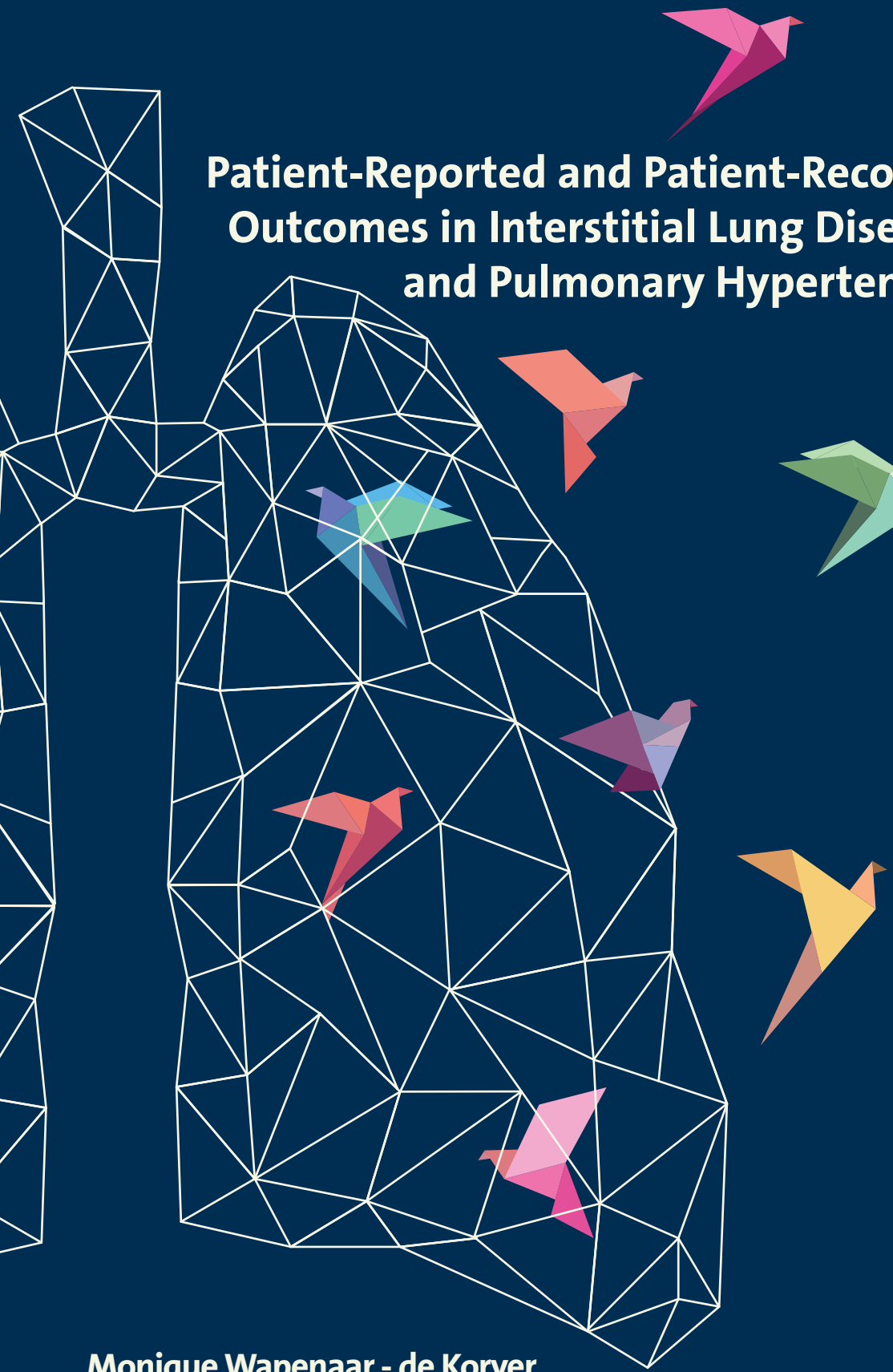
Patient-Reported and Patient-Recorded Outcomes in Interstitial Lung Diseases and Pulmonary Hypertension



Monique Wapenaar - de Korver

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Patient-Reported and Patient-Recorded Outcomes in Interstitial Lung Diseases and Pulmonary Hypertension

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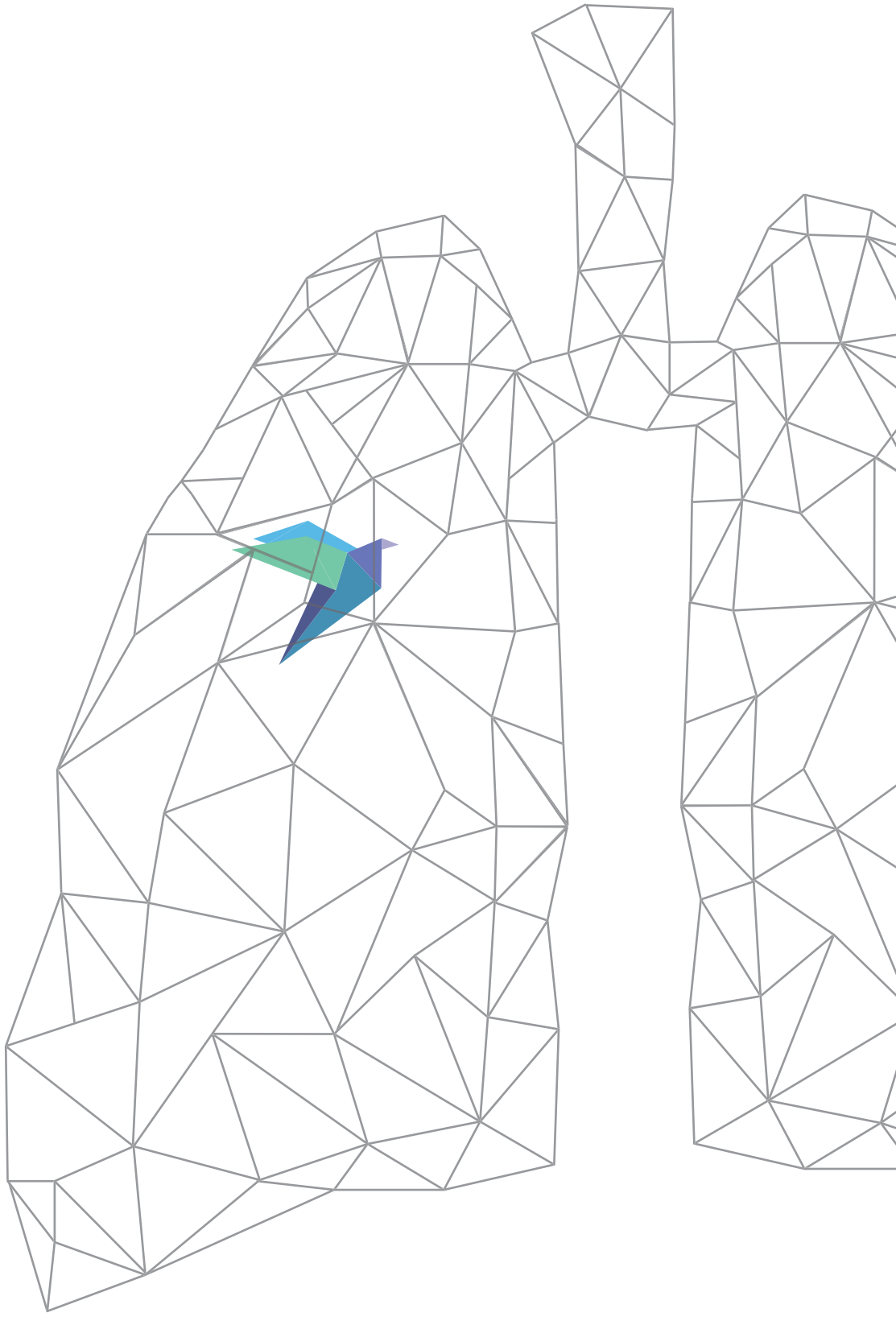
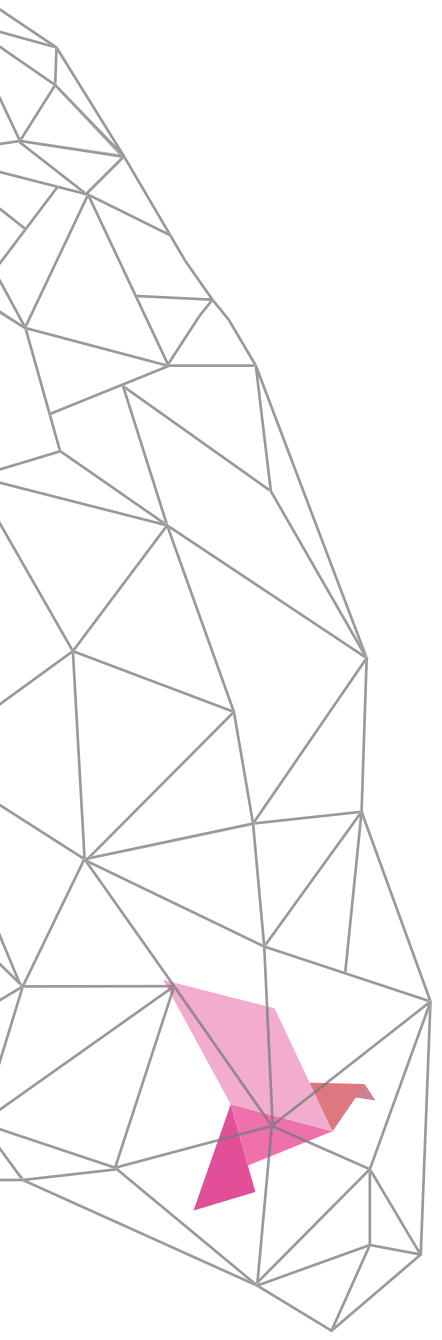


CHAPTER 1

General Introduction



GENERAL INTRODUCTION

Interstitial Lung Diseases (ILDs) and Pulmonary Hypertension (PH) are umbrella terms to describe two groups of chronic and debilitating lung diseases. ILD and PH patients often experience a high symptom burden and deteriorated health-related quality of life (HRQOL). The most commonly encountered symptoms are dyspnea, reduced exercise tolerance, fatigue, and side effects of medication. In ILDs, especially the patients with progressive fibrotic ILD are confronted with a poor prognosis. Although recently new treatment options have been developed that slow down disease progression, many ILDs and all forms of PH are still progressive and incurable. In a small proportion of the patients lung transplantation may be an option.

Traditionally, the effect of medication is assessed using physiologic outcome parameters. However, in both disease areas there is an increasing awareness of the importance to include patient-centered outcomes such as symptoms and quality of life (QOL), when assessing treatment effects. Patients can play a central role in collecting outcome measures, by using patient-reported outcome measures (PROMs) and patient-recorded outcome measures. The most used physiological outcomes and PROMs in the ILD and PH field are shown in Table 1.

There is a paucity of patient-centered outcome measures and interventions aimed at improving QOL, both for patients with ILD and PH. Most of the existing PROMs have been developed in the United Kingdom (UK) or United States of America (USA). The research described in this thesis is focused on translating and validating ILD and PH PROMs for Dutch patients (part 1), develop patient-recorded outcome measures (part 2) and interventions aimed at improving QOL for patients (part 3).

Interstitial Lung Diseases (ILDs)

ILDs comprise more than 200 different disorders, characterized by interstitial inflammation, cellular proliferation, fibrosis or a combination of these processes of the lungs.[1-3] Disease course and prognosis are highly variable between the different ILDs and even between patients with the same disease. Some ILDs are reversible where others show a progressive scarring of lung tissue with rapid decline of lung function and ultimately death.[3] ILDs are categorized into four groups: with a known cause (e.g. drug induced, auto-immune diseases, asbestosis), with an unknown cause (idiopathic interstitial pneumonias-IIPs), granulomatous disorders (e.g. sarcoidosis) and rare ILDs.[4] It is estimated that in the Netherlands around 20.000 people suffer from a form of ILD, with Idiopathic Pulmonary Fibrosis (IPF) and sarcoidosis being the most common ones.[5,6] In this thesis, ILD research is predominantly focused on these two diseases.

Table 1. The most commonly-used clinical outcomes in IPF, sarcoidosis and PAH

Physiologic outcomes	**IPF**	**Sarcoidosis**	**PAH**
Recorded in hospital	FVC	FVC	6MWD
	TLCO	TLCO	peakVO2
	6MWD		V'E/V'CO2
			mean PAP
			PVR
			NYHA Functional class
	Imaging	Imaging	RVSP (echo)
	Biomarkers	Biomarkers	NT-pro BNP
Home-based recorded	FVC	FVC	Physical activity
	Cough	Physical activity	
	Physical activity		
Patient-reported outcomes	**IPF**	**Sarcoidosis**	**PAH**
Generic	SF-36	SF-36	SF-36
	EQ-5D	EQ-5D	EQ5D
	CRQ-SR	WHOQOL-100	NHP
		WHO-BREF	
Disease-specific	K-BILD	KSQ	CAMPHOR
	ATAQ-IPF(-cA)	SAT	MLHFQ
	L-IPF	SHQ	LPH
	SGRQ(-I)	SGRQ	CHFQ
			PAH-SYMPACT®
			emPHasis-10
Domain/symptom-specific			
Depression	HADS	HADS	HADS
Dyspnea	MRC	MRC	Borg
	BDI	BDI	
	Borg	Borg	
	UCSD-SOQB		
Fatigue	FAS	FAS	MFI, Borg
		FACIT-F	
		PROMIS fatigue scale	
Cough	CASA-Q	LCQ	
	VAS	Cough monitors	
	LCQ, CQLQ		
	Cough monitors		

Table 1. The most commonly-used clinical outcomes in IPF, sarcoidosis and PAH *(continued)*
FVC, forced vital capacity; TLCO, transfer factor of the lung for carbon monoxide; 6MWD, 6-minute walk distance; V'O2, oxygen uptake; V'E/V'CO2, ventilatory response (minute ventilation/carbon dioxide production); PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; WHO, World Health Organization; FC, functional class; RVSP, right ventricular systolic pressure; NT-pro BNP, N-terminal pro b-type natriuretic peptide; SF-36, Short-form 36-item Questionnaire; EQ-5D, EuroQol Group 5-Dimension Self-Report Questionnaire; CRS-SR, chronic respiratory disease questionnaire-self reported; WHOQOL-100, World Health Organization–Quality of Life 100; WHOQOL-BREF, short (brief) version of the WHOQOL-100; NHP, Nottingham Health Profile; K-BILD, King's Brief Interstitial Lung Disease; ATAQ-IPF, A Tool to Assess Quality of life in IPF; L-IPF, living with IPF; SGRQ, St George's Respiratory Questionnaire; (-I), IPF; KSQ, Kings Sarcoidosis Questionnaire; SAT, Sarcoidosis Assessment Tool; SHQ, Sarcoidosis Health Questionnaire; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; MLHFQ: Minnesota Living with Heart Failure Questionnaire; LPH: Living with Pulmonary Hypertension questionnaire; CHFQ: Chronic Heart Failure Questionnaire; PAH-SYMPACT, Pulmonary Arterial Hypertension-Symptoms and Impact questionnaire; emPHasis-10: 10-question survey proposed by the Pulmonary Hypertension Association UK; HADS: Hospital Anxiety and Depression Scale; MRC, Medical Research Council; BDI, Mahler Baseline Dyspnoea Index; UCSD-SOBQ, The University of California, San Diego Shortness of Breath Questionnaire; FAS, Fatigue Assessment Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; PROMIS, Patient-Reported Outcomes Measurement Information System; MFI, Multidimensional Fatigue Inventory; CASA-Q, Cough and Sputum Assessment Questionnaire; VAS, visual analogue scale; ; LCQ, Leicester Cough Questionnaire; CQLQ, Cough Quality of Life Questionnaire.

IPF is a fatal lung disease of unknown etiology, characterized by an irreversible decline of lung volume and gas exchange, leading to severe breathlessness, cough and exercise intolerance.[7,8] The prevalence of IPF in the Netherlands is estimated at 20 per 100 000 persons.[5] IPF occurs more frequent in men than in woman and the median age at diagnosis is 65 years.[9,10] Although the clinical course of IPF varies, overall prognosis is poor with a median survival of 2-4 year after diagnosis when not treated.[9] The main symptoms that patients with IPF suffer from are breathlessness, chronic cough, fatigue, anxiety and depression, which often severely impair their QOL.[9,11,12] At the moment there is no cure for IPF except for lung transplantation. Two antifibrotic drugs (nintedanib and pirfenidon) are currently the standard of care. Studies demonstrated these drugs slow down disease progression as measured by a reduced rate of decline of FVC over 1 year, improve survival and reduce excacerbations.[7,13] However, no convincing beneficial effect of these drugs on patients' QOL was found.[7,13] Besides, many patients experience side-effects of these drugs. [14] To gain insight in the balance of treatment effect versus potential treatment disadvantages, patient perspectives should be included, in daily care as well as in in clinical trials.[15,16] Adequate tools are needed to asses these aspects of care. Furthermore, in the absence of a cure, the aim of patient care should not only be to prolong life but also to improve QOL, preserve or at least slow down deterioration of QOL. There is growing evidence that non-pharmacological therapies such as pulmonary rehabilitation (PR) improve exercise capacity and QOL of life of IPF patients.[17,18] However, PR is commonly offered in a hospital setting and the beneficial effect often weans out

after the training is stopped.[19-21] There is a need of practical homebased interventions to improve QOL for patients with IPF.

Sarcoidosis is a chronic systemic inflammatory disease of unknown cause, characterized by the formation of granulomas.[22] Although sarcoidosis can affect any organ, particularly the lungs, eyes, skin, liver and lymphatic system are involved. The occurrence of sarcoidosis varies greatly depending on race and geographic location and is highest in Nordic countries and African Americans.[23] The estimated prevalence in the Netherlands is 50 per 100.000, with approximately 2000 new cases annually.[5] Sarcoidosis predominantly occurs in patients aged 25-45 years but can affect people of any age.[24] Symptoms vary widely depending on the degree of inflammation and organs involved and range from asymptomatic to severe.[22,25] General symptoms comprise fatigue, muscle pain, weakness, aching muscles, fever, lack of appetite.[24,26,27] In 90% of patients with sarcoidosis, the lungs are affected, leading to dyspnea and cough.[22] The majority of patients recovers from sarcoidosis spontaneously, however, in a significant minority disease becomes chronic and progressive.[22]

Sarcoidosis may have a major impact on the lives of patients and relatives. Quality of life is not only influenced by symptoms due to organ impairment, but by many other factors including side effects of medication, fatigue and the anxiety and stress.[22,28] With such a variety in disease courses, organs involved, symptoms and severity of disease, measuring QOL in sarcoidosis is a challenge and sarcoidosis-specific instruments involving the most affected organs are needed.

The main aim of treatment is to limit or prevent organ damage and improve QOL.[27] Corticosteroids are the first choice of treatment; however limited and outdated evidence exists on optimal dosage and timing of this medication.[29,30] Furthermore, corticosteroid use is associated with side-effects such as weight gain, osteoporosis and reduced QOL.[31] More research is needed to optimize and personalize treatment for patients with sarcoidosis, including careful evaluation of the risk-benefit balance and including patient preferences.

Pulmonary Hypertension (PH)

PH is a pathophysiological disorder, characterized by an elevated blood pressure in the pulmonary circulation that will lead to progressive right heart dysfunction and ultimately death.[32,33] The worldwide prevalence of PH is estimated at 1% of the population and 10% of the individuals over 65 years old, mainly due to systolic or diastolic left heart failure (HFpEF).[34] PH is categorized into five groups according to the World Health Organization (WHO) classification, based on clinical presentation, pathophysiological findings,

hemodynamic findings, and treatment strategy: (1) Pulmonary arterial hypertension (PAH), (2) PH due to left heart disease, (3) PH due to lung diseases and/or hypoxaemia, (4) Chronic ThromboEmbolic Pulmonary Hypertension (CTEPH) and other pulmonary artery obstructions and (5) PH with multifactorial or unclear cause.[35] The research in this thesis focuses on PAH and CTEPH.

Pulmonary Arterial Hypertension (PAH) is a rare and incurable condition of the pulmonary vasculature, characterized by endothelial dysfunction, muscularization of the small arteries and thickening of the adventitia, causing narrowing of the pulmonary arteries. This will lead to elevation of the pulmonary arterial pressures which will eventually cause progressive right ventricular failure.[35] PAH can be associated with several underlying diseases, e.g. collagen vascular disease, congenital heart disease, liver disease or HIV. In some cases, an underlying genetic mutation is demonstrated. However, if after careful analysis no underlying cause is found, the disease is called idiopathic. The diagnosis PAH has to be confirmed by means of a right heart catheterization (RHC)[36]; required is a mean pulmonary arterial pressure (mean PAP) ≥25 mmHg at rest, a normal wedge pressure ≤ 15mmHg and a pulmonary vascular resistance (PVR) > 3 Wood units (WU).[35]

In CTEPH, the PVR and the mean PAP are elevated due to thromboembolic obstruction and arteriopathy.[35] PAH affects more females than males. Data on the true prevalence of PAH and CTEPH are lacking due to under diagnosis, but in the Netherlands approximately 1400 patients with PAH or CTEPH are currently being treated (unpublished data).[37] Symptoms initially occur mainly during exercise and include breathlessness and lack of energy.[38] In more advanced disease, patients can experience chest pain with exercise, they will develop peripheral edema and they can experience syncope during exercise. These symptoms severely affect the daily life physical functioning of patients and restricts them from performing everyday tasks.[32]

In PAH the last 10-15 years advances have been made in the medical treatment due to a better understanding of the underlying pathways.[35] Despite these improvements survival rates are still poor. Depending on the underlying cause, the 5-years survival is around 70%.[39] However, in case of CTEPH about 60% of the patients can be treated with a pulmonary endarterectomy.[40] In the majority of these patients this is a curative option. In some cases, patients suffer from rest PAH which can be treated with PAH specific medication. Recently a new treatment option has been developed, a balloon angioplasty (BPA).[41,42] Lesions which are located too peripheral to be reached with pulmonary endarterectomy, may be treated by means of BPA.

Treatment of PAH and CTEPH focuses on achieving a low-risk status, so called "goal-oriented" therapy.[35] This condition is usually associated with good exercise capacity, preserved right ventricle function and a low mortality risk.[35] The goal of treatment is to improve hemodynamics; to reduce pulmonary vascular resistance, herewith improve cardiac output and preserve right ventricle function.[35] However, these last outcomes can only be measured during an invasive RHC. Therefore, alternatively less invasive outcomes measures have been developed which cannot directly determine the above mentioned measures, but provide information on the physical status of the patient. Currently, the most used physiological end-point in clinical trials is the distance walked in the 6-min walk test, to measure changes in exercise capacity.[43] This is a relatively cheap and reproducible test. N-terminal pro B-type natriuretic peptide (NT-pro BNP) is a biomarker often used as marker of right ventricle function.[44] Other important outcomes measures are shown in Table 1.

Despite the advancements in specific treatment in PAH and CTEPH, patients still have a poor prognosis and an impaired HRQOL due to physical, emotional and social problems.[45] In 35% of the PH patients, stressors like delay until a correct diagnosis has been made, uncertainty about the prognosis and physical burden lead to depression, anxiety and panic attacks.[46,47] Therefore, earlier detection of anxiety and depression by using well validated PROMs is needed to start psychological support in time.[48] Only less than 25% of the patients receive supportive treatment for their general wellbeing. Fortunately it has been increasingly acknowledged that the wellbeing of patients should also be evaluated in clinical care and research (6th world symposium on pulmonary hypertension).[49] In clinical trials studying new treatment options, patient-reported outcomes are frequently included as secondary clinical endpoint.[38] However, there is a lack of a PH-specific questionnaires in Dutch.

Generic questionnaires used may be less sensitive to measure HRQOL in PAH. We concluded that a PAH-specific instrument is needed that is able to capture the burden of this specific disease. We therefore translated a PAH-specific questionnaire (CAMPHOR) for the Netherlands. Afterward a validation process was carried out to examine whether the Dutch version retained the measurement properties of the original CAMPHOR. This process and the results are described in part 1, chapter 4.

Apart from treatment with PAH specific drugs, PAH guidelines do recommend adding non-pharmacological therapies such as supervised pulmonary rehabilitation.[35] Several studies demonstrated that beside hemodynamic impairment and ventilation-perfusion mismatches, respiratory and skeletal muscle dysfunction play an important role in exercise limitation in patients suffering from PAH.[50-53] Since muscle impairment limits

PAH patients in daily life activities, it has a strong negative influence on QOL.[52,54] Several studies demonstrated beneficial effects of PR programs in a clinical setting on exercise tolerance, muscle strength, functional status and QOL.[55-57] However, little is known about the safety and effectiveness of a PR program in an outpatient setting. We therefore studied the effectiveness of a multidisciplinary PR program, including psychological intervention, education and contact with peers, in an entirely outpatient setting. The results of this study are described in part 3, chapter 9.

Outcomes

Outcomes can roughly be categorized into physiological outcomes and patient-reported outcomes (PROs). In diseases such as ILD and PH, the crucial clinical outcomes of treatment are disease progression, mortality and QOL. However, use of survival as primary endpoint to evaluate treatment response is often not practicable, unless in end stage disease.[43,58] Therefore, to evaluate treatment response faster and more direct, so called surrogate markers as substitute for clinically meaningful endpoints, are used.[59]

In IPF and sarcoidosis Forced Vital Capacity (FVC) is the most used primary endpoint.[7,13,60,61] FVC is easy to measure, reliable and able to capture changes in disease progression.[9,62-64] Compared to other physiologic markers, FVC best correlates with worsening of fibrosis. Furthermore, a 5-10% decline in FVC predicts worse prognosis.[65] The 6-min walking distance (6MWD) and the transfer factor of the lung for carbon monoxide (TLCO), physiologic markers for respectively functional status and gas exchange, are often used as secondary endpoints.

In PH, the 6MWD is the most used primary endpoint next to hemodynamic data.[66-68] The 6MWT is easy to measure, inexpensive and reproducible.[43] Furthermore, 6MWT evaluates the integrated responses to exercise of the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.[69] 6MWD has prognostic value and is an estimate of daily life functional capacity.[70] Next to 6MWT, NYHA functional class and soluble biomarkers e.g. NT-pro BNP levels are also used as secondary endpoint and as independent factors in risk stratification for survival. [71,72]

Although usually physiological outcomes are recorded in the hospital, technological advances have opened the way for homebased self-recording of physiological outcomes by the patients.

Prolongation of life (survival) as the main goal of new therapies is undoubtedly of utmost relevance to both physicians and patient. However, a reasonable treatment goal

should also be making the patient feel better. Therefore information on this aspect should at least be included as a secondary end-point in therapy trials.[73] Physiological outcomes fail to capture aspects that are most relevant to the patient such as dyspnea (symptoms), level of independence, social functioning, psychological state and QOL. FVC and TLCO for example, poorly correlate with QOL and dyspnea.[16,74,75] Patients, being experts on their disease, are the most reliable source to obtain information on how they feel and function in daily life, and what the effect is of treatment on their wellbeing. These aspects can be measured by tools called patient-reported outcome measures (PROMs). A Patient-Reported Outcome (PRO) is defined as "Any report coming directly from the patient without interpretation by a third party about how they feel or function in relation to a health condition and given intervention".[76] Patient perspectives on these aspects are always subjective, because a true value is never known. However, if validated well, PROMs are reliable tools to assess patient perspectives in a structured way, enabling quantification and interpretation.

PROMs can be questionnaires that measure single dimensions of a patient's wellbeing such as symptoms (breathlessness) or specific domains as functioning, but may also measure broader and more complex concepts like QOL. QOL is defined as an individual's perception of her/his position in life in the context of the culture and value systems in which she/he lives and in relation to her/his goals, expectations, standards and concerns. QOL is affected by the persons physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment.[77] When QOL, impacted by health or by treatment is studied, the term health-related QOL (HRQOL) is used in literature. HRQOL is restricted to the physical, psychological and social domains. Health status concerns the impact of a disease on health-related functioning. Two individuals with the same functional limitation (HS) can evaluate their QOL differently.[78] Although the related concepts QOL, HRQOL and health status have a different meaning, in literature they are often used interchangeably.[79]

PROMs can be divided in generic and disease-specific questionnaires.[80] Generic instruments assess the wellbeing of persons regardless of their disease, giving the advantage to compare outcomes across diseases or to compare outcomes with those of the healthy population (higher generalizability). However, they may be insensitive to treatment effects, resulting in misleading estimates.[81] Disease specific questionnaires are designed to assess the wellbeing of patients with a particular disease. They contain relevant items that were selected by patients with the targeted disease during the development process. This makes the questionnaire responsive and sensitive enough to capture small changes in health status that are important for these patients. Symptom or domain-specific questionnaires focus on specific aspects of the patient's health such as breathlessness, cough, fatigue or

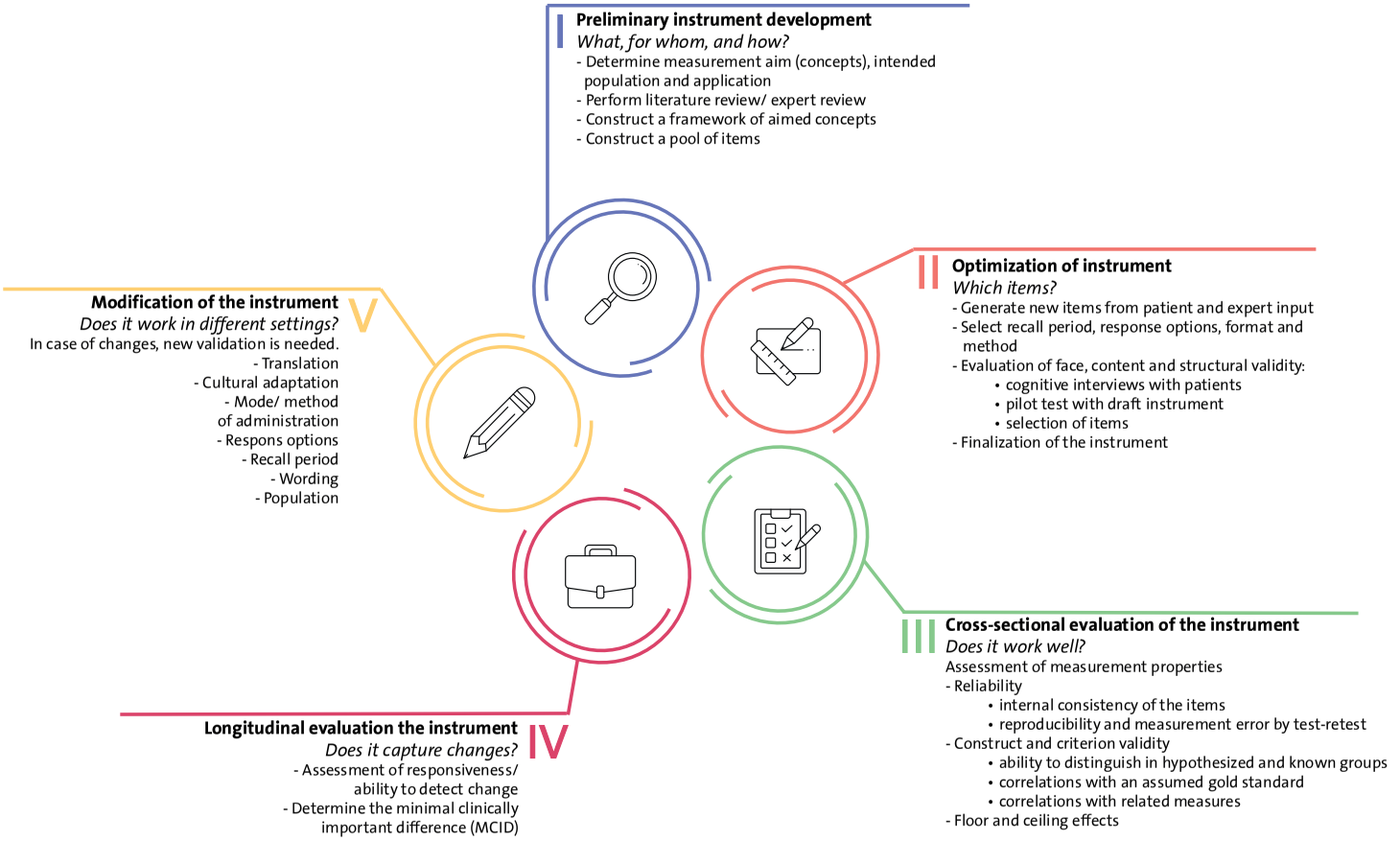


Figure 1. Guidance on how to develop, modify and validate PROMs [90]

depression.[82,83] Although in the last decades many generic and disease-specific PROMs have been developed, well validated ILD and PH questionnaires are still scarce. The most used physiological and patient-reported outcomes in ILD and in PH are shown in Table 1.

Like other clinical endpoints, a PROM must be reliable (producing consistent results), valid (has to measure what is intended to measure), and responsive to changes. To assess its' measurement properties, various standards has been suggested.[76,84-89] The FDA has supplied extensive instructions what properties a PROM must have when used in clinical trials for label claims of new medication.[76,90] The development of a PROM is a multistep and iterative procedure (Figure 1).

I. Preliminary instrument development (for whom and what?)
The first step is to determine the measurement aim and for whom the PROM is needed. This step is followed by making a clear framework of the relevant concepts that need to be measured e.g. symptoms, functional status, general health status or overall QOL. To construct a pool of items that reflect the area of interest, direct input of patients and experts is required (patient interviews, focus groups, expert opinions and literature search).

