control of my lung/respiratory problem	O	O
I do not expect my lung/respiratory problem to get any better	O	O
I have become frail or an invalid because of my lung/respiratory problem.....	O	O
Exercise is not safe for me	O	O
Everything seems too much of an effort	O	O

Section 5:

These are questions about your lung/respiratory medication, including oxygen,inhalers, and pills. If you are not receiving medication, go to Section 6. Please fill in each circle that applies to you now.

	True	False
My lung/respiratory medication does not help me very much	O	O
I get embarrassed using my lung/respiratory medication in public	O	O
I have unpleasant side effects from my lung/respiratory medication	O	O
My lung/respiratory medication interferes with my life a lot.	O	O

Section 6.

These are questions about how your activities might be affected by your breathing problem. For each question, answer True if one or more parts applies to you because of your breathing problem. Otherwise answer False.

	True	False
I take a long time to get washed or dressed	O	O
I cannot take a bath or shower, or I take a long time to do it.....	O	O
I walk slower than other people my age, or I stop to rest	O	O
Jobs such as household chores take a long time, or I have to stop to rest	O	O
If I walk up one flight of stairs, I have to go slowly or stop	O	O
If I hurry or walk fast, I have to stop or slow down	O	O
My breathing problem makes it difficult to do things such as walking up hills, carrying things up stairs, light gardening such as weeding, dancing, playing golf, or light sports such as horseshoes....	O	O
My breathing problem makes it difficult to do things such as carrying heavy loads, digging in the garden or shoveling snow, jogging or walking briskly, playing tennis, or swimming	O	O
My breathing problem makes it difficult to do things such as very heavy manual labor, riding a bike, running, swimming fast, or playing competitive sports	O	O

Section 7. We would like to know how your breathing usually affects your daily life. Please fill-in each circle that applies to you because of your lung/respiratory problem.

	True	False
I cannot play sports or active games	O	O
I cannot go out for entertainment or recreation	O	O
I cannot go out of the house to do the grocery shopping	O	O
I cannot do household chores	O	O
I cannot move far from my bed or chair	O	O

Here is a list of other activities that your lung/respiratory problem may prevent you from doing. (You do not have to fill-in these, they are just to remind you of ways in which your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Having sexual intercourse

Going to church, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your lung/respiratory problem may stop you from doing:

_____

_____

_____

Now, would you fill in the circle (only one) that you think best describes how your breathing problem affects you:

	True	False
It does not stop me from doing anything I would like to do	O	O
It stops me from doing one or two things I would like to do	O	O

It stops me from doing most of the things I would like to do	O	O
It stops me from doing everything I would like to do	O	O

Thank you for completing this questionnaire.
Please check to be sure that you have answered all questions.

Attachment 2

HRCT socring criteria for IPF

Ground **glass score**	**Characteristic**
0	no ground glass change (the whole lung, the same below)
1	ground glass lesion range ＜5% (Least but not normal)
2	ground glass lesion range 5-24%
3	ground glass lesion range 25-49%
4	ground glass lesion range 50-75%
5	ground glass lesion range >75%
Fibrosis score	
0	No fibrosis
1	Interlobular septal thickening, no honeycombing
2	Honeycombing (with or without septal thickening) <25% whole lung field
3	Honeycombing (with or without septal thickening) 25-49% whole lung field
4	Honeycombing (with or without septal thickening) 50-75% whole lung field
5	Honeycombing (with or without septal thickening) > 75% whole lung field

Attachment 3

Standard operating procedure of 6-minute walking test

Location

The 6MWT should be performed indoors, along a long, flat,straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap,should be marked on the floor using brightly colored tape.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test(cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid,appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests.The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following:(*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4*)staggering, (*5*) diaphoresis, and (*6*) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the

event and the technician's
assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg. Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (see the APPENDIX).
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (see Table 1 for the Borg scale and instructions).

TABLE 1. THE BORG SCALE

score	symptom
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard,Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a

long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones.

You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line.

Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement.

Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this:"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"

11. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.

12. Record the number of laps from the counter (or tick marks on the worksheet).

13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

14. Congratulate the patient on good effort and offer a drink of water.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.