Validation of handheld spirometry in Interstitial Lung Diseases (ILD) as part of the European ILD Registry (eurILDreg)

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Table of Contents

1 Introduction:

Interstitial lung diseases (ILDs) are a rare heterogenous group of diseases characterized by inflammatory and fibrotic changes and the irreversible destruction of the alveolar architecture of the lung. This in turn, reduces the available gas exchange area and enlarges the diffusion distance for oxygen transfer between the alveoli and the blood stream with typical symptoms at onset including dyspnea, reduced exercise tolerance and a reduction in the quality of life (1). Despite novel treatment options available, patients are still at an increased risk of significant morbidity and premature death (2).

The etiologies and epidemiology of ILDs are variable, depending on environmental inhalative exposition to certain fumes and dust, genetic predisposition, ethnicity and modifiable risk factors such as smoking. In all, there are over 200 known causes of ILDs, each representing a rarity of the overall plethora of diseases, collectively classifying them as orphan diseases(3).

Next to a careful clinical evaluation and physical examination of the patients, conductance of lung function and diffusion capacity for carbon monoxide (DLco) and/or blood gas analysis as well as High Resolution Computer Tomography (HRCT) remain as the gold standard for the initial diagnosis as well as follow up of ILD (4)(5).

The provision of these diagnostic tools and further adequate care in the western world is usually provided through a specialized multidisciplinary discussion (MDD) board, resulting in a multi-disciplinary deliberation based on the above-mentioned measures and additional serological and histological diagnostic tools. Such MDD boards are most often offered through large tertiary care centers, allowing access to more specialized medications and potential surgical interventions such as lung transplants (1)(6). It is by their very nature that these specialized centers are located around large population clusters, contributing to an inequality in their access for rural communities (7). Additionally, the longitudinal course of disease is highly heterogenous, with acute exacerbations (AEs) in patients precipitating within days, rendering regular follow up within 3- 6 monthly intervals inadequate (8).

With the rise in handheld technology, it has been postulated that a form of portable monitoring could overcome an inadequate monitoring pattern and thereby improve our understanding of disease progression, improve data collection for novel treatment options and reduce healthcare inequality.

A most recent literature review, evaluating the use of home spirometry and exercise testing in various ILDs, has given praise for its potential to improve healthcare inequality and increase the monitoring density of lung function. A common criticism to home monitoring however, has been an array of technical and quality control issues leading to highly variable lung function data (9).

1.1 Epidemiology and Classification of ILDs:

The term ILD is used as an umbrella term for several diseases of different aetiologies. The predominant abnormality common to many ILDs is the pathological infiltration of various inflammatory cells and the activation of fibroblasts. Since the playing field of this intricate pro-fibrotic milieu is principally within the lung interstitium, they are referred to as ILD. If one were to assess the pathophysiology of ILD pedantically however, it should be noted that most forms transcend the infiltration of all three lung compartments (alveolar, interstitial and vascular) (2). The vast majority of ILDs are subsequently a result of either excessive inflammation or fibrosis, or more often than not, a combination of the two.

The exact triggers leading to the destruction of the lung structure can vary widely. Some ILDs develop as a result of systemic autoimmune diseases, such as collagen disease, vasculitis, and rheumatoid arthritis. Some are caused by inhaled toxins, environmental pollutants or medications. Other causes include ILDs characterised by the development of cysts or airspace filling. The most prominent group are those of the Idiopathic Interstitial Pneumonias (IIP)s, of which Idiopathic Pulmonary Fibrosis (IPF) remains the deadliest, with a mortality akin to many malignant diseases (10). In contrast to many other forms of ILDs triggered by chronic inflammatory conditions, IPF seems to be primarily caused by chronic alveolar epithelial injury.

The precise causative disease is determined through an integration of clinical, histopathological, and radiological parameters. However, the classification of ILDs

remains dynamic, as ongoing genetic and biochemical discoveries continue to reshape our understanding of their pathogenesis. Despite significant advances, approximately 10% of ILDs still fail to meet established diagnostic criteria and are categorized as unclassifiable ILD (11).

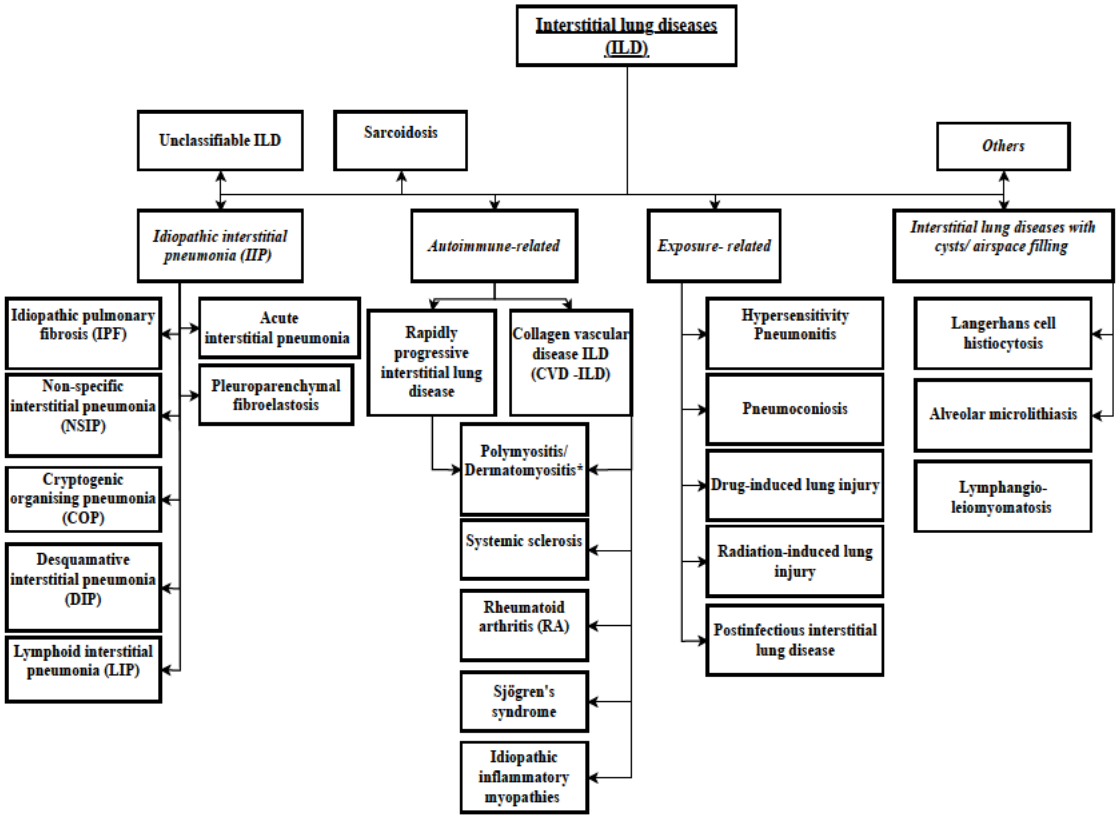


Figure 1: Current classification of ILDs

Adapted from (3)

Abbreviations: COP= Cryptogenic organising pneumonia, CVD-ILD= Collagen vascular disease ILD, DIP= Desquamative interstitial pneumonia, IIP= Idiopathic interstitial pneumonia, ILD= Interstitial lung disease, IPF= Idiopathic pulmonary fibrosis, NSIP= non-specific interstitial pneumonia, RA= Rheumatoid arthritis

1.1.1 IIPs

The most severe and common form of IIP remains IPF with a median survival rate of untreated IPF currently at 2-3 years and an incidence reported at between 0.9- 13.0 cases per 100 000 people within the western world. It is most often associated with older age (>60 years) and male sex (1,13,14).

IIPs distinguish themselves from other ILDs by remaining particularly challenging to study due to their unclear etiologies. Current classifications are primarily based on the consensus guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS). According to the consensus guidelines published in 2002 and 2013 respectively, the diagnosis of IIPs relies on a combination of characteristic imaging findings on HRCT and distinctive histopathological patterns (12,13).

1.1.2 Autoimmune- related ILD

Autoimmune- related ILDs represent a significant subset within ILDs. They are identified by differing degrees of inflammation or fibrosis within the lung parenchyma, reflecting the pulmonary manifestation of systemic autoimmune dysregulation. The chief culprits in this case are the presence of specific autoantibodies and down-stream upregulation of the immune system (14).

The relative risk of developing ILD from autoimmune-related diseases, is highly dependent on the underlying disease. In Rheumatoid arthritis, the relative risk of developing ILD is between 5% to 58% whilst other diseases such as Systemic sclerosis are more likely to develop into ILD with a risk between 40% to 91% (15). For such patients, the 5 year mortality is 3 fold higher than patients with the same disease but without a pulmonary manifestation (16).

1.1.3 Exposure- related ILD

Of the exposure- related interstitial lung diseases, Hypersensitivity Pneumonitis is the most common (17). Hypersensitivity Pneumonitis is based on the development of a type III/ IV allergic reaction against inhaled dusts. Over 200 antigens, largely organic in nature, are known to cause the disease in susceptible patients (18). Whereas mold in hay and straw is known to cause “farmer’s lung”, bird droppings and feathers may lead to “bird breeder’s lung”. Usually, a combination of repetitive exposure to specific antigens and a genetic predisposition leads to disease development.

The pathophysiology follows the path of antigen presentation, immune sensitization and a fulminant inflammatory response, of which specific IgG antibodies form to specific antigens (19). With local inflammation simmering and granuloma formation developing,

fibrotic remodeling can occur with chronic fibrotic HP being akin to IPF in its prognosis (20).

1.1.4 Sarcoidosis

Sarcoidosis holds a unique place within the realm of ILD due to its relative obscurity in both disease progression, etiology and potential for spontaneous resolution. Sarcoidosis is often referred to as a sterile non- necrotizing granulomatous disease where the exact pathogenesis is still unclear. It is speculated that, based on an inherited disposition, patients with sarcoidosis react to cell wall components of gram + bacteria (chord factor e.g. in Propioni Bacteria Acnes) or to other dusts (e.g dusts from the World Trade Center terror attack) with a granuloma formation (21,22)
Common consensus describes a mechanism by which macrophages and activated T cells form granulomas within sites of the body (23). Sarcoidosis usually develops within the lymph nodes, skin or the lungs, though any organ can later be affected. Pulmonary involvement occurs in 90% of all sarcoidosis cases, with between 10% to 40% developing into Stage IV and thus lung fibrosis (24).

1.2 Symptoms and Disease Burden

The hallmark symptoms of ILDs at onset include progressive dyspnea on exertion and a persistent non-productive cough. It is typical that these symptoms progress over time, severely impacting the physical function and quality of life for patients. Although the rate of progression is highly variable, most untreated patients can expect a gradual decline in their lung function capacity over time. In later stages, hypoxemia and fatigue become more pronounced, rendering patients to become dependent on supplemental oxygen (3).

Additionally, patients are at an increased risk of developing AEs, defined as a sudden and unexplained worsening of respiratory function (2). AEs are insidious and unpredictable events associated with significant morbidity and a high mortality rate of up to 50% in IPF patients (25–27). The triggers of AEs can be due to infections, environmental exposures or due to complete spontaneity, rendering timely diagnosis and treatment difficult.

1.2.1 Treatment

Until the advent of specific disease-modifying medications, patients with primarily inflammatory triggered ILDs were dependent on broad immunosuppressive medication in the form of Corticosteroids, Azathioprine or Cyclophosphamide with limited treatment success (28). Additionally, in some rheumatic forms of ILD, biologicals or modern immunomodulatory drugs (e.g mycophenolate mofetil) have some additional benefit (29).
A true paradigm shift was initiated when the Japanese government first licensed the use of Pirfenidone as an anti- fibrotic agent in IPF in the year 2008 (30). In 2020 Nintedanib followed suit, only this time with an American FDA approval to treat patients with Progressive Pulmonary Fibrosis independent of their origin, considerably enlarging the target audience (31).
These treatments have been shown to reduce the annual decline in lung function by approximately 50% in individuals with progressive ILDs (32).
Despite these strides in treatment options and some indication that Pirfenidone and Nintedanib reduce the risk of AEs, the latter still represents a major cause of mortality in ILD patients (33).
The most commonly used treatment for AEs remains a high dosage corticosteroid regime, although never tested and proven beneficial in the setting of a prospective, randomized controlled clinical trial (34). In addition, supportive therapies such as antibiotics are applied should a concurrent infection be present (35). Critically however remains the early recognition of AEs as even short delays are associated with worse outcomes (36).

1.3 Diagnosis

1.3.1 Imaging

The first line diagnostic imaging modality for ILD is the chest X-ray due to its wide availability, relative cost effectiveness and its ability to discern other potential causes for the typical symptoms at onset for ILDs. Typical findings for interstitial lung disease may include increased reticular markings in the basal lung regions or air-filled cavities. Whilst indicative, these changes give only limited information about the underlying form of ILD and the true extent of disease.

It is due to the superiority in image resolution and 3-dimensional aspect ratios, that HRCT remains the gold standard in the diagnosis of ILDs. Standardised protocols, predominantly originating from the consensus paper of the American Thoracic Society/European Respiratory Society (ATS/ERS) from 2018 has led to three distinct image patterns described for ILD (37). Among the three described patterns, the Usual interstitial pneumonia pattern is most commonly associated with diseases in which lung fibrosis is the predominant pathology, such as drug-induced ILD (e.g., amiodarone), ILD related to collagen vascular diseases, and asbestosis. Notably, the presence of a Usual interstitial pneumonia pattern is a prerequisite for the diagnosis of IPF.

1.3.2 Further Investigations

While findings on HRCT form the cornerstone of ILD diagnosis, a range of additional tests and examinations are required to identify the exact subtype and underlying cause. Pulmonary function tests, such as spirometry and DLco, are crucial for assessing lung restriction and gas exchange impairment, with spirometry playing a key role in monitoring disease progression.

Blood tests, including autoimmune serology panels, are instrumental in diagnosing connective tissue disease-associated ILDs. Bronchoscopy and bronchoalveolar lavage provide cellular and microbiological insights in certain cases, while histopathological confirmation necessitates cryobiopsies or surgical lung biopsies, particularly when imaging and clinical findings remain inconclusive (2). Together, these diagnostic modalities enable precise classification and guide tailored management strategies for ILD patients.

1.4 Importance of Lung Function Monitoring

1.4.1 Spirometry

Spirometry plays a vital role in both the initial diagnosis and ongoing monitoring of ILDs. By requiring patients to perform standardized inspiratory and expiratory manoeuvres, it generates data on lung volumes and airflow over specific time intervals. With its widespread availability, reproducibility, and strong correlation with a patient's lung function, spirometry is uniquely positioned to provide valuable longitudinal data, enabling the assessment of lung impairment progression over time.

The following parameters are measured in a spirometry manoeuvre and are typically measured in the unit Litres (L) (38,39):

- Vital capacity
- Forced Vital Capacity (FVC)
- Inspiratory vital capacity
- Inspiratory reserve volume
- Expiratory reserve volume
- Forced expiratory volume in 1 second (FEV_1)
- Peak expiratory flow
- Forced expiratory time
- Tidal volume

In the first instance, spirometry data helps distinguish between obstructive and restrictive lung pathologies, with restrictive patterns being a hallmark of ILDs. Restrictive lung disease is defined by reduced lung expansion, which leads to decreased lung volumes. Key spirometric features of restrictive lung disease include a proportional reduction in both FVC and total lung capacity. In contrast to obstructive lung diseases, such as asthma, where airway narrowing impairs exhalation, restrictive lung diseases preserve the ability to exhale air. As a result, the ratio of FEV_1 to FVC is typically normal or even increased, reflecting a limitation in lung volume rather than airway obstruction.

FVC plays a crucial role in diagnosing and monitoring ILDs, as it measures the total volume of air a person can exhale forcefully after a full inhalation, directly reflecting lung volume. Since ILDs are progressive conditions that reduce lung volume over time, changes in FVC provide a reliable measure of disease progression. For this reason, proportional FVC decline over time is a standard measurement for monitoring the progression of ILDs (40).

1.5 Limitations of Traditional Spirometry

In hospitals and in most pulmonary outpatient clinics, body plethysmography is used instead of spirometry. Next to the parameters outlined above, the body plethysmography additionally allows measurement of further important lung function parameters such as the residual volume and the total lung capacity.

Complementarily, to providing the variables mentioned in Section 1.4.1, they are usually accompanied with a DLco measuring device, yielding high quality all round pulmonary function data (37). They require specially trained staff to operate and maintain the devices as well as instruct patients on the proper technique.

It is for their precision, that body plethysmography and DLco are the mainstream diagnostic modality during regular 3-6 month follow up in specialised clinics for the monitoring of ILD patients.

It has to be considered however, that these devices are notably absent in most small community or primary care practices (41).

Whilst therefore yielding reliable lung function data, the limitation of body plethysmography and DLco lies in its complexity and limited availability, requiring ILD patients to travel considerable distances for regular monitoring (9). Furthermore, their appointments are often made more difficult due to their dyspnoea, need for supplemental oxygen and dependency on assistance by caregivers. Finally, FVC, the key parameter used for characterization of disease progression, can be obtained equally well with spirometry.

Additionally, progressive disease and development of AEs may require tighter monitoring regimes than is possible with currently practiced, intermittent follow up (2). This, combined with the heightened risk of cross-infection among already vulnerable patients during the Coronavirus pandemic, has fostered an increased willingness among healthcare providers to explore alternative solutions (42,43).

1.6 Handheld Monitoring: A New Frontier in ILD Management

With the advent of handheld technology, the option of empowering patients to monitor their own exercise capacity, lung function and symptoms has emerged. Perhaps most promising has been a multimodal approach with a combination of symptoms questionnaires, pulse oximeters, exercise tests and handheld spirometry allowing an in depth analyses of disease trajectory (9,44,45).

It has generally been shown that adherence and compliance to home monitoring is initially high with some reduction in adherence over time (46). Similarly, reliability and reproducibility of home spirometry has been established by a systematic review (47). The advantages of home monitoring are numerous and complementary to the disadvantages of on-site monitoring. There is a reduction in healthcare inequality, less risk of contracting hospital acquired diseases, earlier identification of disease complications, greater patient involvement and empowerment as well as the potential to reduce health care costs associated with unnecessary appointments (7,9,48,49).

Recently the first pilot study assessing a combination of patient reported outcome measurements (PROMs) and exercise testing was able to predict AEs through a reduction in post exertional peripheral capillary oxygen saturation (SpO_2) weeks prior to the diagnosis of an AE in ILDs (50). There was, however, a notable absence of handheld spirometry data.

1.6.1 Current Challenges

Since 2016, when the first study on the use of handheld spirometry was published, numerous research has been conducted on improving the reliability and acceptance of handheld spirometry as well as implementing further objective and subjective outcomes in the form of exercise tests and PROMs (44,50–56). One of the most common criticisms to home monitoring, specifically handheld spirometry, has been inadequate quality feedback mechanisms which assess each spirometry blow individually and provide feedback to patients (9,54,57,58). This has often led to highly variable lung function data, requiring either retrospective correction or crude exclusion of lung function measurements below certain limits.

More crucially however, a lack of instantaneous feedback discourages proper spirometry technique and makes real-time analysis difficult.

Other criticisms have revolved around technical difficulties in connecting multiple devices like the handheld spirometer and pulse oximeter via Bluetooth or a poor integration of the app software (9). It should also be noted that the widespread use of technology inevitably excludes older less technologically informed patients (59).

1.6.2 Algorithm-based Feedback

As of yet, no robust detailed feedback algorithm adhering to the updated 2019 ATS/ERS guidelines for spirometry has been widely implemented in studies evaluating the use of handheld spirometers. This is especially significant since previous findings from 2022 showed that Artificial intelligence quality (ArtiQ) algorithms could retrospectively detect bad-quality spirometry blows with an accuracy of 88,5% in FVC parameters (60). This suggests that a form of an integrated machine learning algorithm could potentially give real-time feedback on any spirometry measurement, therein improving measurement data and blow technique. As of yet, two published protocols have mentioned the implementation of such an algorithm (61,62).

1.6.3 Exercise Testing

Exercise induced oxygen desaturation is seen as an important independent prognostic indicator of mortality by current international guidelines (1). Using the standardised 6 Minute-walk test, it has been shown that significant desaturation was a strong predictor for mortality in IIPs (63) with Japanese guidelines including the results in its severity staging (64). As the name suggests, it involves patients walking continuously for 6 minutes whilst the SpO2 are recorded via a pulse oximeter.

Due to its relative time consumption for patients, numerous studies have proposed an alternative exercise test in the form of a 1 Minute Sit to stand test (1MSTST) with comparable accuracy to the 6 Minute-walk test (65,66). It involves patients placing a standard 46cm high armless chair against a wall whilst the patient attaches a pulse oximeter to his finger. Prior to commencing, patients must sit upright with a right angle between hips and knees. Similarly, the feet must be flat on the ground with the arms resting on their hips. Once a signal is being given, patients continuously sit and stand without the use of their arms within a 1-minute window. The SpO_2 is measured every

second during the test (67). This allows better integration into the lifestyle of patients for home monitoring.

1.6.4 PROMs

Contextualising the subjective wellbeing of patients in the form of questionnaires provides further information to clinicians and aids the holistic treatment while improving patient outcomes (68). There is a wide range of PROMs, ranging from broad quality of life questionnaires such as the EQ 5D 5L (European quality of life 5 Dimensions- 5 Levels) to disease specific questionnaires like he King's Brief Interstitial Lung Disease questionnaire for ILDs (69,70). As of yet, there has been a notable lack of correlating disease specific questionnaires with changes in FVC.

2 Objectives:

This prospective multi- centre sub study conducted under the European ILD register (eurILDreg) aimed to validate the use of handheld spirometry for home monitoring in patients with ILDs in a "real world" population. Recruitment and data collection were done with 64 patients providing written consent across specialty clinics and eurILDreg sites in Gießen, Barcelona and Catania.

Primary Endpoint

The primary objective within this study was the examination of adherence patterns in handheld spirometry and 1MSTST under the complete motivational disengagement of study organisers. The following aspects were considered for this endpoint:

- Impact of low adherence within the first month on further engagement
- Differences in adherence patterns between handheld spirometry and 1MSTST

Secondary Endpoints

As a secondary objective, this study aimed to verify the accuracy of usable handheld spirometry FVC and FEV1 compared to established on-site spirometry measurements. The following aspects were considered for this endpoint:

- Correlation of usable handheld FVC and FEV1 and on-site measurements
- Comparison of the change in slope of usable handheld and on-site FVC over time

Explorative Endpoints

The following further explorative endpoints were examined:

- Evaluation of responses provided by real-time ArtiQ feedback algorithm for handheld spirometry blows.
- Impact of poor initial blow technique reported by ArtiQ on further study engagement
- Significant changes in handheld FVC in response to reductions in EQ 5D 5L score or self-reported respiratory infections.