II. Optimization of instrument: assessment content and face validity (how?)
This step contains assessment of face and content validity. Through cognitive patients interviews and pilot testing, the items are assessed on:

- Clarity (*is the questionnaire easy to read and clearly displayed? how do patients interpret the questions?*)
- Relevance (*do the patients recognize the relevance of the question?)*
- Response range, including floor or ceiling effect, variance of responses (*are the directions of the response scale clear? Is a yes/no answer sufficient? Or should this response scale cover a range of answering possibilities (e.g. frequency of dyspnea: never, seldom….. to most of the time, all of the time?)*
- Recall period *(is this a realistic and relevant time interval to report on?)*
- Item redundancy *(are there overlapping questions, or non-relevant questions?)*
- Relevancy of the items is analyzed using statistical techniques (e.g. impact factor analysis or Rasch analysis). If needed, redundant items are removed, followed by new pilot testing.

III. Cross-sectional assessment of psychometric properties (does it work well?):
The finalized PROM is tested in a substantial group of patients and examined on reliability and validity. The PROM is reliable when the individual items in a (sub) scale correlate well (internal consistency), if it produces stable scores under identical conditions and if it can discriminate between individuals despite measurement error (test-retest, Bland-

Altman plot with limits of agreement, intra class correlation). The PROM is valid when it correlates with related measures (convergent validity), with an earlier validated PROM that is assumed to be the gold standard (criterion validity) and if it captures differences in disease severities (known-groups validity).

IV. Longitudinal assessment of psychometric properties (does it capture changes over time?)
The responsiveness or the ability of the PROM to detect changes in disease status can be assessed over time. This is particularly important when assessing effectiveness of treatment in clinical trials.

For interpretation, an important aspect is to assess its' minimal clinically important difference (MCID); the minimum change in score that is considered relevant for patients. Commonly, the MCID is estimated using anchor variables, linking changes in the PROM to changes in related patient-reported measures and clinically relevant indicators of which the MCID is known (anchor-based method). An alternative or supportive method is distribution-based MCID estimation, which uses statistical measures of variability.

V. Modification of the PROM (does it work in different settings?)
Every time a PROM is modified new testing from step I is recommended to demonstrate that the adapted PROM still is a reliable and valid instrument. In case of modifying the language, translation procedures must be followed in which the developers should be involved to assess whether the translated and adapted questionnaire will still measure what they intended to measure. More details on these translation procedures are shown in chapter 2 , 3 and 4.

In general, it is recommended to use an existing PROM, not only to avoid a lengthy and costly procedure to develop and validate a new one, but also to avoid an abundance of PROMs within one field. With too many PROMs in one field, experience and validation will dilute and comparison and pooling of data hampered. Inclusion of the same disease-specific PROM in clinical trials not only enables to compare outcomes between therapies but also enables to gain insight on the interpretation of scores and score changes and to establish the minimal important clinical differences. Validation is an ongoing process; the more evidence the more valid and applicable a PROM becomes**.**

Advances in physiological outcome measures

Patient-recorded outcome measures
In IPF, the FVC is currently the primary endpoint for clinical trials as it correlates best with fibrosis progression and is considered a surrogate end-point for mortality.[91] Besides, it is a reliable and valid measure, capable to capture changes and the test is easy

to perform. Reliability of FVC measurements in IPF patients has been demonstrated in large randomized trials that showed a stable FVC between screening and baseline visit.[64] However with longer intervals, measurement variation is a potential problem and can vary between 5-9%, even in healthy persons with stable lung function.[92,93] Possible failure to detect changes in FVC in clinical trials due to this variability noise complicates the development of new therapies.[94] Another "problem" that arose with the registration of two drugs for IPF is that current trial design is add-on and not placebo-controlled anymore. This results in the need to detect smaller effect sizes. In IPF the yearly decline without treatment is estimated to be 200 ml. With the current anti-fibrotic treatment this decline is around 100 ml per year. This means that to study the effect of a new drug that is equally effective and halfs the decline in lungfunction, very large trials are needed. Johanssen et al.[94] estimated that with the FVC traditionally recorded during hospital visits at baseline and after 24 weeks, 3840 participants are needed to demonstrate a difference of 50 ml FVC between the two arms with an effect size of 50%. An alternative could be to collect more data points, however, in practice it is not feasible to ask patients to visit the hospital weekly or even daily for a trial. A solution would be to ask patients to self-record lung function at home. Johanssen et al.[94] calculated that with FVCs measured weekly for 24 weeks, the estimated group size can be reduced with 75% to 951 participants, largely improving efficiency and reducing costs for clinical trials. However, data on feasibilty and reliability of homebased measurements of FVC are scarce and not using realtime data collection.[94,95] We aimed to investigate if home monitoring and daily recording of FVC by IPF patients, using an e-health platform with realtime transmission, is feasible and reliable (part 2, chapter 6).

Home monitoring of FVC also is promising in pulmonary sarcoidosis. For the treatment of pulmonary sarcoidosis corticosteroids are first choice.[96] Corticosteroids are associated with multiple side effects for patients such as weight-gain, diabetes, osteoporosis and mood disturbances.[31] Until now treatment and tapering regiments are largely based on expert opinion and longterm treatment is recommended.[22,97] In the study described in chapter 5 we evaluated the effect of prednison on lungfunction change, assessed by daily home-based spirometry. Better insights in response to therapy can help physicians to better tailor treatment, start earlier with tapering of the prednisolon, potentially resulting in less side effects and hence improving QOL.

TLCO

Another hurdle in the current trial landscape for IPF is the inclusion of patients. With many new compounds being studied in a rare disease, there is a need to adequately identify patients that are eligible for trials. The gain is twofold, all possible candidates are identified, but also unneccesary referals for trials and dissapointments for patients

are avoided. One of the important inclusion criteria is the TLCO. TLCO is a measure of pulmonary gas exchange function and is decreased in patients with IPF.[10] Interpretation of the TLCO is usually based on comparisons of measured data with reference values based on healthy subjects.[58] In IPF trials, screen failures are frequently based on a TLCO below lower limits, and are disappointing to patients. In 2017 the Global Lung function Initiative (GLI) group launched a new all-aged and globally derived reference value set for the TLCO.[98] Although this GLI reference value set is currently the most accurate available, many lungfunction laboratories still use older reference value sets. This may not only lead to interlaboratory variability in treatment decisions but also in trial eligibility. In part 2 chapter 7 we assessed the impact of the new GLI TLCO reference equations on trial inclusion for IPF patients.

Interventions aimed at improving QOL

Despite advances that have been made in pharmacological treatment, IPF and PAH patients still suffer from severe exertional dyspnea, exercise intolerance, reduced QOL and decreased life expectancy. Dyspnea and impaired exercise tolerance lead to a downward spiral of deconditioning, and decreased social participation, both affecting QOL. Guidelines on IPF and PAH care promote pulmonary rehabilitation as complemetary non-pharmocological treatments that improve QOL and exercise capacity, with exercise training being a component of pulmonary rehabilitation.[9,35,55]

For a long time PAH patients were recommended to avoid exercise because of risk of further deterioration of the right ventricular dysfunction and sudden cardiac death. However, in 2006 a study of Mereles demonstrated that highly supervised, individualised and low-intensity training is safe and feasible and beneficially effected symptoms, exercise capacity and QOL.[99] Since then many studies and meta-analysis have demonstrated that pulmonary rehabilitation positively effects symptoms, functional capacity, QOL and muscle strenght in PAH patients.[50,56,100-102]

Most of these PR studies in PAH patients are carried out or at least started in a hospital or inpatient setting.[103] However, for most patients this is not feasible. Knowledge about the safety and about the effects of a multidisciplinary aproach in an exclusively outpatient setting is needed.[38,104] In part 3, chapter 9, we evaluate the effectiveness of an entirely outpatient PR program with a multidisciplinary approach on exercise capacity, muscle strenght, soluble markers and QOL in PH patients.

In IPF, exercise capacity is known to be an important prognostic factor and positively correlated with the ease to perform daily physical activities.[105,106] Randomized controlled trials showed that 8-12 weeks PR programs improved functional capacity, dyspnoea,

and QOL in IPF patients, though the longterm effects are still debated.[17-21,107] Due to the relatively poor prognosis, IPF patients are often reluctant to follow inpatient pulmonary rehabilitation programs. Moreover, studies showed the benefical effects wean out after the program stopped, which may be explained by the rapid progression of IPF.[19-21] Therefore we aimed to develop a home-based training modality with the potency not only to improve exercise capacity and QOL of IPF patients but also to retain its' positive effects. In part 3, chapter 8, we evaluate the effectiveness of a walk-bike on QOL and exercise capacity in IPF patients; a pilot study.

Outline of this thesis

The research described in this thesis is focused on validating PROMs for patients with ILD and PH (part 1), development of patient-recorded outcome measures (part 2) and interventions aimed at improving QOL for patients (part 3).

Part 1: Validating PROMs for patients with ILD and PH

In chapter 2 we describe the translation and validation proces of the originally English King's Brief Interstitial Lung Disease (K-BILD) questionnaire into French, Italian, Swedish, and Dutch. In chapter 3 we demonstrate the validation of the English King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population. The translation and validation of the English Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for the Netherlands is described in chapter 4.

Part 2: Development of patient-recorded outcome measures

In chapter 5 we show how we captured the early lung function response on steroid treatment in sarcoidosis patients by daily patient-recording of spirometry at home.
A pilot study on feasibility of daily home monitoring of FVC by IPF patients is described in chapter 6. In chapter 7 we assessed the impact of the new Global Lung Function Initiative TLCO reference values on trial inclusion for patients with Idiopathic Pulmonary Fibrosis.

Part 3: Interventions aimed at improving quality of life for patients

In chapter 8 we describe a crossover pilot study to the feasibility and efficacy of home-based training with a walk-bike on QOL and exercise capacity in patients with idiopathic pulmonary fibrosis. We studied the effectiveness of a multidisciplinary PR program, including psychological intervention, education and contact with peers, in an outpatient setting. The results of this study are described in chapter 9.

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PART 1

Validating patient-reported outcome measures in interstitial lung diseases and pulmonary hypertension

“The King’s Brief Interstitial Lung Disease (K-BILD) questionnaire now available in Dutch, French, Italian and Swedish to structurally assess patient perspectives in care and research.”

CHAPTER 2

Translation and validation of the King's Brief Interstitial Lung Disease (K-BILD) questionnaire in French, Italian, Swedish, and Dutch

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ABSTRACT

No disease-specific instruments exist in Dutch, French, Italian, and Swedish to measure health status in idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs). The King's Brief Interstitial Lung Disease (K-BILD) is a 15-item validated questionnaire assessing health status in patients with ILD. The aim of this study was to translate and validate the K-BILD to French, Italian, Swedish, and Dutch versions. The K-BILD was translated following a forward–backward multistep procedure and tested in structured patient interviews. Subsequently, 195 outpatients with ILD were asked to complete K-BILD, St. George's Respiratory Questionnaire (SGRQ), and Euroqol EQ-5D-5L (EQ5D), twice, 2 weeks apart. Internal consistency, concurrent validity, and repeatability were determined. No major difficulties occurred in the translation processes. The K-BILD was considered comprehensible and relevant by patients. One hundred seventy-six patients (108 IPF and 68 other ILDs) completed the translated K-BILD. Internal consistency was good for all K-BILD modules (Cronbach's α 0.70–0.93). Concurrent validity of K-BILD was strong compared with SGRQ (r = -0.86) and EQ5D (r = 0.68), low with transfer capacity of the lung for carbon monoxide corrected for hemoglobin (r = 0.33) and with forced vital capacity (r = 0.35). The K-BILD and its domains were repeatable over 2 weeks; intraclass correlation coefficients were 0.86–0.93 (n = 159). Known groups validity showed K-BILD was able to discriminate between patients based on severity of disease. K-BILD's validity and reliability for patients with IPF was similar to that of other ILDs. The French, Italian, Swedish, and Dutch translated K-BILD questionnaires were well-received by patients and demonstrated excellent validity comparable to the original English K-BILD.

INTRODUCTION

Health related quality of life (HRQL) is impaired in the majority of patients with interstitial lung disease (ILD) due to symptoms, such as dyspnoea and fatigue, limitations on physical activities, and social isolation.[1–3] HRQL is quantified using disease-specific questionnaires on aspects of life that patients consider important. In clinical research, HRQL is an important endpoint to assess effectiveness of therapeutic interventions.

There are no disease-specific instruments to assess HRQL in idiopathic pulmonary fibrosis (IPF) and other ILD patients available in Dutch, French, Italian, and Swedish. Therefore, the St. George's Respiratory Questionnaire (SGRQ), originally developed for chronic obstructive respiratory disease, is commonly used (50 items).[4–7] In 2012, the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire was made available.[8,9] The K-BILD questionnaire contains 15 questions and is much shorter than the SGRQ and easy to administer. It is well validated and can be used to assess HRQL in a wide range of ILDs. K-BILD also showed a stronger concurrent validity than the SGRQ with pulmonary function in patients with IPF.[8] The availability of the K-BILD in different languages could facilitate collaborative international research aiming to improve the quality of life in these rare diseases.

The aim of this study was to translate and validate the K-BILD to French, Italian, Swedish, and Dutch versions. The linguistic and psychometric validations of the Italian, French, Swedish, and Dutch K-BILD questionnaires are reported.

METHODS

Linguistic validation: translation, patient interviews, and adaptation

The K-BILD is a 15-item validated, self-completed questionnaire on disease-specific health status with a seven point response scale. It has three domains: breathlessness and activities, psychological and chest symptoms, and one question on financial problems. The domain and total score ranges are 0–100, with the higher scores corresponding with better HRQL.[8]

The translation and adaptation of the Dutch, French, Italian, and Swedish K-BILD questionnaires were conducted, respectively, at the pulmonary departments of Erasmus Medical Center in Rotterdam, the Netherlands, Louis Pradel Hospital, Lyon, France, the University of Catania, Italy, and the Karolinska University Hospital Solna, Stockholm, Sweden.

Permission to translate the K-BILD was asked from the copyright holders.[10] The K-BILD questionnaire was translated into Dutch, French, Italian, and Swedish, following a multistep procedure and in collaboration with the developers using their conceptual framework of items to ensure conceptual/semantic equivalence.[11–13] Online supplement 1 provides details on all the 11 steps of the translational procedure. This included an external back translation and review by linguistic services of Mapi Language Services (Lyon, France).

For each country, the translated version was tested with structured interviews in at least five patients (interview questions are shown in the online supplement 2). This was followed by harmonization meetings to reconcile issues raised. The resulting final versions of the Dutch, French, Italian, and Swedish K-BILD are shown in the online supplements 3 to 6.

Psychometric validation of the Dutch K-BILD

Patients and measurements

All consecutive patients with ILD visiting the tertiary outpatient clinic of the pulmonary department of Erasmus Medical Center, between December 2013 and May 2014, were asked to participate. For Sweden, France, and Italy, patients were included between August 2015 and April 2016. Patients were excluded if they had sarcoidosis, emphysema (clinician's judgment, based on lung function and computer tomography scan), or if there was a language or intellectual barrier. ILD was classified consistent with international guidelines.[14,15] Patients willing to participate were asked to complete two questionnaires: K-BILD and SGRQ, and two health status measurements: Punum Ladders and Euroqol EQ-5D-5L (EQ5D), at the day of the current visit and after 2 weeks.[16,17] The sequence of completing the questionnaires was: K-BILD, SGRQ, Punum Ladder, and EQ5D. Patients were instructed to fill in the questionnaires alone in a quiet place. Nonresponders received a phone call to remind them. Patients who did not complete > 85% of the questions were excluded from the study.

If performed in routine care, the results of pulmonary function tests (total lung capacity (TLC), forced vital capacity (FVC), and transfer capacity of the lung for carbon monoxide corrected for haemoglobin (TLCOc)) were recorded from the files.[18,19]

The ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, decided to exempt this study from review according to national and international regulations because of the noninterventional design (MEC-2013-498). All other hospi-

tals approved of this decision. All patients gave written informed consent or approval by voluntarily returning the completed questionnaires.

Validation

For validation, we tested the following five different aspects:

1. Concurrent validity showing correlations between K-BILD scores and SGRQ scores, Punum Ladders, EQ5D, and lung function.
2. Internal consistency reflecting the interrelatedness of items comprising the K-BILD.
3. The test–retest reliability (repeatability) was determined by comparing the K-BILD scores at baseline and 2 weeks in patients whose condition was considered stable.
4. Discriminative validity, reflecting the ability of an instrument to differentiate between groups of patients, was examined by comparing baseline health status scores of "known groups".
5. Effect size (ES) was calculated by determining partial η2 in K-BILD scores between the groups.[20]

Analysis

Data analysis was executed using SPSS version 21. Results are expressed as mean values (± standard deviation) unless otherwise stated. To determine concurrent validity between HRQL variables and clinical variables, we used Pearson correlation coefficient or Spearman's rank correlation coefficients. Internal consistency was determined by calculating the Cronbach's α coefficients for each domain and the total K-BILD. Cronbach's α coefficient > 0.7 is considered a reliable internal validity. The test–retest reliability was assessed with intraclass correlation coefficient (ICC) and Bland–Altman plots. An ICC of 0.7 is considered the minimum standard for reliability.[21] Punum Ladders were used as a measure to assess if patients felt stable at 2 weeks. To assess discriminative validity and ES, students' t-test or one-way analysis of variance was used.

RESULTS

Permission to translate the K-BILD questionnaire was obtained by the copyright holders. Review by the developers of the cognitive interviews, comments, and back translations in each country resulted in minor changes to make sure the translated questionnaires reflected the intention of the original K-BILD. Demographics, translation comments, and changes per country per stage are shown in Table 1 and online supplement 7.

Table 1. Characteristics of participants involved in linguistic validation per country.[a]

Characteristics	France	Italy	the Netherlands	Sweden
	(*n* = 6)	(*n* = 5)	(*n* = 11)	(*n* = 8)
Female	2 (33%)	1 (20%)	4 (36%)	3 (38%)
Age (years)	76 (69-89)	66 (57-77)	59 (39-76)	74 (69-81)
FVC, %predicted	70 (58-92)	70 (52-94)	75 (39-97)	65 (51-81)
TLCOc, %predicted	38 (26-49)	50 (30-80)	42 (33-98)	40 (36-63)
Diagnosis				
IPF	6	3	8	7
NSIP		2	1	
CVD			1	
Other			1	1

FVC: forced vital capacity; TLCOc: transfer capacity of the lung for carbon monoxide, corrected for hemoglobin concentration; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; CVD: collagen vascular disease associated ILD.
[a]Values are numbers (percentages) or medians (range) .

A total of 195 patients were recruited for the psychometric validation of the K-BILD. One hundred seventy-six patients (90%) completed and returned the questionnaire at week zero and 159 patients (82%) at week 2, with 0.2% missing items in the K-BILD questionnaire and 1.9% in the SGRQ. The diagnoses were: IPF (108), collagen vascular disease-associated ILD (19), chronic hypersensitivity pneumonitis (10), unclassifiable ILD (14), idiopathic nonspecific interstitial pneumonia (13), pulmonary alveolar proteinosis (2), obliterative bronchiolitis (3), organizing pneumonia (2), Langerhans cell histiocytosis (1), lymphangioleiomyomatosis (1), respiratory bronchiolitis-associated ILD (1), asbestosis (1), and desquamative interstitial pneumonia (1). Demographic information is shown in Table 2.

Lung function data were used when present; of 139 patients TLCOc data were available, 72 of the 139 patients had a TLCOc below 50% predicted. There were no floor or ceiling effects in the K-BILD total or domain scores; less than 15% of the participants achieved, respectively, the lowest or highest possible score.[21]

Concurrent validity of the K-BILD domain and total scores with the validated SGRQ domain and total scores was strong for all domains. Correlation coefficients with other HRQL measures and lung function variables are shown in Table 3 for the total group and in online supplement 8 for the individual countries. The correlations between SGRQ total score and lung function parameters were comparable (FVC %predicted: $r = -0.38$, forced expired volume in 1 second %predicted: $r = -0.30$, TLC %predicted: $r = -0.33$, and TLCOc %predicted: $r = -0.39$).

Table 2. Demographics, HRQL and clinical findings of participants involved in the psychometric validation of the K-BILD questionnaire: Total for all countries, split by IPF and ILD (non-IPF), and split by individual country.

			All countries		Split by country			
	Total all countries (*n* = 176) Mean (SD) N(%)	Range	IPF (*n* =108) Mean (SD) N(%)	ILD and non IPF (*n* = 68) Mean (SD) N(%)	France (*n* = 22) Mean (SD) N(%)	Italy (*n* = 25) Mean (SD) N(%)	Netherlands (*n* = 96) Mean (SD) N(%)	Sweden (*n* = 33) Mean (SD) N(%)
Female	69 (39.2%)		24 (22.2%)	45 (66.2%)	3 (13.6%)	8 (32.0%)	47 (49.0%)	11 (33.3%)
Age, years	66.8 (9.6)	35-87	70.5 (8.0)	61.7 (9.7)	70.5 (9.0)	67.4 (7.0)	63.6 (9.5)	73.0 (8.0)
Diagnose								
IPF	108 (61%)				20 (91%)	20 (80%)	39 (41%)	29 (88%)
ILD, non-IPF	68 (39%)				2 (9%)	5 (20%)	57 (59%)	4 (12%)
Ethnicity								
Caucasian	165 (93.8%)		101 (93.5%)	64 (94.1%)	21 (95.5%)	25 (100%)	89 (92.7%)	30 (90.9%)
Afro-Caribbean	4 (2.3%)		2 (1.9%)	2 (2.9%)	-	-	4 (4.2%)	-
South Asian	2 (1.1%)		-	2 (2.9%)	-	-	2 (2.1%)	-
Other	5 (2.8%)		5 (4.6%)	-	1 (4.5%)	-	1 (1.0%)	3 (9.1%)
Supplemental Oxygen								
No	117 (66.5%)		63 (58.3%)	54 (79.4%)	17 (77.3%)	13 (52.0%)	64 (66.7%)	23 (69.7%)
If necessary (exercise ,sleep)	34 (19.3%)		27 (25.0%)	7 (10.3%)	4 (18.2%)	7 (28.0%)	18 (18.8%)	5 (15.2%)
Continuous	25 (14.2%)		18 (16.7%)	7 (10.3%)	1 (4.5%)	5 (20.0%)	14 (14.6%)	5 (15.2%)
Perceived health status [a]			[a]	[a]		[a]		
Very good	2 (1.1%)		1 (0.9%)	2 (1,5%)	1 (4.5%)	-	1 (1.0%)	-
Good	38 (21.6%)		19(17.6%)	19 (27.9%)	7 (31.8%)	-	22 (22.9%)	9 (27.3%)
Fair	80 (45.5%)		46 (42.6%)	34 (50%)	11 (50.0%)	-	54 (56.3%)	15 (45.5%)
Poor	23 (13.1%)		17(15.7%)	6 (8.8%)	3 (13.6%)	-	15 (15.6%)	5 (15.2%)
Very Poor	5 (2.8%)		3 (2.8%)	2 (2.9%)	-	-	3 (3.1%)	2 (6.1%)

Table 2. Demographics, HRQL and clinical findings of participants involved in the psychometric validation of the K-BILD questionnaire: Total for all countries, split by IPF and ILD (non-IPF), and split by individual country. (*continued*)

			All countries		Split by country			
	Total all countries (*n* = 176) Mean (SD) N(%)	Range	IPF (*n* =108) Mean (SD) N(%)	ILD and non IPF (*n* = 68) Mean (SD) N(%)	France (*n* = 22) Mean (SD) N(%)	Italy (*n* = 25) Mean (SD) N(%)	Netherlands (*n* = 96) Mean (SD) N(%)	Sweden (*n* = 33) Mean (SD) N(%)
K-BILD								
Breathlessness /activities [0-100]	40.5 (28.4)	0 – 100	36.5 (28.5)	46.8 (27.4)	48.7 (26.7)	27.4 (23.4)	41.6 (27.8)	41.5 (32.5)
Psychological [0-100)]	55.5 (24.3)	0 – 100	52.2 (24.7)	60.8 (22.9)	63.1 (22.1)	40.8 (24.3)	56.2 (23.5)	59.6 (24.5)
Chest symptoms [0-100]	66.2 (23.7)	0 – 100	66.5 (23.9)	65.6 (23.6)	77.9 (15.5)	53.5 (25.6)	64.7 (23.8)	72.2 (21.8)
Total [0-100]	54.5 (22.0)	5.9 – 98.8	51.9 (22.2)	58.7(21.81)	63.6 (16.1)	40.5 (21.8)	54.8 (21.4)	58.3 (22.9)
SGRQ								
Activity [0-100]	63.5 (24.7)	0 – 100	66.2 (24.2)	59.1 (25.1)	55.8 (18.5)	73.2 (22.1)	63.8 (24.4)	60.3 (29.2)
Impact [0-100]	36.8 (22.9)	0 – 92.0	39.3 (23.4)	32.8 (21.6)	30.2 (19.2)	46.7 (23.6)	37.2 (22.1)	32.7 (25.3)
Symptoms [0-100]	43.1 (21.0)	0 – 97.6	46.9 (19.4)	37.1 (22.1)	42.4 (16.1)	42.3 (19.7)	42.6 (22.7)	45.6 (20.4)
Total [0-100]	46.1 (21.1)	2.4 – 85.8	48.9 (20.9)	41.7 (20.8)	40.4 (16.3)	54.3 (20.7)	46.3 (20.9)	43.2 (23.7)
EQ-5D-5L								
Index value[-0.329-1.00]	0.69 (0.22)	-0.27 – 1.0	0.66 (0.23)	0.74 (0.19)	0.59 (0.30)	0.62 (0.24)	0.71 (0.19)	0.77 (0.17)
QOL VAS [0-100]	62.8 (18.5)	10 – 95	60.8 (18.9)	65.8 (17.5)	60.5 (18.4)	60.0 (16.5)	64.0 (17.6)	62.7 (22.9)
Lung function								
FVC % predicted (*n* = 163)	74.8 (18.3)	37 – 116	72.5 (16.8)	79.1 (20.2)	76.9 (17.6)	73.4 (15.1)	77.7 (19.9)	67.0 (14.6)
FEV1 %predicted (*n* = 162)	74.8 (18.3)	18 – 125	75.8 (17.6)	72.9 (19.6)	81.7 (18.6)	74.7 (16.3)	74.3 (19.9)	71.6 (14.7)
TLC % predicted (*n* = 125)	66.0 (15.9)	36 – 114	62.3 (13.3)	72.3 (18.0)	72.8 (13.3)	-	69.1 (16.4)	54.8 (10.2)
TLCOc % predicted (*n* = 139)	51.3 (17.6)	15 – 119	47.1 (15.2)	59.5 (19.2)	45.1 (14.2)	58.1 (13.4)	54.8 (19.7)	43.5 (13.4)

HRQL: health related quality of life; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; K-BILD: King's Brief Interstitial Lung Disease questionnaire; SGRQ: St. George's Respiratory Questionnaire; QOL: quality of life; VAS: Visual Analogue scale; FVC: forced vital capacity; FEV1: forced expired volume in 1 second; TLC: total lung capacity; TLCOc: transfer capacity of the lung for carbon monoxide, corrected for hemoglobin concentration.

[a]In Italy, the perceived health status questionnaire was not administered.table 3

Table 3. Correlation coefficients between K-BILD scores and other HRQL scores and clinical variables, total for all countries.[a,b]

Outcome scales	K-BILD Total	K-BILD breathlessness/ activity	K-BILD psychological	K-BILD Chest symptoms
SGRQ				
Total	**-0.86**	-0.87	-0.72	-0.64
Activity	-0.77	**-0.84**	-0.62	-0.51
Impact	-0.83	-0.81	**-0.70**	-0.62
Symptoms	-0.65	-0.59	-0.55	**-0.59**
EQ-5D-5L				
Index Value	**0.68**	0.69	0.59	0.46
VAS	**0.63**	0.67	0.56	0.40
Lung Function				
FVC %predicted	0.35	0.42	0.29	0.16[c]
FEV1%predicted	0.28	0.37	0.22	0.15[d]
TLC %predicted	0.34	0.37	0.33	0.13[d]
TLCOc %predicted	0.33	0.44	0.26	0.12[d]
Punum Ladder				
Overall	**-0.76**			
Breathlessness/Activity		**-0.76**		
Psychological			**-0.76**	
Chest symptoms				**-0.55**

HRQL: health-related quality of life; K-BILD: King's Brief Interstitial Lung Disease questionnaire; SGRQ: St. George's Respiratory Questionnaire; VAS: Visual Analogue scale; FVC: forced vital capacity; FEV1: forced expired volume in 1 second; TLC: total lung capacity; TLCOc: transfer capacity of the lung for carbon monoxide, corrected for hemoglobin concentration.

[a]The correlation coefficients for the corresponding domains are shown in bold.

[b]Values shown represent Pearson's correlation coefficients, all $p < 0.01$ unless otherwise stated.

[c]$p < 0.05$.

[d]$p > 0.05$.

Internal consistency was good in the chest domain and excellent in the other domain and total scores (Table 4). Repeatability was tested in 159 patients; the average length of time between baseline and measurement at week 2 was 16 days. ICCs for consistency and Bland–Altman plot demonstrated good repeatability and thus reliability of the K-BILD (Table 4 and Figure 1 for the total group and online supplements 9 to 13 for the individual countries). Punum Ladders were completed by 156 patients, 99% had no change or minimal change in Punum scores quality of life between baseline and week 2, which confirmed their stable health status. Removing the two patients with major changes from test–retest analysis did not alter the results.

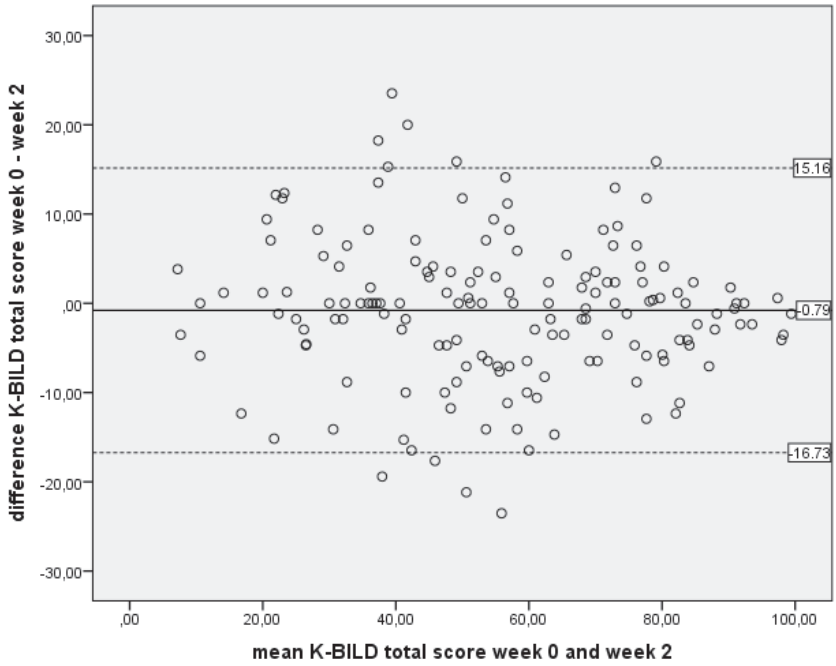

Figure 1. Bland Altman plot of repeatability of the K-BILD questionnaire of all countries. The solid line shows the mean difference and the dashed lines represent the 95% limits of agreement. K-BILD: King's Brief Interstitial Lung Disease questionnaire.

Table 4. Internal consistency and reliability K-BILD (total all countries).[a]

	Internal reliability	ICC	95% CI
K-BILD			
Breathlessness/ activities	0.89	0.90	0.87-0.93
Psychological	0.91	0.90	0.87-0.93
Chest symptoms	0.70	0.86	0.81-0.89
Total	0.93	0.93	0.91-0.95

K-BILD: King's Brief Interstitial Lung Disease; ICC: intraclass correlation coefficient for K-BILD repeatability; 95%CI: 95% confidence interval.

[a]Data shown are Cronbach's α coefficient.

Both K-BILD and SGRQ total scores were able to discriminate between patients based on severity of their disease (Table 5). The discriminative power of the K-BILD and SGRQ is expressed in ES between the known subgroups. The ES is the strongest (0.4) for symptom-based classification of groups and poor for those based on lung function and other non-symptom parameters, which is not surprising as they measure a different aspect of disease. The magnitude of the ES indicates both questionnaires having good discrimina-

Table 5. K-BILD and SGRQ total scores in known groups.[a]

Clinical variables		*N*	K-BILD Total	ES	SGRQ Total	ES
Supplemental oxygen						
	Yes	59	38.3 (15.3)	0.27	60.8 (15.5)	0.25
	No	117	62.6 (20.3)		38.7 (19.7	
Perceived health status						
	Poor/Very poor	28	33.6 (14.1)	0.41	68.5 (11.6)	0.46
	Fair	80	55.4 (17.5)		46.5 (16.6)	
	Very good / Good	40	74.1 (15.1)		26.9 (15.3)	
TLC						
	≤ 60 %predicted	49	48.2 (19.7)	0.14	51.8 (17.9)	0.13
	> 60 %predicted	76	64.6 (19.7)		36.6 (20.5)	
FVC						
	≤ 50 %predicted	15	39.8 (12.7)	0.10	63.6 (14.8)	0.14
	51-90 %predicted	113	53.4 (22.3)		47.1 (20.1)	
	>90 %predicted	35	66.0 (20.3)		33.4 (20.9)	
TLCOc						
	≤ 35 %predicted	27	45.8 (20.1)	0.06	55.6 (16.0)	0.11
	36-70 %predicted	90	56.5 (22.9)		44.0 (22.1)	
	> 70 %predicted	22	64.9 (21.6)*			
ILD						
	IPF	108	51.9 (22.2)	0.02	48.9 (20.9)	0.03
	Non-IPF	68	58.6 (21.1)		41.7 (20.8)	
Gender						
	Female	69	54.6 (21.3)*	0.00	45.4 (20.5)*	0.00
	Male	107	54.4 (22.5)		46.6 (21.5)	

K-BILD: King's Brief Interstitial Lung Disease questionnaire; SGRQ: St. George's Respiratory Questionnaire; ES: effect size; TLC: total lung capacity; FVC: forced vital capacity; TLCOc: transfer capacity of the lung for carbon monoxide, corrected for hemoglobin concentration; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

[a] Values represent mean scores (standard deviation). Statistical tests used to determine difference between groups was student's test or one-way analysis of variance. ES are expressed in partial η^2 : small effect ≥ 0.01, medium effect ≥ 0.06, large effect ≥ 0.14.