3 Methods:

3.1 Study Design and European ILD Register

This study is a prospective multi-centre study with recruitment in this preliminary analysis held between 11.04.23 and 04.08.24 as part of the European ILD register (eurILDreg). The register includes data for patients with interstitial lung diseases from participating centres in Germany, Italy, France, Spain, United Kingdom, Austria, Netherlands, Denmark and Belgium.

The eurILDreg and ILD-Biobank was formed on the 04.08.2021 as an amendment to the previous eurIPFreg formed in 2008 (AZ 111/08, first amendment from 20.03.2013)(71,72). Additionally, the eurILDreg is registered in the German Clinical Trials Register under DRKS 00028968. A further amendment was signed on the 02.12.2021 for the facilitation of this handheld sub study. A protocol for the eurILDreg was published by Krauss et. al in 2024 (73).

Data in this preliminary study under the eurILDreg was restricted to three participating centres in Barcelona, Catania and Gießen with each sites obtaining separate ethical approval from their designated ethics committees. A protocol for the “European ILD registry algorithm for self-assessment in interstitial lung diseases” was also published by Krauss et. al in 2025(62).

The clinical data within the eurILDreg is collected via baseline questionnaires completed both by participating patients themselves and by the treating physicians at the respective sites. The patient questionnaire includes information on demographics, symptoms, comorbidities, and quality of life. The physicians' questionnaire summarizes data from the physical examination, laboratory results, lung function tests, echocardiography, spirometry, right heart catheterization, imaging, comorbidities, and previous therapies. This study limited itself to a select number of on-site measurements with many aspects recorded in the larger register negated for this thesis. Spirometry data measured at the participating sites using large immobile spirometers, is classified as “on-site spirometry” data in this study.

All data regarding questionnaires and demographic are recorded anonymously by the participating sites and stored on the widely used and secure REDCap (Research Electronic Data Capture; Vanderbilt University) web- based platform.

3.2 Handheld Monitoring Software and Devices

Handheld monitoring software is supplied by PatientMpower (pMp), an Irish software developer specialised on patient-led monitoring since 2016. The App was specifically designed in corporation with study organisers and is available on both android and IOS operating systems. The App is available in German, Italian, Spanish and English. The spirometer (Spirobank Smart, MIR, Italy) and pulse oximeter (Nonin Medical, Inc. Plymouth, MN, USA) connect via Bluetooth to the pMp app.

During recruitment, patients are provided with an anonymous pMp account, including the login credentials, the handheld spirometer and a pulse oximeter. In cases where patients do not have a viable mobile phone, they are additionally provided with an Alcatel 1 smartphone. The pMp App amalgamates all aspects regarding handheld spirometry, 1MSTST, PROMs and daily symptoms checks into one platform.

Patients then receive extensive guidance and printed instruction sheets on all the procedures involved. A standardised teaching procedure for patients, available in German, Italian, Spanish and English is utilised by all three participating sites, allowing any initial troubleshooting or questions to be answered. Similarly, study nurses help download the app and connect the spirometer and pulse oximeter via Bluetooth whilst also logging them onto their respective accounts. Most importantly, patients are helped to perform the first handheld spirometry, 1MSTST and PROMs during recruitment.

Patients also receive daily reminders to perform a handheld spirometry manoeuvre, 1MSTST and daily symptoms check on their mobile devices. Typical daily reminders are set in the morning for measurements to be reproducible and to avoid hindering the daily life of patients.

3.2.1 Handheld Spirometry/ ArtiQ Feedback

Following an initial demonstration of the spirometry manoeuvre, patients are made familiar with the ArtiQ algorithm. The ArtiQ algorithm assesses the usability of each spirometry blow in real time against the current ERS/ ATS spirometry guidelines. Should a blow be classified as "rejected", patients receive specific feedback and be asked to perform another manoeuvre. Patients are also familiarised with the battery replacement (every 4-6 months) and cleaning of the mouthpiece and rotor on a weekly basis.

3.2.2 1MSTST

The exercise test is explained to patients as per Section 1.6.3 with the SpO2 and Borg Dyspnoea score being recorded before initiating the test. The app does not initiate the exercise test if the pre- test vitals record a tachycardic heartbeat over 120 beats per minute or the SpO2 is measured below 90%. Additionally, should the SpO2 drop below 85% at any point during the test, an alert will be triggered, and the test will immediately stop. Patients also have the option of pausing the test at any time. Once completed, patients are asked to record the number of repetitions and their Borg dyspnoea score. Continuous SpO2 measurements are automatically recorded in the app. In this study, 1MSTST and exercise testing is used interchangeably.

3.2.3 Daily Symptom Check

Upon opening the app, patients are additionally asked to complete the daily symptom check on a daily basis. To avoid asking unnecessary questions, once patients report a "no" after question 1, they will not be prompted to answer the proceeding questions. Table 1 summarises the questions below

Table 1: Daily symptom check questionnaire

Number	Question/ Answer
Question 1	Do you have a worsening cough?
Answer 1	Yes| No
Question 2	Do you feel as if you have a flu or respiratory infection?
Answer 2	Yes | No
Question 3	Are you producing sputum?

Answer 3	Yes | No
Question 4	Are you producing coloured sputum?
Answer 4	Yes| No
Question 5	Do you have flu-like headaches or muscle pain?
Answer 5	Yes | No
Question 6	Do you have a fever?
Answer 6	Yes| No
Question 7	As you reported a fever, may you please enter your temperature?
Answer 7	[temperature recorded in Celsius]

3.2.4 EQ Visual Analogue Score (VAS)

Patients are asked to complete the European Quality vertical Visual analogue scale (EQ VAS) every 3 months or during periods of distress. The EQ VAS was chosen as opposed to the full EQ 5D 5L questionnaire since it is a direct visual representation in the quality of life a patient perceives, objectified as a numerical digit between 0 to 100, where the latter suggests a “perfect” quality of life.

3.2.5 Data Access

Patients are informed that there will be no active monitoring of their data by study nurses or physicians, and they will not be proactively contacted for motivation or data review during routine follow-up. However, patients are encouraged to access their longitudinal spirometry and exercise test results via the app and to reach out to their treating physician immediately if any significant issues arise or if they feel significantly worse.

3.2.6 Technical Support

Patients are able to contact a technical support line or approach participating sites, should any technical issues arise.

3.2.7 Data Transfer

Handheld data is managed by PatientMpower Ltd (Ireland registration 563516), based in Dublin (D08TCV, The Digital Hub) in accordance with EU regulation 2016/679. No

personally identifiable data are collected or transferred, and measurements are transferred on a monthly basis under the pseudonym provided in the app.

3.3 Patient Cohort, Inclusion and Exclusion Criteria

Participating Centres at the time between the 11.04.23 and 04.08.24 were El Instituto de Investigación Biomédica de Bellvitge in Barcelona, University Hospital "Policlinico - Vittorio Emanuele" in Catania and the Centre for Interstitial and Rare Lung Diseases of the Justus Liebig University Hodpital in Gießen.

Participants considered for the inclusion in this study must be at least 18 years old and have an ILD diagnosis established per current standards, verified by regional MDD panels. Exclusion factors include an inability to fulfil the technological requirements for smartphone and app usage, as determined by either the patient or the investigator, the absence of internet connectivity, and an inability to commit to at least a year of participation. Criteria for discontinuation encompass non-adherence, damage or misplacement of any study-related device, and disease advancement requiring transition to palliative care. Patients recruited within 2 weeks of the study conclusion were retrospectively excluded from further analysis.

3.4 Study Discontinuation

During the length of the study between 11.04.23 and 04.08.24, patients had the option to discontinue the study at will during either routine follow up or upon written confirmation and the return of all devices. Upon discontinuation, patients were approached by study nurses to complete a questionnaire detailing their study experience. Patients who voluntarily discontinued the study before 12 months were classified as “early discontinuation”. Patients discontinuing after 12 months were classified as “late discontinuation”. Table 2 shows the relevant questions and answers for the study discontinuation questionnaire.

Table 2: Bespoke study discontinuation questionnaire

Number	Question/ Answer
Question 1	How would you rate the comprehensibility of the app?

Answer 1	Very good | Fairly good | Poor
Question 2	How often did you experience technical difficulties using the app or performing the measurements (e.g. app not working, missing Bluetooth connection, etc.)?
Answer 2	Always | Often | Rarely | Never
Question 3	On average, how would you rate your motivation to perform the self-measurements?
Answer 3	Highly motivated | Moderately motivated | Hardly motivated
Question 4	How regularly did you compare your current measurement values with previous values?
Answer 4	Always | Often | Rarely | Never
Question 5	Were you able to derive personal benefits from the self-measurements?
Answer 5	Yes | No
Question 6	Do you believe that the results of the self-measurements correspond with your subjective experience of illness and the severity of your symptoms?
Answer 6	Completely agree | Somewhat agree | Do not agree at all

3.5 Analysis of Data

Patient cohort data and on-site spirometry measurements were made available via the eurILD registry. Anonymised handheld measurements were made available by PatientMpower and stored on the eurILDreg Data Warehouse through an encrypted connection. Graphs and statistical analyses were performed with Microsoft Excel and the statistics program R Version 2024.09.1+394 (http://www.R-project.org).

3.5.1 Missing data

Missing data regarding diagnosis or other descriptive aspects regarding the participants, were treated as an absolute exclusion criteria for further analysis in this study. Similarly, non-identifiable handheld data was excluded from further analysis.

3.5.2 Adherence:

Adherence was calculated as the mean number of patients completing at least one spirometry or 1MSTST measurement in the given week. Since patients were continuously enrolled during the study, late enrolment meant adherence was only considered for the time of participation until the due date of this study. The moment in time in which

information was given to discontinue the study, patients were no longer considered for the calculation of adherence.

Patients who had not performed any self-measurement despite having given no written or verbal indication of discontinuing within the study were thus still considered in the calculation of adherence. Patients were further differentiated into an adherent and non-adherent group to aid further analyses. Non-adherence would be defined as patients who had not performed weekly spirometry testing within the first 4 weeks of participation. The former would include all other patients.

3.5.3 Usability of Handheld Spirometry Data

Except for adherence calculations, only "usable" or "acceptable" handheld spirometry data assessed by ArtiQ, hence fulfilling the ATS/ ERS quality criteria, was considered in this study.

3.5.4 Correlation to On-site Measurements:

To correlate the on-site spirometry with handheld spirometry, the mean of the handheld spirometry 7 days before and after the on-site spirometry of each individual patient was considered and compared to the on-site spirometry of each individual patient. When patients were recruited and no handheld data was available for the preceding 7 days, the average of the proceeding 7 days was used, only. To compare the two pairs of spirometry data, the mean average of the handheld spirometry was taken as a percentage of the on-site spirometry.

Correlation analyses was performed using the Pearson's correlation coefficient. Reliability was assessed using the intraclass correlation coefficient. Agreement was calculated and presented by the Bland-Altman plot. Very strong correlation would be achieved with a Pearson's r >0.7. For intraclass correlation calculations, the ICC2 value would be used for reliability calculations. Excellent reliability would be achieved with an ICC2 value of >0.9 with good reliability calculated between 0.75 and 0.9. Bland-Altman analysis was used to evaluate the agreement and consistency between on-site and handheld measurements by determining whether the two modalities produced sufficiently similar results for practical use. For this, the 95% confidence interval (CI) and bias would

be calculated in L and compared to established literature values. Statistical significance for all tests was set at $p = <0.001$.

3.5.5 Handheld/ On-site FVC Change over Time

To maximise statistical significance, patients had to have at least 3 on-site spirometry measurements and over 100 handheld FVC measurements over a time span of at least 6 months. Slope calculations for both handheld and on-site spirometry was based on the time span in which data was available. The slope for the change in FVC over time was calculated using a linear regression analysis with statistical significance achieved with a $p = <0.05$. To detect a statistically significant difference between all on-site and handheld slopes, a paired t-test was performed. A p-value of >0.05 suggested that no statistically significant difference in slopes was observed, indicating that any differences in slopes were likely due to random variation rather than a true effect

3.5.6 Handheld FVC Change in Response to PROMs

To detect statistically meaningful changes in handheld FVC in response to changes in PROMs, an anchor analyses was performed.

To detect a statistically meaningful change in the EQ VAS score, dates were selected in which the score (out of 100) would be lower than the lower bound of the standard deviation (SD) of the mean score of all EQ VAS outcomes of each individual patient. Each date satisfying these specifications were used as an anchor date.

Should patients report a flu or respiratory infection in the symptom survey, the respective date in which it was first reported was used as an anchor date. In cases where patients would continuously self-report respiratory infections beyond 7 days in a row, any date after 7 days was ignored. Similarly, any further date in a 5-week window after the first date of self-reported infection was ignored for correlation testing.

To compare the averages in FVC measurements, around the date of PROMs, the average in FVC of 5 to 1 week preceding the anchor date (the so called “healthy period”) were compared to the average FVC 7 days before and after the anchor date (the so called “sick

period"). It is for this reason that continuous respiratory infections beyond 7 days or within a 5-week window had to be disregarded since it would have allowed "sick days" to be considered in the average calculations of the "healthy" 4-week period.

To detect a statistically significant change in the mean FVC, a one tailed T-test was calculated to compare the mean FVC before and around the anchor date. For the one tailed t-test, a plus or minus indicates the directional change in FVC before and after the anchor date, with higher values generally indicating larger differences relative to the variability in data.

To compare the median in FVC before and around the anchor date, a one tailed Wilcox signed rank test was calculated. The Wilcox signed rank test generally measures whether the median FVC significantly differs from before to after the anchor date with the value itself representing the sum of the signed ranks of differences between paired observations. The test works by ranking the absolute differences between paired values, assigning signs based on whether values increased or decreased, and summing these signed ranks.

Statistical significance for both tests was achieved with a p value of <0.05.

4 Results:

4.1 Descriptive Analyses of Patient Cohort

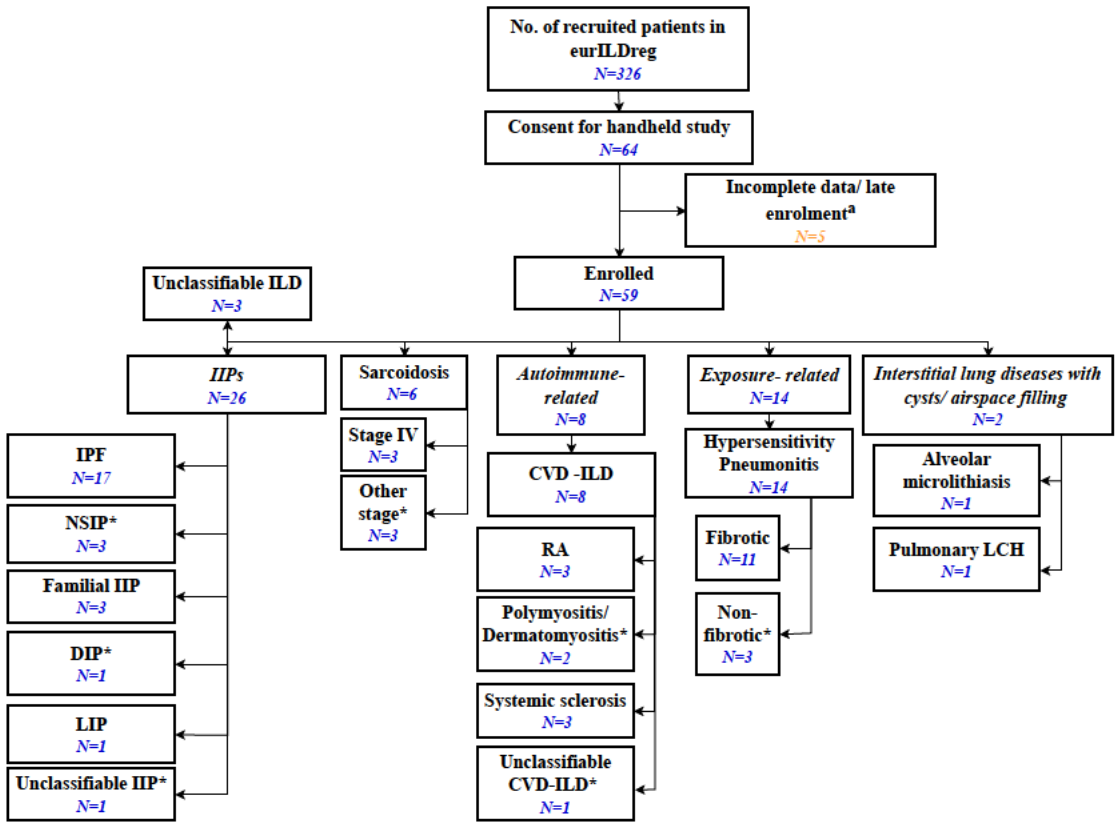


Figure 2: Distribution of ILD subtypes and patient enrolment

[a] 3 patients enrolled within 2 weeks of the conclusion of the preliminary study, yielding insufficient data. 1 patient with insufficient data regarding diagnosis and on-site data. 1 patient with non-matching handheld spirometry data.

* Patients without fibrotic changes on HRCT were excluded from measuring FVC decline over time. Within the NSIP and Polymyositis/ Dermatomyositis cohort, 1 patient each showed no fibrotic lung changes.

Abbreviations: CVD-ILD= Collagen vascular disease ILD, DIP= Desquamative interstitial pneumonia, IIP= Idiopathic interstitial pneumonia, ILD= Interstitial lung disease, IPF= Idiopathic pulmonary fibrosis, LCH= Langerhans cell histiocytosis, LIP= Lymphoid interstitial pneumonia, NSIP= non-specific interstitial pneumonia, RA= Rheumatoid arthritis.

Overall, 326 patients were enrolled within the eurILD registry, of which 64 provided written consent to participate in the handheld sub study at the three participating sites in Catania, Barcelona and Gießen. 5 patients had to be retrospectively excluded from further analyses due to either late recruitment or corrupted identifiable data. 18 patients were recruited at the participating sites in Barcelona, 5 in Catania and 36 patients in Gießen.

The most common ILD subtypes were the IIPs (44.1% of cases) with IPF making up the majority of cases within the group. Exposure and autoimmune-related ILDs (23.7% and 13.6 % respectively) represented a large minority of cases. No specific diagnosis could be established even after review by an MDD board in 5.1% of cases and were subsequently categorized as unclassifiable ILDs.

The demographic data is further shown in Table 3. The vast majority of patients were of male gender (76.3%) and were 62.06 ± 9.73 years old at the time of recruitment. The population had a Body Mass Index (BMI) of 27.63 ± 5.98, in line with the European average.

About 64% of patients were past or active smokers with an average number of pack years of 23.19 ± 15.64. At the time of recruitment, 40.98% of patients had been prescribed anti-fibrotic medication in the form of Nintedanib or Pirfenidone.

About 9.8% of patients had a systolic pulmonary arterial pressure of over 35mmHg suggestive of pulmonary arterial hypertension. The average FVC % of predicted at time t_0 was 78.65 ± 23.54 %.

Table 3: Demographic data of patient cohort

Parameters at time t_0	Patient Cohort
Number of patients enrolled (n)	59
Male gender (%)	76,3
BMI (mean ± SD (kg/m²))	27.63 ± 5.98
Age at time t_0 (mean ± SD (years))	62.06 ± 9.73
Smoker/ Ex-smoker/ Non-Smoker (%)	3.28%/ 60.66%/ 36.07%
Pack years (mean ± SD)	23.19 ± 15.64
Estimated 10-year survival according to Charlson Comorbidity Index (CCI)(mean in % ± SD)	59.96 ± 29.48
Caucasian Ethnicity (%)	95%
Under anti-fibrotic medication* (%)	40.98%
Patients with systolic pulmonary arterial pressure (sPAP) > 35mmHg (%)	9.8%
On site FVC at time t_0 (% of predicted; mean ± SD)	78.65 ± 23.54
On site FEV1 at time t_0 (% of predicted; mean ± SD)	78.78 ± 22.49
EQ-5D-5L Scores (mean ± SD)	64.82 ± 22.76

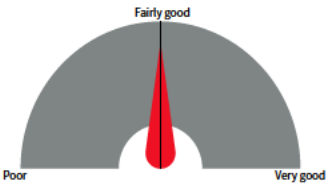
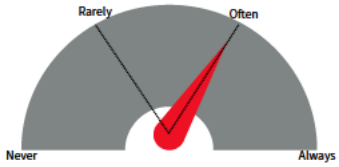
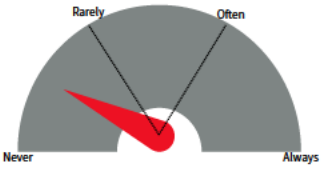
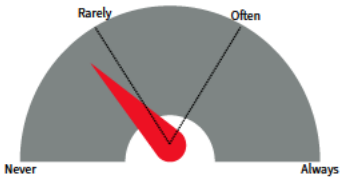
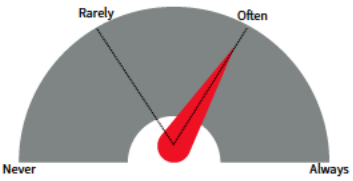
Abbreviations: BMI= Body Mass Index, EQ-5D-5L= European Quality of Life 5 Dimensions- 5 Levels Questionnaire, FVC = Forced Vital Capacity, FEV1= Forced Expiratory Volume in 1 second, kg= Kilogram, m^2= Square meters, mmHg= Millimetre(s) of Mercury, n= Number of Patients, SD= Standard deviation, sPAP= Systolic pulmonary arterial pressure.

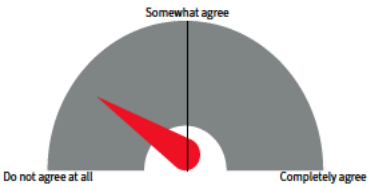
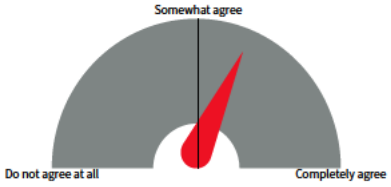
4.1.1 Study Discontinuation Questionnaire

Of the 59 patients within the cohort, 12 patients (20.3%) discontinued their participation within the study. There were 7 patients discontinuing their participation before 12 months (early termination), of which 5 patients (71.4%) responded to the questionnaire. 5 Patients discontinued after 12 months (late discontinuation), of which 4 patients (80%) responded to the questionnaire. Responses to the questionnaire were converted into percentages to standardize and facilitate the interpretation of results.

A response indicating a negative answer (poor, never, hardly motivated, do not agree at all) was assigned a value of 0%, whereas a positive answer (very good, always, highly motivated, completely agree) was assigned a value of 100%. Intermediate responses were treated proportionally where necessary. The answers are visualised in Table 4.

Table 4: Comparison of user experience and perceived benefits between early and late discontinuation groups

Question	Mean of Early Discontinuation (n= 5 patients)	Mean of Late Discontinuation (n= 4 patients)
Q1: How would you rate the comprehensibility of the app?	 Mean:70% SD: ±27.4%	 Mean:50%; SD±40.8%
Q2: How often did you experience technical difficulties using the app or performing the measurements?	 Mean:66.7% SD:±23.6%	 Mean:16.7% SD±33.3%
Q3: On average, how would you rate your motivation to perform the self-measurements?	 Mean:80% SD±44.7%	 Mean:25% SD±28.9%
Q4: How regularly did you compare your current measurement values with previous values?	 Mean:25.7% SD±43.5%	 Mean:66.7% SD±38.5%
Q5: Were you able to derive personal benefits from the self-measurements?	 Mean:40% SD±54.8%	 Mean:25% SD±50%

Q6: Do you believe that the results of the self-measurements correspond with your subjective experience of illness and its severity?	 Mean:20% SD±27.4%	 Mean:62.5% SD±25%

Abbreviations: n= number of patients, SD= standard deviation, Q= question

4.2 Adherence

The reduction in sample size within the adherent group is summarized in Table 5. By week 48, 4 patients had dropped out, and an additional 18 patients did not complete the 12-month study period due to late recruitment. In the non-adherent group, 3 patients had dropped out by week 48, with only 4 patients still formally participating despite providing no readings beyond week 9. Furthermore, 5 patients (27.8% of the non-adherent cohort) were enrolled at a time when completing 4 weeks of spirometry blows was not feasible before the study's conclusion. Of note, it is important to state that participants were not motivated by phone calls or other measures by the study site to keep engaged in hand-held measurements

Table 5: Sample size in adherent group over time

Measurement Type	Baseline at T_0	12 weeks	24 weeks	48 weeks
Handheld spirometry measurement	N= 41	N= 37	N=25	N=19
1 MSTST exercise testing	N= 38	N=34	N=22	N=16

Abbreviations: N= number of patients

4.2.1 Handheld Spirometry

Within the cohort, 41 patients (69.5%) were classified as adherent, while 18 patients (30.5%) were categorized as non-adherent. Among the adherent group, 14 patients (34.1% of adherent cohort) demonstrated >90% adherence over a period of at least 24 weeks.

For the adherent group, the mean weekly adherence rate at 12 weeks was 81.1%. At 24 weeks, the mean weekly adherence decreased to 52.0%. By 48 weeks, the mean weekly adherence further declined to 36.8%.

Figure 3 shows the adherence pattern of the respective cohorts. Based on this figure, it could be observed that the adherence within the adherent cohort stabilised after around 24 weeks. In the non-adherent group, no additional spirometry readings were recorded beyond 10 weeks, showing that adherence during the first month of participation serves as a strong indicator of continued engagement.

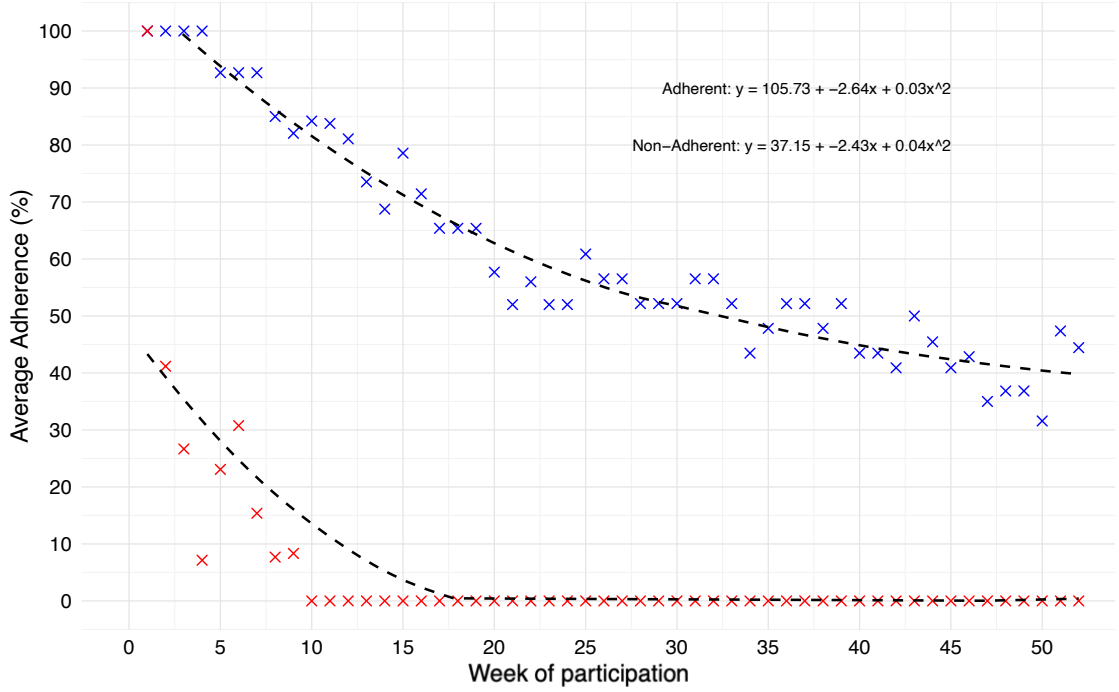


Figure 3: Weekly adherence to spirometry blows stratified by cohort over 52 Weeks

Kaplan- Meier survival graph showing mean adherence stratified by non-adherent cohort (n=18) in red and adherent cohort (n=41) in blue. Quadratic regression lines are labelled by their respective gradient above.

A significant proportion of patients remained within the study despite not performing any weekly blows or showed highly dynamic adherence patterns. Figure 4 represents the adherence pattern within the adherent group over the span of 52 weeks. Several key observations can be drawn from this figure. First, a clear gradient in adherence is evident. Patients with higher adherence, located in the lower rows (rows 27–41), maintained consistent spirometry measurements over extended periods, particularly up to 24–48 weeks.

In contrast, patients with lower adherence, seen in the upper rows (e.g., rows 1–10), exhibited significantly fewer recorded measurements, with spirometry adherence ceasing within the first 10–12 weeks. The figure further shows that for a subset of patients (e.g rows 7, 15, 22) intermittent non-adherence precedes either a complete disengagement or preludes worsening adherence. Other times, patients would exhibit complete adherence prior to complete disengagement (e.g rows 1-5). This finding underscores the challenge of retaining patients and predicting their adherence in the absence of regular motivation and interaction with healthcare professionals.

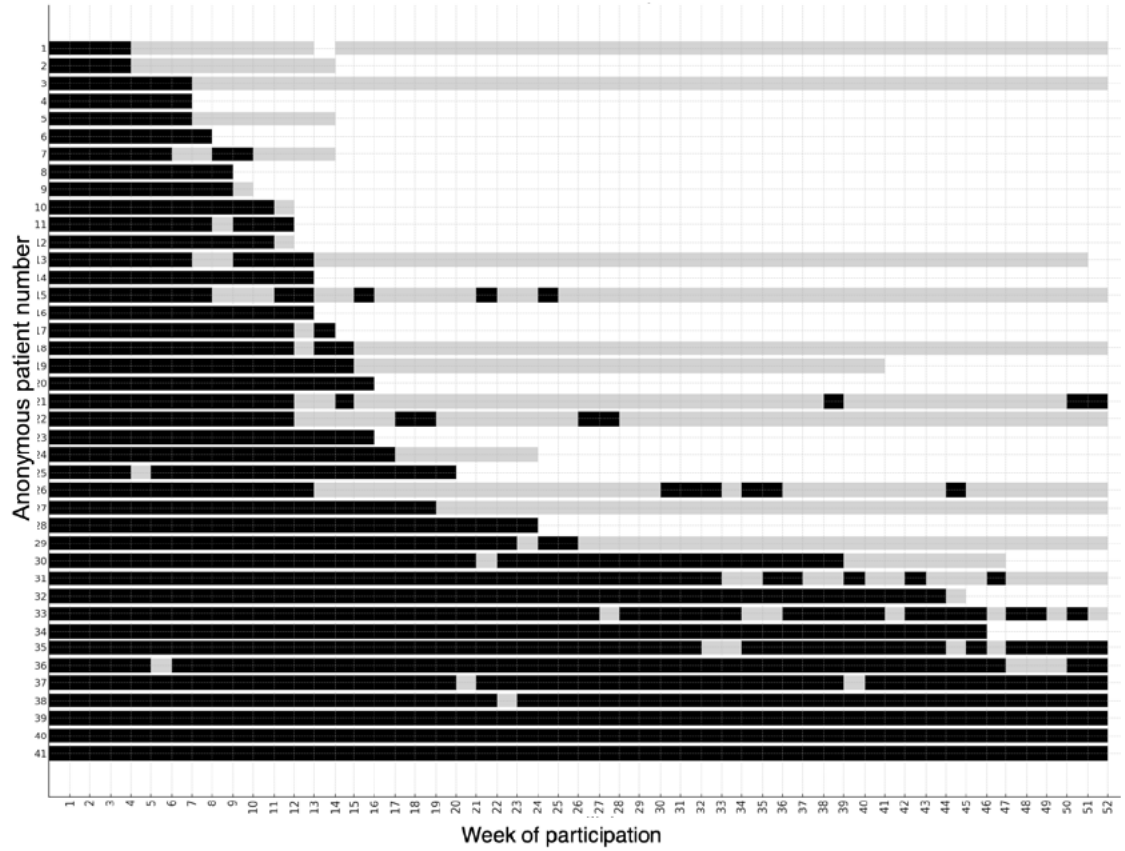


Figure 4: Weekly adherence pattern to spirometry measurements within adherent cohort

Gannt diagram illustrating adherence in given week. black representing adherence, grey indicating non-adherence with missing bars indicating either early study discontinuation or late recruitment.

4.2.2 Exercise Testing/ 1MSTST

Overall adherence to weekly exercise testing was lower than adherence to spirometry measurements. Of the 59 patients, 4 (6.8%) never attempted exercise testing. Among these, 1 patient was unable to provide representative SpO2 data due to the dermatological manifestations of systemic sclerosis, and another reported connectivity issues with the

pulse oximeter. No reasons were identified for the remaining 2 patients. Among the 55| patients who attempted exercise testing, 17 (30.9%) were classified as non-adherent, while 38 (69.1%) met adherence criteria. Notably, 11 patients (28.9% of the adherent group) achieved >90% adherence over 24 weeks.

The rate of decline in adherence is presented in Figure 5. Within the adherent group, the mean weekly adherence rate was 73.5% at 12 weeks, decreasing to 45.5% at 24 weeks, and further declining to 29.4% by 48 weeks. Figure 4 illustrates that adherence within the adherent cohort appeared to stabilize after 24 weeks, mirroring trends observed in spirometry adherence. In the non-adherent group, no additional exercise test readings were recorded beyond week 9. This reinforces the observation that adherence during the first month of participation strongly predicts continued engagement in both exercise testing and spirometry measurements.

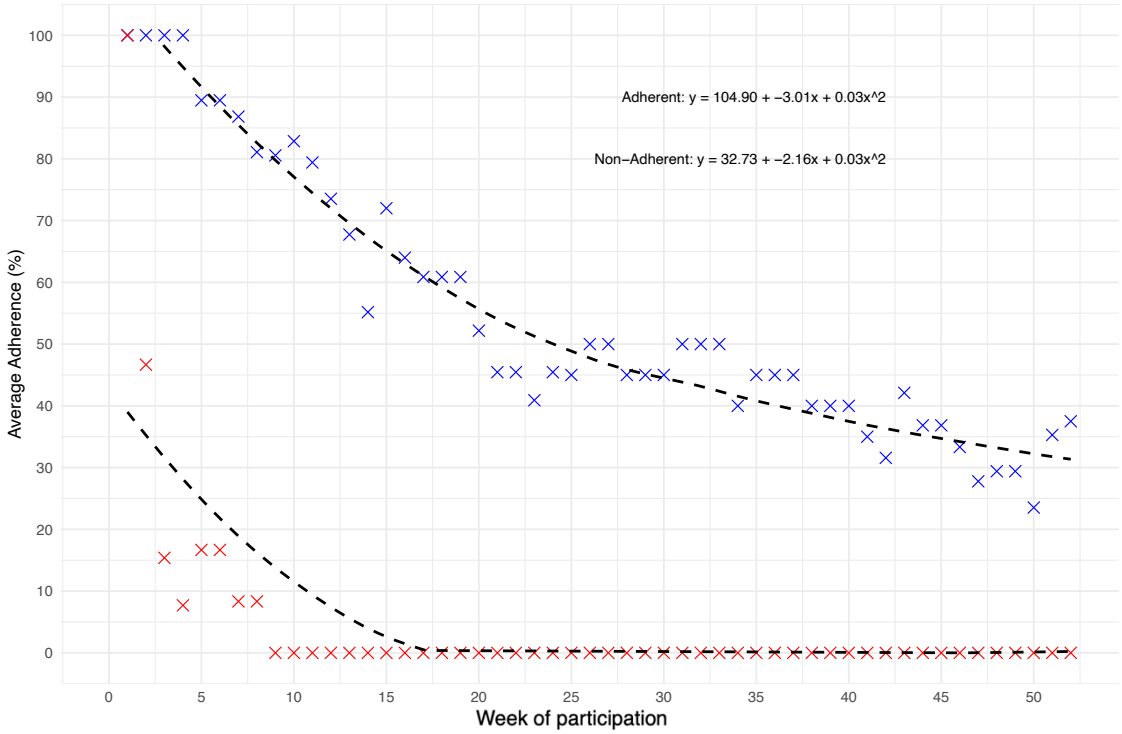


Figure 5: Weekly adherence to 1MSTST stratified by cohort over 52 weeks

Kaplan- Meier survival graph showing mean adherence stratified by non-adherent cohort (n=17) in red and adherent cohort (n=38) in blue. Quadratic regression lines are labelled by their respective gradient above.

Abbreviations: 1MSTST= 1 Minute sit to stand test

Figure 6 illustrates the adherence pattern for performing exercise test measurements among individual patients within the adherent cohort. Patients with higher adherence,

located in the lower rows (e.g., rows 29–38), demonstrated consistent engagement, maintaining exercise test measurements over extended periods, particularly up to 24–48 weeks. In contrast, patients with lower adherence, situated in the upper rows (e.g., rows 1–15), provided significantly fewer recorded measurements, with adherence ceasing predominantly within the first 10–12 weeks.

Similar to the trends observed in spirometry measurements, adherence to the 1MSTST displayed erratic tendencies, with no clear patterns emerging prior to complete disengagement. A direct comparison of the Gantt charts in Figures 5 and 3 reveals that the vast majority of patients exhibited nearly identical adherence patterns across both measurements. However, a small subset of patients demonstrated a preference for

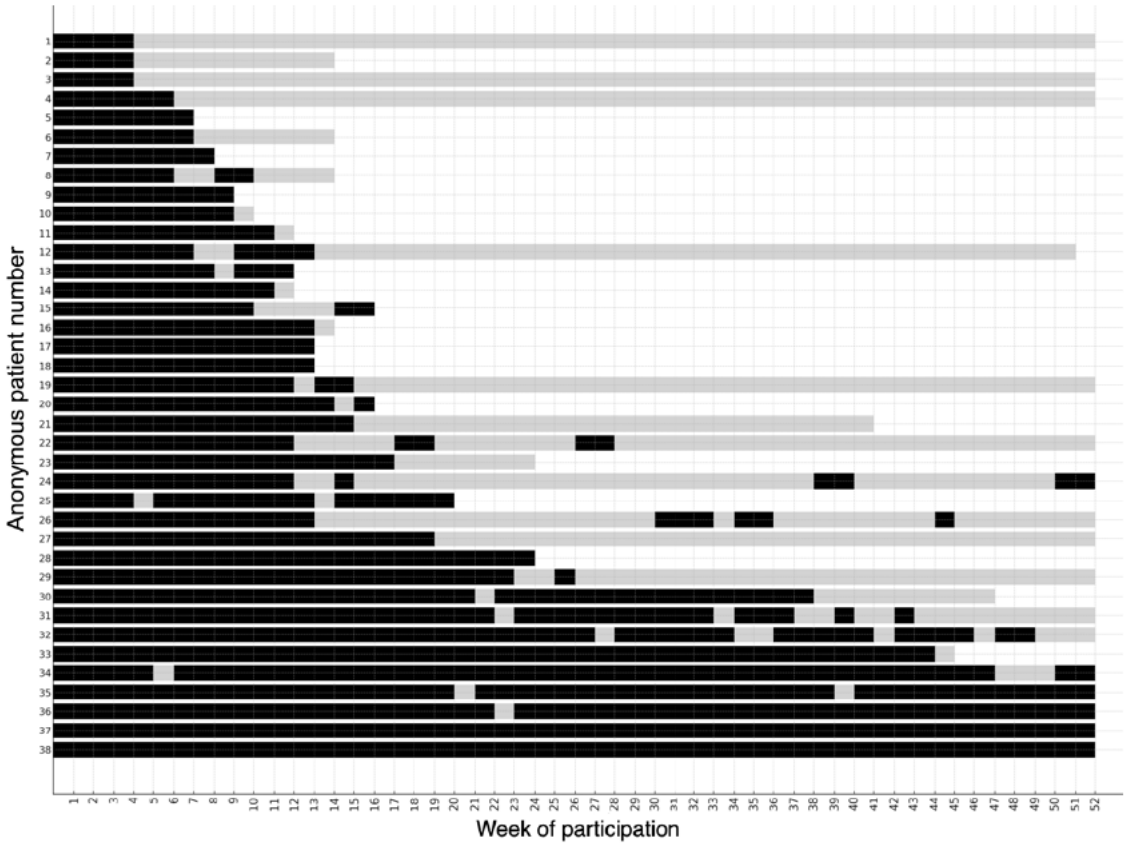


Figure 6: Weekly adherence pattern to 1MSTST within adherent cohort

Gannt diagram illustrating adherence in given week, where black represents adherence, grey indicating non-adherence with missing bars indicating either early study discontinuation or late recruitment.

Abbreviations: 1MSTST= 1 Minute sit to stand test

spirometry measurements over exercise testing, contributing to slight differences in adherence behaviour.

4.2.3 Adherence Across both 1MSTST and spirometry:

The contrast in adherence between spirometry and 1MSTST is visualised in Figure 7. The initial decline in adherence is more considerable for the exercise test, although both exhibit a critical phase of disengagement in the first 12 weeks after which re-engagement is rarely exhibited. Beyond 30 weeks, the engagement to both measurements converge with an adherence of 52.2% for spirometry and 50.0% for the 1MSTST at week 33. At no point during the entire time span does the adherence to exercise testing surpass that of the spirometry readings, suggesting a sustained preference for spirometry.

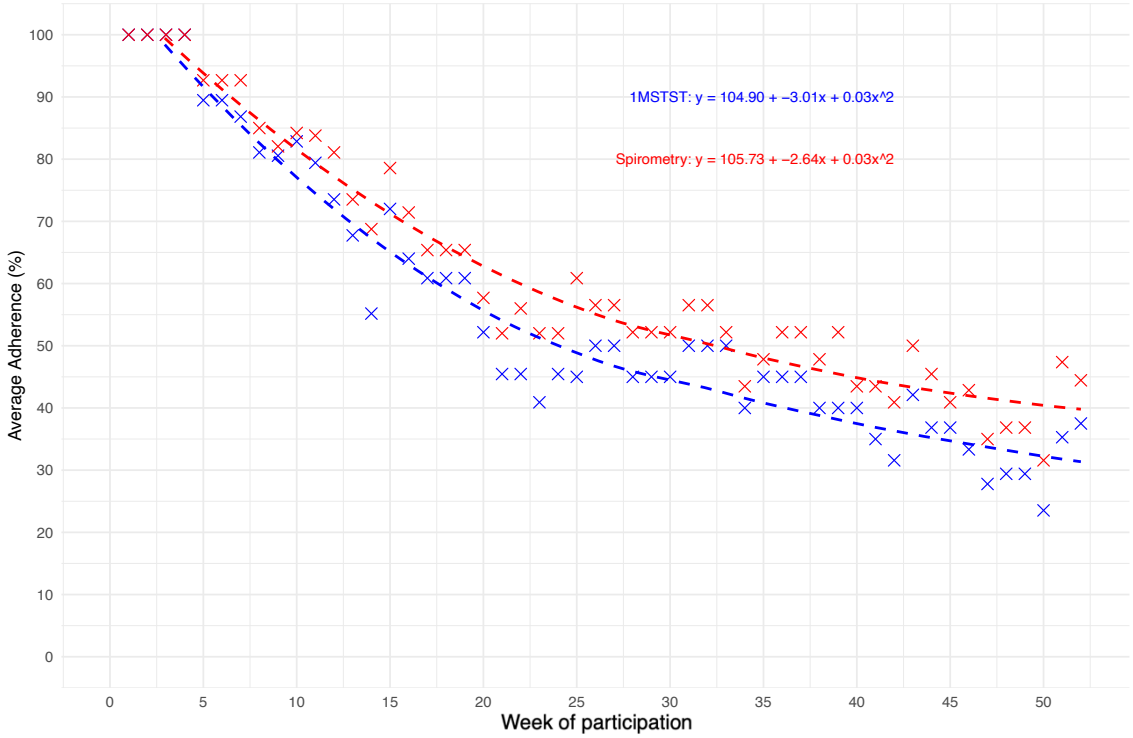


Figure 7: Adherence across adherent cohorts for 1MSTST and Spirometry measurements

Kaplan- Meier survival graph showing mean adherence of adherent groups stratified by 1MSTST in blue and spirometry in red. Quadratic regression lines are labelled by their respective gradient above.