* All groups show significant differences between the scores except those marked with *.

tive power. Table 6 shows the concurrent validity, internal reliability, and repeatability of the K-BILD questionnaire in patients with IPF when comparable to patients with other ILDs (non-IPF).

Table 6. Concurrent validity, internal reliability, and repeatability of K-BILD in IPF in comparison with other ILDs, total for all countries.[a]

	K-BILD total score	
	IPF	ILD, non-IPF
Correlation with		
SGRQ Total	-0.82	-0.91
SGRQ Symptoms	-0.59	-0.71
SGRQ Activity	-0.73	-0.82
SGRQ Impact	-0.79	-0.87
Internal reliability (Cronbach's α coefficient)	0.93	0.93
Repeatability (intraclass correlation coefficient)	0.93	0.94

K-BILD: King's Brief Interstitial Lung Disease questionnaire; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; SGRQ: St. George's Respiratory Questionnaire.
[a]Data shown are Pearson's correlation coefficients unless otherwise stated, $p < 0.01$.

DISCUSSION

In this study, the K-BILD was translated into an Italian, French, Swedish, and Dutch version and psychometrically validated. It is the first health status questionnaire for IPF and other ILDs available in these languages. During the cultural adaptation process, only minor changes were necessary. The K-BILD was brief with only 15 items easy to administer, well-received by patients, and applicable to non-English speaking countries. The K-BILD was also validated for the first time in non-English speaking populations and showed good concurrent validity, internal consistency, repeatability, and discriminative performance, comparable with the original K-BILD. Also a strong correlation of the EQ5D index value with K-BILD was found. This had not been assessed before.

Instruments to measure HRQL have become increasingly important in trials and clinical care. However, major improvements are needed to develop and validate new or existing instruments.[23]

The K-BILD questionnaire is the first disease-specific questionnaire to examine HRQL in patients with IPF and other ILDs. Other questionnaires were not specifically developed

for ILDs; a-tool-to-assess-quality-of-life-in-IPF (ATAQ-IPF) and an IPF specific version of SGRQ-I were only validated in an IPF population.[23,24] The University of California San Diego Shortness of Breath Questionnaire only measures symptoms and was developed in a non-ILD population and tested for content and construct validity in IPF.[25–27]

In the absence of disease-specific measures for ILDs, clinically relevant patient-reported outcome measures for obstructive lung disease such as SGRQ have been used in trial assessing, for example, medication treatment in ILD/IPF.[28]

The current patient population showed reduced HRQL in all domains of K-BILD and SGRQ, with the activity domain most impaired. This is in line with a review by Swigris of three studies that assessed HRQL in IPF and other ILD patients and also showed that HRQL was most impaired in the physical activity domains.[2] The mean (SD) K-BILD total score was 59 (22) in ILD patients and 52 (22) in IPF patients; in the original development study of the K-BILD, these scores were comparable with 59 (25) and 52 (26), respectively.[8]

Concurrent validity and repeatability were comparable with the results of the original version.[8] In the current study, correlation of FVC and TLCOc with the breathlessness and activity domain was weaker than in the original study; FVC (0.42 vs. 0.51) and TLCOc (0.44 vs. 0.52). Correlations of SGRQ total score with FVC and TLCOc yielded comparable correlation coefficients to those of the K-BILD. The weak correlation of FVC with the HRQL questionnaires confirms that HRQL informs us about aspects of disease severity that are relevant to patients but cannot be measured with physiologic measures such as lung function. In other validation studies, the same results were found. In a study that assessed HRQL in 50 patients with ILD SGRQ total score correlated with FVC %predicted $r = -0.45$ and with TLCOc %predicted $r = -0.55$.[7] The SGRQ-I showed in IPF population correlations with FVC %predicted $r = -0.33$.[23] The ATAQ-IPF correlations revealed comparable results.[24]

These findings confirm FVC contributes only partly to the impact ILD or IPF has on quality of life. TLCOc %predicted with a moderate correlation appears to be more related to quality of life in both our study and others.[7,23,24]

It is interesting to note that in the current study, differences in between countries are seen in HRQL. In Italy, more impairment in HRQL is found both with the K-BILD and the SGRQ, while mean FVC values are comparable to the other countries. Also, correlations between FVC and K-BILD differed between countries. This could be due to small numbers; however, in Sweden and the Netherlands, correlations are similar to the original study from the United Kingdom. Although purely speculative, an alternative explanation

could be that factors such as climate and diet influence disease burden or disease perception and consequently HRQL, with the Northern countries having more resemblance in these factors with the original study population from the United Kingdom and more similar outcomes. To the best of our knowledge, no studies have yet been performed in ILD looking at influences of diet and climate on disease and HRQL.

The K-BILD was developed for ILDs, including IPF. To assess more specifically its ability to measure HRQL in IPF, we compared the construct validity, internal reliability, and intraclass correlation between IPF and non-IPF ILD subgroups. These results show that the K-BILD is also a reliable and valid tool in IPF patients. Our study confirms HRQL is more affected in IPF than in other ILDs as has also been previously noted in studies using the generic measure Short Form-36.[2]

The K-BILD questionnaire detected differences in disease severity. HRQL was more impaired in patients using supplemental oxygen (in line with the original study), with lower perceived health status and with lower lung function values (this was not tested in original study). In the original article of Patel et al., no ES are calculated. In our study, ES show that K-BILD discriminates better in the home oxygen and TLC subgroups, and the SGRQ discriminates better in the TLCOc and perceived health status subgroups (based on one question describing general health status). Both questionnaires had acceptable levels of missing items, K-BILD scored better with only 0.2% missing items versus 1.9% in SGRQ. The advantage of the K-BILD is that it is much shorter, 15 questions versus 50 questions.

With the economically challenging climate and new and expensive medications, governmental organizations increasingly investigate cost-effectiveness of treatment, with the benefit of interventions expressed in quality-adjusted life years (QALYs). A generally accepted tool for the calculation of QALYs is the EQ5D, a generic five questions measure of health. EQ5D was used in intervention studies in IPF to assess quality of life and to calculate cost-effectiveness of new treatment options.[29] In our study, K-BILD total score correlated well with EQ5D (0.68). The Dutch general population norm for the EQ5D index value is 0.91.[30] In our study, the mean EQ5D index value was 0.74 for ILD and 0.66 for the IPF subgroup.

A limitation of this study is that it did not assess responsiveness and minimal clinically important difference (MCID). The study of Patel et al. suggests that the K-BILD is a responsive health status outcome measure in ILD with an MCID of around eight; however, as they also state that this was only assessed in a small sample size and only four patients with large changes.[9] A larger study with longer follow up is needed. We therefore cur-

rently follow up a patient cohort prospectively, to gain information about responsiveness and MCID in a bigger multicultural cohort. Another limitation is that both in the original as well as in our study, only small numbers of patients with ultrarare ILDs were included. Only larger international collaborative studies will be able to further validate the K-BILD in specific disease groups.

In conclusion, the current study developed a Dutch, Italian, French, and Swedish version of the K-BILD and demonstrated that the K-BILD is a reliable and valid instrument to measure HRQL in an international cohort of patients with ILD, consistent with the evidence of the original version. With only 15 items, it is easy to use in daily practice, and moreover, its use in different languages could facilitate collaborative international research aiming at improving quality of life in these rare diseases.

SUPPLEMENTAL MATERIAL

The online supplements are available at http://journals.sagepub.com/doi/suppl/10.1177/1479972316674425

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DECLARATION OF CONFLICTING INTERESTS

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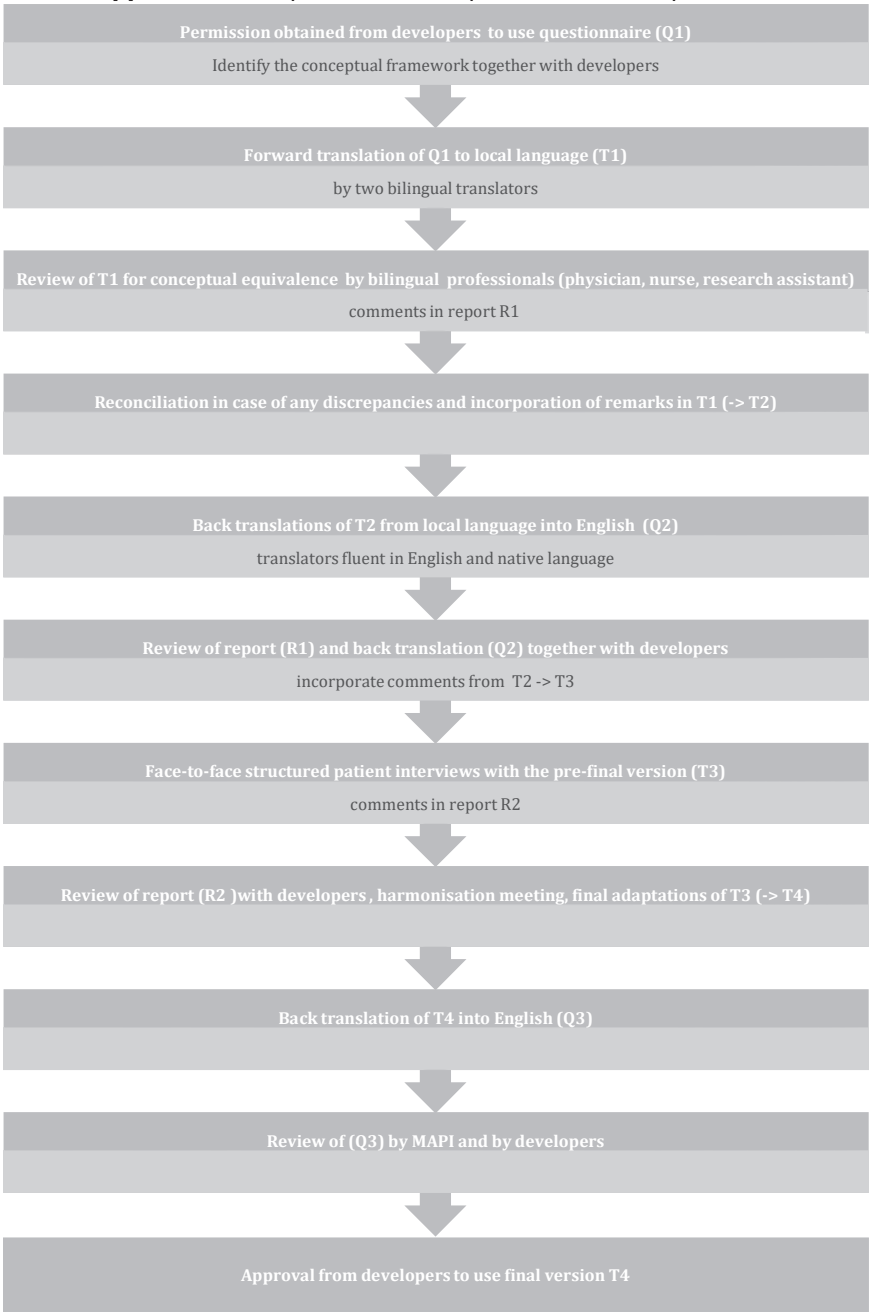
Online supplement 1. Steps in translation procedure K-BILD questionnaire



Q = Questionnaire in English, T = Translation into target language, R = Report with comments

Online supplement 2: Questions patient interviews K-BILD questionnaire

1. Was the questionnaire relevant?
2. Did you understand the question? / What does the question mean to you?
3. Could the question mean more than one thing to you? Could you interpret it in another way?
4. Was the response scale appropriate?
5. Was the questionnaire easy to complete? If not, please can you explain why not?
6. Did you find the questionnaire comprehensive?
7. Did you miss anything in the questionnaire?
8. Do you have suggestions to improve it?
9. Any other comments?

Online supplement 3

King's korte ILD-vragenlijst (K-BILD)

Deze vragenlijst is gemaakt om de invloed van uw longziekte op verschillende aspecten van uw leven te beoordelen. Lees elke vraag zorgvuldig en geef antwoord door de respons die het beste bij u past, te OMCIRKELEN. Beantwoord a.u.b. ALLE vragen zo eerlijk mogelijk.

PATIËNTINFORMATIE:

Naam: .....

Datum: .....

1. De laatste 2 weken was ik buiten adem bij het trappen klimmen of bij het oplopen van een helling of heuvel.

1. Altijd
2. Bijna altijd
3. Verschillende keren
4. Enkele keren
5. Af en toe
6. Zelden
7. Nooit

2. De laatste 2 weken had ik door mijn longziekte een beklemmend gevoel op mijn borst.

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

3. Heeft u zich de laatste 2 weken zorgen gemaakt over de ernst van uw longklachten?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

4. Heeft u de laatste 2 weken vermeden dingen te doen die u buiten adem doen raken?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

5. Had u de laatste 2 weken het gevoel dat u grip hebt op uw longziekte?

1. Nooit
2. Bijna niet
3. Weinig
4. Enkele keren
5. Een groot deel van de tijd
6. Meestal
7. Voortdurend

6. Voelde u zich de laatste 2 weken door uw longklachten futloos of was u het zat?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

7. De laatste 2 weken had ik een gevoel van drang om adem te halen, ook wel "honger naar adem" genoemd.

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

8. De laatste 2 weken maakte ik me zorgen door mijn longziekte.

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

9. Hoe vaak hoorde u de laatste 2 weken piepende of fluitende geluiden uit uw borst?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

10. Hoe vaak had u de laatste 2 weken het idee dat uw longziekte verslechtert?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

11. Heeft uw longziekte de laatste 2 weken invloed gehad op uw werk of andere dagelijkse taken?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

12. Verwachtte u de laatste 2 weken dat uw longklachten zouden verslechteren?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

13. In hoeverre heeft uw longziekte u de laatste 2 weken beperkt in het dragen van dingen, bijvoorbeeld boodschappen?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

14. Heeft u door uw longziekte de laatste 2 weken meer nagedacht over uw levenseinde?

1. Voortdurend
2. Meestal
3. Een groot deel van de tijd
4. Enkele keren
5. Weinig
6. Bijna niet
7. Nooit

15. Bent u financieel slechter af door uw longziekte?

1. Een enorm bedrag
2. Een groot bedrag
3. Een aanzienlijk bedrag
4. Een redelijk bedrag
5. Een klein bedrag
6. Bijna niet
7. Helemaal niet

Hartelijk bedankt voor het invullen van deze vragenlijst!

Online supplement 8. Correlation coefficients between K-BILD scores and other HRQL scores and clinical variables for the individual countries.

The Netherlands				
Outcome scales	K-BILD Total	K-BILD Breath/Activ	K-BILD Psych	K-BILD Chest
SGRQ				
Total	**-0.89**	-0.85	-0.79	-0.65
Activity	-0.81	**-0.83**	-0.70	-0.55
Impact	-0.84	-0.80	**-0.76**	-0.59
Symptoms	-0.71	-0.60	-0.63	**-0.71**
EQ-5D-5L				
Index Value	**0.71**	0.68	0.66	0.48
VAS	**0.66**	0.61	0.62	0.45
Lung Function				
FVC %predicted	0.38	0.45	0.30	0.26[a]
FEV1%predicted	0.28[a]	0.36	0.22[a]	0.19[b]
TLC %predicted	0.33	0.36	0.32	0.17[b]
TLCOc %predicted	0.58	0.59	0.55	0.33
Punum Ladder				
Overall	**-0.80**			
Breathlessness/Activity		**-0.78**		
Psychological			**-0.82**	
Chest symptoms				**-0.72**

Sweden				
Outcome scales	K-BILD Total	K-BILD Breath/Activ	K-BILD Psych	K-BILD Chest
SGRQ				
Total	**-0.87**	-0.93	-0.67	-0.64
Activity	-0.72	**-0.88**	-0.51	-0.44[a]
Impact	-0.85	**-**0.85	**-0.67**	-0.68
Symptoms	-0.76	-0.76	-0.61	**-0.64**
EQ-5D-5L				
Index Value	**0.76**	0.77	0.55	0.66
VAS	**0.69**	0.74	0.56	0.47
Lung Function				
FVC %predicted	0.51	0.53	0.49	0.21[b]
FEV1%predicted	0.44	0.53	0.37[a]	0.13[b]
TLC %predicted	0.54	0.54	0.51	0.29[b]
TLCOc %predicted	0.27‡	0.51	0.06[a]	0.21[b]
Punum Ladder				
Overall	**-0.81**			
Breathlessness/Activity		**-0.81**		
Psychological			**-0.82**	
Chest symptoms				**-0.55**

France				
Outcome scales	K-BILD Total	K-BILD Breath/Activ	K-BILD Psych	K-BILD Chest
SGRQ				
Total	**-0.65**	-0.84	-0.33[b]	-0.20[b]
Activity	-0.46	**-0.79**	-0.14[b]	-0.05[b]
Impact	-0.66	-0.83	**-0.33[b]**	-0.29[b]
Symptoms	-0.52[a]	-0.36[b]	-0.44[a]	**-0.29[b]**
EQ-5D-5L				
Index Value	**0.66**	0.87	0.32‡	0.02[b]
VAS	**0.65**	0.78	0.33‡	0.12[b]
Lung Function				
FVC %predicted	0.29[b]	0.38[b]	0.21[b]	-0.20[b]
FEV1%predicted	0.23[b]	0.34[b]	0.13[b]	-0.14[b]
TLC %predicted	0.41[b]	0.33[b]	0.40[b]	-0.13[b]
TLCOc %predicted	0.37[b]	0.52[a]	0.14[b]	-0.01[b]
Punum Ladder				
Overall	**-0.45[a]**			
Breathlessness/Activity		**-0.65**		
Psychological			**-0.32[b]**	
Chest symptoms				**0.01[b]**

Italy				
Outcome scales	K-BILD Total	K-BILD Breath/Activ	K-BILD Psych	K-BILD Chest
SGRQ				
Total	**-0.81**	-0.81	-0.72	-0.68
Activity	-0.77	**-0.79**	-0.70	-0.56
Impact	-0.77	**-**0.76	**-0.69**	-0.68
Symptoms	-0.53	-0.57	-0.41[a]	**-0.47**[a]
EQ-5D-5L				
Index Value	**0.76**	0.71	0.73	0.66
VAS	**0.63**	0.69	0.59	0.42[a]
Lung Function				
FVC %predicted	0.24[b]	0.26[b]	0.22[b]	0.10[b]
FEV1%predicted	0.18[b]	0.22[b]	0.22[b]	0.14[b]
TLC %predicted	-	-	-	-
TLCOc %predicted	0.16[b]	0.21[b]	0.15[b]	-0.02[b]
Punum Ladder				
Overall	**-0.69**			
Breathlessness/Activity		**-0.60**		
Psychological			**-0.67**	
Chest symptoms				**-0.44**[a]

Values shown represent Pearson's correlation coefficients, all $p < 0.01$ unless otherwise stated ([a] $p < 0.05$, [b] $p > 0.05$). Correlation coefficients for the corresponding domains are shown in bold.
Abbreviations: HRQL = health-related quality of life, K-BILD = King's brief interstitial lung disease questionnaire, SGRQ = St. George's respiratory questionnaire, VAS = visual analogue scale, FVC = forced vital capacity, FEV1 = forced expired volume in 1 second, TLC = total lung capacity, TLCOc = transfer capacity of the lung for carbon monoxide, corrected for haemoglobin concentration.

Online supplement 9. Internal consistency and reliability K-BILD for the individual countries.[a]

The Netherlands			
	Internal reliability	**ICC**	**95% CI**
K-BILD			
Breathlessness/ Activities	0.89	0.88	0.82-0.92
Psychological	0.91	0.89	0.84-0.93
Chest symptoms	0.74	0.84	0.77-0.89
Total	0.93	0.92	0.88-0.95

Sweden			
	Internal reliability	**ICC**	**95% CI**
K-BILD			
Breathlessness/ Activities	0.92	0.97	0.93-0.98
Psychological	0.92	0.86	0.73-0.93
Chest symptoms	0.67	0.73	0.52-0.86
Total	0.94	0.93	0.86-0.97

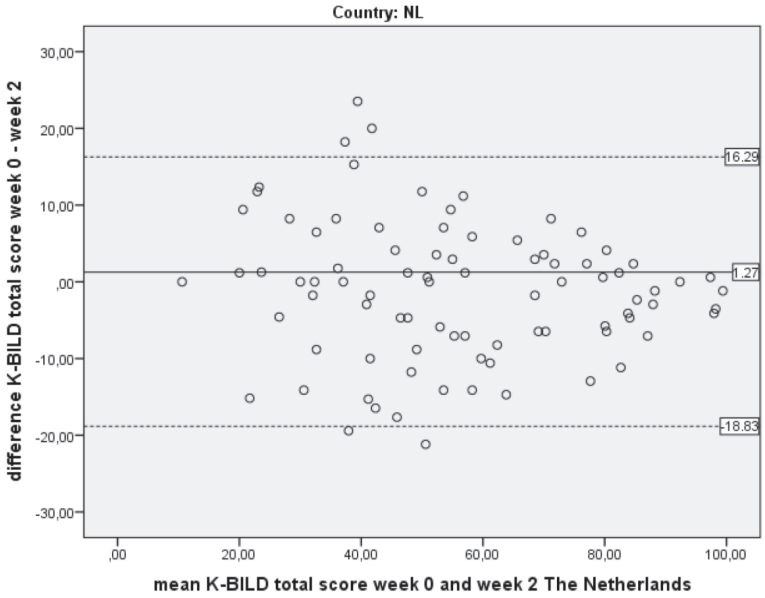
France			
	Internal reliability	**ICC**	**95% CI**
K-BILD			
Breathlessness/ Activities	0.83	0.76	0.46-0.91
Psychological	0.88	0.86	0.65-0.95
Chest symptoms	0.44	0.69	0.32-0.88
Total	0.85	0.87	0.68-0.95

Italy			
	Internal reliability	**ICC**	**95% CI**
K-BILD			
Breathlessness/ Activities	0.88	0.95	0.89-0.98
Psychological	0.95	0.98	0.95-0.99
Chest symptoms	0.69	0.97	0.94-0.99
Total	0.95	0.99	0.97-0.99

K-BILD: King's brief interstitial lung disease questionnaire; ICC = intra class coefficient for K-BILD repeatability, 95%CI = 95% confidence interval

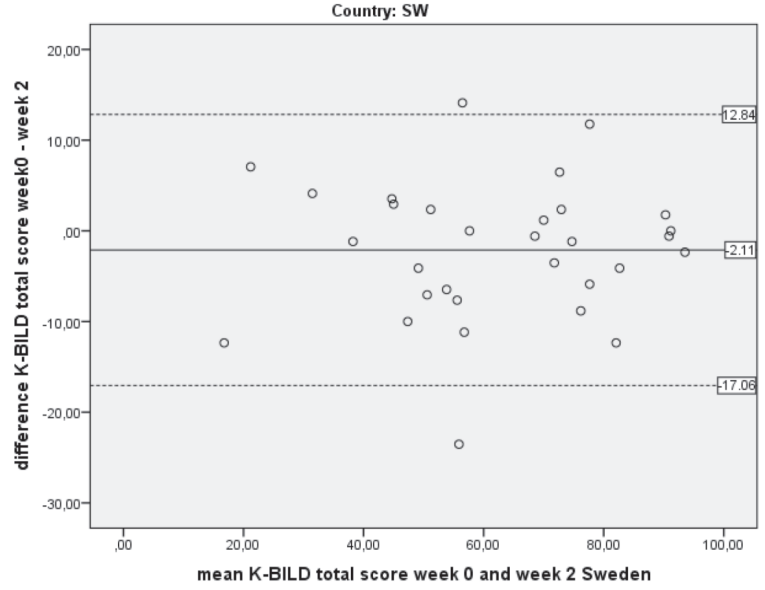
[a]Data shown are Cronbach's α coefficient.

ONLINE SUPPLEMENT 10



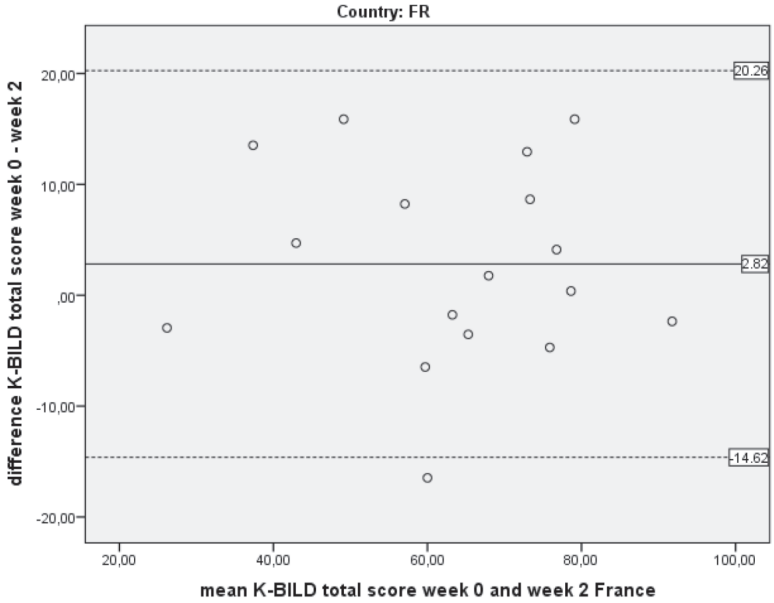
Bland Altman plot of repeatability of the K-BILD questionnaire for the Netherlands. The solid line shows the mean difference and the dashed lines represent the 95% limits of agreement. K-BILD: King's Brief Interstitial Lung Disease questionnaire.

ONLINE SUPPLEMENT 11



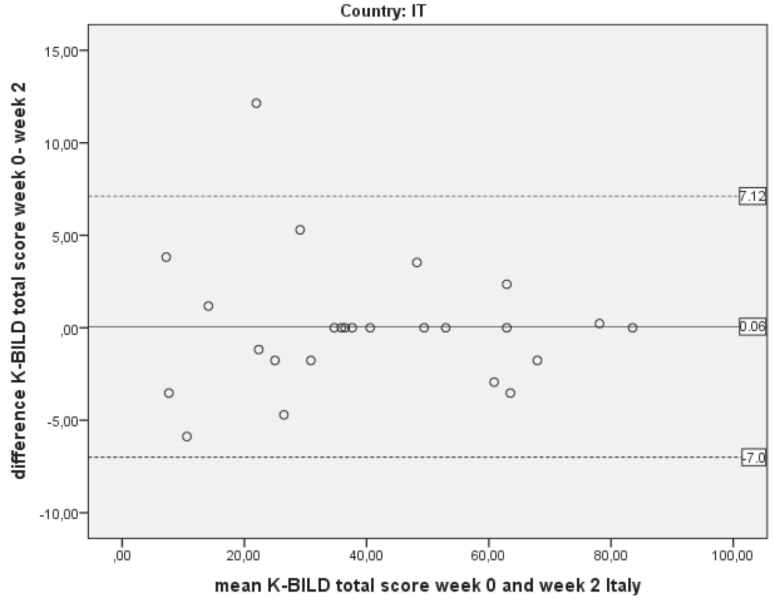
Bland Altman plot of repeatability of the K-BILD questionnaire for Sweden. The solid line shows the mean difference and the dashed lines represent the 95% limits of agreement. K-BILD: King's Brief Interstitial Lung Disease questionnaire.

ONLINE SUPPLEMENT 12



Bland Altman plot of repeatability of the K-BILD questionnaire for France. The solid line shows the mean difference and the dashed lines represent the 95% limits of agreement. K-BILD: King's Brief Interstitial Lung Disease questionnaire.

ONLINE SUPPLEMENT 13



Bland Altman plot of repeatability of the K-BILD questionnaire for Italy. The solid line shows the mean difference and the dashed lines represent the 95% limits of agreement. K-BILD: King's Brief Interstitial Lung Disease questionnaire.

“The King’s Sarcoidosis Questionnaire (KSQ) now available in Dutch to assess patient perspectives in care and research.”

CHAPTER 3

Validation of the King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population

Sarcoidosis Vasc Diffuse Lung Dis. 2016 Mar;33(1):75-82.

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ABSTRACT

Background

The King's Sarcoidosis Questionnaire (KSQ) is a brief questionnaire assessing health status using five modules (General Health Status, Lung, Medication, Skin and Eyes) in patients with sarcoidosis. The KSQ was only validated in one English sarcoidosis cohort.

Objective

The aim of this study was to validate the KSQ in a Dutch sarcoidosis population.

Methods

The KSQ was translated according to international guidelines and tested in interviews with patients. Consecutive outpatients completed multiple questionnaires twice, two weeks apart. Construct validity, internal consistency and repeatability were determined.

Results

Of the 98 patients included 85 had lung, 22 skin and 24 eye disease. There was good construct validity of the KSQ General Health Status module against the World Health Organization Quality of Life-BREF questionnaire. The Medication module correlated weak to moderate with most questionnaires. The correlations with organ-specific questionnaires varied from strong for Eyes (r=0.75), Skin (r=-0.62) to moderate for Lung (r=-0.45 with MRC breathlessness scale). Internal consistency was good for all KSQ modules (Cronbach's α 0.72-0.93). Intraclass correlation coefficients (0.70-0.90) and Bland-Altman plots showed good repeatability of the KSQ.

Conclusion

The Dutch KSQ is the first translation of the English KSQ, validated in a Dutch sarcoidosis population.

INTRODUCTION

Sarcoidosis is a heterogeneous multisystem disease with different clinical phenotypes. Sarcoidosis manifests most commonly in the lungs, but can affect skin, eyes, lymphatic nodes and other organs as well.[1] Health status is impaired in the majority of patients with sarcoidosis due to symptoms such as dyspnea, persistent cough, peripheral pain, fatigue and cognitive dysfunction, leading to limitations in activities, social isolation and depression.[1-3] Therapy for sarcoidosis often leads to side effects impacting health status.[4,5] In recent years patient related outcome measures (PROMs) have gained increasing importance in clinical trials and health status is now a standard outcome measure.[6] Most studies evaluating health status used generic questionnaires such as the World Health Organization Quality of Life-BREF (WHOQOL-BREF) or the MOS 36-item Short Form Health Survey (SF-36), both non-disease specific questionnaires.[7-12] Currently, no sarcoidosis specific instruments measuring health status in patients with sarcoidosis are available in Dutch. In 2012 the King's Sarcoidosis Questionnaire (KSQ) was developed.[13] This self-administered measure for sarcoidosis covers different domains of health status; General Health Status (GHS), Lung (L), Medication (M), Skin (S) and Eyes (E). The aim of this study was to validate the KSQ in a Dutch sarcoidosis population.

METHODS

Translation validation

The KSQ was translated from English to Dutch according to a multi-step forward-backward procedure, following international guidelines [14-16], and was reviewed by sarcoidosis experts and the developers (online supplement 1). The relevance and applicability of the translated KSQ was tested using ten structured patient interviews.

Psychometric validation

Subjects

In July 2014 consecutive sarcoidosis outpatients of the pulmonary department of the Erasmus Medical Center were asked to participate. During the same period sarcoidosis outpatients of the ild care team, Hospital Gelderse Vallei were approached by email. Patients were excluded from the study if they were unable to understand questionnaires due to intellectual impairment or language barrier, when comorbidities that severely impact health status existed (such as malignancies, collagen vascular diseases and cardiac failure other than due to sarcoidosis) or when they had unstable disease as considered by the treating physician. If patients completed less than 85% of a question-

naire they were withdrawn from the study. Formal consultation with the Medical Ethical Committee of the Erasmus Medical Center learnt that, under the Dutch act for medical research involving human subjects (Wet Medisch Onderzoek), approval of this study by the Medical Ethical Committee is not required.

Study procedure

All patients were asked to complete up to seven questionnaires (depending on organ involvement) in addition to the KSQ: WHOQOL-BREF, [7] Fatigue Assessment Scale (FAS), [17] Small Fiber Neuropathy Screening List (SFNSL) [18], Medical Research Council dyspnea scale (MRC dyspnea scale), [19] Dermatology Life Quality Index (DLQI), [20] National Eye Institute Visual Function Questionnaire (NEI-VFQ25) [21] and Euroqol-5D-5 level (EQ-5D-5L). [22] Online supplement 2 shows the organ specific questionnaires and corresponding KSQ modules. Patients also completed two general health status measurements: Punum Ladders [23] and Global Rating of Change-Quality of Life (GRC-QoL).[24] Patients were asked to self-complete the questionnaires at home, two weeks apart.

Results of routinely measured pulmonary function outcomes were gathered from the medical records. The diagnosis of sarcoidosis was established when there was compatible clinical behaviour and pathological or BAL confirmation, according to international guidelines [25]. Patients were asked about their organ involvement during a short face to face interview or interview by telephone.

Statistical analysis

Data are presented as mean values (± standard deviation). KSQ scores were calculated on a logit scale as this scale is more linear and has the potential to perform better at the extreme ends of health related QoL.[26] The validity of the KSQ remains unchanged from the original format.[27] Construct validity between the general and organ specific domains of KSQ and the corresponding questionnaires were determined using Pearson's correlation coefficients. A correlation coefficient of < 0.30 is considered weak, 0.30 – 0.50 moderate and > 0.50 strong.[16] Cronbach's α coefficient was used to determine the internal consistency of the reliability of the KSQ. A minimum of 0.70 is considered a good internal consistency. Bland-Altman plots and intraclass correlation coefficients were used to evaluate the repeatability at baseline and at two weeks, in patients with stable disease. To assess stable disease we used Punum ladders.[23] Patients with ≥ 4 differences in Punum score were excluded in the repeatability analyses. The limits of agreement were calculated as mean ± 1.96 X SD of within-subject differences. Values of $p < 0.05$ were considered statistically significant. All data were analyzed with SPSS version 21.