Abbreviations: 1MSTST= 1 Minute sit to stand test

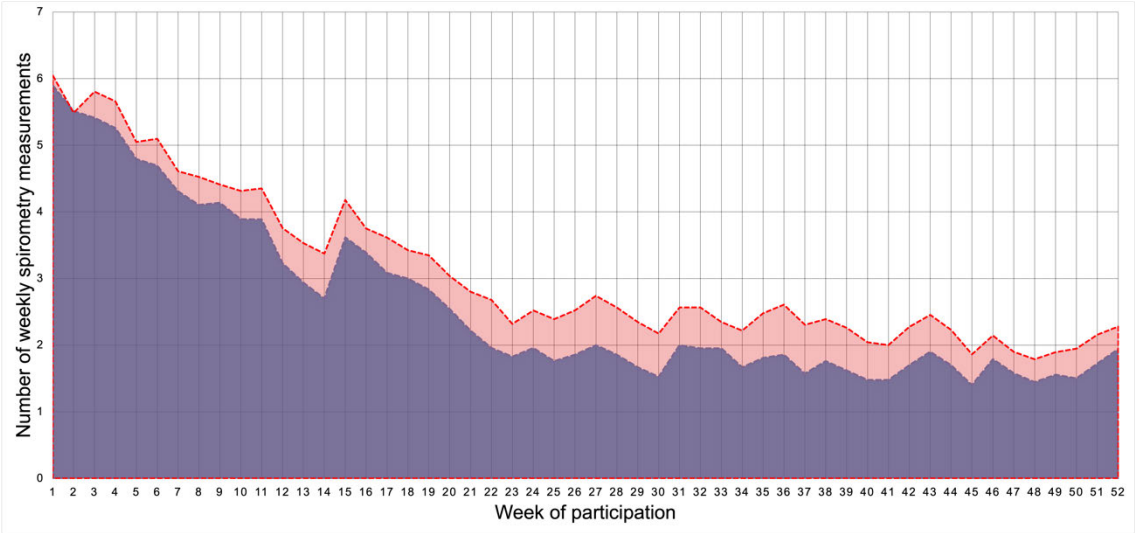


Figure 8: Average number of spirometry vs 1MSTST measurements recorded each week in the adherent group over 52 Weeks

Line graph illustrating the average mean number of weekly recordings for the mentioned tests. Blue= 1MSTST, red= spirometry

Abbreviations: 1MSTST= 1 Minute sit to stand test

Figure 8 provides a more nuanced perspective on patient compliance across both assessments. Consistent with the adherence patterns observed in Figure 7, patients initially demonstrate high engagement, with near-daily testing during the first four weeks. However, this is followed by a marked decline in compliance to handheld spirometry between weeks 4 and 22. Notably, from approximately week 22 onwards, a plateau emerges: patients stabilize their participation, averaging just over 2 spirometry tests per week over the subsequent seven months. A similar trend is evident for the 1MSTST, although it exhibits a steeper initial decline and stabilizes at slightly under two tests per week beyond week 22.

4.3 Handheld Spirometry Quality Control

Out of the total 7427 spirometry blows performed, 5432 blows (73.1%) were recorded as the first spirometry blow of the day. The remaining blows resulted from either failed first attempts or voluntary additional attempts. Table 6 summarises the reasons for failing to perform usable blows and adherence to further blows performed.

Notably, the relative risk of failing a spirometry blow increased from 24.72% on the first attempt to 46.57% on the second attempt. Despite being prompted to perform a second blow following a failed first attempt, only 40.13% of patients proceeded to make a second attempt.

Assuming all patients attempted a second blow, the relative risk of failing both blows on a given day across our cohort averaged 11.51%. Hence, in other words, our current algorithm of hand- held spirometry, with a software-based check of ATS/ ERS quality criteria and one repetition of the attempt in case quality criteria were not met, resulted in close to 90% fulfilment of ATS/ ERS criteria. In most cases, failure to produce a usable measurement was attributed to a multitude of reasons, with early termination of expiration being the most common cause although any combination of the given reasons was seen. The data also suggests that patients adapted to feedback from their failed first attempt, as reasons for failing the second attempt were more specific and involved fewer combinations in the second attempt.

Table 6: Overview for failing to perform usable spirometry blow according to the ATS/ERS guidelines

	First blow* N=5432	Second blow* N= 539
Adherence to 2nd blow after failed 1st blow	Not applicable	40.13%
Acceptable/ usable blow	N= 4089 (75.28%)	N= 288 (53.43%)
Failed blow	N= 1343 (24.72%)	N= 251 (46.57%)
Causes of failed blow		
unsatisfactory start of expiration	N= 410 (30.5%)	N= 101 (18.7%)
Coughing	N= 222 (16.5%)	N= 30 (5.6 %)
Early termination of expiration	N= 1254 (93.4%)	N= 481 (89.2%)
Valsalva maneuver or hesitation	N= 363 (27.0%)	N= 77 (14.3 %)
Obstructed mouthpiece	N= 9 (0.7%)	N= 9 (1.7 %)
Additional air intake	N= 178 (13.3%)	N= 20 (3.7%)

*Refers to the blow of the given day. Abbreviations: N= number of spirometry blows

Abbreviations: ATS= American Thoracic Society, ERS= European Respiratory Society N= Number of blows

4.3.1 Impact of Poor Initial Spirometry Technique and Higher Disengagement

Following the identification of an adherent and non-adherent patient cohort in section 4.2, the following analysis aimed to correlate whether possible dissatisfaction following poor first spirometry blows could drive non-adherence. Before the analysis, patients formally categorized as part of the non-adherent cohort (5 out of 18 patients, or 27.8%) were excluded from this investigation due to their late recruitment, which prevented them from completing the required 4 weeks of handheld measurements. This approach was retrospectively chosen as their continued engagement could not be evaluated and thus no conclusion could be drawn.

On average, the relative risk of failing the first spirometry blow of the day in the first week of participation was highest in the non-adherent group with a mean of 44.9% (SD 36.7%; n=13), as compared to a risk of 38.0% (SD 26.2%; n=23) in the adherent group and 37.2% (SD:23.3; n=14) in patients with a >90% adherence over half a year. Figure 9 illustrates a density curve diagram of the three patient groups for failing the first blow of the day within the first week of participation.

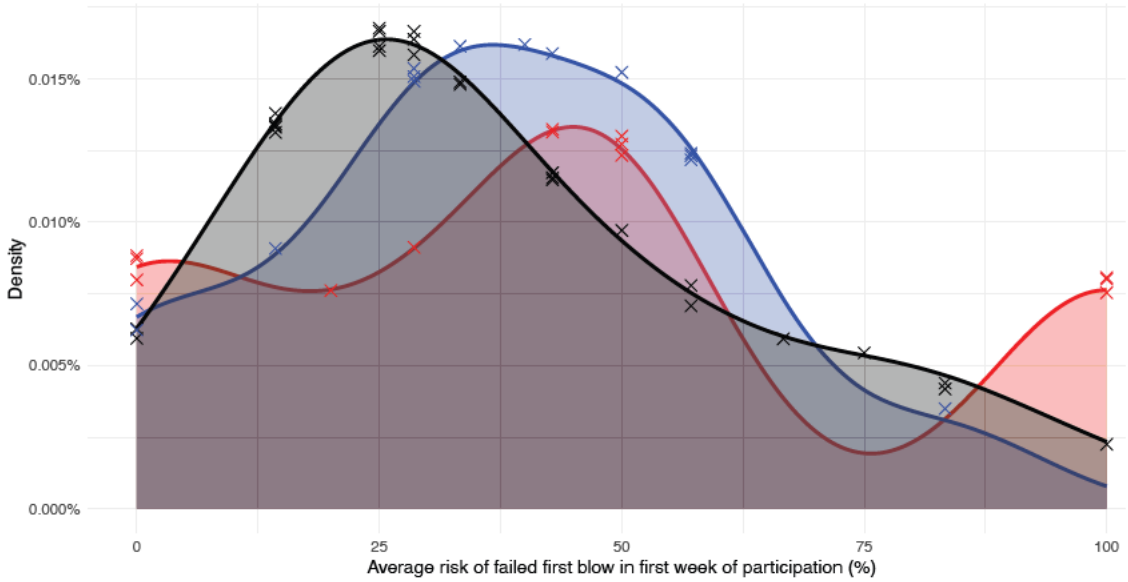


Figure 9: Mean weekly risk of failing the first daily spirometry blow in week 1, stratified by patient and patient cohort

Density calculated by kernel density estimate. Black data points and density curve representing adherent patients (n=23), blue representing >90% adherence over 24 weeks (n=14), red representing non-adherent patients (n=18)

Within the non-adherent cohort, the relative risk of failing the first spirometry blow of the day in the first week had a trimodal distribution with a large minority of patients either having a 100% or 0% risk with the peak shifted further to the right compared to the other

curves at around 45%. It also had the highest density of patients failing to produce any usable blow in the first instance (21.4%). Despite the data suggesting a correlation between poor initial technique and proceeding non-adherence, a Welch Two Sample T-Test of the means of the adherent and non-adherent cohort yielded statistically insignificant results (p= 0.55).

4.3.2 Patient Conditioning and Spirometry Technique Learning

Figure 10 represents the relative decline in the overall risk of performing a failed first spirometry across all patients per week. While some variability in the mean does suggest potentially other factors at play, the general downward trend is supported by a statistically significant (p=0.0004) linear regression analysis. In this regard, the average mean risk decreased from 43.07% (n= 59 patients, SD: 33.02%; median: 36.7%) in week 1 to 12.54% (n= 13 patients, SD:12,72%; median: 14.28%) by 6 months.

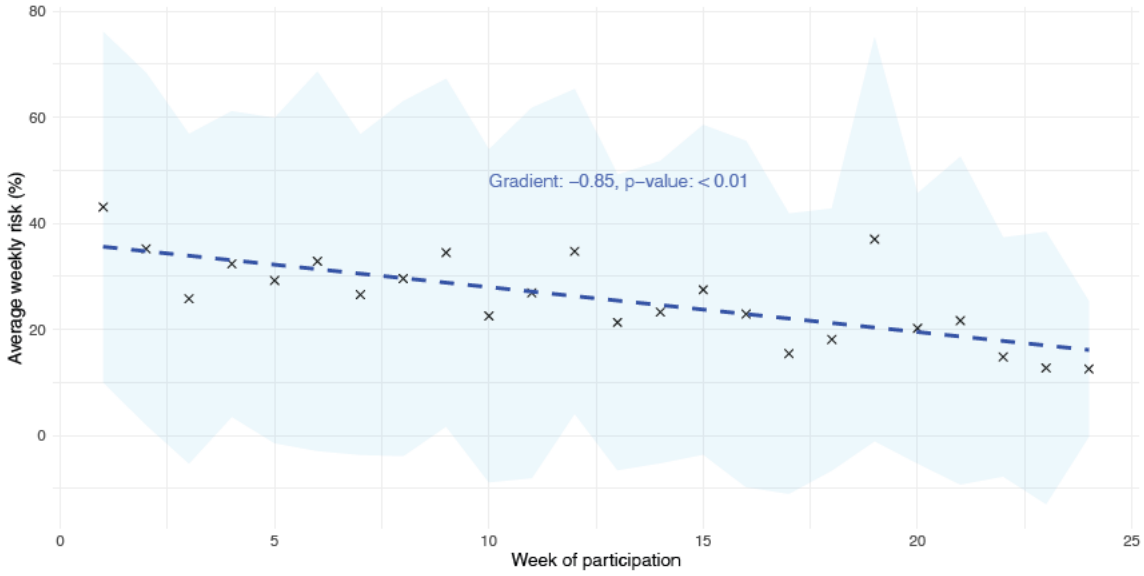


Figure 10: Mean risk of failing first daily spirometry blow per week over 24 weeks across all patients

blue line: linear regression line with respective gradient and p-value. Blue shaded background: standard deviation around the mean of each data point.

4.4 Handheld Spirometry Correlation Testing with On-site

In total, 89 on-site lung function tests from 58 individual patients were available, each accompanied by at least two usable handheld measurements performed within a 7-day window around the on-site spirometry date.

4.4.1 FVC

Figure 11 illustrates a leftward shift in the normal distribution curve relative to the on-site FVC, with the mean of all handheld FVC measurements centred at 95.3% of the on-site FVC. The SD of all handheld measurements spans 78.2% to 112.3 % with 61 of the 89 handheld FVC measurements (68.5%) within one SD of of the mean. 41 out of the 89 handheld FVC measurements (46.1%) were within 10% of the on-site FVC.

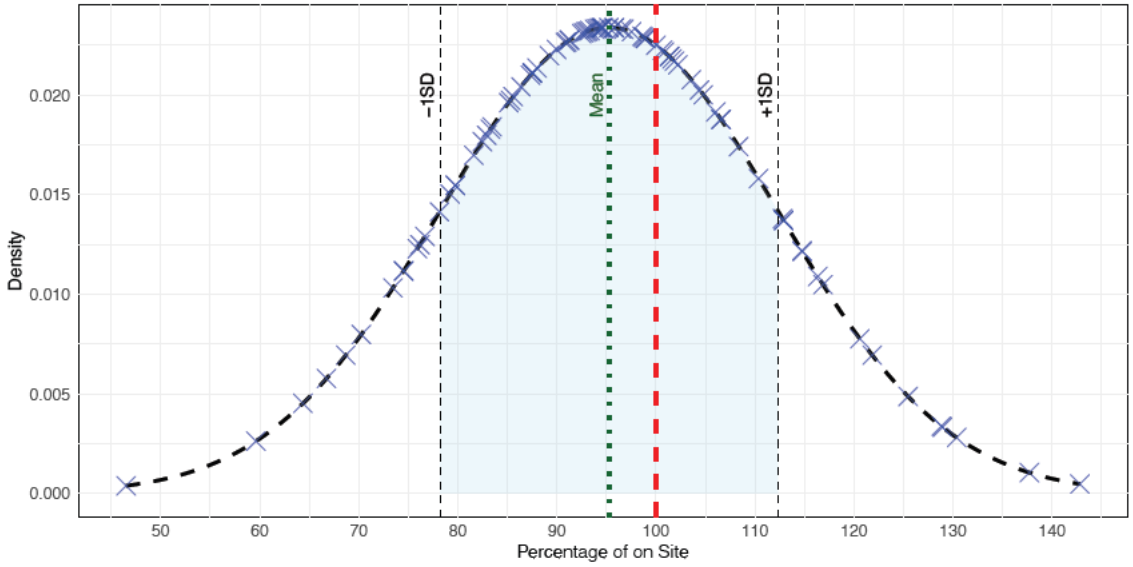


Figure 11: Handheld vs on-site FVC

Handheld FVC was normalised to their individual on-site FVC and presented as a percentage. Blue crosses indicating each individual mean FVC (% of on-site). Green dashed line indicating the mean and the red line showing the on-site FVC (100%).

Abbreviations: FVC= Forced vital capacity, SD= standard deviation,

There is a strong correlation between the on-site and handheld FVC with a Pearson's correlation coefficient of 0.90 (95% CI: 0.850- 0.932, $p < 0.001$). Reliability between on-site and handheld FVC was calculated at 0.89 (lower/ upper bound: 0.809 and 0.929, $p < 0.001$), indicating very good to excellent reliability.

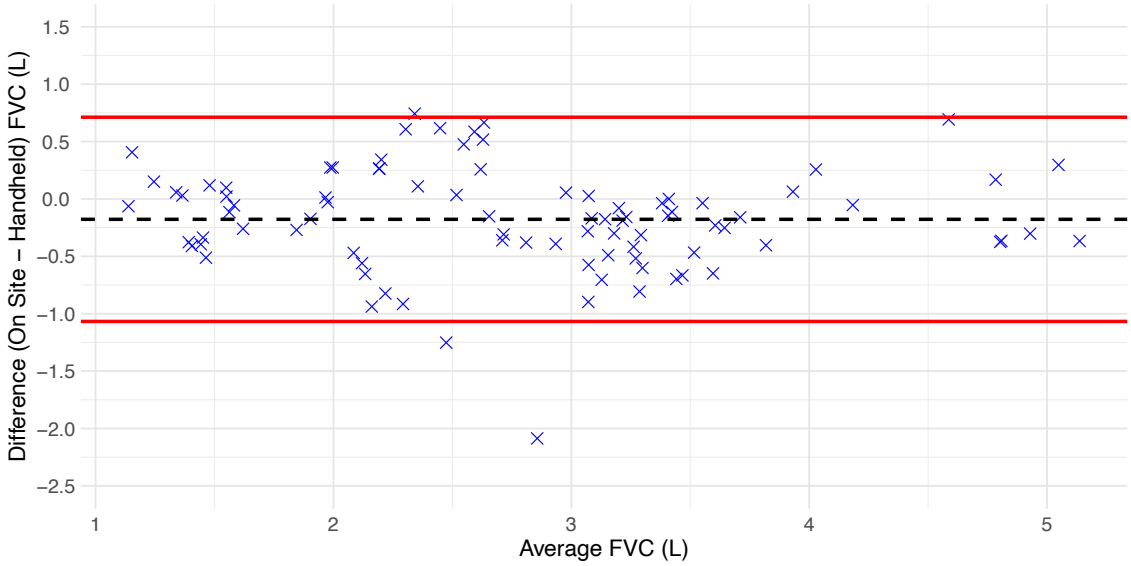


Figure 12: Agreement between handheld and on-site FVC

Bland-Altman analysis where red horizontal line indicating upper bound and lower limit of agreement, each blue cross representing one handheld FVC measurement.

Abbreviations: FVC=forced vital capacity, L= Litre

Figure 12 delineates good agreement (95% CI) across both methods, with a slight bias (mean: -0.177 L), where the handheld spirometer tends to provide slightly lower readings than the on-site readings. 96.6% of all data points are within the level of agreement, with 1 above the limits of agreement (0.712 L) and 2 measurements below the limit of agreement (-1.067 L). The SD of differences remains relatively small (0.454) suggesting that the differences between the two measurements are consistent across the sample. The distribution of the difference between hand-held and on-site measurements versus magnitude of restrictive lung disease is not suggestive of a dependency of this relationship on disease severity.

4.4.2 FEV1

In Figure 13 the leftward shift of the normal distribution of the FEV1 relative to the on-site FEV1 is more pronounced, with the mean in FEV1 at 85.4% of the on-site FEV1. The SD of all handheld measurements spans 68.43% % to 100.56% with 61 of the 89 correlation pairs (68.5%) within one SD of the mean. Notably, the on-site FEV1 is barely encompassed within the upper bound of one SD. 29 of the 89 handheld FEV1 measurements (32.6%) were within 10% of the on-site FEV1, a marked reduction when compared to the alignment handheld and on-site FVC.

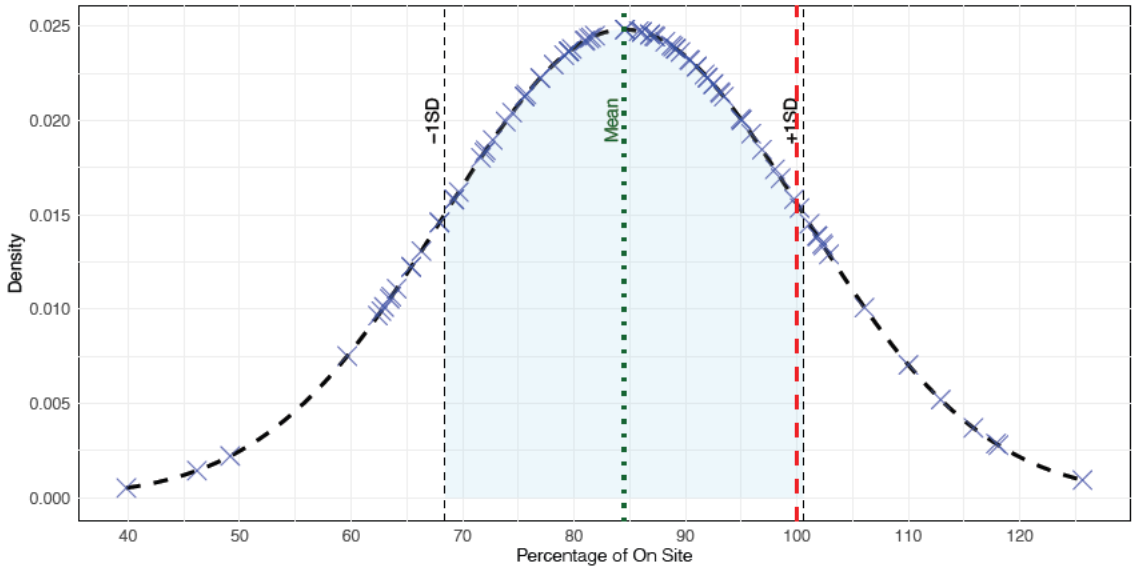


Figure 13: Handheld vs on-site FEV1

Handheld FEV1 was normalised to their individual on-site FEV1 and presented as a percentage. Blue crosses indicating each individual mean FEV1 (% of on-site). Green dashed line indicating the mean and the red line showing the on-site FEV1 (100%).

Abbreviations: FEV1= Forced expiratory volume in 1 second, SD= standard deviation

Correlation between on-site and handheld FEV1 was weaker compared to the FVC with a Pearson's correlation coefficient of 0.87 (95% CI: 0.805- 0.911, $p < 0.001$). Reliability was calculated at 0.77 (lower/ upper bound: 0.25 and 0.90, $p < 0.001$) suggesting moderate reliability, with a large CI indicating some uncertainty about its true reliability.

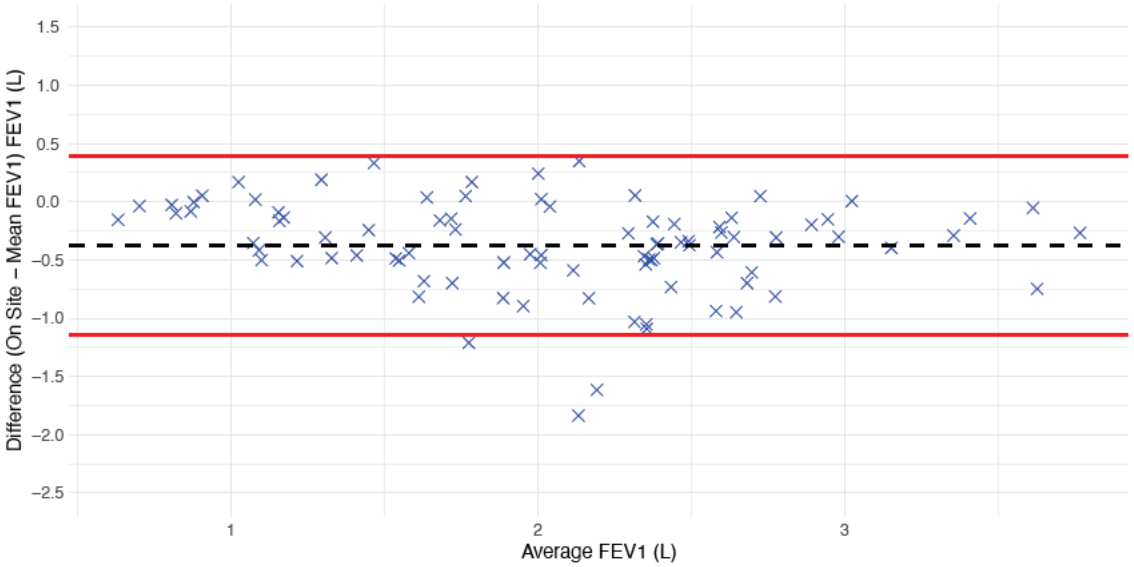


Figure 14: Agreement between handheld and on-site FEV1

Bland-Altman analysis with red horizontal line indicating upper bound and lower limit of agreement, each blue cross representing one handheld FEV1 measurement.

Abbreviations: FEV1=forced expiratory volume in 1 second, L= Litre

Agreement (95% CI) between handheld and on-site FEV1 as shown in Figure 14 could be classified as suboptimal with a significant bias towards an underestimation in the handheld FEV1 (mean: -0.373 L). The upper and lower limit of agreement were calculated at 0.395 and -1.142 L respectively with a SD of differences of 0.392. 96.6% of all data points are within the levels of agreement with 3 points below the level of agreement. Again, there seemed to be no dependency of the distribution on disease severity

4.5 Comparison of the Change in FVC Slope over Time

10 patients were identified to have at least 3 on-site spirometry readings over a time span of 6 months with over 100 acceptable handheld spirometry readings each in the same time frame. Overall, 2985 handheld spirometry readings in the handheld, and 44 on-site spirometry readings were considered for slope calculations. 5 out of the 10 patients were receiving a form of anti-fibrotic medication before and during the time of data collection. Table 7 summarises the individual slope gradients of both, on-site and handheld as well as their respective underlying disease.

Table 7: ILD subtype and intra-individual linear regression slope analyses: on-site vs handheld over time

ILD subtype	Anti-fibrotic medication	Slope on-site (ml/ week)	Slope handheld (ml/ week)
Fibrosing Polymyositis	No	- 0.5 p= 0.923	- 0.1 p= 0.803
Hypersensitivity pneumonitis	No	+ 7.6 p= 0.297	- 3.9 p= 0.048
Hypersensitivity pneumonitis	No	- 4.1 p= 0.030	+ 1.1 p= 0.008
Systemic sclerosis	Yes	- 4.5 p=0.363	- 2.9 p= 0.190
IPF	Yes	- 4.3 p= 0.691	- 7.0 p= < 0.001
IPF	Yes	- 15.6 p= 0.244	- 12.0 p= < 0.001

Familial IIP	Yes	+ 0.3 p=0.868	+ 5.7 p= < 0.001
IPF	Yes	- 4.5 p= 0.423	- 4.2 p= < 0.001
Stage IV Sarcoidosis	No	- 1.5 p=0.458	+ 2.9 p= < 0.001
IPF	No	- 7.1 p=0.059	+ 4.3 p= < 0.001

Slope of weekly FVC change was calculated using linear regression analysis with its respective p value mentioned below

Abbreviations: IPF= Idiopathic pulmonary fibrosis, ml= millilitres, p= P value

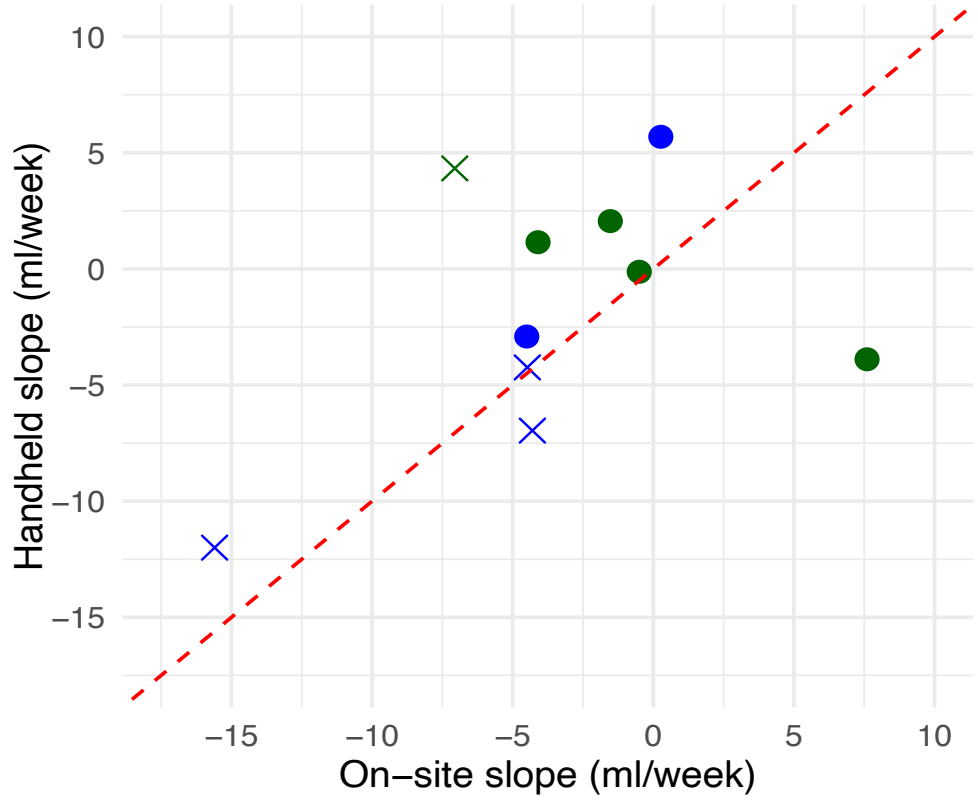


Figure 15: Handheld vs on-site slope analysis

Red dashed line indicating line of equality. Cross= IPF diagnosis, Dot= any other disease. Blue: under anti-fibrotic medication. Green: no anti-fibrotic medication.

Abbreviations: ml= millilitres

In Figure 15, the majority of data points lie to the left of the line of equality, indicating that handheld spirometry generally underestimates declines in lung function or overestimates improvements in lung function compared to the on-site measurements. Notably, there were three cases where handheld spirometry failed to detect a decline in

lung function, despite the on-site FVC slope indicating a negative trend. Conversely, one instance was observed where the handheld spirometry modelled a decline in FVC, whereas the on-site FVC slope reflected a positive trend.

The paired t-test yielded a t-value of -0.912 with a p-value of 0.386, indicating the difference in slopes between the two methods is likely due to random variation. The mean difference in slopes was negligible, with a 95% CI ranging from -6.00 ml/week to 2.60 ml/week, including 0. On average, the handheld device slopes are slightly less pronounced by 1.73 ml/week.

4.6 Handheld FVC Changes in Response to PROMs

4.6.1 Changes in Average Handheld FVC in Response to Changes in the EQ VAS score

Overall, there were 566 individual EQ VAS responses. Of those, there were 9 timeframe(s) with a maximum of 7 days from 5 individual patients in which the EQ VAS score was found to be below the lower bound of their respective individual SD. Table 8 summarises the results of the statistical tests correlating a change in handheld FVC in response to a change in the aforementioned survey.

Table 8: Statistical significance of the change in FVC in response to significant changes in EQ VAS score:

Anchor date	Change in mean FVC (one tailed T-Test)	Change in median FVC (one tailed signed Wilcox rank test)
2023-07-02	-0.96 *p= 0,39*	54.0 *p= 0.81*
2023-08-31	1.7 *p= 0.12*	268.0 *p=0.12*
2023-12-06	-0.60 *p= 0.56*	44.5 *p=0.44*
2024-04-17	-1.49 *p= 0.20*	79.5 *p=0.20*
2024-06-07	-0.94 *p= 0.37*	56.0 *p=0.41*
2023-12-08	0.40 *p=0.69*	259.0 *p=0.92*

2024-01-27	-0.45 *p= 0.66*	110.5 *p=0.62*
2024-01-31	0.54 *p= 0.60*	91.5 *p=0.75*
2024-05-20	1.62 *p= 0.15*	18.5 *p=0.025*

Note: the first values of each box indicate the result of the relevant statistical test. For the second column this reflects the t-test value and for the third column the Wilcox- signed rank test value. The p- value is mentioned for each statistical result.

Green highlighting statistical significance

Abbreviations: EQ VAS= European quality visual analogue scale, FVC= forced vital capacity, p= p-value,

Overall, no statistical test identified a meaningful change in the average FVC in response to a reduction in patients' perceived quality of life. While a statistically significant change in the median FVC was observed on 2024-05-20 using the Wilcoxon signed-rank test, this finding is limited in significance, particularly given the lack of corroboration from the one-tailed t-test.

4.6.2 Changes in Handheld FVC in Response to Patient Reported Infections

Overall, there were 158 individual days, in which patients in the daily symptom log reported of signs of respiratory infections. Of those, there were insufficient handheld measurements for 6 of those days. Additionally, one patient reported a respiratory infection continuously for 115 days. Excluding time frames beyond 7 continuous days and days, in which insufficient handheld spirometry data were available, there were 14 singular episodes of self-reported infections by 9 different patients. Of those 14 periods, a statistically meaningful decrease in the mean FVC was observed in 5 out of 14 cases (35.7%) as delineated in Figure 16.

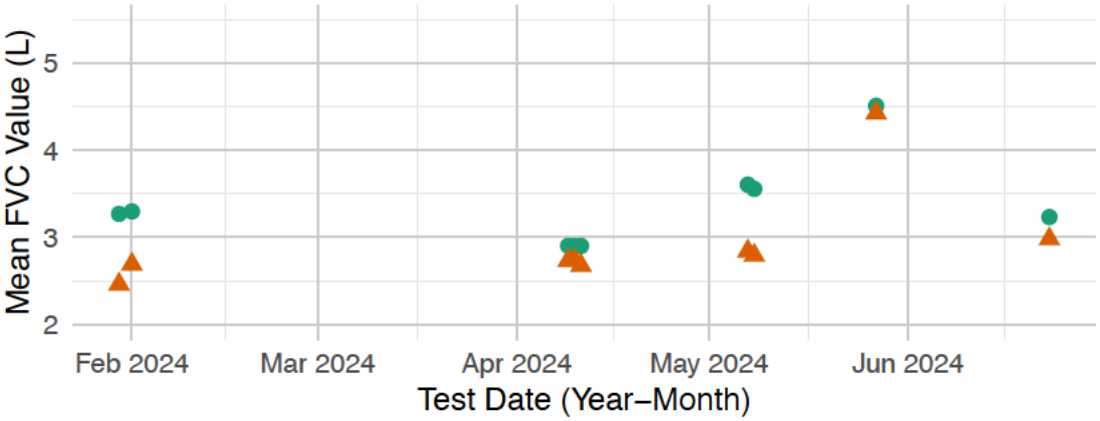


Figure 16: Reduction in the mean FVC in response to self-reported infection

Note: Only statistically significant change in mean FVC (p-value < 0.05) shown.

Green dot: mean FVC 5-1 weeks prior to self-reported infection. Orange triangle: mean FVC 7 days before and after self- reported respiratory infection.

Abbreviations: FVC= Forced Vital Capacity, L= Litres

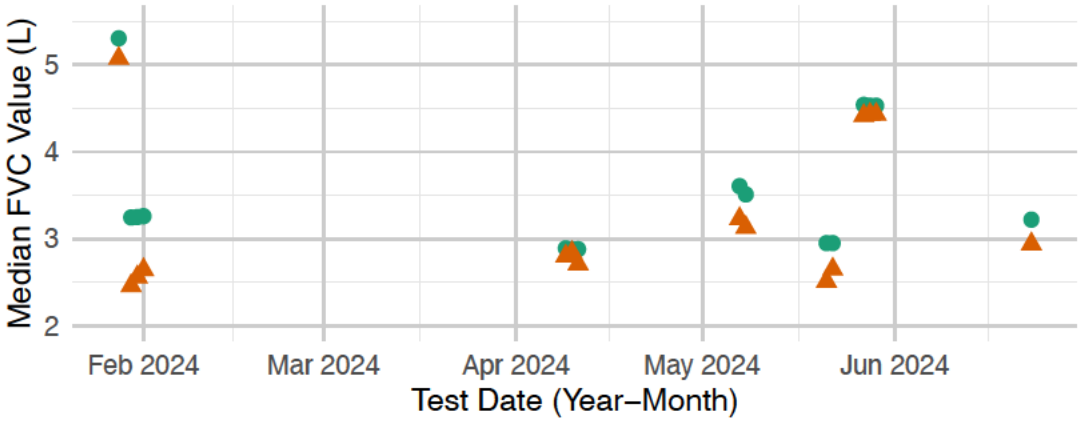


Figure 17: Reduction in the median FVC in response to self-reported infection

Note: Only statistically significant change in median FVC (p-value < 0.05) shown.

Green dot: median FVC 5-1 weeks prior to self-reported infection. Orange triangle: median FVC 7 days before and after self- reported respiratory infection.

Abbreviations: FVC= Forced Vital Capacity, L= Litres

Considering a median change in FVC in the period prior and during the self-reported respiratory infection, a statistically significant decrease could be detected in 7 of the 14 cases (50%; significance measured at p=<0,05). It is of particular interest, that the instances in which a statistically significant decrease in the mean FVC was calculated, the change in median FVC could also detect the same significant change as well as detecting a further 2 instances.

5 Discussion

In this study, home monitoring of lung function and exercise capacity was evaluated as a practical tool to empower patient participation in disease management. It demonstrated acceptable compliance, excellent FVC reliability and good agreement compared to state-of-the-art on-site spirometry in a European cohort of 59 patients. This is the first study to evaluate the use of a novel, ArtiQ feedback algorithm across multiple sites, giving detailed responses to blow technique in real time and accurately eliminating failed blows whilst helping patients improve spirometry technique.

Adherence to weekly spirometry manoeuvres and exercise testing was generally lower than reported values described by Althobiani et. al, Johannson et. al and Barth et. al (46,51,61). While Johannson et al suggested an average adherence to weekly spirometry at around 90% after 24 weeks (51), we found our adherence to decrease to 52% in the same time span. Possible explanations for our lower adherence can be attributed to the methodology employed in this study. In an effort to incentivise continued adherence and peace of mind to patients, most previous studies like Barth et.al involved an element of active surveillance of measurements by physicians (61). Other times, patients were encouraged to report “protocol holidays” in which patients could report off days or weeks in which adherence would be nullified in those reported timespans as suggested in Althobiani et. al (46). In our study, patients were literally left alone with the devices, with the goal of assessing the pure motivational level of patients in absence of assistance and support by the site.

It is therefore reasonable to assume that, had there been an element of active surveillance by the treating physician or an ability to “pause and play”, patients had likely had a higher adherence to home monitoring in our study. Our findings therefore suggest that a “hands off approach” used in this study is likely to negatively impact continued engagement over long periods of times. This finding aligns with a previous 'hands-off' study described by Edwards et al, which reported similar adherence rates (74). Direct comparisons of adherence with Johannson et al. further suggests that the critical phase of early disengagement in the first 20 weeks is more nuanced in studies where active monitoring by physicians was involved (51). This suggests that active monitoring is protective of

some early disengagement, whilst later disengagement is likely unaffected, although research directly correlating this finding has been notably absent.

The early identification of adherent and non-adherent cohorts was a key methodological strength. Non-adherence in the first 4 weeks showed substantial predictive power for continued disengagement, with no patients in the aforementioned group recording either handheld spirometry or 1MSTST measurements beyond 10 weeks.

When evaluating the discontinuation questionnaire, early dropouts described themselves as highly motivated, while those who disengaged after 12 months showed minimal motivation for self-measurements. This demonstrates that the monotony of home monitoring may demotivate continued engagement beyond 6 or 12 months and could explain the more gradual late disengagement beyond 6 months. It may therefore be of critical importance to examine adherence beyond 12 months prior to mainstream adoption of home monitoring by healthcare providers.

This study also aimed to correlate poor spirometry technique, as assessed in real-time by ArtiQ, with a propensity for study disengagement. Although the findings suggested a potential relationship between suboptimal blows and disengagement, statistical significance was not achieved (44.9% vs 38.0%, p= 0.55). Nonetheless, the results indicate that implementing ArtiQ may inadvertently lower overall adherence, as patients might become frustrated by receiving consistent negative feedback. However, it could be argued that this form of selection bias—favouring patients with good spirometry technique—might be beneficial when assessing meaningful spirometry data, as it could enhance data reliability and reduce variability.

Correlation, agreement and reliability with on-site spirometry was high (handheld vs on-site FVC; Pearson's r=0.90, p<0.001; ICC 0.89, p <0.001) and comparable to established literature values characterised by Johannson et al, Althobiani et al, Khan et al and Barth et al. (51,56,57,75). This is especially significant since our correlations were calculated without crude retrospective measurement exclusions but rather using the organic values deemed usable by the ArtiQ algorithm.

In line with the majority of previous studies, handheld FVC measurements were slightly underestimated by 4.7% compared to on-site measurements, with handheld FEV1 showing a particularly pronounced underestimation and subsequently worse correlation in our study. The underestimation observed in this study may be attributed to several factors. The pronounced underestimation of FEV1, in particular, can be explained by its shorter measurement duration, making it more susceptible to inaccuracies caused by device response time and user technique. Additionally, suboptimal patient effort, which is less readily detected by the ArtiQ algorithms, disproportionately impacts FEV1 measurements compared to FVC.
Another factor influencing the underestimation of both handheld measurements is the deviation from the "best of three" approach recommended by good medical practice guidelines for on-site spirometry (39). To minimize patient burden, this study did not employ the "best of three" approach, meaning patients were unable to improve their values once the ArtiQ system deemed a blow usable.

Finally, due to the relative infancy of the ArtiQ system, it was unable to detect potential air leakages during spirometry, such as those caused by an improper lip seal, which could have negatively affected both FEV1 and FVC measurements.
Overall, despite the slight underestimations observed, our findings suggest that handheld spirometry is a reliable alternative to on-site spirometry, with its utility being more pronounced in restrictive lung diseases like ILD. In contrast, its applicability in obstructive lung diseases may be more limited, as FEV1—of greater clinical significance in these conditions—appears to be more susceptible to underestimation.

The correlation between longitudinal FVC decline measured by handheld and on-site spirometry in our study was less pronounced than anticipated. Handheld FVC slope calculations often underestimated declines in lung function or overestimated improvements, a finding consistent with Maher et al. (59). The general FVC trajectory (whether decline or improvement) was similar in a disappointing 60% of cases. A peculiar aspect shown was that handheld and on-site FVC trajectory showed significantly greater alignment in patients taking anti-fibrotic medication, as the general longitudinal trend was corroborated between both diagnostic modalities in all cases (n=5).

Our methodology may however have been ill-suited to assess longitudinal decline. A significant limitation was the insufficient number of on-site spirometry readings available to calculate reliable on-site slopes. With only 3 or 4 measurements per patient and substantial variability among these limited data points, the resulting slope calculations for on-site spirometry failed to reach statistical significance ($p < 0.05$) in 9 out of 10 patients. One could potentially even argue that diurnal or seasonal differences during on-site measurements have impacted the variance in on-site FVC measurements, implicating its usability for trajectory calculations.

Additionally, a sample size limited to 10 patients for longitudinal FVC decline raises scepticism over its applicability to larger cohorts. Despite this, it was found that generally speaking, differences in longitudinal FVC decline between the two diagnostic modalities was likely due to random variation rather than true effect. Further research is needed to assess whether increasing the number of on-site spirometry measurements and patient cohort increases alignment with handheld spirometry and whether active anti-fibrotic treatment increases the corroboration between the two modalities.

Correlation between sudden reductions in EQ VAS scores and FVC measurements were poor with not a single instance showing a direct relationship. Associating sudden changes in FVC and PROMs has not been assessed in ILD in the past and thus sets our findings on speculative footing.

There has, however, been a previous study by Lee et al. assessing the correlation of reductions in disease specific PROMs and clinical outcome such as disease progression in ILDs (76). One study presented by Yuan et al. also assessed the impact of changes in PROMs on FVC measurements in ILDs specifically (77). When extrapolating the results from the two studies, it can be concluded that the specificity of a questionnaire to a particular disease enhances its association with clinical outcomes. This may explain our poor correlation with EQ VAS score since it reports on general wellbeing with other factors such as psychological and social wellbeing also being of impact (78).

However, self-reported respiratory infections, supposed to directly translate in more respiratory symptoms and impaired lung function, did correlate strongly with a simultaneous reduction in FVC in half the instances (n=7) reported. This is significant since Tsuji et al. and Collard et al. have already shown that respiratory infections play a major factor in the development of AEs in ILDs and late treatment being a key contributor

to mortality (36,79). Previous studies assessing this correlation are importantly absent so our findings should be corroborated with a larger patient cohort and more independent variables such as fever, colour of sputum and exercise capacity being also assessed. Should further studies support our findings, it might suggest that incorporating self-reported infections into an algorithm for the detection of AEs prove highly valuable.

In this study, we also found substantial evidence that real-time ArtiQ helps patients improve their spirometry technique over time. Over a matter of 24 weeks, patients reduced the risk of failing the first spirometry blow of the day from over 40% in week 1 down to 12% in week 24. Similarly, findings suggest that patients could accurately interpret and adapt to the feedback presented by ArtiQ. While almost half the patients (46.6%) still failed their second attempt of spirometry blow, feedback on the second attempt became more specific and involved fewer combinations. This shows that patients would still improve certain aspects of their blow technique despite failing to produce a usable blow.

Additionally, in this study we did not evaluate the individual variability in FVC measurements performed by patients, which serves as an indicator of the reproducibility of handheld spirometry. Comparing this variability with values reported in the literature could have provided an objective metric to assess the superiority of ArtiQ over previous algorithms. Assessing other aspects of the ArtiQ algorithms could open a myriad of possibilities in further research. One important question not answered in this study were the associations of poor spirometry technique to patient demographics. Future research could potentially identify patient characteristics which make it unsuitable to produce usable handheld spirometry data. This could help health care providers and physicians decide on which patients should be included in the roll out of handheld monitoring.

This study faced several substantial limitations, ranging from methodological issues to technical challenges associated with the devices and the app used. The inclusion criteria were relatively broad, encompassing any ILD diagnosis confirmed by a MDD board in line with the current ATS/ERS consensus. However, a key exclusion criterion was the inability to effectively use modern smartphones and associated devices. This introduced a significant selection bias, potentially skewing the study population toward younger, more technologically proficient individuals. When compared to other large ILD registries

described by Buschulte et al. and Wälscher at al., the average age of participants in this study was approximately 2 to 2.5 years younger, reflecting this bias (62.06 vs. 64.3 and 64.7 years, respectively) (40,80).