RESULTS

Translation validation

A Dutch version of the KSQ, achieved after forward and backward translation, was approved by the KSQ developers. Following this approval, ten patient interviews with the Dutch version of the KSQ took place (step T3 online supplement 1). Discussion of these interview results with the KSQ developers did not necessitate any further adaptations of the translation and resulted in the final Dutch KSQ-version (online supplement 3).

Psychometric validation

One hundred and four consecutive outpatients in the Erasmus Medical Center were evaluated for participation, 89 were interested and 54 participated in this study. At the same time 117 patients of the ild care team, Hospital Gelderse Vallei were approached by email, 60 patients responded and 44 were recruited. Reasons for exclusion were: clinical instability (15), comorbidity that severely impacted quality of life (14), no PA/BAL confirmation (9), not able to read or write Dutch (5) or other reasons (8) (not willing to participate, not reachable by telephone or by email, participating in another study). Thus in total 98 patients were included. Eighty-eight (90%) of them completed week zero and 83 (85%) week two (Figure 1).

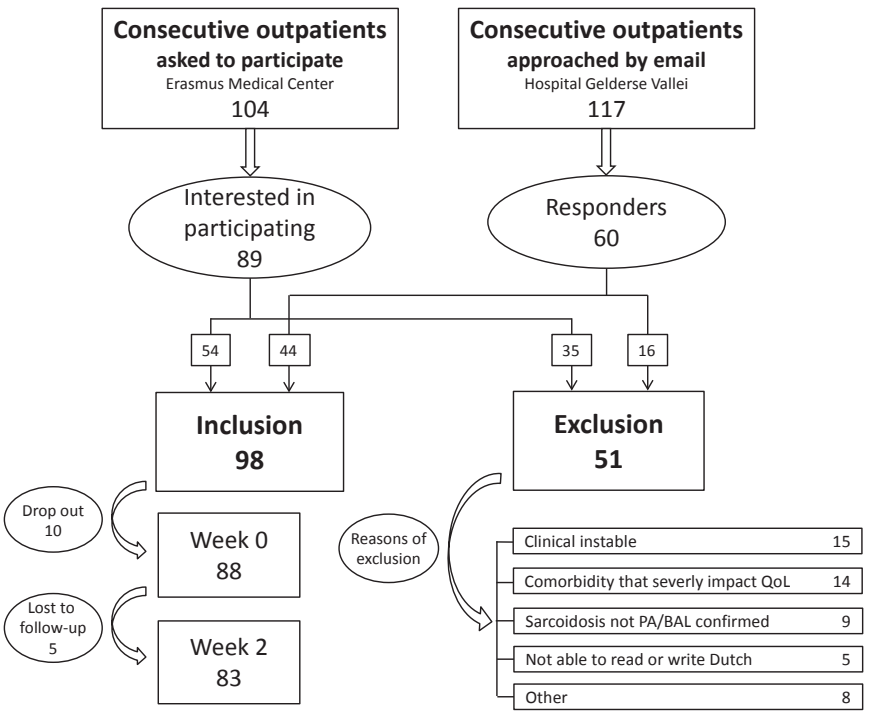

Figure 1. Study design

Demographics

Table 1 shows the demographics of the patients included. Patients with two or more organs involved showed a significantly worse health status than patients with single-organ disease: mean (SEM) KSQ GHS score 53(1.6) versus 68(3.7); mean difference 15; 95% Confidence Interval (CI) 7-23; p = 0.001. No significant difference was found between the KSQ GHS score for females compared with males: mean (SEM) 54(2.5) versus 60(2.3); mean difference 5; 95% CI 1-12, p = 0.115. Patients with more complaints of fatigue (FAS score ≥ 22) have a significantly worse health status (mean (SEM) KSQ GHS 52(1.5)), than those with lower FAS scores (mean (SEM) 76(3.2); mean difference KSQ GHS -24; 95% CI -30 to -17, p = 0.000).

Construct validity

The correlations between the KSQ GHS domain and all generic questionnaires (WHO-QOL-BREF and EQ-5D-5L) were strong (r= 0.50 – 0.84). KSQ organ modules combined with the GHS module all showed a moderate to strong correlation with the WHOQOL-

Table 1. Patient demographics

		Organ involvement		
	All patients	Lung	Skin	Eyes
Number	88	85	22	24
Age, years, mean (SD)	52 (11)	51 (11)	52 (11)	52 (13)
Women, n (%)	36 (41)	35 (41)	10 (46)	11 (46)
Ethnicity, n (%)				
Caucasian	70 (80)	67 (79)	17 (77)	16 (67)
Afro-American	2 (2)	2 (2)	-	-
Surinamese-Hindi	13 (15)	13 (15)	4 (18)	5 (21)
Morrocan	2 (2)	2 (2)	1 (5)	2 (8)
Unknown	1 (1)	1 (1)	-	1 (4)
Smoking status, n (%)				
Current	3 (3)	3 (4)	-	1 (4)
Ex	15 (17)	15 (18)	5 (23)	8 (33)
Never	64 (73)	61 (72)	15 (68)	12 (50)
Unknown	6 (7)	6 (7)	2 (9)	3 (13)
Time since diagnosis, years, mean (SD)	8.0 (8.8)	8.1 (8.9)	7.4 (10.5)	8.4 (11.2)
Organs involved, n (%)				
Lungs	85 (97)			
Skin	22 (25)			
Eyes	24 (27)			
Small nerve fibers	26 (30)			
FVC % predicted, mean (SD), [n]	92 (20) [84]	91 (20) [81]		
FEV1/FVC ratio % predicted, mean, [n]	76 (13) [74]	76 (13) [72]		
TLCOc % predicted, mean (SD) , [n]	81 (21) [73]	81 (21) [70]		
TLC % predicted, mean (SD) , [n]	86 (18) [57]	86 (18) [56]		

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; TLCO, diffusing capacity of the lung for carbon monoxide, corrected for hemoglobin level; TLC, total lung capacity as % predicted.

BREF and EQ-5D-5L (r= 0.44 – 0.85). The Medication module showed a weak to moderate correlation with the generic questionnaires (r= 0.26 – 0.47) (Table 2).

All KSQ modules correlated moderately to strongly with the FAS. The relationship between the KSQ organ-specific modules and their corresponding organ-specific questionnaires was also moderate to strong. The Lung module was weakly correlated with the FVC% predicted (r= 0.24) (Table 2).

Reliability

All domains of the KSQ had good internal consistency, Cronbach α; 0.90 (GHS), 0.91 (Lung), 0.72 (Medication), 0.84 (Skin), and 0.93 (Eyes). With regard to the repeatability (test-retest) 83 patients (lung n= 80, skin n= 20 and eyes n= 22) completed the KSQ twice. The following intraclass correlations were found: GHS 0.85, Lung 0.74, Medication 0.70, Skin 0.77, Eyes 0.90, suggesting a good reliability. Twelve patients in the GHS and 13 patients in the Lung module groups were excluded from the analysis for repeatability, because they did not show stability in their Punum scores. The Bland-Altman plots in figure 2 and 3 show the repeatability of the KSQ GHS and Lung module, respectively.

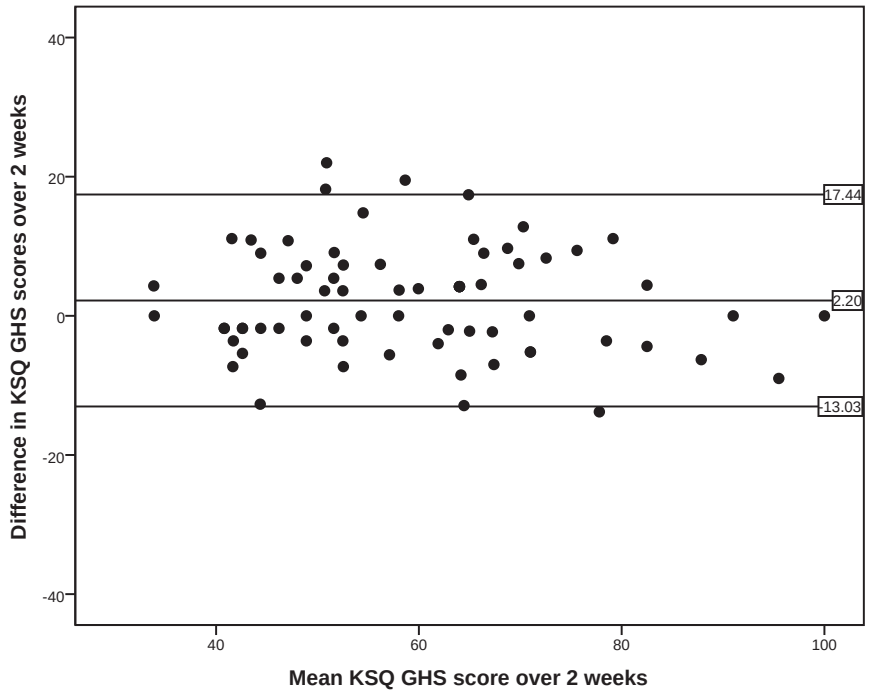

Figure 2. Bland Altman plot of repeatability of King's Sarcoidosis Questionnaire General Health Status module. Solid line represents mean difference and dashed lines represent 95% limits of agreement

Table 2. The relationship between KSQ and disease-specific outcome measures

	Generic QoL						Fatigue	Lung		Skin	Eye	SFN
	WHOQOL-BREF				EQ-5D-5L		FAS	FVC	MRC	DLQI	NEIVFQ-25	SFNSL
	DOM1	DOM2	DOM3	DOM4	Index Value	VAS	Total	%Pred	Breathlessness	Total	Total	Total
KSQ modules												
General Health Status	0.84	0.70	0.61	0.50	0.69	0.67	-0.81	-	-0.29	-0.43*	0.52	-0.60
Lung	0.55	0.52	0.47	0.44	0.55	0.39	-0.63	0.24*	-0.45	-	-	-0.56
Skin	0.37**	0.46*	0.35**	0.44*	0.48*	0.32**	-0.50*	-	-	-0.62	-	-0.37**
Eyes	0.36**	0.32**	0.51*	0.45*	0.49*	0.28**	-0.56	-	-	-	0.75	-0.59
Medication	0.47	0.31	0.28*	0.36	0.30	0.26*	-0.39	-	-0.19**	-0.45**	0.66	-0.33
Overall Health Status												
Lung + GHS	0.79	0.68	0.60	0.52	0.68	0.59	-0.79	0.15**	-0.40	-	-	-0.64
Skin + GHS	0.85	0.83	0.70	0.64	0.61	0.44*	-0.76	-	-	-0.51*	-	-0.63
Eyes + GHS	0.72	0.56	0.62	0.58	0.81	0.68	-0.74	-	-	-	0.75	-0.69
Lung + Skin + GHS	0.77	0.76	0.65	0.65	0.58	0.35**	-0.72	0.18**	-0.13**	-0.60	-	-0.64

Data shown are Pearson's correlation coefficients for organ-specific comparisons. All $p<0.01$ except *$p<0.05$ and >0.01 and **$p>0.05$ (not significant). WHOQOL-BREF, World Health Organization Quality of Life-Brief questionnaire; DOM1 = physical, DOM2 = psychological, DOM3 = social relationships, DOM4 = environment; EQ-5D-5L, Euroqol-5D-5 level; FAS, Fatigue Assessment Scale, FVC, forced vital capacity; MRC, Medical Research Council dyspnea scale; DLQI, Dermatology Life Quality Index; NEIVFQ-25, National Eye Institute Visual Function Questionnaire-25; SFN, small fiber neuropathy, SFNSL, Small Fiber Neuropathy Screening List.

Both plots have a few outliers (outside the 95% of limits of agreement). We found a mean difference between the first and second measurement of 2.20 in the KSQ GHS module and 2.45 in the Lung module.

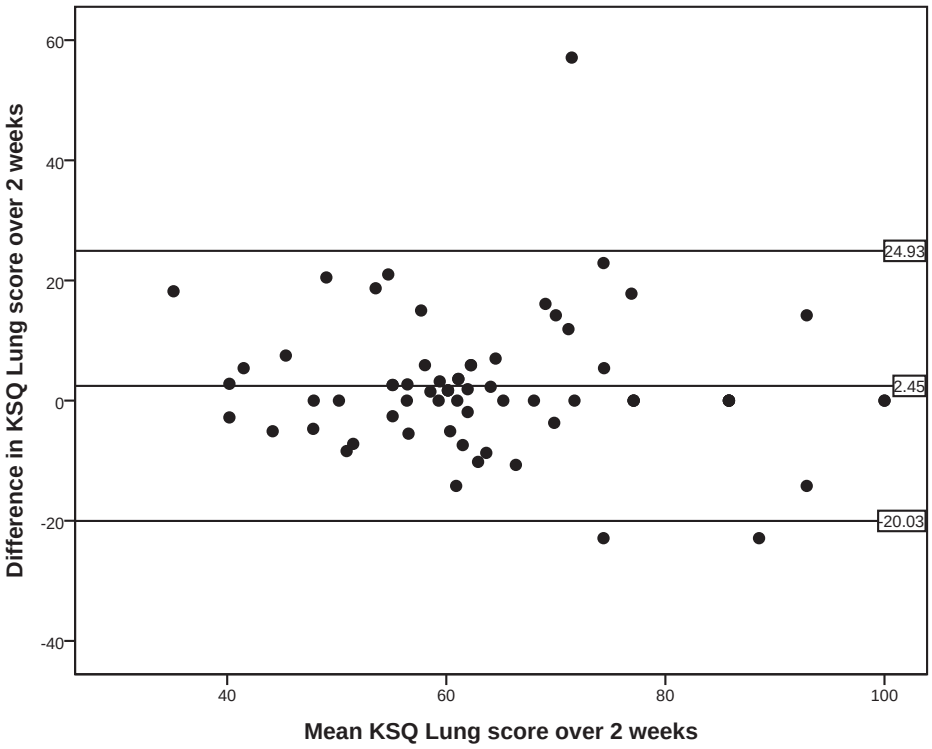

Figure 3. Bland Altman plot of repeatability of King's Sarcoidosis Questionnaire Lung module. Solid line represents mean difference and dashed lines represent 95% limits of agreement

DISCUSSION

The Dutch KSQ is the first health status questionnaire for sarcoidosis in the Netherlands. It is also the first non-English validation of the questionnaire. The KSQ is simple to administer, adaptable to individual organ involvement and shown to be a valid and reliable health status measurement in Dutch patients with sarcoidosis.

PROMs are becoming more important in clinical trials and daily care.[6] Health status is nowadays a standard outcome measure. Most sarcoidosis studies use non-disease specific questionnaires such as the WHOQOL-BREF and the SF-36.[10-12] The KSQ is a self-administered sarcoidosis specific instrument. The KSQ questionnaire was originally developed in the UK and was not available in languages other than English. The availabil-

ity of the KSQ in other languages could facilitate international collaboration aiming at measuring, comparing and improving health status in patients with sarcoidosis, which is often severely affected. During translation in Dutch and the patient interviews no major cultural difference was noted and the questionnaire was considered comprehensible and relevant by Dutch patients.

The patient demographics of the current Dutch study population were in line with the original study, though there were slightly more Caucasians in our study and lung function was less severely affected.[13] Quality of life was worse in females similar to Patel et al. but in contrast did not reach statistical significance.[13,28]

The following domains of health status are covered in the KSQ: General Health Status, Lung, Medication, Skin and Eyes. Construct validity of the organ-specific questionnaires with their corresponding modules is similar to the development paper.[13] The KSQ Lung module showed a weaker correlation with the MRC. In the original article from Patel et al. the MRC dyspnea scale as well as the St. George Respiratory Questionnaire (SGRQ) was used. They found a Pearson's correlation of -0.58 for the MRC dyspnea scale and -0.85 for the SGRQ. It therefore seems that the MRC dyspnea scale is a less reliable tool to assess construct validity in this population. We did not include the SGRQ, because of the high number of questionnaires patients had to complete for validation and we feared this would lead to 'questionnaire fatigue'. Moreover, the SGRQ is a disease-specific questionnaire developed for chronic obstructive pulmonary disease, with 50 items and no questions about skin or eye involvement.

We found a difference in study population between Patel et al. and ours; our population had less patients with a severe impairment of the lungs, which is shown in the difference in TLCOc% predicted (63 vs. 81 in our group)[13] This could also explain the weaker correlation found between the Lung module and FVC% predicted (r= 0.24). To date, this lack of correlation between health status questionnaires and lung function has often been reported in other pulmonary diseases as well. [29] This underlines the idea that health status questionnaires measure different aspects of disease severity and therefore are very important additional outcome measures. When combined with the KSQ GHS module all organ-specific KSQ modules showed a better correlation with the generic questionnaires. This supports the use of organ-specific modules in combination with the GHS module.

Fatigue is a major problem in patients with sarcoidosis with an important impact on health status.[30] This was reflected by a strong correlation between the FAS and GHS. This confirms that the KSQ also captures influence on health status caused by fatigue.[13] Our

results are in line with other studies showing the major effect of fatigue on the wellbeing of patients.[30]

Small fiber neuropathy related symptoms, which are disabling and difficult to control, can also significantly reduce health status.[31] We chose to include the SFNSL questionnaire to evaluate if the KSQ also captures this problem as this had not been evaluated before. Strong correlations with the SFNSL were found by combining the KSQ GHS and the organ-specific KSQ modules. This suggests that the KSQ captures the small fiber neuropathy related influences on health status.

In line with Patel et al. findings, weak to moderate correlations were found between the optional Medication module and almost all questionnaires.[13] Therapy for sarcoidosis, as for instance corticosteroids, often causes burdensome side effects. It is tempting to speculate that these side effects may have affected health status more than the symptoms of sarcoidosis. In both Patel et al. and the present study the Medication module does not contribute much. Longitudinal studies are needed with changes in medication to see if the KSQ captures influences of medication on health status.

According to the study of Patel and colleagues, we found that the KSQ has a good internal consistency.[13] Reliability was also assessed with Bland-Altman plots showing good repeatability (test-retest) in measurements.

At the time of this study, the Sarcoidosis Health Status Questionnaire (SHQ) was the only alternative sarcoidosis health status questionnaire.[32] In our view this 29-item instrument, developed in 2001, has some important limitations. It contains only few organ-specific questions, has not been validated for eye and skin disease and can, therefore, not be tailored to individual clinical phenotypes. Furthermore, the SHQ is mostly longer than the KSQ, because most patients do not have to fill in all the organ-specific KSQ modules.

Recently, Judson et al. validated a new patient reported outcome measure, the Sarcoidosis Assessment Tool (SAT).[31,33] The SAT was constructed in a similar way as the KSQ and also consists of organ-specific modules. With 51 questions it is considerably longer than the KSQ. The SAT was validated in an interventional study giving the advantage that the MCID has been calculated.[5] However, to our knowledge repeatability has not yet fully been assessed making it difficult to conclude if a difference in scores indicates a low repeatability or a true change in health status. It would be valuable to compare the different sarcoidosis questionnaires prospectively.

In sarcoidosis any organ can be involved and it remains unclear if the KSQ will also capture the impact of more rare forms of sarcoidosis on health status. Another limitation of our study is the lack of follow-up after two weeks. Responsiveness of the questionnaire can thereby not be assessed. Further research, through longitudinal studies in larger patient cohorts, is warranted to determine the responsiveness, the influence of rarer disease forms and the value of the Medication module.

In conclusion, the Dutch KSQ is the first translation of the English KSQ, validated in a Dutch sarcoidosis population.

ACKNOWLEDGEMENT

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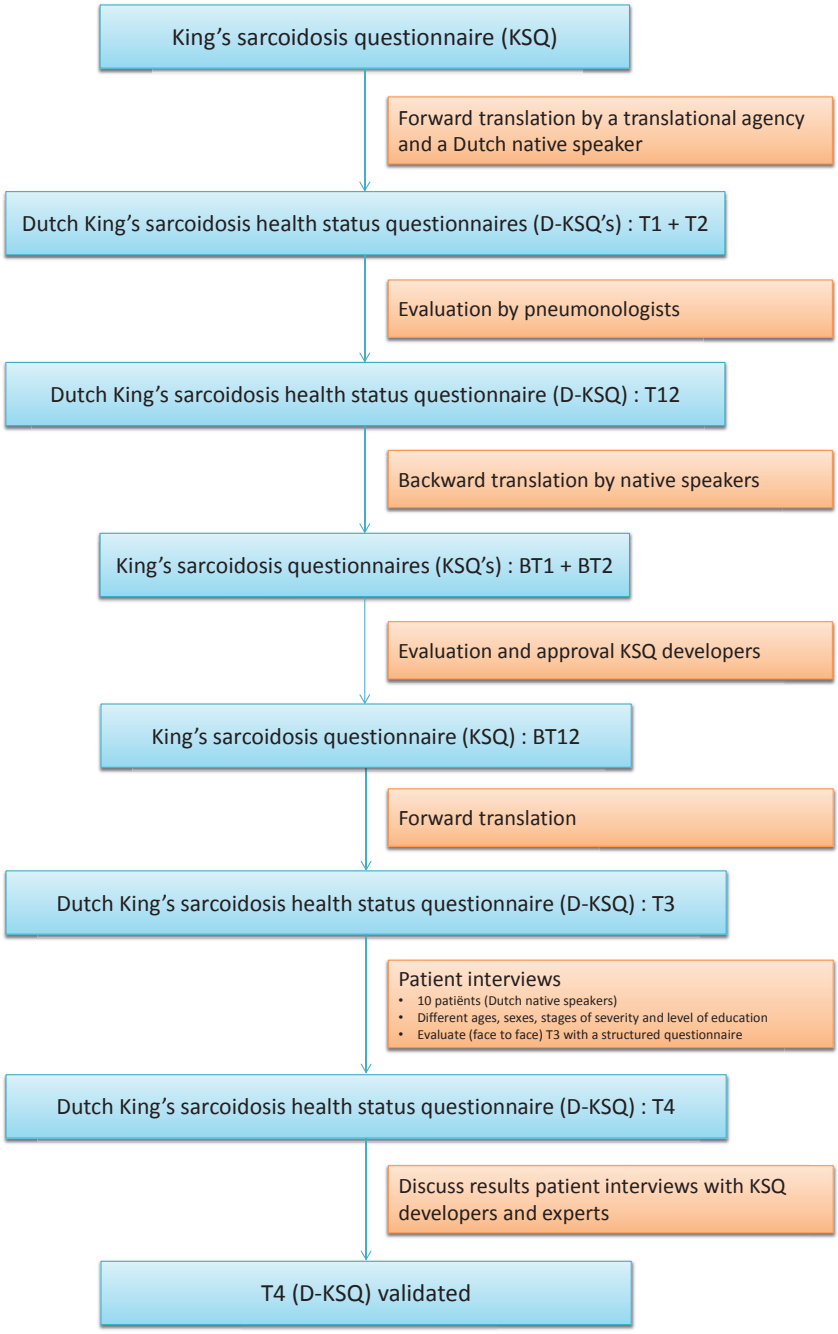

Online supplement 1. Translation procedure

Online Supplement 2. Depending on their organs affected patients will be asked to complete specific questionnaires

Questionnaire	KSQ (GHS + M)	KSQ (L)	KSQ (S)	KSQ (E)	MRC	DLQI	NEI-VFQ25
Organ(s) affected							
Lung	X	X			X		
Skin	X		X			X	
Eyes	X			X			X
Lung, Skin	X	X	X		X	X	
Lung, Eyes	X	X		X	X		X
Skin, Eyes	X		X	X		X	X
Lung, Skin, Eyes	X	X	X	X	X	X	X

KSQ, King's Sarcoidosis Questionnaire; GHS, General Health Status; M, Medication; L, Lung; E, Eyes; MRC, Medical Research Council; DLQI, Dermatology Life Quality Index; NEIVFQ-25, National Eye Institute Visual Function Questionnaire-25

Online supplement 3. The Dutch King's Sarcoidosis Questionnaire

King's Sarcoïdose Vragenlijst (KSQ)

Invuldatum: .....

Het doel van deze vragenlijst is het bepalen van de invloed van sarcoïdose op verschillende aspecten van uw leven. Lees elke vraag zorgvuldig door en omcirkel het antwoord dat het meest op u van toepassing is. Beantwoord ALLE vragen zo eerlijk mogelijk. Deze vragenlijst is vertrouwelijk. Alle vragen hebben betrekking op de manier waarop **SARCOIDOSE** uw gezondheid heeft beïnvloed.

ALGEMENE GEZONDHEIDSTOESTAND

	In de laatste 2 weken ...	De hele tijd	Het grootste deel van de tijd	Een flink deel van de tijd	Een deel van de tijd	Een klein deel van de tijd	Heel zelden	Helemaal niet
1	Heb ik me gefrustreerd gevoeld	1	2	3	4	5	6	7
2	Heb ik moeite gehad me te concentreren	1	2	3	4	5	6	7
3	Heb ik onvoldoende motivatie gehad	1	2	3	4	5	6	7
4	Heb ik me moe gevoeld	1	2	3	4	5	6	7
5	Heb ik me zorgen gemaakt	1	2	3	4	5	6	7
6	Heb ik last of pijn in mijn spieren/gewrichten gehad	1	2	3	4	5	6	7
7	Heb ik me geschaamd	1	2	3	4	5	6	7
8	Heb ik me zorgen gemaakt over mijn gewicht	1	2	3	4	5	6	7
9	Heb ik me zorgen gemaakt over mijn sarcoïdose	1	2	3	4	5	6	7
	In de laatste 2 weken ...	**Zeer sterk**	**Behoorlijk sterk**	**Matig sterk**	**Enigszins**	**Weinig**	**Zeer weinig**	**Niet**
10	Heeft vermoeidheid mij gehinderd bij mijn normale sociale activiteiten, zoals uitgaan met vrienden of familie	1	2	3	4	5	6	7

LONG

	In de laatste 2 weken …	De hele tijd	Het grootste deel van de tijd	Een flink deel van de tijd	Een deel van de tijd	Een klein deel van de tijd	Heel zelden	Helemaal niet
11	Heb ik pijn/ongemak gehad door het hoesten	1	2	3	4	5	6	7
12	Ben ik buiten adem geraakt als ik de trap op klom of een flauwe helling op liep	1	2	3	4	5	6	7
13	Heb ik diep moeten ademhalen, ook bekend als “snakken naar adem”	1	2	3	4	5	6	7
14	Heb ik me benauwd op de borst gevoeld	1	2	3	4	5	6	7
15	Heb ik perioden van benauwdheid gehad	1	2	3	4	5	6	7
16	Heb ik last gehad van pijn op de borst	1	2	3	4	5	6	7

MEDICATIE

Gebruikt u medicatie voor uw sarcoïdose?

JA O NEE O (ga naar het volgende onderdeel)

	In de laatste 2 weken …	Zeer sterk	Behoorlijk sterk	Matig sterk	Enigszins	Weinig	Zeer weinig	Niet
17	Heb ik me zorgen gemaakt over bijwerkingen van mijn medicijnen	1	2	3	4	5	6	7
18	Heb ik me slechter gevoeld door mijn medicijnen voor sarcoïdose	1	2	3	4	5	6	7
19	Ben ik aangekomen door mijn medicijnen voor sarcoïdose	1	2	3	4	5	6	7

HUID

	In de laatste 2 weken …	Zeer sterk	Behoorlijk sterk	Matig sterk	Enigszins	Weinig	Zeer weinig	Niet
20	Heb ik last gehad van mijn huidproblemen	1	2	3	4	5	6	7
21	Heb ik me zorgen gemaakt over veranderingen in de kleur van mijn huidafwijkingen	1	2	3	4	5	6	7
	In de laatste 2 weken …	**De hele tijd**	**Het grootste deel van de tijd**	**Een flink deel van de tijd**	**Een deel van de tijd**	**Een klein deel van de tijd**	**Heel zelden**	**Helemaal niet**
22	Heb ik mij geschaamd vanwege mijn huid	1	2	3	4	5	6	7

OGEN

	In de laatste 2 weken …	De hele tijd	Het grootste deel van de tijd	Een flink deel van de tijd	Een deel van de tijd	Een klein deel van de tijd	Heel zelden	Helemaal niet
23	Heb ik droge ogen gehad	1	2	3	4	5	6	7
24	Heb ik problemen gehad met fel licht	1	2	3	4	5	6	7
25	Zijn mijn ogen rood geweest	1	2	3	4	5	6	7
26	Heb ik pijn in of rond mijn ogen gehad	1	2	3	4	5	6	7
27	Heb ik moeite gehad met lezen	1	2	3	4	5	6	7
	In de laatste 2 weken …	**Zeer sterk**	**Behoorlijk sterk**	**Matig sterk**	**Enigszins**	**Weinig**	**Zeer weinig**	**Niet**
28	Heb ik last gehad van wazig zien	1	2	3	4	5	6	7
29	Heb ik me zorgen gemaakt over mijn gezichtsvermogen	1	2	3	4	5	6	7

Einde vragenlijst

“The Dutch version of the CAMPHOR is a reliable and valid questionnaire to measure quality of life and health status in patients with PAH and CTEPH.”

CHAPTER 4

Adaptation and validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for the Netherlands

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ABSTRACT

Background

The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is the first disease-specific instrument for pulmonary arterial hypertension (PAH) to assess patient-perceived symptoms, activity limitations and quality of life. To be able to use this questionnaire in the Netherlands, the aim of the study was to translate and validate this instrument for the Dutch-speaking population.

Methods

First the CAMPHOR was translated into Dutch (by means of a bilingual and a lay panel) and field-tested by means of cognitive debriefing interviews with ten PAH patients. For psychometric evaluation, 80 patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) were asked to complete the CAMPHOR twice over a two-week period. To test for construct validity, participants also completed the Nottingham Health Profile (NHP).

Results

The Dutch version of the CAMPHOR showed high internal consistency for all scales (Cronbach's alpha 0.89–0.91) and excellent reproducibility over two weeks (reliability coefficients 0.87–0.91). Concurrent validity showed that the CAMPHOR scales correlated as expected with the NHP scales. The CAMPHOR was able to distinguish between patient groups based on self-reported general health status, disease severity and NYHA classification demonstrating evidence of known group validity. The CAMPHOR activity limitations scale correlated moderately with the distance walked during the 6-minute walk test ($r = -0.47$, $p < 0.01$) and the symptoms scale with the Borg dyspnoea score ($r = 0.51$, $p < 0.01$).

Conclusion

The Dutch version of the CAMPHOR is a reliable and valid measure of quality of life and health status in patients with PAH and CTEPH is recommended for use in routine care and in clinical research.

BACKGROUND

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature, leading to increased pulmonary vascular resistance ultimately resulting in right heart failure and premature death.[1] PAH can affect persons of all ages, and females are more affected than males.[1,2] Symptoms include breathlessness, fatigue, chest pain, palpitations, ankle oedema and syncope.[1] Unfortunately, it is not possible to cure the disease with the currently available treatments. The aim of therapy is to lengthen survival time, to ameliorate symptoms, to improve quality of life and to reduce the number of hospitalisations.[3] Chronic thromboembolic hypertension (CTEPH) is a form of precapillary PH. Patients with non-operable CTEPH suffer from the same symptoms as patients with PAH and despite treatment with specific PAH medication have a poor life expectancy.[4,5]

In spite of the current treatment options, health-related quality of life (HRQL) is impaired in most patients suffering from PAH.[6-9] HRQL should be measured with an appropriate questionnaire.[10] Generic HRQL measures employed in PAH populations are of limited value in the assessment of PAH, since these do not take into account all aspects of the disease and its treatment.[11-14] Therefore, a disease-specific outcome measure for patients with PAH has been developed, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[15] The questionnaire comprises three scales that assess overall symptoms (25 items), activity limitations (15 items) and quality of life (25 items). This tool is designed for use in clinical practice as well as clinical trials. This questionnaire has been used as an outcome parameter in studies concerning PAH over the last years.[16-18] The CAMPHOR health questionnaire has been translated and validated in several languages for several countries.[19-23] This paper describes the adaptation and the validation of CAMPHOR for Dutch-speaking population in the Netherlands.

METHODS

The adaptation of the CAMPHOR questionnaire was conducted in two PH centres in the Netherlands, the Erasmus University Medical Center in Rotterdam and the VU University Medical Center in Amsterdam. The process consisted of three stages: translation (by means of a bilingual and a lay panel), cognitive debriefing interviews with ten PAH patients and validation by means of a postal validation study. The study was approved by the ethics committees of both centres.

Translation process

A professional translation panel of six individuals who were fluent in both English and Dutch, led by the local investigator's representative and a research scientist from Galen Research, produced the first translation. A separate lay panel consisting of five individuals of average educational level (3 men and 2 women aged between 21 and 67 years) discussed the proposed wording of the items and decided whether these were acceptable or required adjustments to improve the clarity and to make the sentences sound more natural. The local investigator evaluated and discussed the changes made with the scientist from Galen Research.

Cognitive debriefing interviews

The draft version of the instrument was tested with ten patients, via one-to-one semi-structured interviews. A representative selection of PAH patients was made based on gender, age, severity of PAH and social background. The respondents were asked to complete the questionnaire in the presence of an interviewer who observed whether any problems were experienced. Respondents were required to provide feedback on their comprehension of the measure and the relevance of the items.

Postal validation survey

During a consecutive three-month period from September 2014 to December 2014, 80 Dutch-speaking patients (who were able to read the Dutch language), suffering from pre-capillary PAH (WHO group 1) or CTEPH (WHO group 4), were asked to complete the new language version of the CAMPHOR and the Nottingham Health Profile (NHP) on the day of their clinic visit and the CAMPHOR questionnaire again after two weeks.

The NHP is a generic measure of perceived distress consisting of 38 items divided into six sections (energy level, pain, emotional reactions, sleep, social isolation and physical ability).[24,25] In both questionnaires higher scores indicate worse health status.