In this study, we encountered compatibility issues between Chinese smartphones and the PatientMpower app. Due to retaliatory measures implemented by the U.S. government against Chinese phone manufacturers, Bluetooth connections with spirometers and pulse oximeters were blocked, rendering these devices non-functional. While attempts were made to supply new smartphones at no cost to patients, this came with a host of further technical issues. Overall, this problem had a substantial impact on the recruitment of possible patients.
Additionally, many findings were based on a limited number of patients who provided continuous handheld data over long periods of times. This inevitably imputes a degree of selection bias since patient dropout was substantial, especially beyond 6 months.

In conclusion, in our study we successfully validated home spirometry as a powerful tool in the monitoring of ILDs. Adherence was generally acceptable and comparable to previous studies when adjusted for differences in methodology. Similarly, the agreement and correlation with current state of the art spirometry supports its use and gives testament to the value of employing ArtiQ algorithms. Also, this novel approach regarding ArtiQ and PROMs gives substantial insight into the direction of home monitoring for detecting disease progression and AEs whilst integrating well with the current gap of literature. Our interpretation of the data is that combined assessment of PROMs, indicators of respiratory infections and hand-held spirometry / saturation at rest or exercise holds great promise to be applied to a larger set of patients and to be implemented as novel tool to monitor ILD patients and to detect much earlier life-threatening acute exacerbations.

6 Summary

Background: Interstitial lung diseases (ILD) are a heterogeneous group of diseases characterized by frequent irreversible destruction of the alveolar structure in the lungs. ILDs are often progressive in nature, leading to an incremental worsening of dyspnoea, reduced exercise tolerance, and a reduction in the quality of life over time. Despite novel treatment approaches, most forms are severely life-limiting, and the course of the disease is highly disparate, rendering current monitoring regimes for ILDs inadequate. While regular spirometry monitoring is the standard approach for tracking disease progression, handheld monitoring has been shown to cater more effectively to the variable progression of ILDs.

This study aimed to validate mobile over-App handheld spirometry and home monitoring to effectively monitor lung function in ILDs. Using a novel artificial intelligence (ArtiQ) based algorithm, lung function data was assessed in real time, providing immediate feedback on measurement quality. Patient adherence, correlation to established on-site spirometry measurements, and longitudinal FVC changes were evaluated in a European multi-center study as part of the European ILD Registry (eurILDreg)

Results: Data from 59 eurILDreg patients who provided consent for handheld monitoring were considered. Weekly adherence for handheld monitoring decreased to 81.1% and 73.5% after 3 months, 52.0% and 45.5% after 6 months and 36.8% and 29.4% at 12 months for handheld spirometry and exercise testing respectively. Correlation to on-site FVC was calculated at $r=0.90$ ($p<0.001$), reliability at 0.89 ($p<0.001$) and agreement with a bias of -0.177 L (upper/ lower limit 0.712 L and -1.067 L respectively). Correlation to on-site FEV1 was calculated at $r=0.87$ ($p<0.001$), reliability at 0.77 ($p<0.001$) and agreement with a bias of -0.373 L (upper/ lower limit 0.395 L and -1.142 L respectively). Direction of longitudinal FVC change was corroborated between handheld and on-site spirometry in 60% of cases ($t= - 0.912$, $p=0.386$, 95% CI: - 6.00ml/week to 2.60 ml/week).

Conclusions: We reported acceptable and comparable adherence pattern to previous studies when adjusted for the methodology. Similarly, agreement and correlation with current state of the art spirometry supports its use, a testament to the value of employing ArtiQ algorithms. Also, our novel approach regarding ArtiQ gave substantial insight into the direction of home monitoring for detecting disease progression and AEs whilst integrating well with the current gap of literature.

7 Zusammenfassung:

Hintergrund: Interstitielle Lungenerkrankungen (ILD) sind eine heterogene Gruppe von Erkrankungen, die durch oftmals irreversible Zerstörung der alveolären Struktur der Lunge gekennzeichnet sind. ILDs verlaufen häufig progressiv, was zu einer zunehmenden Verschlechterung der Dyspnoe, einer reduzierten Belastungstoleranz und einer Verschlechterung der Lebensqualität führt. Trotz neuer Behandlungsansätze sind die meisten Formen prognostisch ungünstig, und der Krankheitsverlauf ist äußerst unterschiedlich, was aktuelle Überwachungsstrategien für ILDs erscheinen lässt. Um der variablen Progression von ILDs gerecht zu werden, sind mobile Überwachungsmethoden zunehmend in der Diskussion. Diese Studie hatte das Ziel, eine App- basierte, mobile Heimüberwachung zu validieren, um die Lungenfunktion bei ILDs effektiv zu überwachen. Mithilfe eines neuartigen, auf künstlicher Intelligenz (ArtiQ) basierenden Algorithmus wurden dazu die Lungenfunktionsdaten in Echtzeit ausgewertet. Zur Auswertung wurden Patientenadhärenz, die Korrelation zu etablierten vor-Ort-Spirometrie-Messungen und longitudinalen FVC-Veränderungen in einer europäischen multizentrischen Studie im Rahmen des Europäischen ILD Registers (eurILDreg) untersucht.

Resultate: Daten von 59 eurILDreg-Patienten, die ihre Einwilligung zur mobilen Überwachung gegeben hatten, wurden berücksichtigt. Die wöchentliche Adhärenz für die mobile Überwachung sank nach 3 Monaten auf 81,1 % bzw. 73,5 %, nach 6 Monaten auf 52,0 % bzw. 45,5 % und nach 12 Monaten auf 36,8 % bzw. 29,4 % für mobile Spirometrie und Belastungstests. Die Korrelation zur vor-Ort-FVC wurde mit r=0,90 ($p<0,001$), die Zuverlässigkeit mit 0,89 ($p<0,001$) und die Übereinstimmung mit einem Bias von -0,177 L (oberes/unteres Limit 0,712 L bzw. -1,067 L) berechnet. Die Korrelation zur vor-Ort-FEV1 wurde mit r=0,87 ($p<0,001$), die Zuverlässigkeit mit 0,77 ($p<0,001$) und die Übereinstimmung mit einem Bias von -0,373 L (oberes/unteres Limit 0,395 L bzw. -1,142 L) berechnet. Die Richtung der longitudinalen FVC-Veränderung wurde zwischen mobiler und vor-Ort-Spirometrie in 60 % der Fälle bestätigt (t = -0,912, p=0,386, 95%-KI: -6,00 ml/Woche bis 2,60 ml/Woche).

Schlussfolgerung: Wir berichteten über akzeptable und mit früheren Ergebnissen vergleichbare Adhärenz Muster, wenn unterschiedliche methodische Ansätze berücksichtigt werden. Ebenso unterstützen Übereinstimmung und Korrelation mit der aktuellen Spirometrie den Einsatz mobiler Systeme, was den Wert der Verwendung von

ArtiQ-Algorithmen unterstreicht. Darüber hinaus lieferte unser neuartiger Ansatz in Bezug auf ArtiQ wesentliche Einblicke in die Richtung der Heimüberwachung zur Erkennung von Krankheitsprogression und unerwünschten Ereignissen (AEs) und fügt sich gut in die aktuelle Forschungslücke ein.

8 Supplements

8.1 Abbreviations:

1MSTST	1 Minute sit to stand test
AE	Acute exacerbation
ArtiQ	Artificial intelligence quality
ATS	American Thoracic Society
BMI	Body mass index
CI	Confidence Interval
Dlco	Diffusing capacity for carbon monoxide
EQ 5D 5L	European quality of life 5 Dimensions- 5 Levels
ERS	European Respiratory Society
eurILDreg	European Interstitial Lung Disease register
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HRCT	High resolution computer tomography
ICC	Intraclass correlation coefficient
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
Kg	Kilogram
L	litres
MDD	Multidisciplinary discussion
PROM	Patient reported outcome measurements
SD	Standard deviation
SpO2	Peripheral capillary oxygen saturation

8.2 List of Figures

8.3 List of Tables

8.4 Bibliography

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8.5 Ethics Applications

8.5.1 Ethics Application eurIPFreg

JUSTUS-LIEBIG UNIVERSITÄT GIESSEN

FACHBEREICH 11 MEDIZIN

Ethik-Kommission, Gaffkystr. 11c, D-35385 Gießen

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Gießen, 16. September 2008
Dr. Kr./erb

AZ.: **111/08**

Titel: *Europäisches IPF-Register (eurIPFreg).*

Sitzung am 04.09.08

Sehr geehrte(r) Antragsteller/Antragstellerin [redacted]

wir bedanken uns für die Vorstellung Ihres Forschungsprojektes. Im Folgenden erhalten Sie das Votum der Gießener Ethik-Kommission zur oben genannten Studie:

Es handelt sich um eine Erstbegutachtung für den Leiter der Klinischen Prüfung (LKP) ☒
Es handelt sich um eine Anschlussbegutachtung ☐

Eingesandte Unterlagen:

- ☒ Formalisierter Antrag
- ☒ Ausführliche Darstellung des Vorhabens (detaillierte Beschreibung)
- ☒ Datenschutzkonzept
- ☒ Patienten/Probanden-Information und Einwilligungserklärung, Version 1.3 vom 27.08.2008
- ☒ Patientenfragebögen „Baseline" und „Follow-up", Version 06-06-08
- ☒ Arztfragebögen „Baseline" und „Follow-up", Version 06-06-08
- ☒ Vertragsentwurf mit Teilnehmern des Forschungsvorhabens, Version 1.2 vom 13.08.08
- ☒ Consortium Agreement No. 202224, final version 2008-01-22
- ☒ Abteilungsleiter-Haftpflicht-Versicherung

Der Antrag wurde unter ethischen, medizinisch-wissenschaftlichen und rechtlichen Gesichtspunkten geprüft. Soweit betreffend, wurde **das auf Seite 2 wiedergegebene Protokoll** unter Berücksichtigung des Good Clinical Practice for Trials on Medicinal Products in the European Community (ICH-GCP) erstellt. Es bezieht sich auf die vorgelegte Fassung des Antrags.

Forderungen der Ethik-Kommission, soweit darin aufgeführt, wurden inzwischen erfüllt. ☐
Sie stimmt dem Vorhaben zu. ☒
Sie stimmt dem Vorhaben unter Auflagen zu (siehe S. 2). ☐
Sie stimmt dem Vorhaben nicht zu (siehe S. 2). ☐

Die Ethik-Kommission erwartet, daß ihr bis 2011 ohne Aufforderung ein kurzer Bericht auf beigefügtem (roten) Formblatt übermittelt wird. Er soll mitteilen, ob das Ziel der Studie erreicht wurde, ob ethische, medizinisch-wissenschaftliche oder rechtliche Probleme aufgetreten sind, und ob das Ergebnis publiziert ist/wird. Unabhängig davon ist die Ethik-Kommission über alle Änderungen des Prüfplans zu unterrichten. Ihr sind alle schweren unerwünschten Wirkungen mitzuteilen, soweit sie im Bereich der Zuständigkeit dieser Ethik-Kommission aufgetreten sind. Bei überregionalen Studien sind sie auch dem LKP mitzuteilen.
Die ärztliche und juristische Verantwortung des Leiters der klinischen Prüfung und der an der Prüfung teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethik-Kommission durch unsere Stellungnahme unberührt.

Auszug aus dem Protokoll der Kommissionsitzung vom 04.09.2008:

Prof. Dr. Günther trägt vor. Das Europäische IPF-Register (eurIPFreg) wird vom Europäischen IPF-Netzwerk (eurIPFnet) aufgebaut und betreut; dies wiederum ist ein von der Europäischen Union im Rahmen des 7. Rahmenprogramms geförderter Forschungsverbund, dem derzeit 10 Universitäten und ein industrieller Partner in 5 europäischen Staaten angehören. Der Koordinator dieses Forschungsverbundes ist Prof. Günther. Das Europäische IPF-Register hat zunächst zum Ziel, möglichst umfassend den natürlichen Verlauf verschiedener Formen der idiopathischen interstitiellen Pneumonien, hier vor allem der idiopathischen pulmonalen Fibrose (IPF) und der nicht-spezifischen interstitiellen Pneumonie (NSIP) zu charakterisieren (klinisches Spektrum mit Beschwerden, Veränderungen über die Zeit, Faktoren, die eventuell auslösende oder beschleunigende Wirkung haben). Langfristig soll das Register einem besseren Verständnis der IPF dienen und zur Entwicklung neuer wirksamer Therapieansätze beitragen. Neben Informationen von den Patienten (Fragebogen) werden alle im Rahmen der Routinediagnostik erhobenen medizinischen Befunde strukturiert erfasst und in einer zentralen Datenbank gespeichert. Die Befragungen werden mehrfach durchgeführt. Blut, Lungenspülflüssigkeit, Atemproben und Gewebeproben, die im Rahmen von Routinemaßnahmen oder für Forschungszwecke gewonnen wurden, werden in einer Biobank in Gießen archiviert. Geplant sind auch genetische Untersuchungen und Genexpressionsstudien zur Erfassung eventueller genetischer Faktoren. Es wird vermutet, dass 15% der Lungenfibrosen einen genetischen Hintergrund haben. Die bisher nur in englischer Sprache vorliegenden Fragebögen werden von autorisierten Übersetzern ins Deutsche übertragen.
Die Kommission stimmt dem interessanten, für Gießen sehr wichtigen Vorhaben zu; die Betrauung von Prof. Günther mit der Funktion des Koordiators stellt für Klinikum und Fachbereich auch eine große Ehre dar.

(Ende)

Wir wünschen Ihnen für Ihr Forschungsprojekt viel Erfolg.

[redacted]

Prof. Dr. K. L. Schmidt
Vorsitzender

Die Namen der bei dieser Sitzung anwesenden Mitglieder sind durch Unterstreichung hervorgehoben.
Mitglieder: Frau Dr. Blüthers-Sawatzki (Pädiatrie); Dr. Bödeker (Informatik); Herr Brumhard (Pharmazie); PD Dr. Gödicke (Bürgerliches Recht); Prof. Linn (Innere Medizin), Dr. Repp (Pharmakologie), Prof. Schmidt, Vorsitzender, (Rheumatologie), Prof. Schwemmle, stv. Vorsitzender (Chirurgie); Prof. Rüße (Rechtsmedizin).
Vertreter: Prof. Dreyer (Pharmakologie, Prof. Dudeck (Informatik); Prof. Federlin, (Innere Medizin), Prof. Schapp (Bürgerliches Recht); Frau Prof. Kemkes-Matthes (Innere Medizin); Frau Kreckel (Pharmazie); Prof. Künzel (Gynäkologie); Prof. Lasch (Innere Medizin); Prof. Weiler (Rechtsmedizin).

P.S.: Bitte informieren Sie die Ethik-Kommission unter Benutzung des beigefügten Formulars über den Beginn der Studie!

8.5.2 Ethics Amendment for eurILDreg

JUSTUS-LIEBIG UNIVERSITÄT GIESSEN

FACHBEREICH 11 MEDIZIN

ETHIK-KOMMISSION
des Fachbereichs Medizin

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Gießen, den 2. Dezember 2021
Az.: Dr. Kr./

Ethik-Kommission, Klinikstr. 29 (Alte Chirurgie), D-35385 Gießen

Prof. Dr. med. Andreas Günther
Leiter der Plattform Biobanking des DZL
Koordinator des europäischen IPF-Registers
Med. Klinik und Poliklinik II
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Ihre Einreichung vom 15. August 2021
Erweiterung des IPF-Registers auf das neue ILD-Register

Sehr geehrter Herr Prof. Günther,

im Gegensatz zum bisherigen eurIPFreg sollen im neuen eurILDreg jetzt grundsätzlich alle Formen interstitieller Lungenerkrankungen in das Register aufgenommen und ein erweitertes Spektrum an "big und ~omics data" erhoben werden. Neben dem "Formalisierten Antrag" wurde das sehr umfangreiche Registerprotokoll eingereicht, das auch 7 Anhänge aufweist, hierunter die Parameterliste, das Lastenheft der hand-held-Spirometrie und -Sättigungsmessung, die Geschäftsordnung, den Site Investigator-Vertrag, die Antragsbeschreibung RARE-ILD, das Datenschutzkonzept sowie die Patientenaufklärung und Einwilligung.

Die genannten Unterlagen wurden gemeinsam mit 1 weiteren Mitglied der Kommission, Herrn Dr. Krämer, besprochen. Die Ethik-Kommission hat keinerlei Einwände gegen die Änderungen.

Mit freundlichen Grüßen

[redacted]

Prof. Dr. H. Tillmanns
Vorsitzender der Ethik-Kommission

8.5.3 Ethics Amendment for Handheld Study

JUSTUS-LIEBIG UNIVERSITÄT GIESSEN

FACHBEREICH 11 MEDIZIN

ETHIK-KOMMISSION
des Fachbereichs Medizin

Vorsitz: Prof. Dr. H. Tillmanns

Klinikstr. 29 (Alte Chirurgie)
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Tel.: (0641)99 42470
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Gießen, den 2. Dezember 2021
Az.: Dr. Kr./

Ethik-Kommission, Klinikstr. 29 (Alte Chirurgie), D-35385 Gießen

Prof. Dr. med. Andreas Günther
Leiter der Plattform Biobanking des DZL
Koordinator des europäischen ILD-Registers
Med. Klinik und Poliklinik II
Klinikstr. 33
D-35392 Gießen

Ihre Einreichung vom 15. August 2021
Evaluierung einer Lungenfunktions- und Sättigungs-Monitoring App bei interstitiellen Lungenerkrankungen im Rahmen einer Registerstudie (eurILDreg)

Sehr geehrter Herr Prof. Günther,

Sie reichen das Konzept einer im Rahmen des eurILDreg geplante Register-/Pilotstudie ein, bei der es um eine Überprüfung der Nutzbarkeit von kleinen Spirometriegeräten und Sättigungsmessgeräten durch die Patienten selbst geht. Diese Pilotstudie soll dem breiten Einsatz dieser Geräte innerhalb des eurILDreg vorweggehen. Dazu ist gepant, etwa 1000 Patientenjahre an hand-held-Geräten zu erfassen, um dann in einer retrospektiven Auswertung zu überprüfen, ob mit diesen Geräten ILD-spezifische Unterschiede bei der Patientenselbstmessung festgestellt werden, und ob subtile Änderungen bei den täglichen Selbstmessungen in der Lage wären, klinisch relevante Verschlechterungen im weiteren Verlauf anzuzeigen. Weder bei der Pilotstudie, noch bei der breiteren Anwendung soll das klinische Patientenmanagement, also insbesondere die Frage einer Vorstellung im Zentrum oder des Aufsuchens des Hausarztes, von Ergebnissen der hand-held-Spirometrie abhängig sein.

Die genannten Unterlagen wurden gemeinsam mit einem weiteren Mitglied der Kommission, Herrn Dr. Krämer, besprochen. Die Ethik-Kommission hat keinerlei Einwände gegen die Durchführung der Pilotstudie, die Ziele des Registers werden nicht verletzt.

Mit freundlichen Grüßen

[redacted]

Prof. Dr. H. Tillmanns
Vorsitzender der Ethik-Kommission

8.6 eurILDreg: Patient Information and Declaration of Consent

Patient information sheet and informed consent form for the research project entitled

European ILD Registry (*eur*ILD*reg*)

Patient Information

You will be given a long version and a short version. You should read both versions.

SHORT VERSION

Project summary

There are some lung diseases, called interstitial lung disease (ILD), that cause fibrosis (scarring) in the lungs. In order to enable research to be conduction into the progression, risk factors and reasons for ILDs we would like to collect together as many cases and patient samples of interstitial lung diseases in Europe as possible. This project is called European ILD Registry. If you consent to this study, your clinical information, your CT scans and your blood and other samples may be shared with other expert doctors, scientists and health care companies including drug companies that are partnered with this project. Your identity will be protected and will not be shared and the study is approved by an ethics committee. This research may not benefit you directly or immediately but will help us in the future.

More information, including information specifically for patients, and up-to-date contact details can be found on the research association's website (www.pulmonary-fibrosis.net).

What is the study about?

The European ILD registry is aimed at characterising ILDs as comprehensively as possible. The project involves anaWe will be storing information and samples from you during the course of your lung condition. For comparison, we will also be collecting information and samples from patients with other lung conditions (e.g. lung cancer, COPD etc) and from healthy people without lung disease.

What are we doing with your clinical information (data)

We will be collecting and storing information that is relevant to your lung condition. This includes medical history, breathing tests, CT scans, other investigations and drug treatments. We will share this information with other members of the European ILD registry team and partners including drug companies. We will use ethically approved measures to protect your identity so you cannot be identified from the information and samples we collect and share.

What are we doing with your samples including genetic samples?

We will store and analyse your blood, including DNA, fluid from lung washings, breath samples, and lung tissue samples at our central biobank in Giesen. We will study various molecules that we think may be involved with lung disease. If there is a particular test that we cannot perform on your blood or lung sample, the sample may be given to another University or a drug company that can perform the tests. Lung fibrosis is uncommon so in order to make sense
of results, we will have to share your samples, including genetic samples with qualified doctors and scientists who have expertise in this area. The genetic tests are for research and so until we know for certain if they are useful we won't be able to use them as a routine test.
How long are we going to keep your information and your samples?

We do not have a time-limit for how long we would like to keep your data and your blood, genetic and lung fluid samples. This means we can use the information and samples for future studies. without asking for your permission again.

Where do I find more information?
Information on the activities conducted in the field of lung research as part of the eurILDreg and the medical research projects involving biological samples from the registry can be found on the eurILDreg website on www.pulmonary-fibrosis.net. If you find research projects you do not approve of on this link, you may withdraw your consent at any time.

Participation in this study/research project is voluntary. You may stop participating at any time without giving reasons and without suffering any disadvantages with regard to your medical treatment or relationship with your treating physician. On the other hand, you may also be withdrawn from the study should this be necessary on medical or organisational grounds.

What do we need from you?

For all participating patients with ILD, if you consent to this study, we will ask you to do the following:

Fill questionnaire at the start of the study. This will take you around 1 hour to complete and will record relevant information on your medical history and quality of life.

Complete another questionnaire at regular intervals (at least once a year but every 3 months would be best). This questionnaire will take around 15 minutes to complete and includes questions on your quality of life.

Allow the doctor that is treating you to send any relevant medical information and results from investigations with the Euro-ILD registry. This includes blood tests, lung washings and biopsies, breathing tests, CT scans reports and the scans themselves and other relevant tests.