Baseline characteristics were obtained (sex, age, employment status) and illness information (duration of PH, perceived general health, self-perceived disease severity, oxygen use) was also collected. The NYHA functional class was determined, a six-minute walk test (6MWT) was performed and the NT-pro BNP level was measured.

Patients were asked to complete the questionnaires at home and to return the questionnaires by post in pre-addressed, stamped envelopes. After two weeks, they received a phone call to remind them to fill in the second CAMPHOR questionnaire and to inquire about possible changes in their physical health.

Withdrawal of patients

Patients who did not complete more than 85 % of a questionnaire were withdrawn from the analysis. For the test-retest reliability, patients were excluded if they were not clinically stable.

Data analysis

Continuous variables are expressed as mean ± SD. Internal consistency of the CAMPHOR adaptation was evaluated by determining Cronbach's alpha coefficient. An alpha coefficient >0.7 is considered to be the minimum value required to indicate sufficient internal consistency.

Test re-test reliability (patient-specific agreement between two repeated administrations) was examined using Spearman's rank correlations. Correlation coefficients above 0.85 indicate good reproducibility.[26] Convergent validity was assessed with the NHP as the comparator instrument using Spearman's rank correlations. Known group validity was tested by Mann-Whitney U test. Correlation between CAMPHOR scores, demographic factors, the results of the 6MWT (including Borg scores) and NT-pro BNP levels was assessed using Spearman's rank correlations. A p-value of <0.05 was considered statistically significant.

RESULTS

Bilingual panel

The group reached consensus on the appropriate wording for most items. A few phrases could not be translated literally. For example, one item from the symptoms scale; 'My stamina levels are low' was translated as 'Mijn lichamelijke conditie is slecht' (literally: 'My physical condition is weak'). For a few items consensus could not be reached and alternative versions of these items were taken forward for consideration by the lay translation panel.

Lay panel

Some expressions were altered from the original translation into more commonly used Dutch. For example, for item 9 of the symptoms scale: 'I soon run out of energy'. This sentence was translated as; 'Mijn energie is snel op'. The panel felt that this translation was too literal. They instead proposed: 'Ik heb weinig energie' (literally: 'I have little energy').

Cognitive debriefing interviews

Ten patients were interviewed (6 females, 4 males, mean age 49.1, range 20–77 years, PH symptoms ranged from mild to quite severe). Average time for completion was 12.6 minutes (range 6–24 minutes, median 11.5 minutes). Overall patients thought the questionnaire was appropriate and applicable. Some patients found it hard to choose between the 'Yes' or the 'No' response format, and would have liked the option of 'Sometimes'. For the activity limitations scale, the response option 'Doing it on your own with problems' was changed into 'With difficulties doing it on your own'. In the quality of life section item 17; 'I feel that I'm losing my role in life', translated as; 'Ik voel dat ik mijn rol(len) [verantwoordelijkheden] in het leven verlies' was considered to be a difficult question by the majority of the patients.

Postal validation survey

From the 80 patients who were asked to participate, 76 completed and returned the questionnaires. Of these only 0.14 % of the items were missing. Missing items from the CAMPHOR as well as the NHP questionnaire were handled according to the manuals. Demographic and disease characteristics of the respondents are listed in Table 1. The cohort consisted of 59 females and 17 males, which is consistent with the gender ratio in a PAH population. Disease information is listed in Table 2. The descriptive statistics for the questionnaires at both time points are shown in Table 3. High floor effects (high number of patients scoring the minimum) were observed in the NHP subscales, but not in the CAMPHOR scales.

Table 1. Demographic and patient characteristics

Characteristics		Patients ($n = 76$)	Percentage (%)
Sex	Male	17	22.3
	Female	59	77.7
Age in years	Mean	56	
	Median	59.5	
	Range	20–79	
Diagnosis in years	Mean	7.1	
	Median	4.2	
	Range	0–50	
Aetiology	IPAH	26	34.2
	HPAH	4	5.3
	Congenital heart disease	5	6.6
	Connective tissue disease	11	14.5
	HIV	3	3.9
	Porto pulmonary	3	3.9

Table 1. Demographic and patient characteristics (*continued*)

Characteristics		Patients ($n = 76$)	Percentage (%)
	PVOD	1	1.3
	Other	3	3.9
	CTEPH	20	26.3
NYHA classification	1	0	0
	2	56	73.7
	3	20	26.3
	4	0	0
Treatment	ERA monotherapy	13	17.1
	PDE-5 inhibitor monotherapy	7	9.2
	Riociguat	2	2.6
	Duo therapy: ERA and PDE-5 inhibitor	30	39.5
	Prostacyclin monotherapy	6	7.9
	Prostacyclin and PDE-5 inhibitor	2	2.6
	Prostacyclin and ERA	1	1.3
	Triple therapy: prostacyclin, ERA and PDE-5 inhibitor	11	14.5
Require oxygen	No	61	81.3
	Yes	14	18.7
6-minute walking distance in meters	Mean	466	
	Median	472	
	Range	232–647	
	Missing	4	
NT-pro BNP in pmol/ml	Mean	53.4	
	Median	24.8	
	Range	3.9–439.2	

IPAH idiopathic pulmonary arterial hypertension, *HPAP* heritable pulmonary arterial hypertension, *PVOD* pulmonary veno-occlusive disease, *CTEPH* chronic thromboembolic pulmonary hypertension, *ERA* endothelin receptor antagonist, *PDE-5 inhibitor* phosphodiesterase-5 inhibit

Internal consistency

For all three CAMPHOR scales, Cronbach's alpha coefficients were above 0.8, indicating high internal consistency (detailed in Table 4).

Test-retest reliability

Test-retest reliability was excellent for all three scales, (0.87 for symptoms, 0.91 for activity and 0.87 for quality of life), which demonstrates low levels of random measurement error.

Table 2. Disease information at time 1 ($n = 76$)

	Number of patients	Percentage (%)
Self-reported general health		
Poor	6	7.9
Fair	32	42.1
Good	32	42.1
Very good	6	7.9
Self-reported severity of disease		
No symptoms	8	10.7
Mild	28	37.3
Moderate	35	46.7
Quite severe	3	4.0
Very severe	1	1.3
Flare up		
No	72	94.7
Yes	4	5.3

Table 3. Questionnaire descriptive statistics

	n	**Median (IQR)**	**Mean (SD)**	**Min–Max**	**% scoring minimum**	**% scoring maximum**
Time 1						
CAMPHOR symptoms	76	4.0 (2.0–8.0)	5.3 (4.6)	0.0–25.0	13.2	0.0
CAMPHOR activities	76	4.0 (2.0–9.0)	5.6 (4.9)	0.0–30.0	14.5	0.0
CAMPHOR QoL	76	4.0 (1.0–8.0)	5.1 (4.9)	0.0–25.0	14.5	0.0
NHP						
Energy scale	74	0.0 (0.0–33.3)	19.8 (32.6)	0.0–100.0	66.2	9.5
Pain scale	75	0.0 (0.0–0.0)	7.0 (18.4)	0.0–100.0	78.7	0.0
Emotional Reactions	75	0.0 (0.0–11.1)	10.8 (18.7)	0.0–100.0	58.7	1.3
Sleep scale	75	20.0 (0.0–40.0)	25.3 (30.2)	0.0–100.0	46.7	2.7
Social isolation	74	0.0 (0.0–0.0)	5.1 (13.7)	0.0–100.0	85.1	0.0
Physical mobility	74	12.5 (0.0–25.0)	15.4 (19.0)	0.0–100.0	47.3	0.0
NHP–D	73	2.0 (0.0–4.0)	2.9 (3.9)	0.0–24.0	32.9	0.0
Time 2						
CAMPHOR Symptoms	74	6.0 (1.8–9.0)	5.9 (5.0)	0.0–25.0	16.2	0.0
CAMPHOR Activities	75	4.0 (2.0–9.0)	5.9 (5.1)	0.0–30.0	17.3	0.0
CAMPHOR QoL	74	3.0 (1.0–8.3)	4.9 (5.2)	0.0–25.0	21.6	0.0

Table 4. Cronbach's alpha coefficients

	Time 1	Time 2
CAMPHOR symptoms	0.89	0.89
CAMPHOR activities	0.91	0.90
CAMPHOR QoL	0.89	0.91

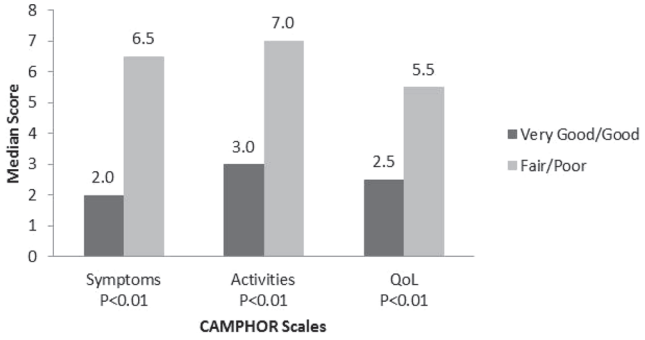

Figure 1. Median CAMPHOR scales scores for self-reported general health tested with Mann Whitney U. Interquartile ranges (IQR) for the Camphor scales scores for very good/good and fair/poor, respectively, are: Symptoms 0.8–4.3 and 4.0–11.0; Activities 1.0–5.0 and 3.0–10.0; Qol 1.0–5.0 and 1.8–10.0

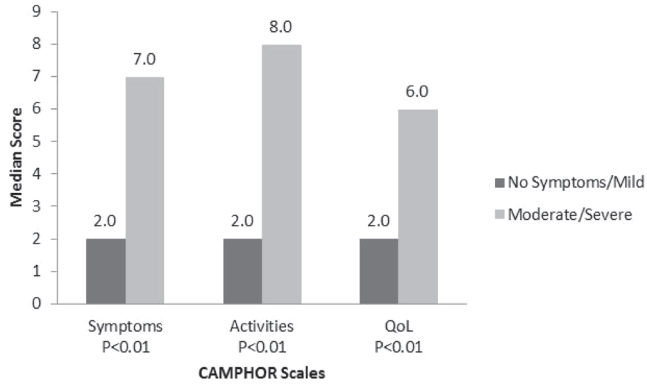

Figure 2. Median CAMPHOR scales scores for self-reported disease severity tested with the Mann-Whitney U test. Interquartile ranges (IQR) for the Camphor scales scores for no symptoms/mild and moderate/severe, respectively, are: Symptoms 0.0–3.0 and 5.0–11.0; Activities 0.3–5.8 and 3.0–10.0; Qol 0.0–5.0 and 3.0–10.0

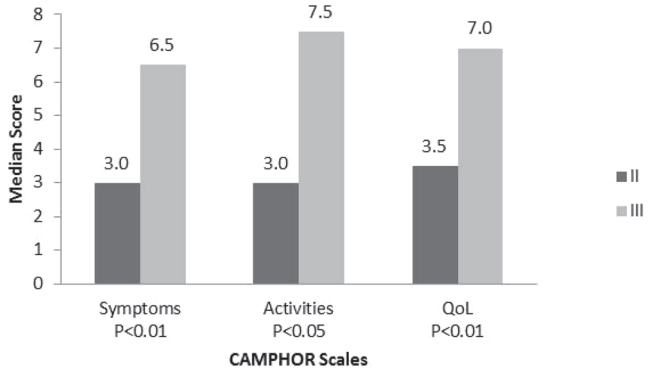

Figure 3. Median CAMPHOR scores and NYHA classification tested with the Mann-Whitney U test. Interquartile ranges (IQR) for the Camphor scales scores for class II and class III, respectively, are: Symptoms 1.0–7.0 and 4.0–11.8; Activities 2.0–8.0 and 3.0–12.5; Qol 1.0–5.8 and 2.3–11.5

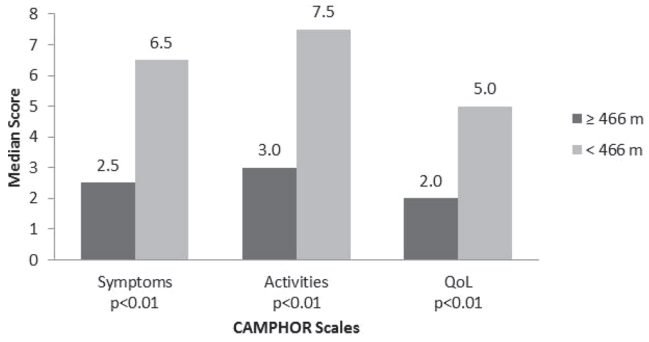

Figure 4. Group validity of six-minute walk distance ≥ 466 m and < 466 m and median CAMPHOR scales scores using the Mann-Whitney U test. Interquartile ranges (IQR) for the Camphor scales scores for ≥466 m and 466 m, respectively, are: Symptoms 1.0–3.0 and 3.0–9.8; Activities 1.0–5.0 and 3.0–12.8; Qol 0.0–5.8 and 4.0–8.0

Convergent validity

The CAMPHOR symptoms scale correlated strongly with the energy and physical mobility scales of the NHP, showing the importance of these factors on PAH symptomatology. It also correlated moderately with Borg dyspnoea scores. There were significant correlations between the CAMPHOR QoL scale and the NHP energy scale, physical mobility and NHP-D (summation of sub-set of NHP items scores) indicating that multiple factors influence QoL. As expected, the activity limitations scale showed the strongest correlation with the NHP physical mobility and 6MWT. The correlation coefficients between CAMPHOR scales and the NHP are listed in Table 5.

No significant correlations were demonstrated between the CAMPHOR scales and the NT-pro BNP (Table 5).

Table 5. Correlation coefficients between CAMPHOR scales and NHP, 6MWT and NT-proBNP

	Symptoms	Activities	QoL
NHP			
Energy scale	0.71*	0.65*	0.66*
Pain scale	0.38*	0.38*	0.42*
Emotional reactions	0.43*	0.24**	0.37*
Sleep scale	0.32*	0.22	0.38*
Social isolation	0.23	0.34*	0.39*
Physical mobility	0.67*	0.76*	0.61*
NHP-D	0.58*	0.49*	0.63*
6MWT			
Distance walked(m)	−0.34*	−0.47*	−0.42*
Borg dyspnoea score	0.51*	0.49*	0.32*
NT-proBNP	−0.08	−0.08	0.10

Values shown represent Spearman's rank correlation coefficients
*$p < 0.01$; **$p < 0.05$

Association of CAMPHOR scores and demographic factors

No significant differences in the CAMPHOR scores were found between patients grouped by age. However, significant differences were shown in the scores of symptoms and QoL scales between males and females. Females scored higher on these two scales compared with males. A chi-square test of independence was performed to assess the relation between gender and self-reported severity of disease. No significant association was found between these variables (χ^2 (1, n = 75) = 0.08, p = 0.93). Similarly, no significant relationship was found between gender and NYHA class (χ^2 (1, n = 76) = 1.1, p = 0.74). The relation between gender and cause of PH was also investigated, but again no significant association was found (χ^2 (7, n = 76) = 8.5, p = 0.29).

Known group validity

CAMPHOR scales scores were able to discriminate between patients based on perceived general health ('very good/good' versus 'fair/poor') and severity of disease ('no symptoms/mild' versus 'moderate/severe'). Patients with worse perceived general health (Figure 1) and more severe PAH (Figure 2) had higher scores for all three scales of the CAMPHOR.

Patients in NYHA class 3 showed significantly higher scores on all three CAMPHOR scales compared with patients in NYHA class 2 (Figure 3).

Patients grouped based on the distance walked during 6MWT (below and above the mean value of 466 metres) showed significant differences in all CAMPHOR scales (Figure 4).

No differences were observed in the CAMPHOR subscales between PAH and CTEPH patients (16 patients in NYHA class 2 and four patients in NYHA class 3), tested by the Mann-Whitney U test: CAMPHOR symptoms $p = 0.59$, CAMPHOR activities $p = 0.92$ and CAMPHOR quality of life $p = 0.94$.

DISCUSSION

This study demonstrates that the new adaptation of the CAMPHOR for Dutch-speaking participants in the Netherlands is valid and reliable. The objective of adapting the questionnaire is to ensure that items are understood in the same way in different countries and that conceptual equivalence rather than linguistic equivalence is achieved in the translated items. Moreover, it is vital that translated items are expressed in common (everyday) language. No major problems were encountered during the translation process.

Descriptive statistics showed the CAMPHOR had low floor effects and no ceiling effects, which indicates the CAMPHOR is well targeted to the PAH population. Consequently, the measure should be sensitive and responsive in clinical studies (e. g. in longitudinal studies). In contrast, the NHP showed very high floor effects indicating patients with the lowest possible score cannot be distinguished from each other, which reduces sensitivity.

Cronbach's alpha coefficients were above 0.8 for the three CAMPHOR scales, indicating that the items were related adequately to form scales. Test-retest reliability was excellent for all three scales showing the scales have low levels of random measurement error.

The CAMPHOR scales showed different levels of association with the scales of the NHP, demonstrating evidence of convergent validity. As expected, CAMPHOR activities correlated most strongly with the NHP physical mobility scale and 6MWT as was also shown by Cima et al. in the German adaptation of the CAMPHOR.[22]

Patients with worse perceived general health and more severe PAH had higher scores for all three scales of the CAMPHOR scores showing that the scales could distinguish appropriately between groups of known importance.

Females scored higher on the scales of symptoms and QoL compared with males. Further analyses were performed to investigate this difference. The relation between gender and self-reported severity of disease as well as gender and NYHA class and gender and cause of PAH was assessed. No significant association was found between gender and the investigated variables. Based on these findings it was unclear what contributed to the differences between gender groups. However, due to the relatively small sample of males the results could be spurious.

The sample of patients included in this study seemed to have less severe disease than the sample included in the original paper describing the development of the CAMPHOR questionnaire. One explanation may be that with the currently available treatment, including triple therapy, less patients are now in NYHA class 4. Another explanation might be that only patients who visited the outpatient clinic were asked to participate in the study. In this way the very severe patients, who were hospitalised during this period (for example those waiting for lung transplantation), were not included.

However, the CAMPHOR scores were able to clearly distinguish between patients in NYHA class 2 and NYHA class 3. Moreover, the results of the 6MWT correlate well with the CAMPHOR scale scores.

CONCLUSIONS

The new Dutch language version of the CAMPHOR is a valid and reliable instrument for assessment of health-related quality of life in PAH and CTEPH patients and is recommended for use in clinical practice. Moreover the CAMPHOR provides a valid tool for a single-point measurement in cross-sectional studies.

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Conflict of interest

M. Wapenaar, J. Twiss, M. Wagenaar, P. Seijkens, L. van den Toorn, J. Stepanous, A. Heaney, A. van den Bosch and K. A. Boomars state that there are no conflicts of interest.

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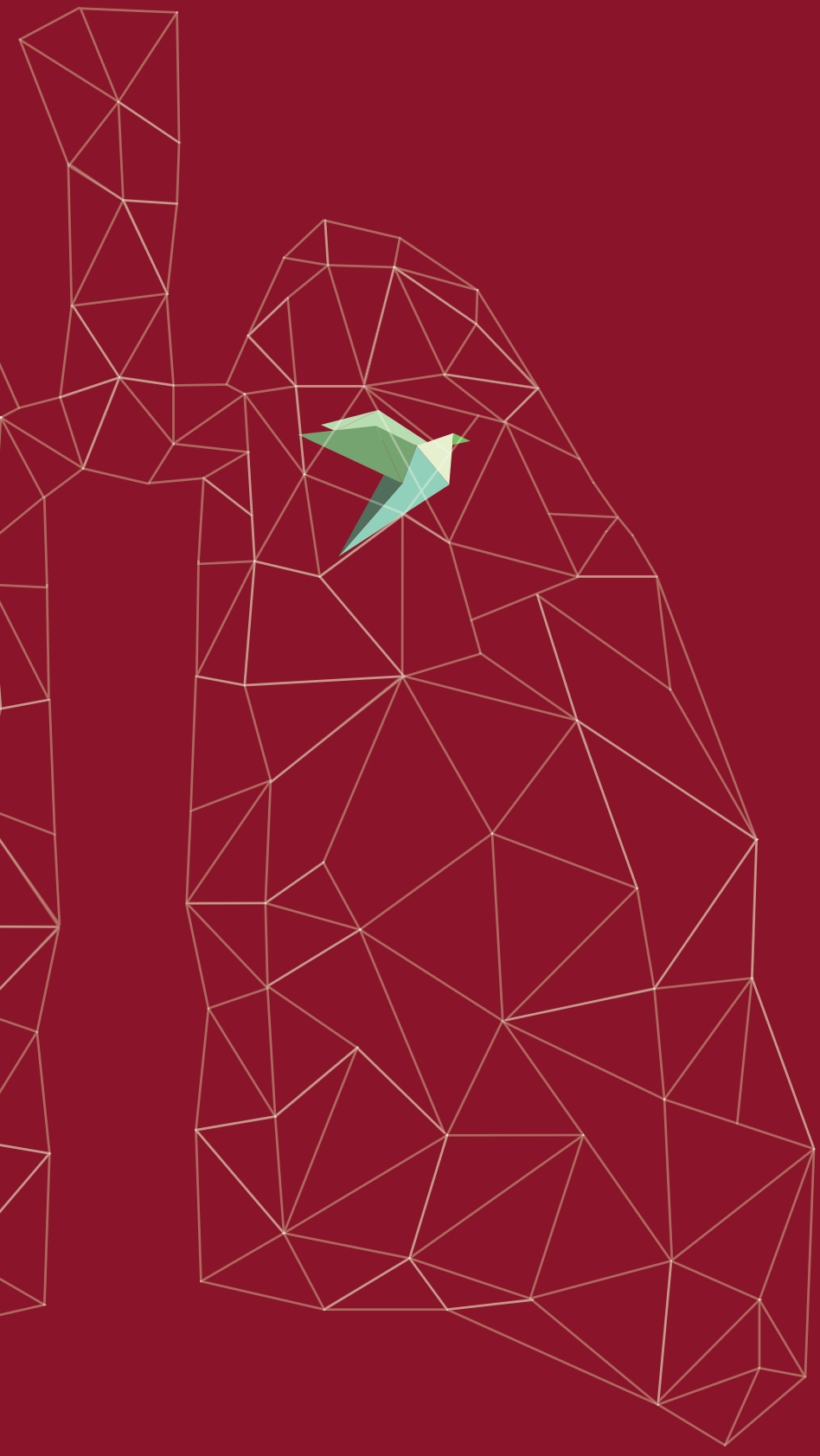
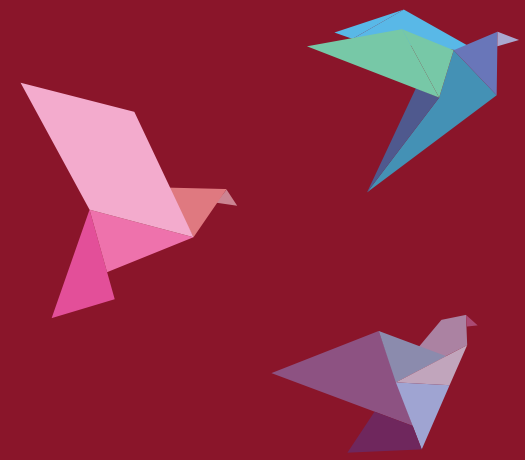
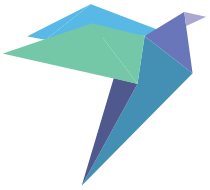




PART 2

Development of patient-recorded outcome measures



“Daily home spirometry detected that the major treatment effect of prednisone on FVC and symptoms is reached within 2 to 3 weeks in newly treated sarcoidosis patients.”

CHAPTER 5

Daily home spirometry to detect early steroid treatment effects in newly treated pulmonary sarcoidosis

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Prednisone is the mainstay of sarcoidosis treatment. However, prednisone treatment optimisation is warranted, since prolonged high-dose prednisone therapy is associated with burdensome and harmful side-effects.[1,2] Early prednisone dose tapering has the potential to reduce side-effects. Gaining insight in the early treatment response can help to determine when tapering could be initiated. To date, there are no prospective studies that look at early treatment response to prednisone in sarcoidosis by monitoring clinical symptoms and daily patient-administered lung function. Therefore, we initiated a multicentre, prospective and observational study with daily home spirometry to detect early steroid treatment effects in newly treated pulmonary sarcoidosis (Dutch National Trial Register NTR4328; www.trialregister.nl/trialreg).

Treatment-naïve sarcoidosis patients in whom prednisone therapy was about to be initiated for a pulmonary indication were eligible. Patients were intended to be treated with the following prednisone regimen: 4 weeks 40 mg·day^{-1}, 2 weeks 30 mg·day^{-1}, 2 weeks 20 mg·day^{-1}, 2 weeks 15 mg·day^{-1}, 2 weeks 10 mg·day^{-1} (unless the treating physician decided that the clinical situation demanded deviation). During these 3 months, daily home monitoring of forced vital capacity (FVC) was performed by the patient on a calibrated hand-held spirometer (Micro Diary; Carefusion, Hoechberg, Germany). Additionally, patients were asked to fill out a Medical Research Council (MRC) dyspnoea and Fatigue Assessment Scale (FAS) score at the end of each week in a diary. Data are presented as mean±SD unless stated otherwise. More details on the study design can be found in the trial register online.

The study group consisted of 21 patients (13 male and eight female; age 43±11 years). The majority of the patients (76%) were diagnosed with Scadding stage II sarcoidosis. Routine in-hospital lung function monitoring showed a significant FVC increase following treatment from 69.7±13.9 to 81.5±13.7 % predicted at month 1 (mean change 11.8±9.2, $p<0.001$) (figure 1a). A smaller FVC improvement was observed between month 1 (81.5±13.7) and month 3 (84.8±13.2) (mean change 3.3±6.4, $p=0.039$) (figure 1a). The estimated mean FVC change obtained using daily home spirometry over time was calculated using a fixed effect model, meaning that the regression lines of all 21 individual patients were incorporated (figure 1c). A maximal mean increase of 9.7 (95% CI 8.4–10.9) % pred FVC was estimated after treatment initiation. Interestingly, a plateau of FVC increase was observed at 24 days (95% CI 14–33) and 90% of the total FVC increase was already reached by day 18 (95% CI 10–28).

Together, these data show that most of the improvement in FVC occurs within 2–3 weeks after prednisone therapy initiation in a cohort of newly treated sarcoidosis patients.

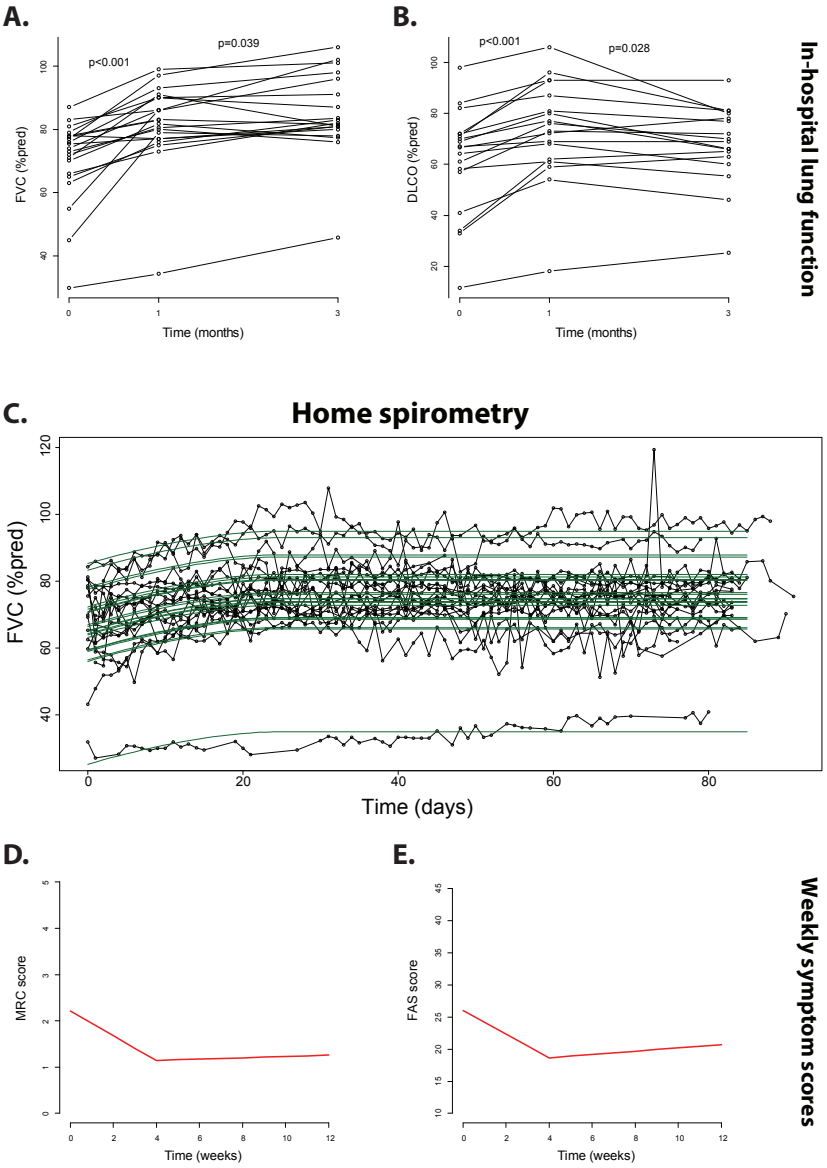

FIGURE 1. a) In-hospital clinical monitoring of forced vital capacity (FVC; n=19) and b) diffusing capacity of the lung for carbon monoxide (D_{LCO}) (corrected for haemoglobin levels; n=17) values at baseline, month 1 and month 3 during prednisone treatment of patients with data available at all three time-points. Lines represent paired results from one patient. Significance was determined using a two-tailed paired t-test. c) Daily best FVC measurements recorded on the home spirometer (Micro Diary; Carefusion) per individual patient over time (in days) as % predicted, including regression lines of all 21 individual patients. Daily FVC measured during home monitoring was used as the outcome in a fixed effect model (fixed effect nonlinear least squares model). Regression line of all d) weekly Medical Research Council (MRC) dyspnoea scores and e) Fatigue Assessment Scale (FAS) scores filled out in a home diary per individual patient over time (in weeks). A multilevel model was used that modelled linear splines with a knot at 4 weeks

Our results are in line with other studies that have suggested that the major increase in FVC during prednisone treatment in sarcoidosis occurs within 1 month.[3,4] However, these studies were either performed retrospectively in patients experiencing an exacerbation who previously were shown to be responsive to prednisone and/or evaluated changes on in-hospital lung function equipment at pre-determined time-points, possibly missing early and daily changes in FVC.[3,4]

No single clinical test has been found to accurately assess disease burden in pulmonary sarcoidosis.[5] Therefore, it is important to evaluate whether other outcomes improve as well. Multilevel analyses of the weekly filled out MRC scores showed that dyspnoea symptoms decreased significantly with 0.3 (95% CI 0.2–0.4) MRC points per week ($p<0.001$), stabilising after 1 month (figure 1d). Similarly, FAS scores decreased significantly with 1.8 (95% CI 1.5–2.2) FAS points per week ($p<0.001$), stabilising after 1 month (figure 1e). Importantly, this is the first study to evaluate early therapy effects on dyspnoea (MRC) and fatigue (FAS)[6], and the early improvements observed strengthen our home spirometry data.

In a sub-cohort of patients, participating at a select number of study sites, diffusing capacity of the lung for carbon monoxide (*D*LCO) (corrected for haemoglobin level) was measured. A significant increase in *D*LCO % pred was observed within 1 month from 60.4±20.6 to 72.5±19.7 (mean change: 12.0±8.5, $p<0.001$). However, *D*LCO decreased somewhat again between month 1 and 3 to 67.5±15.6 (mean change −5.0±8.5, $p=0.028$) (figure 1b). These data may indicate subclinical worsening of the disease during prednisone tapering, as *D*LCO measurements may reflect earlier interstitial changes in sarcoidosis.[7] However, we cannot be certain that this is a relevant change, as reproducibility of *D*LCO measurements is well known to be lower than FVC measurements, and only a major change (>15%) in *D*LCO has been suggested to reliably exclude confounding by measurement variation.[5] Furthermore, daily home spirometry and weekly dyspnoea and fatigue scores showed that the initial improvement was retained in the majority of patients up to 3 months while prednisone dose was tapered. In addition, inflammatory markers that are thought to reflect disease activity in sarcoidosis, such as angiotensin-converting enzyme and soluble interleukin-2 receptor[5,8], decreased significantly within 1 month, also remaining stable up to 3 months (data not shown). However, it remains to be investigated whether these outcomes remain stable in the long term.