Allow your samples (DNA, blood, lung etc) to be sent to a medical centre (in Germany) who may then send on to other researchers and partners associated with the Euro ILD registry. The samples you provide will be 'spare' samples left over from routine clinical tests that would normally be thrown away. We won't take any blood samples or biopsies for research purposes.

Allow your doctor to fill in a questionnaire describing your medical condition now and in the future item and send this to Euro-ILD

Allow for the data collected and results from data analyses to be forwarded to partners in Euro-ILD (including drug companies) in an ethically approve way so it will not be possible to identify you.

For some specific patients with ILD we will be performing we ask you to do the following:

To provide additional blood samples (up to 25ml, around 5 teaspoons). This blood sample will be taken once and we will try to take the sample at the same time as a routine blood test.

To provide urine samples. These samples may be taken several times during the study.

Allow us to take measurements to detect the molecules in the air and condensation you breathe out. This involves breathing into a machine. These samples may be taken several times during the study and each samples will take less than 10 minutes to obtain.

If you are one of a randomly-selected group of patients we will ask you to do daily breathing tests at home over the course of one year. These test will take no longer than 20 minutes a day we would like to ask to take these measurements regularly. You will be provided with the relevant measuring devices. The device to measure oxygen levels is around the size of a matchbox and the device to measure breathing volumes which is around the size of a mobile phone. We will assist you with installing an app on your phone, as well as with connecting your phone to the measuring devices via Bluetooth. The app is interactive and will guide you through your daily measurements, record the values measured and forward these to our database. As there is a certain effort involved in taking these measurements every day, we will ask you to tell us during the informed consent discussion whether you are prepared to take these home measurements over the course of one year.

FOR PATIENTS WITH OTHER TYPES OF LUNG DISEASE
Unlike the procedure for patients with interstitial lung diseases, we shall only collect key clinical data from you. We also wish, where possible, to store either samples taken during routine medical procedures (blood, fluid from lung lavage, breath samples and/or tissue samples) or those taken specifically for research purposes (blood samples only) at our central biobank in Gießen. We shall conduct genetic tests on blood samples, with the objective of identifying the factors that lead to different types of lung disease.

FOR RELATIVES OF PATIENTS WITH LUNG FIBROSIS THAT APPEARS FREQUENTLY WITHIN THE FAMILY AND FOR HEALTHY VOLUNTEERS
In order to reliably identify the genetic factors responsible for lung fibrosis which occurs frequently within families, we need to take either your blood or cells from the lining of your mouth. In addition, we will store urine and blood as well as breath samples. We also ask you fill out a patient questionnaire, undergo a clinical evaluation conducted by physicians at our centre and take a lung function test. The information collected from you will be processed in the same way as those collected from patients.

4) What are the benefits associated with participating in this study? There are no direct benefits in terms of your treatment associated with participating in this study and providing samples and data. Your data and samples are analysed exclusively for the purposes of research and not to draw any conclusions about your health. As a patient who participates in the registry, you will automatically be informed about the option of participating in clinical trials if you meet their inclusion criteria and wish for this to happen. Finally, you may also be able to benefit from new findings on the causes of your disease, should you so wish. If such new, important findings are discovered during the study, you shall be informed immediately after the ethics committee have been consulted and, if you have any doubts, you can request for these factors to be clarified in relation to your individual circumstances. This shall also apply to any results from genetic testing if you agree for such testing to be conducted and wish to be informed of the results. If relevant results are obtained in this regard, the ethics committee, together with the governing body of the European IPF Registry, will come to a decision on how you should be informed about these results and which supportive measures you should be offered (e.g. genetic counselling). All the medical-scientific

research projects which have been conducted to date, as well as those to be conducted in the future, are aimed at improving our understanding of how the diseases are caused and how to diagnose them, then using this improved understanding to develop new and improved options for treatment and prevention. Against this backdrop, participating in this study would result in a great benefit to society. Information on the activities involved in the eurILDreg can be found on the eurILDreg website on www.pulmonary-fibrosis.net.

5) What are the risks associated with participating in this study?

a. Health-related risks:

To create a biobank, we only wish to use samples taken as part of diagnostic and therapeutic procedures that you would have to undergo in any case, with these samples normally being disposed of as leftover material. As such, providing these samples would pose no additional health-related risk to you.

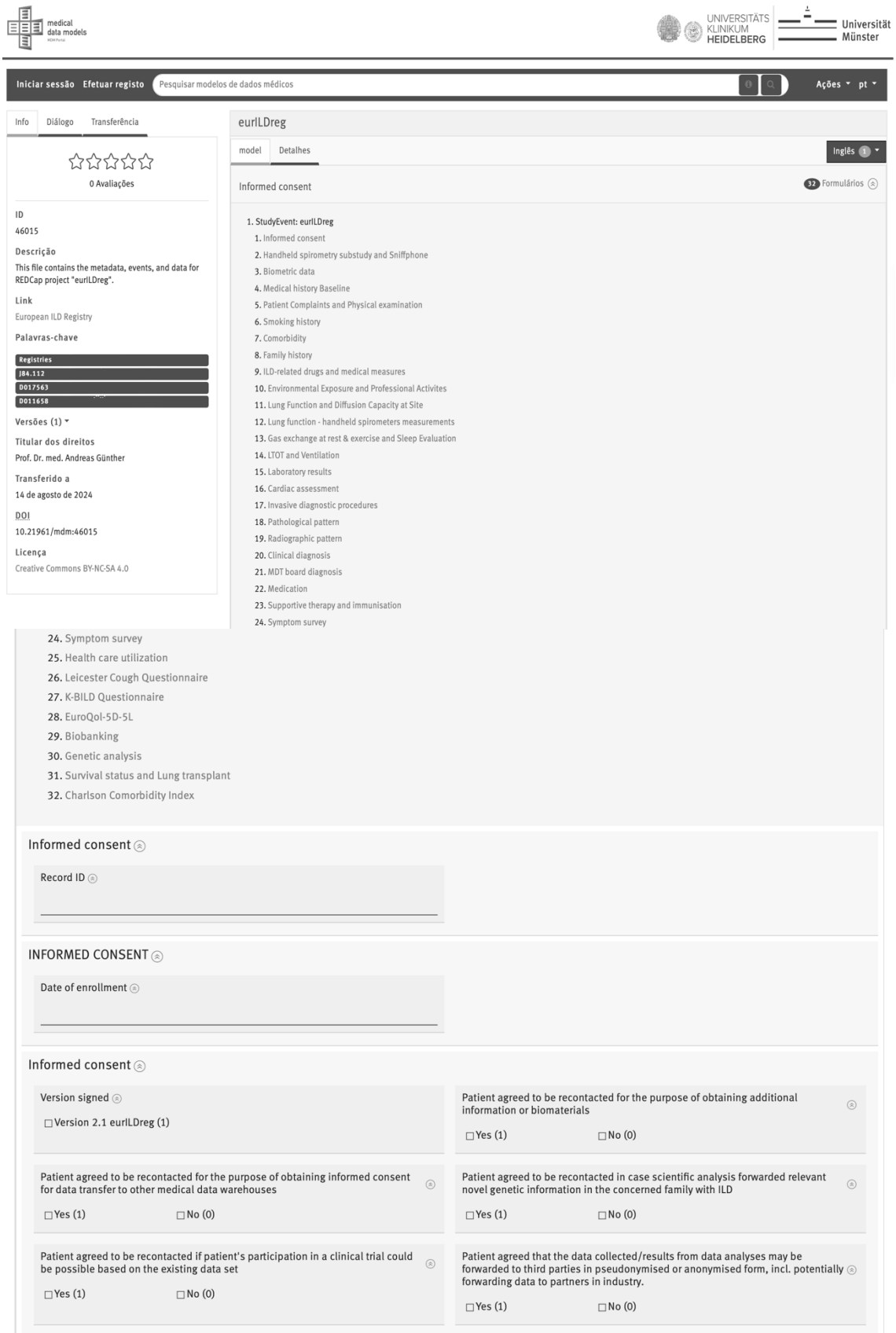
If, as part of a routine diagnostic procedure, e.g. taking blood, up to an additional 25ml of blood is taken (around 5 teaspoons), your treating physician will deem that this is not associated with any additional risk to your health.

b. Other risks:

Every time data from your biological samples are collected, stored and passed on as part of research projects, there are risks that confidentiality could be compromised (e.g. there is a possibility that you could be identified), especially with regard to your genetic material. These risks cannot be completely
ruled out and increase as more and more data can be linked together, especially if you publish genetic data on the internet yourself (e.g. ancestry research).

The eurILDreg can assure you that all measures possible according to the state of the art are taken in order to protect your privacy. More detailed information can be found under item 6 “Who has access to your biological samples and data?”

8.7 eurILDreg Informed Consent and Variables assessed



8.8 PatientMpower App Interface – User Journey

Task 2 - Easy instruction and handling

App push notifications will remind the patient to record their measurements at their chosen time between 7-10am

Task 3 - Introduction

An In-app message will welcome the patient when the log in for the first time

The *More Info* button can direct patients directly to the EQ-5D-5L survey, a webpage hosted by patientMpower or the Registry with full patient instructions. See sample here

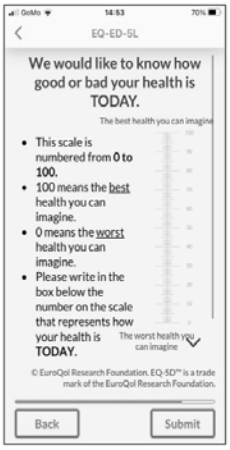
Task 4 - Introduction - EQ-5D-5L

The patient will find the EQ-5D-5L questionnaire in the Surveys section

The patient will be brought through the survey with one question per screen. Each screen will have a progress bar to give patient visual feedback on their progress. Patients click *Next* to navigate to the next question

Task 4 - Introduction - EQ-5D-5L

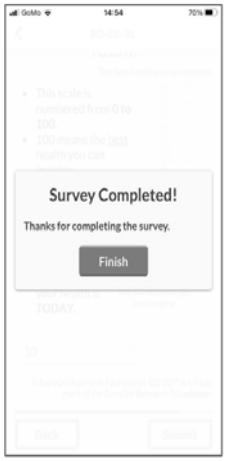
The survey ends with the patient asked to rate their wellness



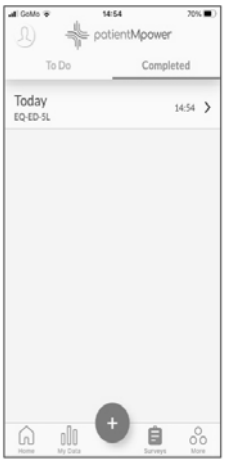
The patient will indicate their score on the scale as well as inputting the value in the text box

Task 4 - Introduction - EQ-5D-5L

When the patient has completed the questionnaire they will see this completion message



The survey will then appear in the *Completed* section, showing the date and time stamp. Patients will be able to review their answers, but not edit them.



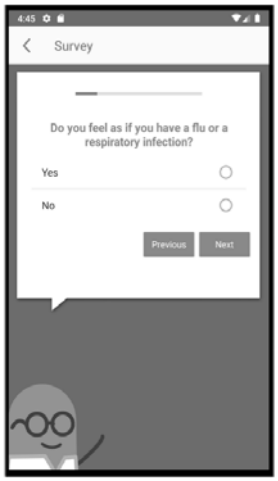
Task 4 - Introduction - Symptom Survey

The patient will find the *Symptom Survey* in the Surveys section

Patient is asked a series of symptom questions, beginning with a question regarding their cough

Task 4 - Introduction - Symptom Survey

Followed by a question regarding flu or a respiratory infection

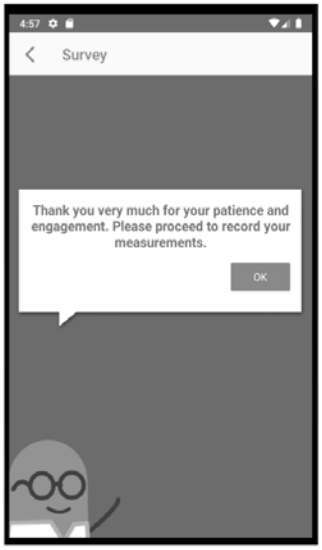


If a patient answers *No* they will see the following message that concludes the survey

Task 4 - Introduction - Symptom Survey

If a patient answers *Yes* they will be brought through 3 more questions regarding sputum, colored sputum and fever.

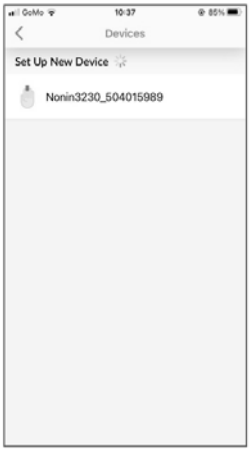
At the end of the symptom survey they will see this message



Task 4 - Introduction - Error Handling

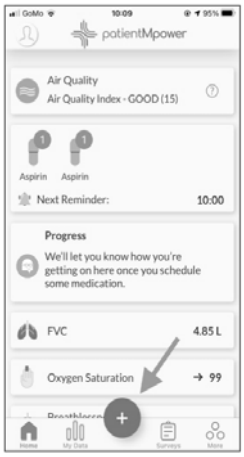
If connection issues occur, this screen will appear informing patients that their device is not connected

Clicking the *Devices* button will direct the patient to the Bluetooth connection page where they can connect their devices

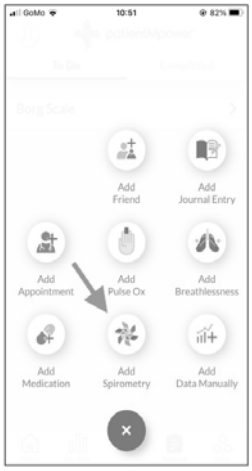


Task 7 - Spirometry

Patients will click the + sign



Patients will select Add Spirometry



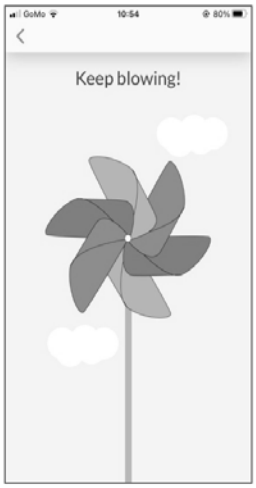
Task 7 - Spirometry

Patients will see the following instructions on screen along with an audio version

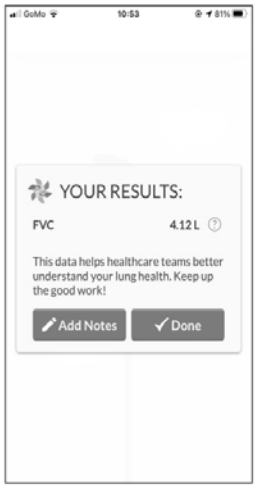
Patient presses *Understood* and is prompted on the next screen to begin their blow

Task 7 - Spirometry

Patients will see the pinwheel spinning on screen and be encouraged by audio to keep blowing



Once the blow is complete the results will appear on screen. If the patient has no other symptoms to report they will click *Done* to finish the measurement



Automated & Real-time assessment of spirometry

patientMpower

Session ID: 40477639

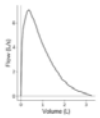
Analysed on: 2021-08-19 18:31:25

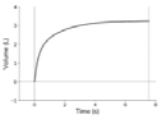
Session Evaluation

Session Grade
FEV1 = E
FVC = E
Overall = Borderline

Best Test Results
FEV1 = 2.32 L
FVC = 3.25 L

Best trial : 1





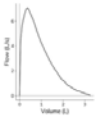
Trial Overview

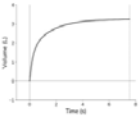
	Acceptable	Usable*
Trial 1	Yes	-

*Usability refers to FEV1 only

Trial Evaluation Details

TRIAL 1 - Acceptable





BEV Criteria: True
EOT Criteria: True
Plateau Criteria: True
(19.8 mL change in last second)
tFE > 6s: True

No artefact on MEFVC

Warnings
No second inspiration

Session ID: 40401551

Analysed on: 2021-08-19 18:31:23

Session Evaluation

Session Grade
FEV1 = E
FVC = F
Overall = Rejected

Best Test Results
FEV1 = 2.24 L
FVC = None L

Best trial : None

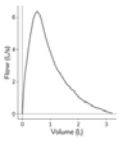
Trial Overview

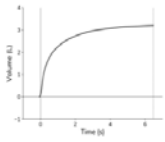
	Acceptable	Usable*
Trial 1	No	Yes

*Usability refers to FEV1 only

Trial Evaluation Details

TRIAL 1 - Usable (failure of EOT criteria)





BEV Criteria: True
EOT Criteria: False
Plateau Criteria: False
(29.7 mL change in last second)
tFE > 6s: True

No artefact on MEFVC

Warnings
No second inspiration

Session ID: 40401550

Analysed on: 2021-08-19 18:31:21

Session Evaluation

Session Grade
FEV1 = F
FVC = F
Overall = Rejected

Best Test Results
FEV1 = None L
FVC = None L

Best trial : None

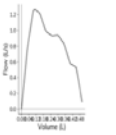
Trial Overview

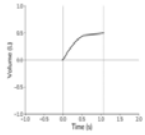
	Acceptable	Usable*
Trial 1	No	No

*Usability refers to FEV1 only

Trial Evaluation Details

TRIAL 1 - Not Acceptable or Usable (No effort)





BEV Criteria: None
EOT Criteria: None
Plateau Criteria: None
tFE > 6s: None

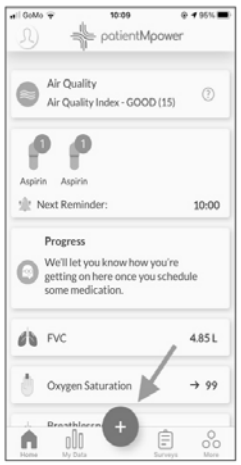
Artefact on Entire MEFVC (No effort)

Warnings

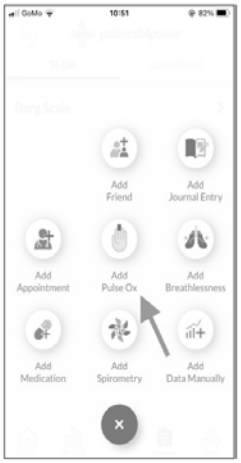
1. without an unsatisfactory start of expiration, characterised by excessive hesitation or false start extrapolated volume or EV .5% of FVC or 0.150 L, whichever is greater
2. without coughing during the first second of the manoeuvre, thereby affecting the measured FEV1 value, or any other cough that, in the technician's judgment, interferes with the measurement of accurate results
3. without early termination of expiration
4. without a Valsalva manoeuvre (glottis closure) or hesitation during the manoeuvre that causes a cessation of airflow, which precludes accurate measurement of FEV1 or FVC
5. without a leak
6. without an obstructed mouthpiece (e.g. obstruction due to the tongue being placed in front of the mouthpiece, or teeth in front of the mouthpiece, or mouthpiece deformation due to biting)
7. without evidence of an extra breath being taken during the manoeuvre.

Task 8 - 1 Minute Sit to Stand Test

Patients will click the + sign



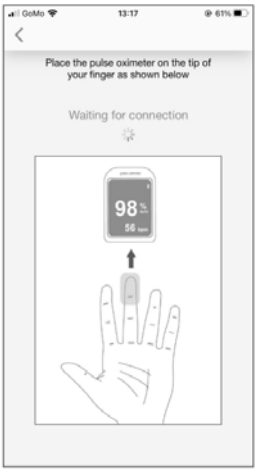
Patient will select an icon that says 1MSTS in this menu



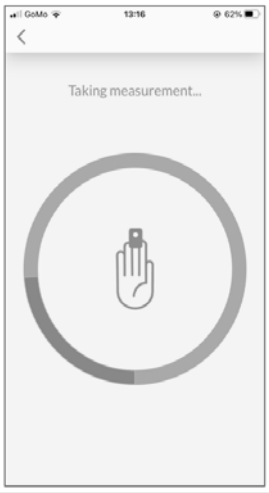
Task 8 - 1 minute Sit to Stand Test

Please note this user flow is subject to change and these are sample designs

Patient will be instructed to place the oximeter on their finger



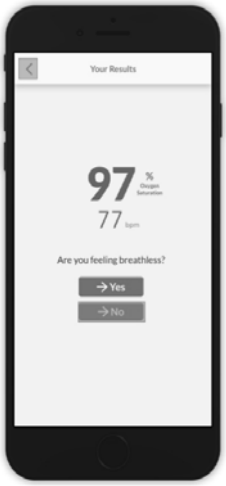
Recording measurement screen



Task 8 - 1 minute Sit to Stand Test

Please note this user flow is subject to change and these are sample designs

Patient will see their result and be asked to report any breathlessness



If a patient selects *Yes* they will indicate rate their breathlessness on the BORG scale which follows on the next screen

8.9 Standardised Teaching Procedure

eurILDreg
European ILD Registry

Center for Interstitial and Rare Lung Diseases Gießen
Klinikstrasse 36 • 35392 Giessen

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Justus-Liebig-Universität Giessen
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Fax +49 6 41 985-4 25 08
Andreas.Guenther@innere.med.uni-giessen.de

Phone specific exclusion criteria:
(Updated as of June 2023)
Chinese phone manufacturers currently exhibiting Bluetooth connectivity issues. Please find a (not complete) list of known problematic phone manufacturers:

- Huawei
- Xiaomi
- Redmi
- Poco

List of other Chinese phone manufacturers which may exhibit similar issues but haven't been tested so far:

- Oppo
- Vivo
- Oneplus
- Lenovo

eurILDreg
European ILD Registry

Recruitment process

This document is not meant as a directive for participating centres but rather a suggestion on how to explain the handheld spirometry/ exercise test study to patients.

What the research team requires:

- MIR Spirometer smart
  - **[to be given to patient]**
- Nose clip
  - **[to be given to patient]**
- NONIN Pulse Oximeter
  - **[to be given to patient]**
- Email & Password slips for signing into patientMpower
  - **[given to patient]**
  - **PLEASE** retain the bottom half of the paper where the 5-digit code is stated and transfer the number to _____
- Written step by step instructions for patients – a video will be released later.
  - **[given to patient]**
- Confirmation of acceptance signed & dated by patients with the Serial Number of the Pulse oximeter and Spirometer.
  - **[Retained by the centre]**

Setting up the app and devices:

1. Ask patient whether they have a smartphone and internet connectivity.

2. Ask the patient if they are willing to participate in **this 1-year study** which will ask them to perform **daily lung function tests and exercise tests** in the **morning around the same time**.
   a. You may elaborate to inform them that the lung function tests take about 30 seconds with the exercise test requiring a total of about 2 minutes.

   b. Should they seem unsure and give the impression that they will discontinue within a short period of time, it might be wise to suggest that they don't take part.

eurILDreg
European ILD Registry

Either before or after the patient has consented to take part:

- ⇨ This study is part of the European registry for interstitial lung diseases. This study aims to correlate the use of the handheld device with the device used in the clinic. Furthermore, we hope to establish an algorithm to diagnose exacerbations earlier than the current devices used. All data will be strictly confidential, and no identifiable data will be collected by the app.

- ⇨ This study will provide the patient with a nose clip, a spirometer, and a pulse oximeter with the latter two both connecting to the phone via the patientmpower app.

- ⇨ You may want to elaborate even further and explain that it may be beneficial for the patient themselves to participate in the study as it allows patients to understand their own illness better.

3. Ask the patient to go on the App Store/ Google Play store and search for patientmpower in the search bar and download the app.

patientMpower

4. In the meantime, take your time to explain the devices:

Spirometer

- Insert batteries.
- Explain that the device does not need to be turned on, as it is always ready to pair – AAA batteries should be changed after about 4-6 months.
- Explain and show how the mouthpiece and the rotor may be taken out to clean about once a week in soapy water **without** a direct jet of water.
- Show how the device should be held.

Nonin Pulse oximeter:

- Insert batteries. Be aware that the +/- combination on one side is different to what is expected -> follow the +/- signs on the device.
- AAA batteries should be changed after about 6 months or longer.
- Explain that the device turns on automatically once a finger is inserted into the device.
- Advice patient, that when using the pulse oximeter, they should have a dry and clean finger.

5. Open the app and click on the red 'login' sign, then click on 'I already have an account'.

6. Type in the email and password credentials provided.

⇨ Tell the patients that they will not have to repeat the login steps once they have been logged in. Nevertheless, the patients should still take the email and password with them as phone updates might delete their credentials.

   a. I suggest typing the email and password in yourself as elderly patients often struggle with typing it themselves.

7. Explain that the screen shown once the app is logged in, will be the same home screen that patients will find once they open the app.

8. **Connecting the devices:**

   a. Make sure, Bluetooth is switched on.

   b. Press on 'more' at the bottom right of the screen and select Bluetooth devices.

   c. Select the spirometer (device starting with Spirobank Smart Z1xxxxxx) – please make sure to select the correct one, the number corresponds with the serial number written on the device.

   d. To connect the pulse oximeter, place the device on the patients finger for it to switch on. A device called Nonin 3230_ (Serial number).

   e. A message should appear for each device being successfully paired.

eurILDreg
European ILD Registry

Spirometry

9. Prior to navigating to the spirometry icon on the app, I suggest you show the patient a run-through on how to perform a good lung function test, either using your own device or pretending to have a device. **This instruction is directed at the relevant doctor/ study nurse:**
    a. Please remain seated for the duration of the test.
    b. Please hold the spirometer such that the mouthpiece is facing up.
    c. Please be careful not to block the turbine with their hand.
    d. Please wear loose clothing, they should avoid clothing that restricts their breathing.
    e. Please perform the spirometry test whilst sitting in a standard chair without an arm rest:
        - Feet parallel to each other and flat on the floor
        - 90-degree angle between thighs and lower legs
        - Free arm dangling down their side
    f. Please **fasten your nose clip** so that the nostrils are closed tightly.
    g. Please breathe in and out twice as deeply as possible – After the second breath:
    h. Place the spirometer in your mouth and close your lips tightly around it.
    i. Exhale as quickly and deeply as you can - remember to continue exhaling for **at least 6 seconds**.
    j. Please note that there is less than 2 seconds between inhalation and the start of maximum exhalation.

10. Once having shown a run through, advice patient to press on the red 'plus' sign at the center of the home screen and select 'add spirometry'.
    a. It may take a moment for the app to connect to the spirometer.
    b. As soon as the device has connected, a brief set of instructions will appear on the screen.
    k. When ready, advice patient to click "understood" at the bottom of the screen. **The test starts automatically as soon as the patient exhales into the device.**
        i. Please note that I have noticed that the test may begin prematurely if the patient handles the spirometer with too much heist as it may prompt the rotor to rotate and give a false reading.
    c. Ask the patient to repeat the steps from point 9.

11. After a short loading period, the screen should display the result of the patient's spirometry measurement.
    a. Should the app detect a faulty exhalation, an error should be delineated below explaining which part of the procedure was done inadequately.

Exercise Test:

12. As previously, I suggest you show the patient a run-through on how to perform a good Exercise test, either using your own device or pretending to have a device. **This instruction is directed at the relevant doctor/ study nurse:**

    a. Place the chair back against a wall to keep it from moving while the test is being performed.

    b. Attach the Pulse oximeter on the finger if not already done so.

    c. Prior to commencing, remind yourself that you should always remember to count the number of sit to stand repetitions as you will have to enter the amount later.

    d. Before the test
        i. Shortness of questionnaire will appear (BORG)
        ii. Oxygen saturation and pulse frequency will be measured.

    e. After completing those steps, a screen will appear in which upon pressing start, a 10 second countdown will automatically count down.
        i. Before pressing start, make sure the pulse oximeter is well-adjusted your finger and the phone is placed face up on the floor in front of the chair.

    f. After leaning forward to press start, you have 10 seconds to adjust your seating position:
        i. Feet parallel on the floor with 90 degrees between lower and upper thigh
        ii. Pulse oximeter should be kept at breast-height.
        iii. Other arm should be hanging freely.
        iv. They should not be using any aids to help them with standing up.

    g. Once the 10 seconds have elapsed, the 1-minute timer starts automatically.

    h. Stand up from the chair and stretch your legs fully. Do not use your hands or arms to help. Then sit back down. This counts as one sit-stand repetition.

    i. In one minute, sit and stand up in the chair as many times as possible.
        i. During the minute, the app will display the current oxygen saturation and pulse

    j. Rest a few seconds during the test, if necessary, then resume as soon as you can

k. You can stop the test at any time if you feel uncomfortable.

l. The test will be aborted if there are technical problems or if the readings are outside the safety parameters.

m. After completing the test, enter how many sit-stand reps you performed in one minute.

n. You will then be asked again to measure your shortness of breath using the BORG scale.

The following instructions repeat some of the points from instruction 12, as it includes the exact measures which must be followed on the App:

13. Once having shown a run through; from the main screen, click on the "Plus" sign in the bottom center.

14. Although not strictly required, I suggest the patient attaches the pulse oximeter at this stage as some devices may show Bluetooth connectivity issues if they attach it later on. Similarly, they should place the chair up against the wall.

15. Advise patient to click on "Add exercise test" on the bottom left.
    a. A welcome screen will appear, repeating the preparation tips previously explained.

16. Advise patient to click on "next" three times as the preparatory steps are explained on screen.

17. Advise patient to click on "Start" at the bottom right - to start the questionnaire.
    a. Patients should answer the following two questions and click on "continue".

18. A short loading screen should appear - during which time the patient's oxygen saturation and pulse are measured at rest.

19. After the results are displayed, tell patient to click on "next".

    a. Advise patient to follow steps 12.E to 12.F

b. During the 60 seconds, the patient should perform instruction 12.G to 12.L

c. At the same time, the patient's current oxygen saturation and pulse are displayed above the timer.

20. Once the 60 seconds have fully counted down, an automatic screen will appear asking the patient to type in the number of repetitions.

21. After they have entered the number, please advise patient to click on "continue"

22. Now they will be asked again to answer the BORG shortness of breath scale, please advise patient to click on "next" each time.

23. After the last question, advise patient to click Submit after answering the last question.

24. a pop up will appear stating "Test Complete", please ask patient to click OK.

Viewing data

25. For patients to view their data, they must press "my data" at the bottom of the screen when navigating from the home screen.

26. Patients can select the timeframe in which they want to view their data by selecting the relevant time frame at the top of their screen.

Further points:

- **Thank Patient** for participating.
- Ask patient to sign the declaration form that they have received both the spirometer and pulse Oximeter
- Ask patients to always bring their devices to follow up meetings, so patients have the option to ask questions regarding any issues.
- Should any issues occur while using the device, the patient may call the relevant clinic which handed out the devices.
- Don't forget to record the patientmpower Username and serial numbers of the devices in redcap.

8.10 Patient instruction for handheld monitoring

Centre for interstitial and rare lung diseases
Klinikstrasse 36 ● 35392 Giessen ● Germany

Prof. Dr. med. A. Günther
European IPF/ILD Registry & Biobank (eurIPFreg)
Universities of Giessen and Marburg Lung Center
Member of the German Center for Lung Research (DZL)
Justus-Liebig-University
Klinikstr. 36, 35392 Giessen, DE

Performing a Measurement with the MIR Spirobank Spirometer

Dear participant,
We kindly request your participation in daily lung function measurements and physical exercise tests. This test should be carried out every morning.
Prior to conducting these measurements, we ask you to assess your daily well-being. Please begin by opening the "Symptom Test" questionnaire and responding to the questions provided. Once you have completed the "Symptom Test," proceed to open the "EQ-5D-5L" questionnaire and fill it out. Additionally, we request your completion of two additional questionnaires every three months, namely K-BILD and LCQ.

First activity: Completion of the "EQ-5D-5L" and "Symptom check" questionnaires

The first activity involves completing the "EQ-5D-5L" and "Symptom Check" questionnaires. Here's a simple guide, on your smart phone open the PatientMpower App:

- Click on the "Surveys" tab at the bottom, then select the "Symptom Check" questionnaire.
- Answer the questions truthfully and click "Finish" at the end.
- Next, select the "EQ-5D-5L" questionnaire, answer the questions, and press "Finish" at the end.
- Every three months, complete two additional questionnaires: K-BILD and Leicester Cough Questionnaire (LCQ).

General Tips:

- Perform measurements between 7 am and 10 am daily.
- Follow PatientMpower app instructions for accurate results.

To ensure a successful day of measurements:

- Wear loose clothing.
- Sit on a comfortable chair without armrests.
- Ensure a right-angle seating position.
- Place the chair against a wall for stability.
- Open the PatientMPower app on your smartphone; the App has already being set up from your outpatient clinic appointment.

Second activity: Performing Lung Function Measurement

- Click the red plus sign, then select "Add spirometry."
- Once the device has connected, follow the on-screen instructions and click on "Got it"

Steps for a correct measurement:

1. **Remain Seated:**
   Ensure you stay seated throughout the test.
2. **Nose Clip Application:**
   Attach the nose clip securely to close your nostrils.
3. **Holding the Spirometer:**
   Hold the spirometer handle with the mouthpiece facing upwards.
4. **Avoiding Turbine Blockage:**
   Be cautious not to block the turbine with your hand.
5. **Foot Placement:**
   Position your feet parallel and flat on the floor.
6. **Free Arm Position:**
   Let your free arm hang loosely during the test.
7. **Breathing Technique**:
   Inhale deeply twice after the second inhalation.
   Position the spirometer in your mouth and enclose it tightly with your lips.
   Exhale forcefully for at least six seconds in total.
   Ensure less than two seconds between inhaling and starting the maximum exhalation.

The test initiates automatically upon exhaling into the device.

- Following a brief loading period, the screen will reveal the results of your spirometry measurement.
  - **Faulty Execution:**
  - In case of an execution error, an error message will be displayed.
  - **Retesting Protocol:**
  - If an error occurs, perform the test once more, but limit retesting to only one additional attempt.
  - **Successful Test:**

If the test is successful and accurate, proceed by pressing the **"Finish"** button.

Third activity: Physical Exercise Test Guidelines:

Attention:
Before proceeding with the exercise test, please ensure the following conditions are met:

1. Well-being:
   - Perform the exercise test only if you are feeling good.
2. Health Status:
   - Refrain from the exercise test if you experience fever, chest pain, nausea, leg cramps, or notice yellowish/greenish sputum.
3. Medical Advice:
   - Confirm that your doctor has not advised against undergoing the exercise procedure.
4. Environmental Conditions:
   - Consider the outside temperature; it should be moderate for a safe exercise environment.

Using the Pulse Oximeter during the Physical Exercise Test.

Preparation:
Ensure optimal preparation for accurate pulse oximetry results:

1. **Warm and Dry Hands:**
   - Confirm your hands are warm and dry before initiating the measurement.
2. **Consistent Finger Use:**
   - Always utilize the same finger for the oximeter measurement. If you regularly check your blood glucose level on your fingers, keep this finger free from needlesticks.
3. **Proper Device Placement:**
   - Hold the oximeter at the height of your belly button during the measurement.
4. **Maintaining Stillness:**
   - While the oximeter is on your finger, avoid touching it. Hold your hand loosely at a right angle in front of you.
5. **Caution for Oxygen Users:**
   - If you use oxygen under load, set the flow rate to the value determined by your healthcare provider.

Execution of the Physical Exercise Test:
Follow these steps for a successful execution of the exercise test:

1. **Accessing and introducting the Physical Exercise Test:**
   - Click on the red plus sign at the bottom center of your screen.
   - Select - Add exercise test.
   - An introduction to the physical exercise test will be provided.
2. **Initiating the Test:**
   - When ready, click "Next" at the bottom of your screen.
3. **BORG Scale Assessment:**
   - Rate your breathlessness and fatigue using the BORG scale.
   - After answering, a 10-second countdown begins.
4. **Preparing for the Test:**
   - Utilize this time to place your smartphone within sight.
5. **Commencement of the Exercise Test:**
   - Stand up from the chair, fully extending your legs without using your hands or arms.
   - Sit down, marking one sit-to-stand repetition.
   - Repeat the sit-to-stand movement as many times as possible in one minute.
   - If needed, take short rests during the test.
   - Continue only when comfortable, and feel free to stop the test at any time if discomfort arises.
6. **Data Entry:**
   - After completing the test, enter the number of sit-to-stand repetitions performed in one minute.
7. **BORG Scale Reassessment:**
   - Rate your shortness of breath and level of fatigue using the BORG scale.
8. **Submission:**
   - Click on "Submit" after answering the last question.
   - "Test completed" will then be displayed.

Support:

If you have any further questions or problems with the mobile app or the devices provided, please feel free to contact us. We will be happy to help you!

Telephone:
E-Mail: support@eurildreg.net

8.11 MIR Spirometer Patient Brochure

Compatible SOFTWARE

MIR SPIROBANK APP

Mobile App (iOS and Android), for real time Spirometry test, directly on your Smartphone via Bluetooth Smart 4.0

Add Oximetry results manually on the APP

GET IT ON Google Play

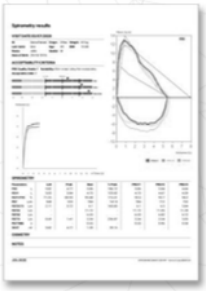
Download on the App Store

REAL TIME TEST

Spirometry: PEF, FVC, FEV1, FEV1/FVC, FEF25/75, FEV6, VEXT, DTPEF, FEF75, FEF25, FEF50

MEDICAL REPORT

Professional PDF report Including Acceptabilty Messages, Quality Control Grade, Acceptable Trials, Variability of FEV1 and FVC, Pictograms



SHARE RESULTS

Share results in PDF With anyone at anytime via eMail, Whatsapp, SMS, Cloud, Drive Bluetooth, Airdrop and other Apps

PERSONAL TREND

E-diary, symptoms and notes can be added for each test.
Oximetry results can also be added manually on the App

INCENTIVE

Real time animation on Smartphone, to improve personal compliance during the test

Compatible TURBINES

	Mouthpiece	Turbine Disinfection	Turbine Calibration	Packaging	Antiviral Filter
Single Patient Reusable Turbine	Included Reusable	Not required	Not required	Individually sealed: 1 unit / box	Not required
flowMIR™ Disposable Turbine	Included Disposable	Not required	Not required	Individually sealed: 60 or 10 units / box	Not required

PLAY VIDEO

SCIENTIFIC PUBLICATIONS

Rev.6

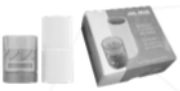
TECHNICAL datasheet

PRODUCT CODE 911105

Technical specification

Width	49 mm
Length	109 mm
Thickness	21 mm
Weight	60.7 g (batteries included)

Turbine



Reusable Turbine with plastic Mouthpiece (code 910013)

Disposable Turbine (code 910004)

Power supply	2 batteries AAA 1.5 V	
Consumption	max 12 mA Stand by 8 μA medium	
Backup battery voltage	none	
Batteries charger	none	
Autonomy	5-10 years (Stand by)	
Connectivity	Bluetooth® 4.0	
Mouthpieces	Ø 30 mm (1.18 inch)	
Type of electrical protection	Internally powered	
Safety level for shock hazard	Type BF Apparatus	
IP protection level	IP22	
Conditions of use	Apparatus for continuous use	
Storage conditions	Temperature:	MIN -25 °C, MAX +70 °C
	Humidity:	MIN 10% RH; MAX 93%RH
Operating Conditions	Temperature:	MIN +5 °C, MAX +40 °C
	Humidity:	MIN 10% RH, MAX 93%RH
Shipping conditions	Temperature:	MIN -25 °C, MAX + 70 °C
	Humidity:	MIN 10% RH; MAX 93%RH

Applicable standards	IEC 60601-1:2005+Amd1:2012 EN 60601-1-2: 2015 EN ISO 14971: 2019 ISO 10993-1: 2018 2011/65/UE Directive EN ISO 15223:2016 IEC 60601-1-6:2010+Amd2013 IEC 60601-1-11: 2015 ATS/ERS Guidelines ISO 26782: 2009 ISO 23747: 2015

Spirometry

Flow sensor	bi-directional digital turbine
Flow range	±16L/s
Volume accuracy	±2.5% or 0,05 L
Flow accuracy	±5.0% or 0,20 L/s
Dynamic resistance	<0.5 cm H2O/L/s
Temperature sensor	none
Test available	FVC,
Measured parameters	FEV1, PEF, FVC, FEV1/FVC ratio, FEV6, FEF2575
Additional parameters available with F/V version	FIVC, FIV1, PIF FEF25, FEF50, FEF75, EVol, FEV05, FEV075, FEV2, FEV3, FET, PEF Time
Memory capacity	the application on the smart phone memorizes data

Certificates & Registrations

CE 0476	MED 9826 by Kiwa-Cermet
FDA 510(k)	K072979
CND code	Z12150102
GMDN code	46906

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8.12 List of Publications and Conferences

Publications:

European ILD registry algorithm for self-assessment in interstitial lung diseases (eurILDreg ASA-ILD)

Ekaterina Krauss, Laurenz H Claas, Silke Tello, Jennifer Naumann, Sandra Wobisch, Stefan Kuhn, Raphael W Majeed , Karen Moor, Maria Molina-Molina, Oisin Byrne, Rebecca Borton, Marlies S Wijsenbeek, Nik Hirani, Carlo Vancheri, Bruno Crestani, Andreas Guenther; eurILDreg investigators

PLoS One. 2025 Jan 29;20(1):e0316484. doi: 10.1371/journal.pone.0316484. eCollection 2025.PMID: 39879227

Future Publications (soon to be published):

Digital Health in ILD: Assessing Adherence to the Self-Assessment Algorithm in the European ILD Registry (eurILDreg ASA-ILD)

Laurenz H. Claas, Maria Molina-Molina, Silke Tello, Jennifer Tschernucha, Katrin Becker, Sandra Wobisch, Stefan Kuhn, Raphael W. Majeed, Oisin Byrne, Rebecca Borton, Nik Hirani, Poornima Mahavadi, Phillipe Bonniaud, Juergen Behr, Bruno Crestani, Carlo Vancheri, Ekaterina Krauss, Andreas Guenther equal contribution

Conference Contributions:

European Respiratory Congress 09/2023 | Milan

- **The European ILD Registry algorithm of self-assessment (eurILDreg-ASA): pilot study data on prospective, patient-centered capture of symptom burden, quality of life, spirometry, oximetry and exercise capacity**

  Laurenz H. Claas, Karen Moor, Maria Molina-Molina, Keerthana Siebert, Silke Tello, Jennifer Naumann, Rebecca Borton, Marlies Wijsenbeek-Lourens, Bruno Crestani, Andreas Guenther, Ekaterina Krauss

  European Respiratory Journal 2023 62(suppl 67): PA429; DOI: https://doi.org/10.1183/13993003.congress-2023.PA429

American Thoracic Society (ATS) Congress 05/2024 | San Diego

- **Striving for Patient-Centered Care: Interim Analysis of Feasibility and Adherence to the European ILD Registry Algorithm for Self Assessment (eurILDreg ASA)**

  E. Krauss, L. H. Claas, K. Moor, M. Molina-Molina, S. Tello, R. Borton, M. S. Wijsenbeek, B. Crestani, N. Hirani, C. Vancheri, A. Guenther

  Conference: American Thoracic Society 2024 International Conference, May 17-22, 2024 - San Diego, CA

  DOI:10.1164/ajrccm-conference.2024.209.1

8.13 Declaration

„Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten sowie ethische, datenschutzrechtliche und tierschutzrechtliche Grundsätze befolgt. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, oder habe diese nachstehend spezifiziert. Die vorgelegte Arbeit wurde weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt und indirekt an der Entstehung der vorliegenden Arbeit beteiligt waren. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.“

_____ _____

Ort, Datum Unterschrift

8.14 Acknowledgements

I would like to express my heartfelt gratitude to everyone who supported me throughout the completion of this thesis.

First and foremost, my deepest thanks go to Prof. Dr. med. Andreas Günther for his unwavering personal and professional support during this project. His provision of the study concept and invaluable insights were crucial to the success of this work.

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My sincere appreciation extends to the entire team at the "Ambulanz für interstitielle Lungenerkrankungen," particularly Dr. Silke Tello and Jennifer Naumann, for their vital assistance during the data collection phase of this research.

A special thank you goes to my parents, Andrea and Jan, who have provided me with all the opportunities one could ever wish for. Their unwavering love and encouragement have been the foundation of my achievements. I am also immensely grateful to my sister, Antonia, for her constant support, understanding, and for always being there to lend an open ear whenever needed.

I would also like to express my gratitude to my grandparents, Marianne, Edel, and Herbert, for their enduring love and support throughout my life. My deepest thanks also go to my girlfriend, Lia, for her boundless motivation, devotion, and love, which have been invaluable over the past two years.

Finally, I would like to extend a big thank you to my friends in Kassel, Kaspar, Tom and Nick with whom I shared a home during this time. Their support and the much-needed moments of distraction brought balance and joy to the challenging process of this study.