Quality of life was also captured in this study during hospital visits at baseline, month 1 and month 3. The St George's Respiratory Questionnaire improved significantly at 1 month, exceeding the reported minimal clinically important difference (table 1).[9,10] Interestingly, questionnaires that were more focused on general health status, such as

the Short-Form Health Survey and King's Sarcoidosis Questionnaire general health status, showed either no or less pronounced changes during prednisone treatment in our study group than scores purely including physical symptoms such as the MRC, FAS and King's Sarcoidosis Questionnaire lung scores (table 1). This may have been caused by concurrent side-effects that occur during prednisone treatment, counterbalancing the positive outcomes of prednisone treatment. Indeed, in our study a number of adverse events were reported that are associated with prednisone treatment, including weight gain. Weight significantly increased within the first 3 months of treatment (mean increase 5.2±4.1 kg, p<0.001). These data confirm that it remains relevant to continuously evaluate benefit–risk ratio of prednisone treatment in consultation with the individual patient.[2,11,12]

This study is the first to perform daily home spirometry in pulmonary sarcoidosis. Daily home spirometry could facilitate a personalised approach to treatment for each patient, aiming at achieving the maximum effect of lung function and symptom improvement

Table 1. Symptoms and quality of life (QoL) assessed during prednisone treatment

Symptom and/or QoL-related questionnaire	Patients	Baseline	Month 1	Month 3[#]
MRC score	18	2.44±1.04	1.33±0.91*	1.39±0.92*
FAS score	18	27.4±10.8	21.0±6.6*	20.7±7.6*
SGRQ				
Symptoms	17	45.0±21.1	29.7±22.4*	27.5±25.1*
Activity	17	55.9±24.9	38.8±27.0*	36.8±28.4*
Impact	17	28.4±23.5	18.5±15.7	18.2±15.1*
Total	17	40.2±21.8	26.5±18.1*	25.4±19.1*
SF-36				
PCS	15	39.0±6.9	40.2±6.9	37.4±6.9
MCS	15	33.5±6.3	36.2±7.0	39.2±8.0*
KSQ				
GHS	11	61.9±14.5	72.0±18.2*	67.0±15.0[¶]
Lung	10	59.0±13.5	70.4±23.1	70.1±20.2*

Data are presented as n or mean±sd. MRC: Medical Research Council; FAS: Fatigue Assessment Scale; SGRQ: St George's Respiratory Questionnaire; SF-36: Short-Form health survey; PCS: physical component score; MCS: mental component score; KSQ: King's Sarcoidosis Questionnaire; GHS: general health status. [#]: none of the values are statistically significant at month 3 compared with values at month 1; [¶]: p=0.055; *: p<0.05 compared with baseline, using a paired sample t-test.

with the lowest possible dose of prednisone, in order to minimise side-effects. This study shows that reliability of daily measured home spirometry in sarcoidosis patients is high;

Pearson correlation between FVC measurements on the home spirometer and the in-hospital lung function equipment was 0.98 ($p<0.001$).

Together, our data argue that monitoring FVC changes at approximately 2–3 weeks after initiation of therapy, either at home or in clinic, can help physicians to better evaluate response to therapy in newly treated sarcoidosis patients. Consequently, physicians might decide on earlier dose tapering and/or the need for initiation of second-line steroid-sparing therapies than is now advised.[13,14] Future studies are needed to evaluate whether home monitoring of prednisone treatment (including FVC and symptom scores) and personalised dose titration[15] will allow for a non-inferior treatment effect compared to current clinical practice, while reducing side-effects and increasing the quality of life for patients with pulmonary sarcoidosis.

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Footnotes

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Conflict of interest: None declared.

This study was registered in the Dutch National Trial Register as NTR4328.

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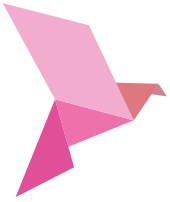

“A home monitoring program including wireless home spirometry, is highly feasible and appreciated by patients with IPF, and enables real-time detection of change in FVC and symptoms, facilitating personalized care.”

CHAPTER 6

A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers

Respir Res. 2018 May 29;19(1):105.

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ABSTRACT

In idiopathic pulmonary fibrosis (IPF), home monitoring experiences are limited, not yet real-time available nor implemented in daily care. We evaluated feasibility and potential barriers of a new home monitoring program with real-time wireless home spirometry in IPF. Ten patients with IPF were asked to test this home monitoring program, including daily home spirometry, for four weeks. Measurements of home and hospital spirometry showed good agreement. All patients considered real-time wireless spirometry useful and highly feasible. Both patients and researchers suggested relatively easy solutions for the identified potential barriers regarding real-time home monitoring in IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, devastating disease with a poor prognosis.[1] Symptoms as increasing shortness of breath and immobility make regular hospital visits a challenge for many patients. New eHealth technologies hold great potential for research and care by facilitating real-time, frequent data collection at home. In IPF, home monitoring experiences are limited and not yet implemented in daily care. Few studies using daily handheld spirometry have been performed in patients with IPF. [2,3] These studies showed that home spirometry in IPF is feasible, may allow for better disease prediction and decrease sample size for future trials.[2,3] However, earlier studies using home spirometry in interstitial lung diseases used paper-based collection or central read-out of Forced Vital Capacity (FVC) results. [2-4] This limits possibilities to control quality of measurements, or respond directly to FVC decline or non-adherence.

We assessed feasibility of a pre-developed home monitoring program in IPF [5], integrated with real-time, wireless home spirometry. Furthermore, we evaluated potential barriers and solutions for implementation of wireless home spirometry in this mostly elderly patient population.

METHODS

This was a prospective pilot study at the Erasmus Medical Center in 2017. Consecutive outpatients with IPF were invited to participate. Approval of the Medical ethics committee was obtained, and participants provided written informed consent. Patients were asked to test the home monitoring program "IPF-online" (www.ipfonline.nl) for four weeks on a tablet. IPF-online is a secured online personal platform, following European safety regulations. The program consists of daily home spirometry, online patient-reported outcomes (PROs) at baseline and after four weeks, weekly reporting of side-effects and symptoms on visual analogue scales, an information library, medication coach and eConsultations. The bluetooth-enabled spirometer (MIR Spirobank Smart, Italy) transmits data real-time via a secure encrypted connection, enabling patients and healthcare providers to access data directly **(Figure 1)**. The system generates email alerts when patients report bothersome side-effects or FVC declines >10% for three consecutive days. If patients fail to perform spirometry or record symptoms, they receive a reminder. Incorporated PROMs are King's Brief Interstitial Lung Disease health status questionnaire, Hospital Anxiety and Depression Scale, Euroqol 5D-5L and an evaluation questionnaire.[6-8] At start, patients received standardized instructions about the correct use of home spirometry and the different components of the online tool. Patients were

considered trained when they were able to perform three good, reproducible FVC measurements, with less than 150 ml difference in the two highest FVCs. Before start of the study, potential barriers of the system were identified based on literature and own experiences. At baseline, potential barriers were discussed with patients. After four weeks, their experiences and suggestions were evaluated. Furthermore, patients performed hospital spirometry at baseline and after four weeks.

Pearson correlation and Bland-Altman plots were used to compare home with hospital spirometry, Wilcoxon signed ranked test was used to compare baseline with follow-up

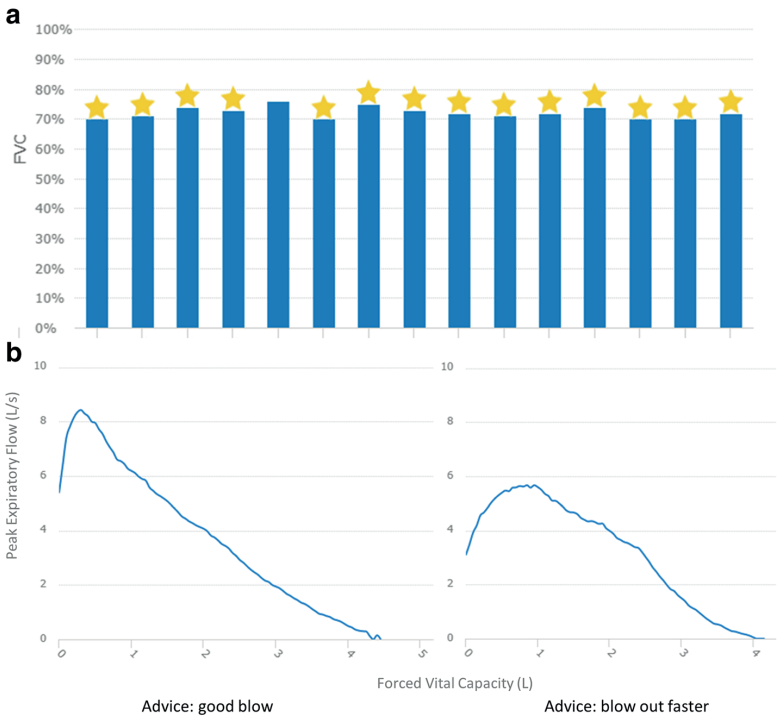

Figure 1a. Daily FVC in % predicted of one patient during two weeks. A star on top of the bar corresponds with a forced expiration > 6 s, and is intended as extra motivation for patients. **b.** Two examples of flow volume loops including daily remarks/advices.

scores. Data are presented as mean (SD) or median (range).

RESULTS

Of 12 patients invited to participate, 10 patients were included (9 men), with a mean age of 71 years (5). All patients were on disease-modifying medication (60% nintedanib, 40% pirfenidone). The mean FVC was 3.28L (1.04) or 79% of predicted (16).

Reliability of home spirometry

Measurements of home and hospital spirometry for FVC (r=0.94 (p<0.001)) and FEV1 (r=0.97 (p<0.001)) were highly correlated, and a Bland-Altman plot showed good agreement (**Figure 2**). Median difference between hospital and home spirometry was 0.22L (0.01-0.69L) with overall lower readings for home spirometry. To evaluate within-subject reproducibility, the median SD for 28 measurements was calculated (0.13L (0.05 -0.39L)). The median coefficient of variation was 3.76% (3-12%).

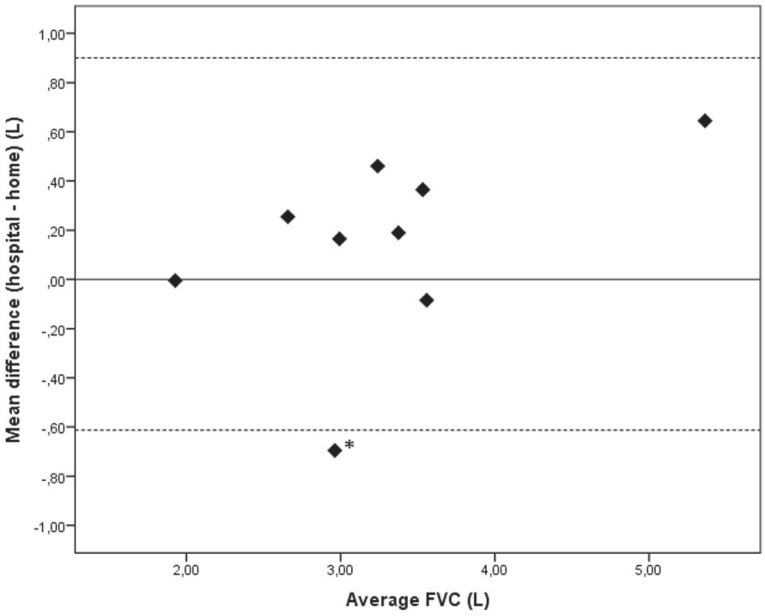

Figure 2: Bland-Altman plot comparing hospital and home spirometry. The value for hospital FVC is the mean of the hospital-based FVC at baseline and after four weeks. The value for home spirometry is the mean of 28 home FVC readings. The solid line represents the mean difference and the dashed lines 95% limits of agreement (-0.61 to 0.90L).* This patient did not use the mouthpiece correctly leading to more variable and higher readings compared to hospital spirometry.

Feasibility and potential barriers of home spirometry in patients with IPF

The vast majority of patients considered daily spirometry easy (80%) and not burdensome at all (90%), the other patients were neutral. The mean adherence to home spirometry was 98.8% (2.5). Most patients (80%) found it pleasant to see their FVC results, 20%

was neutral. All patients considered real-time spirometry useful and would recommend it to others, 90% wished to continue home monitoring after the pilot: "It helps me feel more in control", "I like to monitor my own disease and be monitored" and "I hope this program can replace outpatient clinic visits in the future". Daily home monitoring did not lead to higher anxiety levels (HADS anxiety score at baseline 4.5, score after 4 weeks 4.3, p=0.57), and quality of life remained stable (K-BILD total score at baseline 59.2, score after 4 weeks 60.3, p = 0.65). **Table 1** provides a comprehensive overview of potential barriers, experiences and solutions for use of the home monitoring system.

Table 1. A comprehensive overview of the identified potential barriers for use of the home monitoring system (wireless and real-time), experiences from the pilot study, and possible solutions as suggested by patients and staff.

Potential barriers for the use of real-time home spirometry	Findings in our pilot experiment	Possible solutions
No internet access	Patient who never used internet before had no problems using the tablet and perform spirometry because of the simple design.	- Provide patients with a smartphone or tablet with 4G SIM card during study to guarantee internet access - Use a simple application without too much information
Quality of measurements is difficult to control	All patients performed mostly good quality flow volume loops, which could be checked real-time.	- New wireless spirometers have automated quality control and provide advice to patients - Use a device that shows a flow volume loop accessible to patient and researchers to review quality
A handheld spirometer may be difficult to use	A few patients had to get used to handheld spirometry the first days. Only one patient had variable results, due to technical difficulties with the standard mouthpiece. After providing an additional mouthpiece the readings were comparable to hospital readings.	- Provide a clear instruction manual and good training at start of the study. Patients should be able to perform 3 good quality measurements with ≤ 150 ml difference in the 2 highest FVC's. - Assess individual patients' needs - Consider using an extra/other mouthpiece - Use a video consultation or clinic visit for refreshment training
Motivation	A 6 seconds countdown and FVC target value is always shown during a forced expiration. This motivated patients to blow as good and long as possible.	- Do not use an FVC of 100% predicted as target value as this might demotivate patients - Provide an individual target value for each patient and adjust target value during study if necessary

Table 1. A comprehensive overview of the identified potential barriers for use of the home monitoring system (wireless and real-time), experiences from the pilot study, and possible solutions as suggested by patients and staff. (*continued*)

Potential barriers for the use of real-time home spirometry	Findings in our pilot experiment	Possible solutions
Home spirometry might induce coughing	Some patients mentioned more urge to cough compared to hospital spirometry, but one measurement a day was not a problem at all.	- Advise patients to perform spirometry after a period of rest - Advise patients to try again later that day when a measurement failed because of coughing
Patients might get worried seeing their own results	Anxiety and depression scores were not higher after this short pilot. Almost all patients considered it pleasant to see their daily results.	- Incorporate automated email alerts to the researchers and explain to patients that they will be contacted if FVC declines significantly - Provide an extra option that blinds patients from their results
Daily home spirometry can be bothersome to patients	None of the patients in the pilot considered once daily spirometry bothersome, because it was not time consuming and became part of their routine.	- Advise patients to perform spirometry at almost the same time every day to create a routine - Explain that the whole process takes less than two minutes
Compliance	Patients got motivated by keeping track of their own results and almost all patients continued home spirometry after the pilot.	- Send patients email reminders when they do not perform spirometry or report their symptoms

DISCUSSION

This pilot study shows that a home monitoring program integrated with real-time wireless home spirometry is feasible in patients with IPF. In line with other studies, home-based measurements were slightly lower than hospital-based FVC, which may partly be equipment-related, but also effort-related [2,4]. We tried to minimize the risk for 'underperforming' at home by motivating patients through graphically displaying their personal target value and prior results, a six seconds countdown and advices to technically improve the measurements. However, home and hospital readings are highly correlated and the relative variability of home-based FVC is low, indicating that home spirometry is a reliable tool to monitor patients at a distance. In a patient population with progressive breathlessness and decreasing mobility this enables close monitoring, while lowering the burden of hospital visits, especially in countries with long distances to the hospital. Moreover, real-time uploading of results and automated email alerts not only allow quality review of measurements, it also enables real-time detection of

FVC decline. For example, we already observed a decrease in FVC two days before a patient reported symptoms of a respiratory tract infection. Early detection may potentially improve efficiency and quality of care for patients. Besides spirometry, patients also recorded symptoms and validated questionnaires online, which could be important additional features for future studies.

All patients in our study supported the usefulness of home monitoring, and appreciated being actively involved in monitoring their disease. One patient experienced technical problems with spirometry, highlighting the importance of good instruction. No effects on anxiety or quality of life were observed, however, we believe that the duration of the study is too short to draw definite conclusions on this. We found no major barriers regarding use of real-time wireless home spirometry; relatively easy solutions were suggested by patients and investigators for potential issues.

A limitation of this study is that it is a single center study, with 10 out of 12 consecutive patients willing to participate. In the Netherlands, use of internet amongst elderly people is rather high, however, also in other countries internet use among people over the age of 65 is steadily growing. [9] With worldwide increasing internet use and technological advances, we envision that relatively simple and low-cost systems like this, will facilitate access to care and research for a wider group of patients, also in remote areas and lower socio-economic settings. Further limitations of this pilot are the small sample size and short duration. Although this was sufficient to evaluate reliability and potential barriers of a home monitoring program with real-time wireless home spirometry, larger studies are required to assess whether it improves care, allows for earlier detection of exacerbations, and enhances data collection in clinical trials.

CONCLUSION

A home monitoring program including wireless home spirometry, is highly feasible and appreciated by patients with IPF, and enables real-time detection of change in FVC and PROs facilitating personalized care.

List of abbreviations

IPF: Idiopathic Pulmonary Fibrosis
FVC: Forced Vital Capacity
PROs: Patient Reported Outcomes

Declarations

Ethics approval and consent to participate

Approval of the Medical ethics committee of the Erasmus Medical Center in Rotterdam was obtained (MEC-2017-388), and all participants provided written informed consent.

Competing interests

CM, MW, JM, JG and PC declare no conflicts of interest. MSW reports grants from Erasmus MC Thorax Foundation, Hoffman- la Roche, and Boehringer – Ingelheim related to the submitted work, and other from Galapagos, outside the submitted work.

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“Adopting the new Global Lung Function Initiative TLCO reference values may positively impact clinical trial eligibility for IPF patients.”

CHAPTER 7

The impact of the new Global Lung Function Initiative *T*LCO reference values on trial inclusion for patients with idiopathic pulmonary fibrosis.

Eur Respir J. 2019 Jan 31;53(2).

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We read the paper by Derom et al.[1] with great interest. This paper describes the nationwide introduction and implementation of the new Global Lung Function Initiative (GLI) reference equations for spirometry and transfer factor of the lung for carbon monoxide (*T*LCO) in Belgium.[2,3] Convinced of the advantages of using these all-age and globally most accurate reference value set available[4], the Belgium Thoracic Society applied a stepwise approach to launching them. The aimed nationwide collective transition is currently ongoing, involving pulmonologists, lung function technologists and equipment manufacturers.

Although one could comment that this approach delayed the implementation of the GLI 2012 spirometry equations in Belgium compared to other countries, we fully endorse the importance of a nationwide implementation based on our findings in a study described below. In daily practice, there are many reference value sets implemented and it is acknowledged that use of different sets may lead to interpretation differences of equal measured *T*LCO values within an individual patient. For example, this may happen when a patient is referred from one hospital to another. Uniformity in reference sets will not only avoid potential erroneous effects on treatment decisions; it will also provide clarity to patients and investigators for research purposes, especially when looking at eligibility for trial participation. Below, we describe the impact of the new GLI *T*LCO reference values on trial inclusion for patients with idiopathic pulmonary fibrosis (IPF).

IPF is a progressive and life-threatening interstitial lung disease. Scarring of the lung tissue leads to a restrictive lung function pattern and impaired gas exchange, causing dyspnoea and desaturation on exertion.[5] The *T*LCO, indicator of the gas exchange function of the lungs, is almost always decreased in patients with IPF.[6,7] There is no cure for IPF, except lung transplantation in a select group of patients. Two anti- fibrotic drugs slow-down disease progression but do not stop or reverse the fibrosis.[8] Multiple clinical trials in IPF are ongoing in search for better treatment. IPF patients are often keen to participate in these clinical trials that may give them a chance to improve their disease outcome.[9] Inclusion criteria for these trials usually include a threshold for the *TLCO* %predicted. Screen-failures are frequently based on *TLCO* below lower limits, and are disappointing to patients. Many lung function laboratories still use older reference values of the European Community for Steel and Coal ("ECSC", 1993)[10], Crapo and Morris ("Crapo", 1981)[11], Miller and co-workers ("Miller", 1983)[12] or Neas and Schwartz (National Health and Nutrition Examination Survey 1971-1975; "NHANES-1", 1996).[13] Therefore, we assessed the impact of the new GLI *T*LCO reference equation on trial inclusion for IPF patients.

In a retrospective cohort study, we collected lung function data of consecutive IPF patients, routinely measured in 2017. The *T*LCO %predicted was calculated using the older prediction equations and the new GLI (2017) equations. Predicted values were extrapolated if the age of the patient was beyond the data range of the reference population (ECSC, Miller). Only NHANES-1 has different *T*LCO reference equations for adults with African-American and Caucasian background.[13] We compared the number of patients eligible for clinical trials that use a threshold of *T*LCO ≥30% predicted. SPSS 24 was used for statistical analysis. The ethics committee of our center exempted this study from review because of the noninterventional design (MEC-2018-1383).

We included data of 145 patients, 118 (81%) male, mean±SD age 72±8 years, 11 (8%) non-Caucasian. The mean forced vital capacity (FVC) was 75±16% predicted, Z-score −1.6±1.0, using GLI 2012 spirometry equations. Calculated with the different equations, the median % predicted values and Z-scores for the *T*LCO, the transfer coefficient (*K*CO) and the alveolar volume (*V*A) are shown in Table 1.

Table 1. Values for transfer factor of the lung for carbon monoxide (*T*LCO), transfer coefficient (*K*CO) and alveolar volume (*V*A) as calculated using the different reference equations

	***T*LCO % pred**[#]	**Z-score**	***K*CO % pred**	**Z-score**	***V*A % pred**	**Z-score**
GLI[3]	37% (29–46)	−5.0	64% (52–73)	−2.5	60% (53–69)	−3.5
ECSC[10]	35% (28–44)	−3.9	66% (55–78)	−1.8	55% (48–64)	−4.1
Crapo[11]	30% (24–38)	−4.4	55% (46–64)	−2.5	54% (47–62)	−4.0
Miller[12]	36% (29–45)	−3.3	65% (54–75)	−1.9	55% (48–63)	−3.5
NHANES-1[13]	33% (26–41)					

Data are presented as median % predicted values with interquartile ranges. The Z-score represents the difference between the measured value and the reference population mean in standard deviation units. For example; a Z-score of −3 means that the measured value is far below the 2.5th percentile in a healthy population. [#]: *T*LCO % predicted values from all older equations were significantly lower than the Global Lung Function Initiative (GLI) *T*LCO % predicted (p<0.001, Wilcoxon signed ranks test). [¶]: Z-scores, *K*CO % predicted and *V*A % predicted could not be calculated. ECSC: European Community for Steel and Coal; NHANES-1: National Health and Nutrition Examination Survey 1971–1975.

With an inclusion threshold of *T*LCO ≥30 %predicted, the number of patients eligible using GLI equations was significantly higher than using the older equations, except for those derived by Miller (McNemar's Test); GLI 104/145 (72%) patients, ECSC 96/145; (66%; p= 0.008), Crapo 73/145 (50%; p<0.001), Miller 102/145 (70%; p=0.69), NHANES-1 81/145 (56%; p<0.001). Figure 1 shows that for all individual patients, GLI *T*LCO %predicted values are consistently higher than *T*LCO %predicted values using older equations, except for those of Miller. Using GLI, eligibility status would have changed positively in 2-31 of patients (depending on reference set).

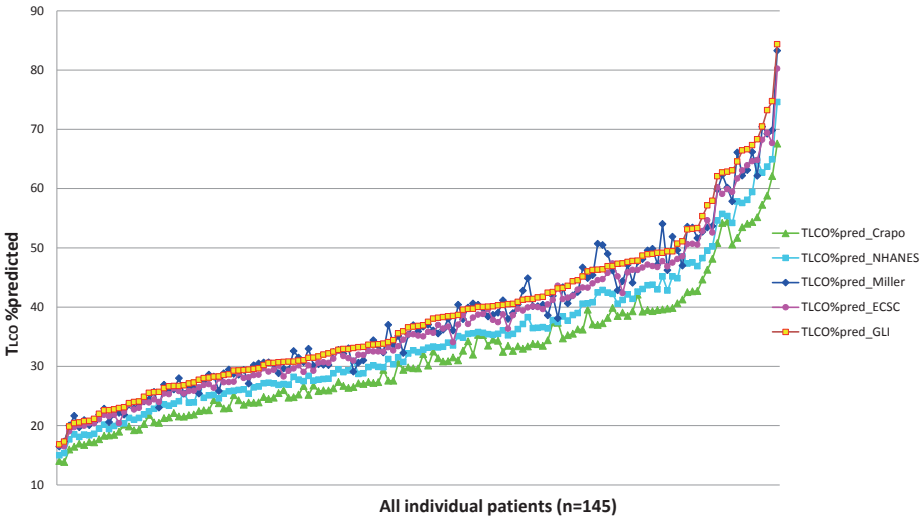

Figure 1. Transfer factor of the lung for carbon monoxide (*TLCO*) % predicted values for all individual patients
calculated by the different reference equations. ECSC: European Community for Steel and Coal; NHANES-1: National Health and Nutrition Examination Survey 1971–1975; GLI: Global Lung Function Initiative.

Our results show that switching to the new GLI *T*LCO reference equations may a have significant positive effect on trial inclusion for IPF patients. This difference in eligibility may have large implications for the individual patient on clinical trial participation. Not only physicians should be aware of this impact of the choice of reference equations, but also sponsors of clinical trials when writing the study protocol.

Systematic differences between the several predicted values have been explained from differences in sample size, population characteristics and distribution of the ages, equipment and setting, measurement techniques and applied statistical methods.[3,14] In our study the Miller *T*LCO % predicted values and number of eligible patients were closest to the GLI. This is remarkable considering that 57% of our patients were >70 years of age, outside the age range of Miller's reference population, and reference values were extrapolated. The largest shift in trial eligibility occurred when changing from Crapo to GLI. The higher Crapo predicted values may be explained by physiologic adaptations of the reference subjects due to altitude (1400 m).[12]

Our study shows that urgent adoption of the globally derived and applicable GLI reference set is needed to reduce variability in trial eligibility between laboratories. Currently GLI *TLCO* equations are only available for Caucasians, which limits their validity. Collecting data to expand the equations are ongoing. However, being derived from the largest dataset ever, measured on modern equipment and representing all-ages, this should

not prevent adoption of the GLI equations in their current form. The implementation strategy as described by Derom et al.[1] should hopefully encourage other national societies to follow this path as well, as in the end patients, healthcare providers and researchers will benefit.

Conflict of interest: M. Wapenaar, J.R. Miedema, C.J. Lammering and F.W. Mertens have nothing to disclose. M.S. Wijsenbeek reports institutional fees and grants from Boehringer Ingelheim and Hoffman la Roche, and institutional fees from Galapagos, outside the submitted work.

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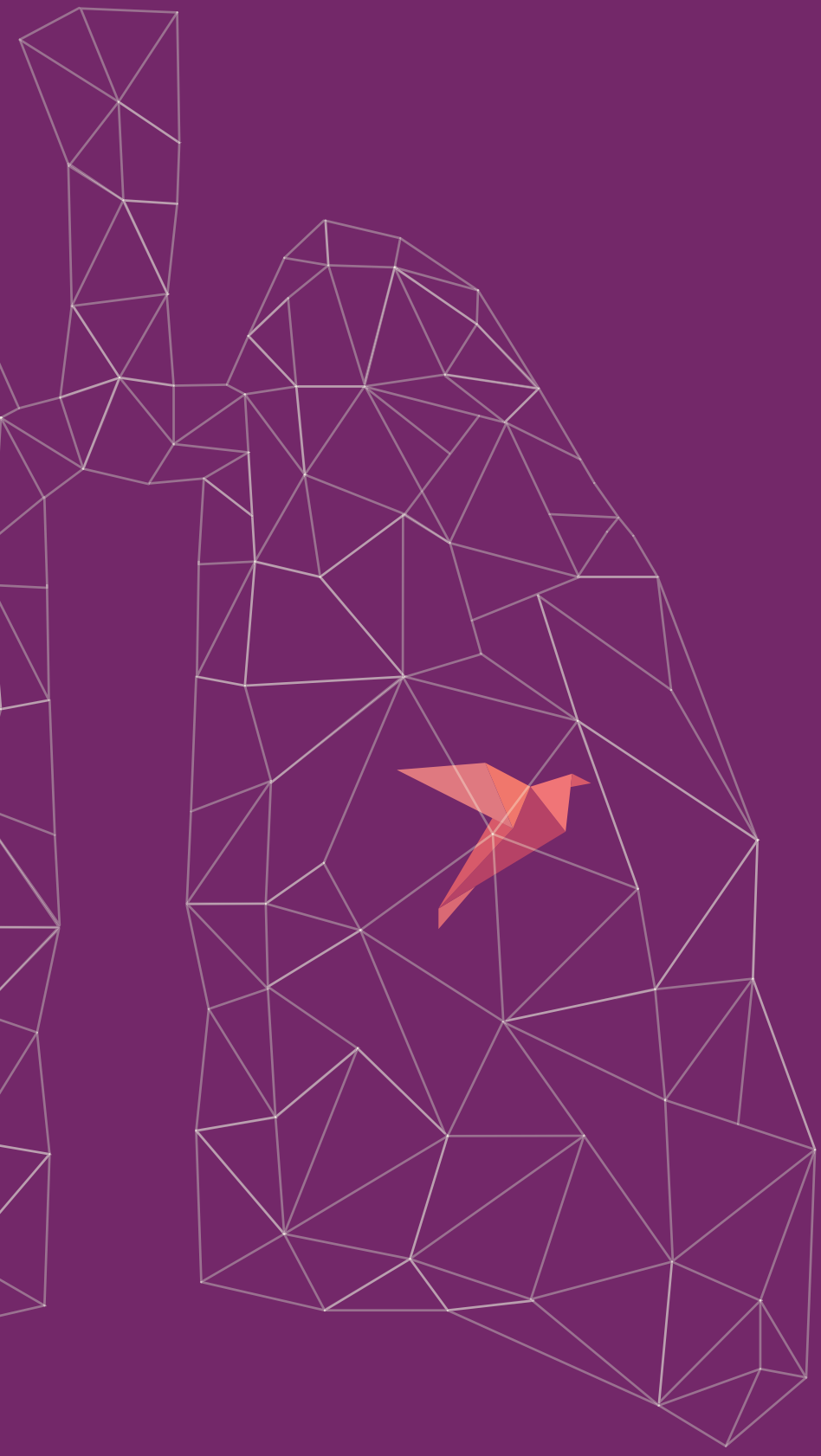

PART 3

Interventions aimed at improving quality of life for patients

“A home-based pilot study showed that individual IPF patients may benefit from a walk-bike, as it improved action radius and tended to improve QOL. No effect on exercise capacity was observed. A larger study seems not feasible due to practical barriers.”

CHAPTER 8

The Effect of the Walk-bike on Quality of Life and Exercise Capacity in Patients with Idiopathic Pulmonary Fibrosis: a Feasibility Study.

Submitted

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ABSTRACT

Purpose: Idiopathic pulmonary fibrosis (IPF) is characterized by progressive loss of pulmonary function and exercise capacity, leading to loss of quality of life and often social isolation. A new walking aid, the walk-bike, showed an improvement in exercise performance in COPD patients. Aims of this pilot study were to evaluate the feasibility of a homebased walk-bike intervention study in IPF patients and to explore the effect of the walk-bike on quality of life (QoL) and exercise capacity.

Methods: We conducted a randomized multicenter, crossover study in patients with IPF with 8 weeks of standard care and 8 weeks of walk-bike use at home. Feasibility outcomes and patients' satisfaction and experience with the walk-bike were collected. Health-related QoL (St. George's Respiratory Questionnaire - SGRQ, King's Brief Interstitial Lung Disease questionnaire - K-BILD) and 6-minute walk test (6MWT) were recorded. An additional 6MWT was performed to compare the distance covered with and without the walk-bike.

Results: Ten patients completed both periods. Potential barriers for feasibility of the study included reluctance to participate and external factors (e.g. weather and road conditions) that hampered adherence to the protocol. Patients' satisfaction and experience with the walk-bike varied greatly. After training with the walk-bike, SGRQ and K-BILD questionnaire scores demonstrated a tendency towards improvement, exercise capacity did not. A clinically important difference was found between the 6MWT with the walk-bike and the standard test; median (range) respectively 602 m (358-684) and 486 m (382-510).

Conclusions: A larger study on walk-bike training-effects in IPF patients does not seem feasible. Patient experience and satisfaction with the bike greatly varied, which seems to limit its use to a small minority of patients. The walk-bike improved action radius and showed a tendency towards improvement in QoL. No effect on exercise capacity was observed.

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive and life-threatening disease of unknown cause.[1] As the disease progresses, worsening of lung function and gas exchange impairment cause hypoxemia during physical activity, resulting in a downward spiral; dyspnea, cough and fatigue lead to a reduction of daily physical activities, exercise tolerance, muscle strength and quality of life. Problems reported by IPF patients are social isolation, increased level of dependency and immobility.[1-5]

Pharmacologic treatment options are limited.[5] There are two drugs that reduce pulmonary function decline in patients with IPF, however their effect on quality of life is not convincingly established.[6-8] In a selected, limited group of patients with IPF, lung transplantation can be an option. Non-pharmacologic treatments that could improve quality of life are increasingly investigated.[4,9-11] Pulmonary rehabilitation programs are recommended by expert opinion for the majority of IPF patients to improve QoL and exercise tolerance.[1,5,12] Cochrane reviews on physical training in patients with different interstitial lung diseases (ILD), including IPF, indicate pulmonary rehabilitation has a beneficial effect on quality of life and functional exercise capacity in IPF patients.[3,13,14] Another problem is that the long-term effects of PR are debated.[15-18] Furthermore, pulmonary rehabilitation programs are offered in outpatient clinics and specialized rehabilitation centers with a duration of usually 6 -12 weeks.[16,19-21] Due to the limited life expectancy of IPF patients and practical problems with decreased mobility and transport, patients are often hesitant to participate in these external programs. Therefore, in recent years homebased (supervised) training has become increasingly investigated.[22] An earlier study has demonstrated that a new-walking aid, the walk-bike or modern draisine, improved exercise performance in Chronic Obstructive Pulmonary Disease (COPD) patients due to the more efficient way of moving without excessive metabolic demand.[23] To our knowledge no (large) randomized controlled trials in IPF patients have been performed with homebased supervised training, nor for the walk-bike intervention. To assess whether a study using this new method for homebased training is feasible and of benefit for IPF patients, we designed a crossover pilot study. We hypothesized that use of this walk-bike in daily life extends the range and everyday mobility of IPF patients, thereby decreasing the level of dependency and social isolation and improving quality of life. If daily activities of IPF patients increase, exercise capacity might improve too. The objectives of this pilot study were (1) to evaluate the feasibility of a homebased walk-bike intervention study in IPF patients, and (2) to explore the effect of the walk-bike on quality of life and exercise capacity.

METHODS

Subjects

Patients were eligible to participate in this study if they were diagnosed with IPF according to American Thoracic Society (ATS) / European Respiratory Society (ERS) criteria, had a diffusing capacity of the lung for carbon monoxide (TLCO) ≥ 25 % predicted, a Forced Vital Capacity (FVC) ≥ 50 % predicted, a 6-minute walk distance (6MWD) ≥ 150 meters and were clinically stable without a decline in TLCO and FVC of 10% or more in the past six months.[1,5] If TLCO could not be measured because of cough or other reasons, FVC should be ≥ 50% and no history of known pulmonary hypertension should be present to include patients in the study.

Patients were excluded if they participated in an official rehabilitation program < 4 months before the start of the study, if they suffered from musculoskeletal disorders, severe cardiac diseases (an ejection fraction < 30%, daily angina, or otherwise specified by treating cardiologist), if they were unable to understand informed consent or if there were other conditions that could hamper the use of a walk-bike. Patients were recruited at the outpatient clinics of three respiratory medicine departments in the Netherlands, Denmark and Spain. The study was approved by ethic committees of all participating sites and all patients gave written informed consent to participate (MEC-2014-047, Erasmus University Medical Center). The study was registered in the Dutch Trial Register, NTR number 5334 (www.trialregister.nl).

Study design

This prospective multicenter pilot study followed a 2-period crossover design with an intervention period and a control period of each 8 weeks. The intervention was a home-based training program using a walk-bike in daily life during 8 weeks, with the aim of a minimum of 1 hour per day. Patients were asked to record the time of real use of the walk-bike in a diary. At baseline, instructions and training under supervision were given. During the control period patients received standard treatment only. The walk-bike is an ambulation aid, a form of a bicycle but without pedals (Figure 1). By sitting on the seat the load on the muscles of ambulation is reduced which results in a lower cost of transport (oxygen uptake in mL/min per meter distance).[23]

Study procedure

Prior to randomization clinical stability was assessed by the physician. Pulmonary function and exercise performance were tested by spirometry, TLCO and 6MWT. Patients were randomly allocated to start with the intervention- or control period by an independent research nurse, not involved in the study and using sealed nontransparent envelopes.

Figure 1. Walk-bike

Block randomization was used to ensure that the numbers of participants assigned to each group were equally distributed during the different seasons. After 8 weeks of intervention- or control period, patients were asked to cross over. Outcome variables were measured at baseline, after 9 weeks and at the end of the study at 18 weeks. Pulmonary function tests including FVC and TLCO were done as part of the routine medical follow up of treatment.

Feasibility outcomes

Outcomes of feasibility comprise the number of patients assessed for eligibility, the proportion of patients that were randomized, the number of patients that finished both periods of the crossover study and adherence with the intervention (1 hour use of the walk-bike per day). Throughout the study, comments and suggestions for improvement from patients and the medical team were collected to explore potential barriers of this study for future research. After the study, patients were asked about their experience and satisfaction with the use of the walk-bike. Feasibility outcomes of all patients that signed informed consent were used.

Patient-reported outcomes

The primary outcome was change in total score in health-related QoL measured with the St. George's Respiratory Questionnaire (SGRQ) after 8 weeks of standard of care and after 8 weeks of walk-bike use at home. Although designed for patients with obstructive disease, the SGRQ has been found to be a valid measure of health-related QoL in patients with restrictive disease including IP.[24,25] The SGRQ is a self-administered questionnaire with 50 items comprising the three domains symptoms, activity and impact, each scored from 0-100, with higher scores corresponding to worse health-related QoL. A change of 7 points in SGRQ total score (0-100) is known to be the minimal clinically

important difference (MID) for IPF patients.[26] Secondary outcome was change in total score of the disease-specific King's Brief Interstitial Lung disease health status questionnaire (K-BILD). The K-BILD questionnaire comprises of 15 items and has three domains; psychological, breathlessness & activities and chest symptoms.[27] The K-BILD domain and total score ranges are 0-100, with higher scores indicating better health-related QoL. The MID range in ILD for the total score is 6-10 units.[28] Other secondary outcomes are change in SGRQ and K-BILD domain scores, and in scores measured with the General Anxiety Disorder Screener (GAD-7). The GAD-7 measures the presence and severity of general anxiety disorder and contains 7 self-rated items, total score range is 0–21 with higher scores indicating more anxiety.[29]

Exercise capacity

Additional secondary outcomes were change in functional exercise capacity, determined by the 6MWD after 8 weeks of standard of care or 8 weeks of walk-bike use at home, and change in the number of steps per day as a proxy for daily physical activities, measured with a pedometer. To compare exercise performance with or without the walk-bike, patients were asked to perform an additional 6MWT using the walk-bike, after the regular 6MWT. This was done at the visit after the intervention period (in week 9 or week 18 depending on allocation). The 6MWT was administered according to ATS criteria.[30] The assessor that measured the regular 6MWT at 9 and 18 weeks was blinded for the allocation and patients were instructed not to inform the care provider. Patients were asked to wear a pedometer (Yamax Digiwalker SW-200) for a week at baseline, at the crossover moment and after the study. This small device worn on the belt detects the steps taken by vertical accelerations of the hip during gait cycles and gives an indication of the volume of physical activity.[31]

Pulmonary function tests

PFT's were performed according to ATS/ERS 2005 criteria.[32,33] FVC and TLCO were recorded and expressed as percentage of the predicted value (%pred).

Analysis

Due to the explorative nature of this pilot study, no sample size calculations were done and results are given in a descriptive way. As it concerns a small group of patients, results are described without statistical analysis.

RESULTS

Feasibility outcomes

One hundred and twenty five outpatients with IPF were assessed for eligibility for the study, 23 (18%) were interested in participating, signed informed consent, and were randomized. Twelve patients were allocated to start in the intervention group and 11 patients to the control group. Sixteen patients finished the first phase of 8 weeks of the study and after crossover, 10 patients also completed the second phase. Two patients who started in the intervention group did not crossover because they wanted to continue using the walk-bike. Other reasons for not completing the full protocol are shown in Figure 2**.**

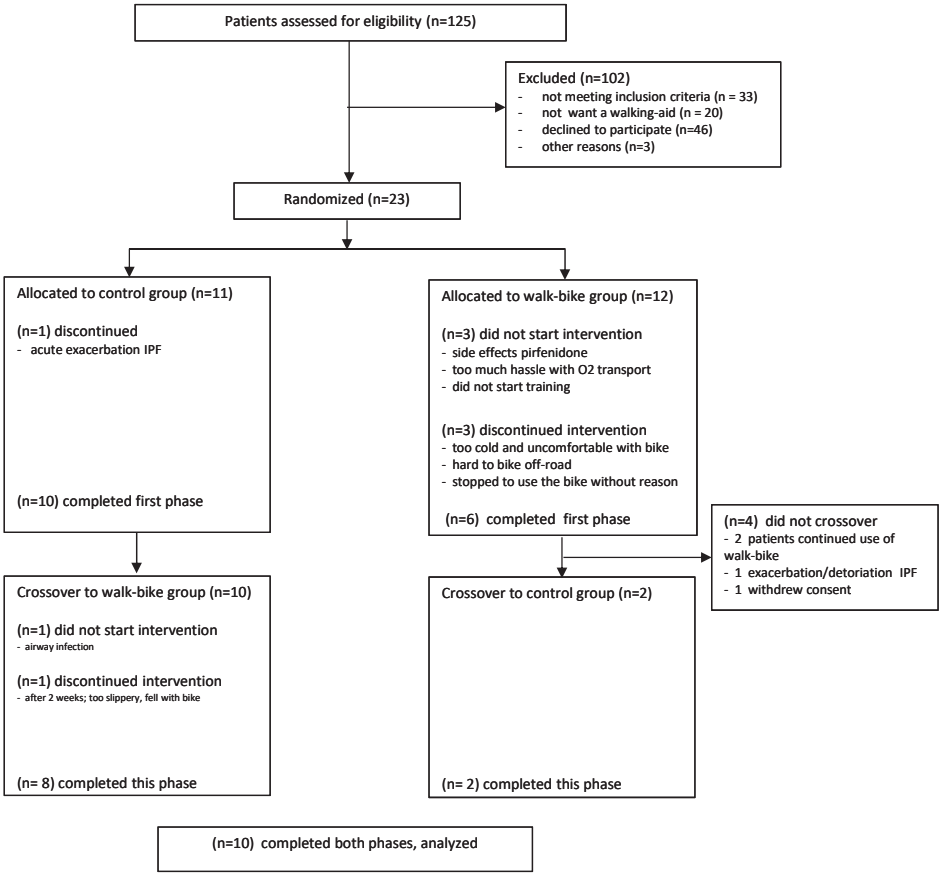

Figure 2. Study flow chart of patients screened and enrolled

Table 1. Overview of detected potential barriers for homebased use of the walk-bike for research as detected by patients and the medical team.

Potential barriers	Findings in this study	Possible solutions
Weather conditions	Patients frequently recorded not using the bike due to rain, storm, snow, slipperiness, heat and humidity.	Additionally offering a homebased indoor trainings program
Transport of oxygen device (a small bottle of oxygen can be attached with Velcro to the rear of the frame below the saddle).	One patient stopped 1 week after the start because he experienced attaching the oxygen to the bike was too much hassle. Another patient solved her problem with transportation of the oxygen bottle by transporting a smaller oxygen device in a back pack.	Ask the vendor to add a larger basket at the rear of the bike to facilitate oxygen transport or providing the option of a back pack.
Hills and unpaved roads	A patient recorded that even a minor hill makes using the walk-bike heavier than regular walking. Another patient mentioned the walk bike is most useful when the road is smooth or goes downhill and uphill, it is useful as a support object, like a walker. Another patient living in the countryside stopped using the bike because it was too heavy to use on unpaved roads.	The walk-bike seems more fit for paved roads and flat countries. The option of electrical support to switch on would be an option to overcome hills.
Compliance/ motivation	Some patients were very compliant and recorded they used the bike every day for at least 60 minutes, others were hampered by external factors or symptoms and didn't use the bike for days.	Using accelerometers and new e-health technologies may help the medical team to detect barriers in use of the walk-bike at an earlier stage enabling them to contact and coach or support the patient in finding solutions.
Fear of stigmatization	Some patients didn't want to participate as they (or their spouse) where being afraid to be stigmatized for using an assistive device.	For some patients the potential benefit of the walk-bike will not outweigh the impact of making their disease visible by using an assistive device. Similar findings have been reported for ambulatory oxygen and careful discussion may help but in the end it is the patient who decides.
Saddle pain	Some patients were bothered by saddle pain or felt the saddle was uncomfortable	Provide silicone gel saddles
Limitations to use the walk bike in public places and public transport	None of the patients mentioned these problems	Patients were provided with a card that the walk-bike is an assistive device in case they would get questions.

Ten of the 14 patients that completed the walk-bike period, recorded the actual use of the walk-bike in a diary; the median (min-max) use of the walk-bike was 5.3 (2.0- 6.9) days a week and 43.9 (11.3-60.6) minutes per actual usage day. An overview of potential barriers and solutions as reported by patients and medical staff during this study is provided in Table 1.

Patient satisfaction and experience with the walk-bike are shown in Table 2. Comments differed from very satisfied with continuation of using the walk-bike after the study, to not satisfied because using the walk-bike was too heavy or because of feelings of embarrassment.

Table 2. Comments on the walk-bike

Positive comments
Bike is really good for training; feel fit after 8 weeks of training
Although not comfortable with the bike because of shoulder pain, would like to continue using it
Able to walk further with less dyspnea
Enables me to leave the house and e.g. go to the bakery without being dependent of my spouse
Easier and nicer to walk
Able to walk further; it is more comfortable and gives possibility to rest
The walk bike has been a good means of contact with other people, it has the interest of news.
Negative comments
Too heavy in combination with oxygen; difficult to use with oxygen bottle
Difficult way of making steps
Able to walk further because of better stability but feel embarrassed when using walk bike
Uncomfortable with bike, roads are too slippery
For small hills walking with the help of the walk-bike is more difficult than without

One patient reported two fall-incidents due to wet and slippery roads, without any physical complaints, and decided to stop with the study.

Baseline characteristics (Table 3) demonstrate that patients were predominantly male with a decreased FVC, TLCO, exercise tolerance and health-related QoL. The patients who dropped out during the study showed on average worse scores in diffusing capacity, exercise measures and health status. The results of the 10 patients that followed the complete protocol are given in Table 4.

Table 3. Baseline characteristics of the study patients

	Randomized (N=23)	Completed study (N=10)	Drop outs (N=13)
Male	18 (78%)	8 (80%)	10 (77%)
Age (years)	71 (54-88)	71 (60-88)	72 (54-88)
Pulmonary function			
FVC (%pred)	69 (48-97)	69 (53-87)	72 (48-97)
TLCO (%pred)	43 (26-67)[a]	51 (26-62)	40 (26-67)[g]
Exercise measures			
6MWD (m)	443 (278-593)[a]	481 (360-540)	433 (278-593)[g]
Nadir SpO2 (%)	87 (78-96)[a]	89 (81-95)	85 (78-96)[g]
Average steps/day	3521 (478-9869)[b]	4016 (707-9636)[e]	3185 (478-9869)[h]
Health status scores			
SGRQ total [0-100][j]	50 (16-62)[c]	44 (32-52)[f]	55 (16-62)[i]
K-BILD total [0-100][k]	63 (30-83)[a]	66 (56-78)	58 (30-83)[g]
Perceived health status [1-5][l]	3 (2-4)[d]	3 (3-4)	3 (2-3)[i]
GAD-7 [0 –21][m]	2 (0-11)[a]	2 (0-8)	5 (0-11)[g]

Data are presented as absolute number (%) or median (min-max). FVC: forced vital capacity (% predicted), TLCO: diffusing capacity of the lung for carbon monoxide (%predicted), 6MWD: distance walked in a 6-minute walk test (meters), SpO_2: oxygen saturation from pulse oximetry measured during 6MWT, SGRQ: St George's Respiratory Questionnaire, K-BILD: King's Brief quality of life questionnaire for Interstitial Lung Diseases, GAD-7: Generalized Anxiety Disorder 7-item scale. a: n=22, b: n=17, c: n=19, d: n=21, e: n=7, f: n=8, g: n=12, h: n=10, i: n=11, j: SGRQ lower scores indicate better health-related QoL, k: K-BILD lower scores indicate worse health-related QoL, l: Assessed with the SGRQ, m: GAD-7 higher scores indicate more anxiety.

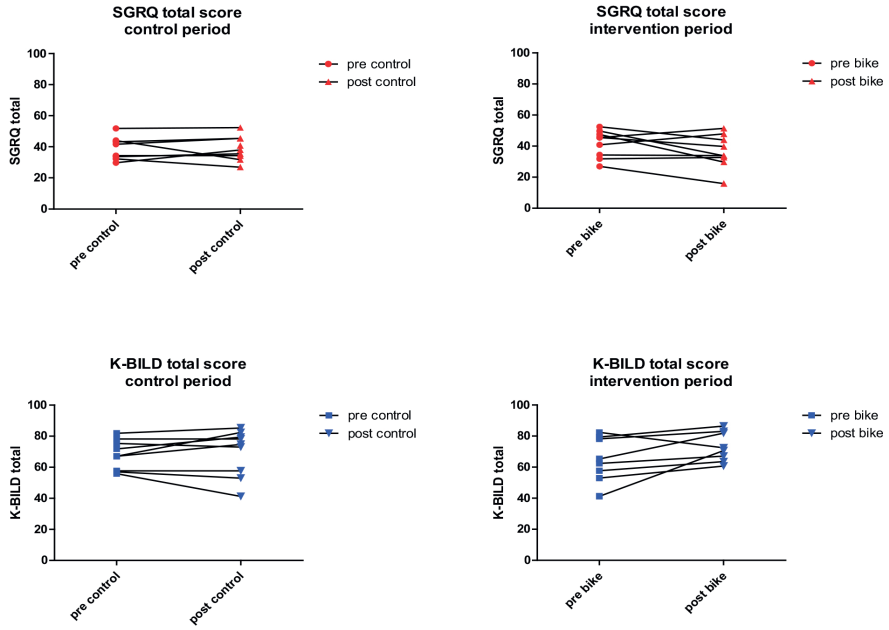

Figure 3. Individual changes in SGRQ- and K-BILD total scores during control and intervention period. A negative change in SGRQ score indicates an improvement in quality of life, a positive change in K-BILD score indicates an improvement in quality of life.

Table 4. Change in health status and exercise measures of patients that completed both phases (*N*=10)

	ΔControl period	ΔWalk-bike period
SGRQ [a]		
Total (*n* = 8)	1.2 (-12.3 - 8.3)	-7.1 (-17.8 - 5.9)
Symptoms (*n* = 9)	6.7 (-22.7 - 38.9)	-7.9 (-42.6 - 16.0)
Activity (*n* = 9)	0.0 (-18.1 - 6.3)	-5.2 (-14.2 - 1)
Impact (*n* = 8)	0.3 (-12.3 - 8.9)	-7.4 (-22.3 - 9.9)
K-BILD [b]		
Total (*n* = 8)	1.8 (-14.7 - 15.3)	6.5 (-10.0 - 29.4)
Chest (*n* = 8)	0.0 (-25.0 - 25.0)	12.5 (0.0 - 37.5)
Breathlessness & activity (*n* = 9)	0.0 (-29.8 - 14.9)	0.0 (-21.8 - 46.8)
Psychological (*n* = 8)	0.0 (-11.1 - 23.5)	6.2 (-16.1 - 18.5)
Other		
GAD-7 (*n* = 9)	0 (-2 - 6)	0 (-2 - 0)
Perceived health status (*n* = 9) [c]	0 (-2 - 0)	0 (-2 - 2)
Exercise measures		
6MWD (m) (*n*=7)	-4 (-25 - 28)	-3 (-34 - 23)
Nadir SpO2 (%) (*n* =7)	-1 (-3 - 6)	-3 (-7 - 2)
Average steps/day (*n* =6)	132 (-903 - 3056)	-461 (-4335 - 1063)

Data are presented as median (min-max) [n]; FVC: Forced vital capacity (%predicted), TLCO: transfer capacity of the lung for carbon monoxide (%predicted), 6MWD: distance walked during 6-minute walk test, SpO2: oxygen saturation from pulse oximetry, SGRQ: St George's Respiratory Questionnaire (MID for total score is 7 points) , K-BILD: King's Brief quality of life questionnaire for Interstitial Lung Diseases (MID range for total score is 6-10 points), GAD-7: Generalized Anxiety Disorder 7-item scale. a: A negative change in SGRQ score indicates an improvement in health-related QoL, b: A positive change in K-BILD score indicates an improvement in health-related QoL, c: Assessed with the SGRQ.

SGRQ- and K-BILD total score, as well as the domain scores, tended to improve after training with the bike (Figure 3), with the most striking improvement in SGRQ symptoms- and K-BILD chest scores.

No change after training was observed in exercise capacity measured with the 6MWD. Training with the walk-bike did not change the anxiety score or perceived health status (Table 4).

A meaningful difference in distance covered was found between the 6MWT performed with the walk-bike and the unaided 6MWT with a median (min-max) 6MWD of 602 meters (358-684) vs. 486 meters (382-510); (Figure 4). The lowest oxygen saturation during the 6MWT with the walk-bike and unaided did not differ with a nadir SpO2 of 86% (80-91) vs. 87% (78-90).

During the study, the lung volume remained stable with a median (min-max) FVC at baseline of 69 %pred (53-87) vs. 70 %pred (57-86) in week 18. Gas exchange parameters

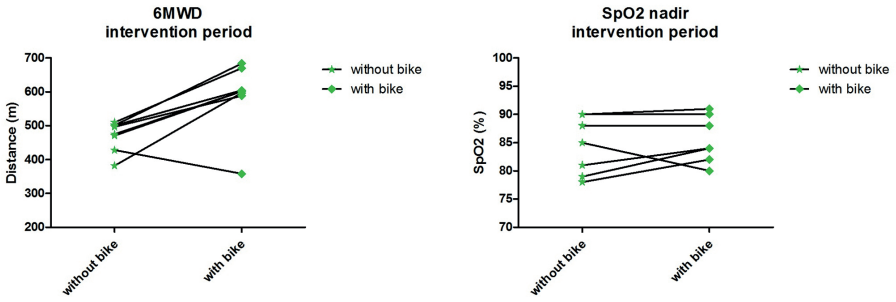

Figure 4. Individual differences in 6MWD and lowest SpO2 during 6MWT with and without walk-bike.

showed a tendency toward decline with a TLCO at baseline of 50 %pred (26-62) vs. 45 %pred (25-59) in week 18.

We also analyzed the data including the four patients that did not cross over; no changes in results were found.

DISCUSSION

In this crossover pilot study, we explored the feasibility of a homebased walk-bike intervention study in IPF patients, and evaluated its effects on quality of life and exercise capacity.

The feasibility outcomes demonstrate that a homebased walk-bike intervention study in its current design is difficult to accomplish. Potential barriers for feasibility of the study include reluctance to participate in the study, but also external factors such as weather and road conditions that may hampered adherence to the protocol. Patients satisfaction with the bike greatly varied. Despite the moderate usage intensity of the walk-bike, we found a tendency towards improvement in quality of life after the 8-week homebased training program with the walk-bike. Functional exercise capacity did not change. Mobility increased with an average of 116 meters in distance covered when using the walk-bike during the 6MWT, compared to an unaided regular 6MWT. Use of the walk-bike proved to be safe.

A larger future RCT to detect clear walk-bike training-effects on quality of life and exercise capacity does not seem feasible unless potential barriers detected in our study

are being solved. We chose a crossover design as it holds the advantage over a parallel study that the patient is its own control, thereby reducing the influence of confounding variables and sample size. However, this crossover design warrants a longer duration of study for the individual patient (16-18 weeks). Despite the block randomization to account for seasonal changes, weather changes during the study period turned out to affect the use of the walk-bike. A study incorporating both walk-bike use as well as a homebased indoor training alternative, maybe be a better design for a homebased training program. As table 1 shows, another potential barrier is the collection of correct information of the intensity of training. In our pilot study patients recorded the time of walk-bike use in a diary. However, this patient-recorded time may have included time spent waiting and resting on the bike without movement. Accelerometers are devices that if worn by the patient, can record intensity duration and frequency of activities and makes assessments of the potential effects of the walk-bike more accurate.

Patient satisfaction with the walk-bike varied greatly from positive to negative. Patients positively evaluated the walk-bike because it enabled them to walk further with less dyspnea, or made it possible to leave the house again. The feeling of an increased level of independence and social participation are both important aspects of IPF patients' quality of life.[9,34] Negative comments related to being afraid to be stigmatized when using the walk-bike. Swigris et al. investigated how IPF affects quality of life from patients' perspective and noted many patients feel the need to try to hide the fact that they have a chronic illness when they are in public.[34] This aspect, together with unfamiliarity with this new walking-aid, may also have played a role in the difficult inclusion of patients in our study. Other patients noted that the walk-bike was too heavy when used outdoors e.g. on hilly roads. It might well be that when the road includes obstacles or hills, use of the walk-bike is more complicated, which was also observed in another study.[35]

In this pilot study, the use of the walk-bike led to improvement of the SGRQ total equal to the MID of 7 points, with a median difference in change of 8.3 points between the intervention period and control period. This improvement in SGRQ scores is comparable with the effects reported in a recently published systematic review on pulmonary rehabilitation in IPF.[36] Meta-analysis on the results of three studies demonstrated a weighted mean difference SGRQ total score of -8.34 (95% CI, -11.30 - -5.39; n = 82) between intervention - and control groups, favoring pulmonary rehabilitation. In our study, we also assessed quality of life with the ILD specific K-BILD questionnaire and found similar results in magnitude and direction of changes compared to the SGRQ. The K-BILD holds advantages for clinical use, being much shorter and disease specific.

We found no effect in exercise capacity (6MWD). In studies that assessed the effect of exercise training or pulmonary rehabilitation programs in patients with IPF, 6MWD usually improved. [14] The previous mentioned review of Gomes-Neto et al.[36] showed a weighted mean difference in 6MWD of 44 meters (95% CI, 5.3-82.8; n = 113) favoring pulmonary rehabilitation. Most pulmonary rehabilitation- or physical training programs contain supervised exercise protocols with a combination of endurance and resistance training.[37] In our walk-bike intervention, the primary aim was to increase quality of life. Participants were encouraged to use the walk-bike for at least one hour daily, and it was up to the discretion of the patients whether to use it continuously or in intervals. Practical factors such as weather conditions and day to day changes in wellbeing turned out to limit participants from using the walk-bike stringently and may have minimized the effect on exercise capacity. In patients with severe COPD it was shown that interval training at low burden could still have a positive effect on exercise capacity.[38] We hypothesized that by increasing daily activities, patients would also exercise more at low burden which may eventually result in improving or maintaining exercise capacity and improving Qol.

The advantage of a home-based physical exercise program is increasingly recognized. It remains to be evaluated if a more structured and supervised use of the walk-bike could play a role in such programs. We found a meaningful improvement of 116 meters in distance covered during a 6MWT with use of the walk-bike, compared to an unaided test. This is in line with the improvement found by Vaes et al. who assessed the effects of the walk-bike on exercise performance in COPD patients.[23] Improvement of mobility by using the walk-bike could potentially lead to a higher level of independence and social participation. These factors may have been the main contributing factors to the tendency toward improvement in quality of life in our study, even though exercise capacity did not improve.

One of the limitations of our study is the small sample size. We aimed to include 22 patients, enrolled 23 patients but after randomization, a part of the patients did not start or discontinued. Only 10 patients completed both phases which underlines the difficulties encountered when trying to set up an interventional study for such a vulnerable patient group. If patients still had a reasonably well-preserved exercise tolerance, they did not wish to use a walk-bike. On the other side, when patients were more impaired and wished to use the walk-bike, risk of dropout increased, leaving a small subgroup that potentially benefits from this intervention. A potential limitation of the study design could be a carry-over effect. However, we believe this can be neglected as 8 patients were allocated to the control period in the first phase and trained with the walk-bike in the second phase, only 2 patient participated in the reverse order. Moreover, with gas exchange parameters that tended to decline across the study, a potential order ef-

fect might have led to underestimation of the effect of the walk-bike. Furthermore, 2 patients that started with the walk-bike decided to continue with the walk-bike instead of crossing over to the control arm.

In conclusion, this pilot study showed that a larger RCT may not be feasible unless most of the potential barriers are being solved. Despite the small group studied we found that the use of a walk-bike led to a meaningful improvement in quality of life for patients with IPF after an 8-weeks homebased training program. Use of the walk-bike also increased mobility for patients but did not result in an improvement in exercise capacity. Patient satisfaction varied greatly and the use of the walk-bike seems only beneficial for a small selected group of patients with IPF.

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“An exclusively outpatient multidisciplinary pulmonary rehabilitation program improves exercise capacity, muscle strength and quality of life of pulmonary hypertension patients.”

CHAPTER 9

The Effects of a 10-wk Outpatient Pulmonary Rehabilitation Program on Exercise Performance, Muscle Strength, Soluble Biomarkers, and Quality of Life in Patients with Pulmonary Hypertension

J Cardiopulm Rehabil Prev. 2019 (in press)

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ABSTRACT

Purpose

Pulmonary arterial hypertension (PAH) is characterized by right ventricular failure, leading to exertional dyspnea, skeletal muscle weakness, and poor quality of life (QOL). Apart from treatment with PAH-specifi c drugs, guidelines recommend pulmonary rehabilitation (PR). Clinical PR programs have shown improvement in functional capacity and QOL. However, little is known about the effectiveness of an outpatient PR program. The aim of our study was to assess effectiveness of a multidisciplinary outpatient PR program.

Methods

Patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH), who were in a stable condition on optimized drug therapy, followed a 10-wk outpatient program in a rehabilitation center. The PR program was designed to improve exercise capacity and health status by means of low load cycling, walking, and muscle training twice a week combined with psychological counseling. QOL was measured by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire.

Results

Twenty-one patients (13 women) with PAH (n = 16) or CTEPH (n = 5) completed the study. All patients were in New York Heart Association (NYHA) functional class III, and their mean age was 45 ±16 yr. After PR, the mean cycling endurance time increased by 4.4 min ($P < .001$), 6-min walk distance by 12.2 m ($P < .05$), and maximum inspiratory pressure by 5.8 cm H_2O ($P = .01$). Skeletal muscle function increased significantly. The CAMPHOR questionnaire demonstrated significant decrease in symptoms and improvement in QOL. Soluble biomarkers did not show any change before and after PR.

Conclusions

Outpatient PR could be an effective instrument to improve exercise capacity and health status in patients with PAH or CTEPH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and incurable condition of the pulmonary vasculature, characterized by increased pulmonary vascular resistance and elevated pulmonary arterial pressure leading to progressive right ventricular (RV) failure. Despite improvement in specific medical treatment of PAH over the last years, patients with PAH still suffer from significant dyspnea, fatigue and skeletal muscle weakness, resulting in exercise limitation/intolerance and poor quality of life (QOL).[1] Exercise intolerance is a key feature in PAH for which the underlying hemodynamic impairment is primarily responsible.[2] Several studies however demonstrated that beside hemodynamic impairment and ventilatory - perfusion mismatches, respiratory and skeletal muscle dysfunction plays an important role in exercise limitation in PAH patients[3-8] and therefore is an important determinant for exercise limitation.[9-12]

Since muscle impairment limits PAH patients in their daily life activities it has a strong negative influence on QOL.[4,13,14] Reduction in muscle dysfunction and exercise intolerance are therefore recognized to be important goals in the treatment of PAH patients. Exercise programs have been shown to improve muscle function by increasing type 1 fiber surfaces.[6,15] Moreover, previous studies have shown both a shift from type IIx to type IIa fibers and a total increase in type II fibers. Furthermore, exercise programs have been demonstrated to improve muscle capillarization,[6,15] muscle strength and exercise capacity in PAH patients.[5,16,17] This not only results in a higher physical activity level but also results in improvement in health-related QoL measured by the 36- item Short Form Survey (SF-36).[18-20]

Historically, patients with PAH were recommended to restrain from physical activity, including pulmonary rehabilitation (PR) because of poor prognosis and risk of sudden cardiac death. In 2006, Mereles et al.[18] were the first to demonstrate in a small randomized controlled trial that exercise training is safe and has beneficial effects on functional capacity and QOL.

Little is known so far about the effect of exercise training on RV function. Most studies did not show a significant effect, while some showed a minor decrease in systolic RV pressure measured by echocardiography.[18,20-22] The underlying mechanism has not yet been elucidated, although in a rat model it was shown that exercise training may lead to less pronounced pulmonary vascular remodeling, and only high intensive training lowered RV systolic pressure and RV hypertrophy.[23,24] Biomarkers such as N-terminal pro B-type natriuretic peptide (NT-pro BNP) and high sensitive troponin-T (HsTnT), are recognized as markers of RV function and are negatively associated with outcomes in

patients with Pulmonary Hypertension (PH).[1] We therefore investigated these markers in our patient group before and after PR program as a marker of RV function.

In recent years, evidence for the beneficial effects of PR is increasing.[25-27] The European Respiratory Society (ERS) and the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PH recommend supervised rehabilitation programs in expert centers for PAH patients in stable condition on optimized PH specific drug therapy.[1] However, most programs so far have been carried out in a hospital setting or were at least started in a hospital setting. Unfortunately, programs in a hospital setting are not always feasible for patients.

We know that PAH as a disease that has great impact on the QOL of these patients.[28] This has also been shown by a QOL questionnaire specifically designed for patients with PAH, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[29,30] We therefore decided to offer a PR program with a multidisciplinary approach including: educational sessions, psychological counseling, advice by an occupational therapist, dietary advice, and group sessions with fellow patients.

Since knowledge about the safety and effectiveness of a PR program in an exclusively outpatient setting is still lacking, our goal was to develop an achievable multidisciplinary outpatient PR program.

We considered withholding PAH patients from a PR program at this stage not to be ethical. This study has therefore specifically been designed as a prospective cohort study.

The aim of our study was to assess the effectiveness of such an outpatient PR program on exercise capacity, muscle strength, soluble biomarkers and QOL.

METHODS

Study design

This prospective cohort study was conducted from January 2016 until December 2017 as a collaboration between the Erasmus University Medical Centre (Rotterdam, The Netherlands) and the Revant Rehabilitation Centre (Breda, the Netherlands). Patients underwent an evaluation at the rehabilitation center before entering the program. They followed an outpatient PR program for 10 wk consisting of 2 sessions per week. Immediately after the PR program an assessment was performed for the effectiveness of the program.

Study procedure

All patients were diagnosed according to the ERS/ESC guidelines.[1] Patients in World Health Organization (WHO) groups I and IV were eligible for the study. Patients had to be in a clinically stable condition under optimized PH drug therapy for ≥3 mo before entering the study (see Supplemental Digital Content 1, available at: http://links.lww.com/JCRP/A119). No changes in PH specific medication were made during the PR program. Patients were excluded if they had participated in a rehabilitation program previously, if they were not able to give informed consent, or if they were younger than 18 y. This protocol was approved by the medical ethical committee, Erasmus MC Rotterdam, the Netherlands (protocol MEC-2011-392). All participating patients signed an informed consent form before commencing the program.

Outcome measures

Patients were evaluated at baseline and week 10, immediately after the PR program. Primary outcome measures were changes at week 10 compared to baseline in exercise capacity, determined by cycling endurance time (CET), and change in QOL as measured by the CAMPHOR.

The PR program was designed to focus on both muscle strength and endurance for cycling and walking. Therefore, we chose the measured CET (min) as primary endpoint to investigate the effect of PR on endurance and exercise capacity. The CET was measured by a sub-maximal constant work rate exercise test at a constant load 75% of the baseline peak workload.

The CAMPHOR is a self-administered PH-specific health status questionnaire with 3 scales to assess symptoms, activity and quality of life. It also contains three symptom-subscales for energy, breathlessness and mood. Scores for symptoms and QOL range from 0-25, higher scores indicating worse QOL. Activity scores range from 0-30, higher scores indicating more physical limitations. Prior research validated the CAMPHOR questionnaire and the correlation between 6MWD and NYHA classification.[30] The CAMPHOR questionnaire was taken at baseline and after 10 weeks of PR.

Secondary outcome measures were changes at week 10 compared with baseline in 6MWD, respiratory muscle strength maximal inspiratory mouth pressure and skeletal muscle strength (quadriceps force and biceps force). The 6-min walking test (6MWT) was carried out according the ERS/American Thoracic Society (ATS) technical standards.[31] The maximal inspiratory mouth pressure was measured during a forced inspiratory effort from residual volume, using a respiratory pressure meter (MicroRPM).[32] Quadriceps

force and biceps force were assessed using a handheld dynamometer (MicroFET2) during maximal isometric knee extension and elbow flexion, respectively.[33]

The maximal peak cycling workload was measured during a maximal incremental symptom-limited cardiopulmonary exercise test (CPX) carried out in semi-supine position. The CPX was performed according to ATS guidelines,[34] with 3 min of rest, 3 min of unloaded cycling, followed by a progressive increase of the workload (5-25 W/minute). Ventilation oxygen-uptake and carbon dioxide output were measured breath-by-breath using a Jaeger CPX metabolic cart. Ventilatory efficiency was derived from the measured ventilation and carbon dioxide output).

Pulmonary rehabilitation program

The 10-wk PR program with 2 group training sessions/wk was especially developed for PH patients. The program included program endurance training (walking and cycling), lower- and upper-limb strength training, individualized psychological counseling, dietary advice, advice by an occupational therapist, educational group sessions, and interaction sessions with fellow patients. Once a week, the group would go out- doors during a physical training session to train activities in a real-life setting, for example, going to a supermarket or walking. The duration of the different activities of both weekly training sessions is shown in Supplemental Digital Content 2 (available at: http://links.lww.com/JCRP/A120). During educational sessions, information was provided by various members of the multidisciplinary team on pathophysiological changes in PH, the importance of dietary advice on the intake of proteins and vitamins, acceptance and coping of the disease, and how to manage energy distribution (breathing techniques etc). Specific PH questions from the patients were collected and answered by the PH special- ized pulmonologist and PH specialized nurse.

To individualize the training program and determine the training intensity at the start, patients performed exercise tolerance tests during the 2 to 3 d of baseline assessments. A symptom-limited maximal incremental CPX was performed to assess the maximal workload (Wmax) and two 6MWTs to evaluate distance walked and speed.

The training program contained the following components: bicycle *occupational training* by a stepwise schedule. Steps 1 and 2 started with exercise-rest interval training at 40% of the maximal workload achieved during the incremental CPX at baseline (Wmax). Steps 3 to 10 comprised continuous cycling for 15 to 20 min at 40% to 80% of Wmax. Training intensity progressed to the next step if perceived exertion during exercise remained <5 on the Borg dyspnea scale, if fatigue did not last >24 hr after the previous training session, and if existing physical complaints did not increase.

Walking training was performed on a treadmill ac- cording to a protocol with the same stepwise approach as mentioned earlier. Steps 1 to 3 comprised interval training at 60% to 75% of the speed achieved during the 6MWT at baseline. Steps 4 to 10 comprised continuous walking during 10 to15 min at 60%-75% to 75%-100% of the baseline 6MWT-speed.

Resistance training consisted of training leg-, arm and abdominal muscles on weight training equipment (Technogym). During the baseline assessment, the1 repetition maximum (1RM) training weight that could correctly be moved with appropriate breathing was determined for each exercise. During subsequent sessions, the training was intensified by gradually increasing repetitions of movements and weight/load to improve muscle strength and endurance respectively, according to ATS/ERS statement on PR.[25]

Once weekly the training sessions included a 60-min outdoor group activity, such as walking or cycling. Physiotherapists supervised all training sessions and, if needed, educated the patients in perceiving their physical limits and optimal breathing technique. Symptoms, heart rate and oxygen saturation to exercise, were closely monitored following specific PH rehabilitation guidelines.[1,25]

Blood samples were collected on the first and last days of the PR program. Biomarker assessment was performed for C-reactive protein, cystatin C, hemoglobin, red cell distribution width, NT-pro BNP, HsTnT, iron, and uric acid. Biomarkers were measured in peripheral blood samples within <1 hr after venous puncture at the clinical chemistry department at the Erasmus MC (Rotterdam, the Netherlands).

Statistics

Values are reported as mean (standard deviation) unless otherwise indicated. Changes in exercise capacity, muscle strength and QOL from baseline to 10 weeks were assessed using paired t-test or Wilcoxon signed rank test. P-values <.05 were considered statistically significant. All statistical analyses were performed using Prism (GraphPad Software, La Jolla, CA, USA) or SPSS version 24.

RESULTS

In this study, 21 patients were included with either PAH (n = 16) or inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (n = 5). The demographics of the study group, which consisted of 8 men and 13 women, are provided in Table 1. All study

Table 1. Demographic and Patient Characteristics[a]

Characteristic	Patients with pulmonary hypertension (*n* = 21)
Gender, female	13 (62)
Age, yr	45.1 ± 15.5
Height, cm	166.7 ± 9.4
Weight, kg	79.9 ± 23
BMI, kg/m^2	28.5 ± 7.1
WHO functional class III	21 (100)
Cause of pulmonary hypertension	
CTEPH	5 (24)
PAH	16 (76)
IPAH	7 (33)
CHD	5 (24)
SLE/SSc	3 (14)
PVOD	1 (5)
PH-specific drugs	
PDE-5 inhibitor	18 (86)
ERA	19 (90)
Prostacyclins	4 (19)
Selexipag	4 (19)
Drug combination therapy	
Monotherapy	3 (14)
Dual therapy	10 (48)
Triple therapy	7 (33)
Echocardiography (<6 mo prior to PR)	
RV pressure, mm Hg	55.8 ± 22.9
RA pressure, mm Hg	5.4 ± 3.3
RVSP, mm Hg	61.2 ± 23.4
6MWT, m	465 ± 98
6MWT, % predicted	84 (73, 79)
6MWT Borg fatigue/dyspnea scores (end of test)	4.4 ± 2.3/ 5.4 ± 2.8
CPX	
Peak workload, W	70.8 ± 37.9
Peak V'O_2, % of predicted	55.3 ± 18.3
Peak V'O_2, mL/kg/min	13.7 ± 3.4
RER	1.13 ± 0.13
V'E,max, L/min	50.2 ± 16.1
HRmax, % of predicted	73.1 ± 12.6
Peak V'E/V'CO2	43.1 ± 10.8

Abbreviations: BMI, body mass index; CHD, congenital heart disease; CPX, cardiopulmonary exercise test; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PDE-5, phosphodiesterase-5 inhibitor; RA, right atrial; RER, respiratory exchange ratio; RV, right ventricular; RVSP, right ventricular systolic pressure; 6MWT, 6-min walk test; SLE/SSc, systemic lupus erythematosus or systemic sclerosis–associated PH patient; V'CO2, carbon dioxide output; V'E , ventilation; V'O_2, oxygen uptake; WHO, World Health Organization.

[a]Data are reported as mean ± standard deviation, median (interquartile range), or n (%).

subjects tolerated the exercise testing and training well. No adverse events, defined as an increase in symptoms, progression of PH, or need for hospital admission, took place during the program.There was no withdrawal or loss to follow-up of patients during the PR program.

Mean CET increased significantly by 4.4 min (+92%) after 10 wk of PR (Figure 1, Table 2).

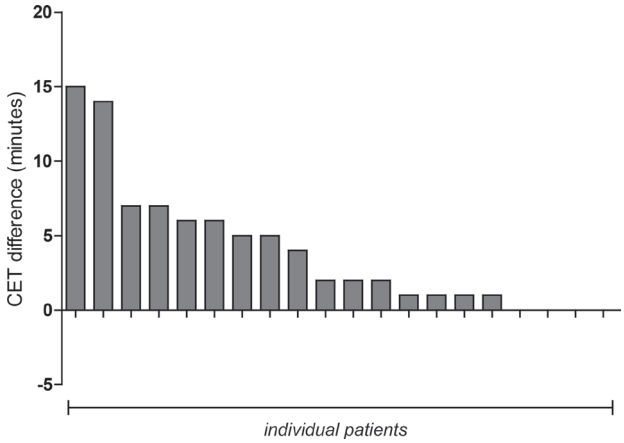

Figure 1. Change in CET for individual patients at baseline and after a 10-wk outpatient pulmonary rehabilitation program. CET indicates cycling endurance time.

Comparing results of the CAMPHOR questionnaire before and after PR, our study group showed an improvement in scores for symptoms and QOL (Figure 2).

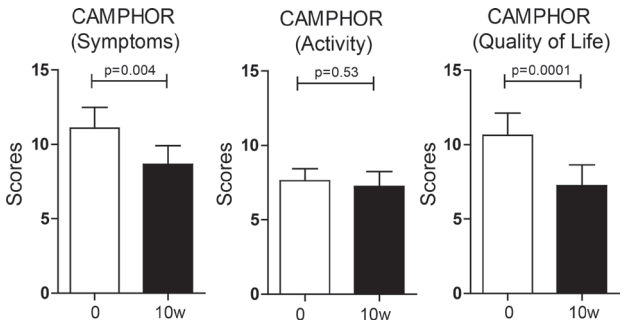

Figure 2. Health-related quality-of-life scores (CAMPHOR) at baseline (white bars) and after a 10-wk outpatient pulmonary rehabilitation program (black bars). Values are mean ± standard error of mean. CAMPHOR indicates Cambridge Pulmonary Hypertension Outcome Review.

Table 2. Test results at baseline and after a 10-wk outpatient pulmonary rehabilitation program[a]

Characteristic	Baseline (N=21)	Post-rehabilitation Therapy (N = 21)	*P* Value
CET, min	4.8 ± 2.1	9.2 ± 5.5	<.001
6MWT, m	465.2 ± 97	477.4 ± 92	.01
6MWT Borg fatigue score	4.4 ± 2.3	4.8 ± 2.0	.38
6MWT Borg dyspnea score	5.4 ± 2.8	5.3 ± 2.1	.89
MIP, cm H_2O	97.6 ± 17.5	103.40 ± 20.1	.01
MIP, % of predicted	102.95 ± 17.9	109.45 ± 22.3	.01
Soluble biomarkers			
Hemoglobin, mmol/L	8.1 ± 1.3	7.9 ± 1.3	.06
RDW, %	15.2 ± 2.9	14.9 ± 2.2	.36
Uric acid, mmol/L	0.3 ± 0.1	0.3 ± 0.1	.78
Iron, micromol/L	15.2 ± 2.8	14.9 ± 2.2	.36
Cystatin C, mg/L	1.2 ± 0.5	1.2 ± 0.3	.98
CRP, mg/L	6.1 ± 7.2	5.2 ± 6.7	.43
Hs-TnT, ng/L	11.2 ± 9.5	12.1 ± 11.0	.46
NT-pro BNP, pmol/L	86.8 ± 173.8	88.7 ± 155.4	.87

Abbreviations: CET, cycling endurance time; CRP, C-reactive protein; Hs-TnT, high sensitive troponin-T; MIP, maximal inspiratory pressure; NT-pro BNP, N-terminal pro B-type natriuretic peptide; RDW, red cell distribution width; 6MWT, 6-min walk test.

[a]Data are given as mean ± standard deviation. 6MWT Borg score values were end-of-test scores.

Secondary endpoints

After 10 wk of PR, the 6MWD increased by 3% (12.2 ±20.4 m; Table 2). After PR therapy, mean muscle function of the dominant quadriceps side increased by 78 N (+ 23%). In the nondominant quadriceps, mean muscle function increased by 62 N (+ 18%) after PR therapy (Figure 3A). Similarly, biceps dominant muscle function increased by 11 N (+ 6%) after PR therapy. In the nondominant biceps, muscle function increased by 16 N (+ 9%) after PR therapy (Figure 3B). Changes in the percentage of predicted values of the muscle function tests are shown in Figure 3. After10 wk of PR, maximal inspiratory mouth pressure increased significantly compared with baseline (Table 2).

Soluble biomarker levels were measured in all study subjects at baseline and after the PR program. However, no significant changes were seen in the soluble biomarker profiles (Table 2).

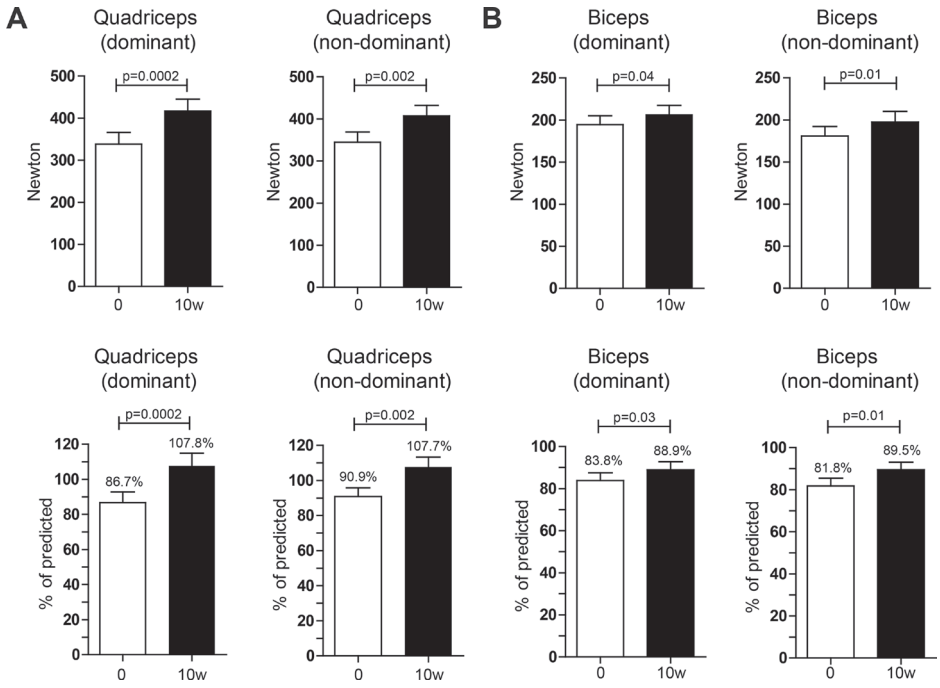

Figure 3. Skeletal muscle function of quadriceps (A) and biceps (B) (dominant and nondominant) at baseline (white bars) and after a 10-wk outpatient pulmonary rehabilitation program (black bars). Values are shown as mean percentage of predicted ± standard error of mean.

DISCUSSION

In this study we demonstrated that our multidisciplinary outpatient PR program is safe for PH patients, since no adverse events occurred during the 10-wk training period. Moreover, there was a positive effect on primary outcome parameters, including exercise capacity and endurance measured by the CET, as well as QOL in 2 out of 3 scales measured by the CAMPHOR questionnaire. In addition, all secondary outcome measures improved, including 6MWD, respiratory muscle strength and skeletal muscle strength.

While several studies have shown effectiveness of PR in an inpatient setting,[18,19,35] our study also shows beneficial effects for PR in an exclusively outpatient setting. The most beneficial effect was found in functional endurance measured by bicycle endurance (increase in the CET of 288 seconds). This result can be considered as a clinical meaningful effect since in a study by Laviolette et al.[36] in patients with chronic obstructive pulmonary disease (COPD), a difference of 100 to 200 sec in the CET was regarded as a clinical significant result. A significant, however small increase in the 6MWD was demonstrated as well. This relatively limited effect compared with the larger effect shown in

other rehabilitation studies,[18,22] could be due to a "ceiling" effect in the 6MWT as shown by Frost et a.l[37] The mean 6MWD at baseline in our cohort was 465 m. Since all other outcome parameters (CET, skeletal muscle function, QOL) changed significantly with a larger improvement and considering the findings by Frost et al., we assume that a ceiling effect in the 6MWT is a more logical explanation of our data than different exercise volumes.

Since assessment of daily activity may be more clinically meaningful to a patient than the 6MWD,[38] accelerometry may be an even better indicator of physical activity in daily life.[39] Therefore, accelerometry could be considered for all PR programs as an instrument for quantifying physical activity.

Consistent with other PR programs, [19,21,35] we observed no changes in soluble biomarkers levels before and after the PR program. A small decrease in RV systolic pressure has been seen in just a few, but not all studies. More studies investigating the effects of exercise training on pulmonary vascular remodeling, RV function and RV remodeling are needed, as well as studies assessing possible underlying mechanisms.

QOL, as measured by the CAMPHOR questionnaire, also improved significantly in our study group for the categories "symptoms" and "quality of life". The "activity" category, however, did not show a significant change. Individual patient evaluations on the contrary showed an increased capacity for activity. This observed difference by the CAMPHOR questionnaire might be due to a lack of discriminative power in a relatively small patient group. In a PR study by Chan and colleagues,[40] the "functioning" category from the CAMPHOR questionnaire did not show a significant improvement either. This study group however, was even smaller .

At the end of this PR program, all patients received a personalized training program to continue physical training under supervision of a first line physiotherapist to enhance the duration of the beneficial effect. Future studies are needed to evaluate the duration and clinical implications of our PR program.

Our study however also has several limitations. First, the study group consisted of PAH patients WHO class 1 with different underlying causes and WHO class 4, CTEPH patients. Analysis of the data of solely the PAH/WHO group I showed similar results. The study unfortunately lacks power to draw conclusions for specific PAH sub-groups. Second, only NYHA class III patients were included, which was not our initial intention. However, NYHA class III patients are undoubtedly clinically impaired in their functioning in daily life, more so than NYHA class I and II patients. They might therefore be more motivated

to participate in an extensive PR program. Moreover, NYHA class III patients are still able to participate in an intensive outpatient PR program, which might not be possible in the case of NYHA class IV patients. This possible explanation was also shown by Hayton et al.[41] in a study where COPD patients showed decreased PR attendance when either their disease was too mild or the COPD too severe to benefit from PR.

Finally, in a paper by Spruit and colleagues,[25] training 3 times/wk was regarded to be even more effective. However, our aim was to maximize training efficiency and to minimize the impact of the PR program on daily life activities of the participating PH patients.

CONCLUSION

This study demonstrates that a 10-wk multidisciplinary PR program has considerable beneficial effects on functional capacity, functional endurance, skeletal muscle function and health-related QOL. While many studies have shown effectiveness for inpatient rehabilitation programs for PH patients, our study demonstrated that an exclusively outpatient PR programme for PH patients is effective and safe. Long-term durability of these improvements and implications must be further evaluated in future studies.

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The authors declare no conflicts of interest .

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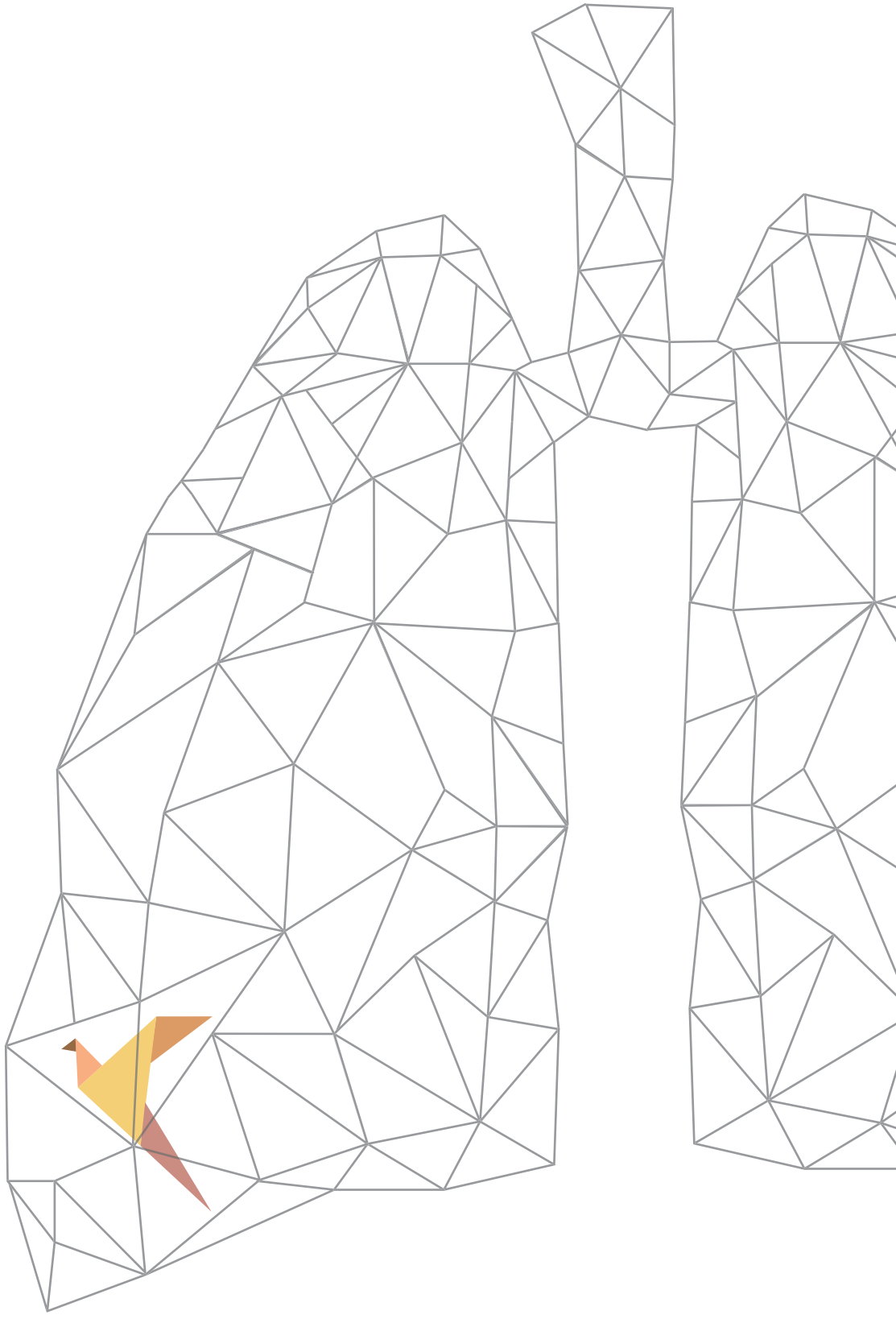
Supplementary Digital Content 1. Patient characteristics; right heart catheterization values at diagnosis.

Characteristic	Patients with pulmonary hypertension (n = 21)
Right heart catheterization (at diagnosis)	
Mean pulmonary artery pressure, mmHg	46.0 ± 15.6
Right atrial pressure, mmHg	8.4 ± 4.4
Pulmonary capillary wedge pressure, mmHg	8.7 ± 4.3

Data reported as mean ± standard deviation

Supplementary Digital Content 2. Group training session schedule.

Group training - Session 1		*Group training - Session 2*	
45 min	Treadmill walking Cycling Fitness training	45 minutes	Treadmill walking Cycling Fitness training
15 min	Rest	15 minutes	Rest
60 min	Outdoor walking or cycling	60 minutes	PH specific education on health
15 min	Rest		
45 min	Treadmill walking Cycling Fitness training	45 minutes	Treadmill walking Cycling Fitness training
15 min	Rest	15 minutes	Rest



CHAPTER 10

General discussion

GENERAL DISCUSSION

Interstitial Lung Diseases (ILDs) and Pulmonary Hypertension (PH) are two entities of chronic lung disorders, that are known to decrease survival and that have a negative impact on health-related quality of life of patients. Patients suffer from a wide variety of symptoms such as dyspnea, fatigue, cough, reduced exercise tolerance and side effects of medication, restricting them to live a normal life.[1-7]

In the research of this thesis we describe: (1) the translation and validation process of instruments that measure patient-reported outcomes in patients with ILD and PH, (2) the development of patient-recorded outcome measures in ILD and (3) interventions that aimed to improve quality of life of ILD and PH patients.

Validation of ILD and PH patient-reported outcome measures (PROMs)

Traditionally disease progression and effect of treatments are assessed by physiological outcomes measured in hospital. However, it is increasingly acknowledged that patient-reported outcomes (PROs) on symptoms and wellbeing should also be examined, in order to quantify the impact of the physical constraints to the patients wellbeing.[8-11] In clinical trial settings, PROs are mandatory nowadays.[12] Patient-reported outcome measures (PROMs) are formal instruments that, if properly validated, are able to measure and quantify these subjective values in a reliable manner. Some PROMs asses a single-item e.g. a symptom, other PROMs have multiple outcomes with various domain scores and a global score on quality of life. As shown in table 1 of the introduction section there are various PROMs available in the ILD and PH field.

What PROM is needed?

For use in routine clinical care, the questionnaire should preferably be short, target sufficient relevant aspects of the disease and be able to detect changes in health status in the individual patient. A brief questionnaire facilitates the physician to rapidly monitor the disease, identify problems and if necessary, respond to this. Often a physician lacks time during a routine consult to interview a patient about how the disease impacts his/her life; a PROM may improve communication between the patient and physician. Despite these advantages, use of PROMs in clinical practice in ILD and PH is scarce and could be improved.

For use in clinical trials the questionnaire should be sensitive enough to detect the effect of a treatment at group level within the trial duration and identify clinically relevant differences between groups with different disease severities. There must be enough evidence that the PROM has valid measurement properties in the studied patient

population.[12,13] Furthermore, the minimal clinically important difference (MCID) is preferably known, to understand what minimal change in PROM score is meaningful for the patient.[14,15] Ideally, a PROM meets all these conditions and could be used both in clinical practice as well as for clinical trials.

How do we get the ideal PROM?

Nowadays, there is a wealth of PROMs and new ones are still being developed. To avoid dilution of experience and validation, a balance should be sought between developing new and better PROMs and using older, extensively validated ones. If a PROM does not exist for the area of interest, a new questionnaire could be developed, ideally from the start with a group with broad diversity, consisting of patients and experts. Being a very timely and costly process, it may be preferable to look for an existing questionnaire and for instance translate a foreign suitable questionnaire. However, when the translation process is not performed properly, the meaning of a question or answer can easily be lost. To be able to compare scores from questionnaires when they are used cross-cultural in global clinical trials or in international collaboration projects, it is crucial that the meaning of questions (as intended by the original developer) is preserved throughout the translation process. [16] Cross-cultural adaptations of the questionnaire may be necessary. The questions and responses of the translated version should be understood similarly by the aimed population as by the population of original development, despite potential cultural differences. In chapter 2, 3 and 4 of this thesis, we describe the translation procedures of respectively the King's Brief Interstitial Lung Disease (K-BILD) questionnaire, the King's Sarcoidosis Questionnaire (KSQ) and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). To ensure the aforementioned equivalence between the original questionnaires and the translated versions of the K-BILD, KSQ and CAMPHOR, we followed a rigorous validation process in three phases: (1) a multistep translation procedure (2) cognitive debriefing interviews with patients; and (3) psychometric assessment of the PROM in repeated tests, 2 weeks apart, in the targeted patient population.[17,18] If there is enough evidence that the PROM performs well in different languages and settings, only phase 1 and 2 (linguistic validation) may be sufficient. This holds also true for PROMs that have been developed in such a way that they can be applied globally, despite known cultural differences.[19,20] In this case only translation of the questionnaire is needed, which may accelerate its global use. Performing phase 3 of the translation procedure, each time the PROM is translated, may hinder its use in global clinical trials as it is time consuming to repeat the psychometric assessment in at least 50 persons of the target population.[21,22]

Psychometric assessment of a translated PROM, may also yield interesting new insights. Recently the 29-item KSQ (described in chapter 3) was translated in German and psy-

chometric properties were tested.[23] Using exploratory factor analysis and item response modeling, the authors found that measurement properties of all domains of the KSQ improved when 5 items were removed. This is an interesting finding considering that a 24-item instead of 29-item questionnaire takes less time to complete and is therefore more convenient for clinical care. However, to adapt this questionnaire for one country has disadvantages as it will hamper collaboration and comparison internationally, as the longer KSQ version has already been translated in 14 languages.[23-25] This is why often, even though a better version of the initial questionnaire exists, people tend to keep working with the original version. A similar situation occurred with the often used SGRQ.[26] Even though this questionnaire has been shortened and adapted for idiopathic pulmonary fibrosis IPF (SGRQ-I)[27], in clinical trials the 50-item originally COPD questionnaire remains used as this allows for comparison with previous studies and has been accepted by policy makers as the Food and Drug Administration (FDA) and European Medicine Agency.[28]

In PH, no such example exist. The CAMPHOR was the first disease-specific questionnaire (described in chapter 4). Currently the CAMPHOR questionnaire is available in at least 23 languages.[29-37] However, since the questionnaire is quite lengthy and not freely accessible, its use is limited in a clinical setting. Recently two much shorter PH specific questionnaires (Pulmonary Arterial Hypertension-Symptoms and Impact -PAH-SYMPACT®-questionnaire and EmPHasis-10), have been developed.[20,38,39] However, they still need further validation. Giving its brevity, especially the EmPHasis-10 may be an attractive indicative tool to monitor the impact of PH in clinical care. In an ongoing prospective study in PAH and CTEPH patients we incorporate both the CAMPHOR and the EmPHasis-10 to examine how they correlate with clinical outcome parameters and to compare the outcome of both questionnaires.

As illustrated above, even though better and more practical PROMs may be available, this will not automatically lead to incorporation of these PROMs in clinical trials and daily practice. Therefore, researchers, pharmaceutical companies and policy makers should stimulate the use of newer PROMs in trials as the outcomes they measure are important for patients. Even when used as an explorative endpoint, these data may contribute to their validation and acceptation.

New technologies to measure PROMs

Also new technologies, may facilitate use of PROMs. An innovative way to assess health status with the shortest possible PROM, could be Computer Adaptive Testing (CAT). CAT is a type of measure which tailors the questions to the individual patient. The questions are drawn from an Item Response Theory-based item bank; a large set of questions mea-

suring the same construct e.g. fatigue. The questions are ranked in order of difficulty. With each response, the computer refines a person's score and determines what the next relevant (most informative) question would be. Irrelevant questions are skipped allowing that the number of questions is kept to a minimum (4-10 items), without losing precision. Until now there is insufficient experience with the application of this CAT in ILD or in PH. Also, its use in clinical trials outside ILD and PH has been limited.[40-42]

Another way of implementing digital technologies is to administer electronic PROMs. Instead of spending valuable time in clinic on completing questionnaires, patients can do this at home, online or in the clinic on a computer or handheld device before the consultation. Scores and trends are immediately available, which allows the patient and the medical team to use these in the consultation and as guidance for management decisions. The big advantage of this system is that it allows patients to see the results of the PROs, whereas in paper version, these questionnaires are often handed in and patients have little insights in their own scores. In the research presented in this thesis we describe a pilot study to the feasibility of a home monitoring program in IPF patients, which also incorporated PROs collection by the patient at home. The data were transmitted real-time to a secured platform, making data immediately accessible for the patient and the physician. This allowed the medical team to monitor the patient at a distance. For instance, if bothersome symptoms or side-effects of medical treatment were reported, the medical team automatically received a notice and could contact the patient via the digital tool or by phone. It also allowed patients to self-evaluate the effect of changes in management. Patients were very satisfied with the program, felt more in control of their disease and wished to continue home monitoring after the pilot study stopped. With increasing digitalization, we have to adapt to these developments as healthcare providers. Currently, there are many initiatives and apps, but only very little research about their effect on patient wellbeing, medical outcomes and implication for healthcare consumption, and economical burden. This will need research about the optimal use of digital platforms and preferably randomized controlled trials.

Development of patient-recorded outcome measures.

In addition to home monitoring of PROs, also home recording of spirometry and other physiological parameters, has the potential to improve medical care and research. In patients with IPF, real-time home recordings of FVC, allows for monitoring of disease progression and identification of patients with fast deterioration, as shown by Russell et al.[43] Potentially, it could also play a role in the early detection of acute exacerbations . In patients with IPF, this is currently investigated in a national trial in Germany, using the system we have developed.

Home spirometry to evaluate effects of treatment

In chapter 5 we describe the use of daily home spirometry, to monitor time needed for optimal treatment response in patients with sarcoidosis. Daily FVC recordings, performed by newly treated patients with sarcoidosis, demonstrated that the greatest improvement in FVC occurred within 2-3 weeks after starting steroid treatment. This would have been missed with the standard frequency hospital measurements (every 3-6 months). As prolonged high-dose steroid therapy is associated with negative side-effects, this finding is important suggesting that physicians could start earlier with dose tapering. Future research in patients with sarcoidosis is needed to evaluate if personalized dose titration based on home recorded FVCs and PROMs will lead to a reduction of side-effects and improvement of quality of life.

Home monitoring; additional benefits

In chapter 6 we describe the development of a daily home monitoring program with real-time wireless spirometry. Though experience with home-based spirometry in ILD is currently limited to IPF and sarcoidosis, we have expanded clinical use and research to the broader population of patients with ILD. Whether home monitoring of FVC and PROs improve quality of life (measured with the K-BILD questionnaire) is currently being investigated in a national randomized controlled trial (NCT03420235).

For use in clinical trials, home monitoring of FVC holds additional benefits. Johannson et al. have modelled that weekly recording of FVC compared to 6-monthly hospital spirometry, importantly reduces the required sample size necessary to demonstrate an effect of potential new IPF therapies in clinical trials.[44] In our research project to the feasibility of a home monitoring program in IPF patients, the median variation coefficient of daily FVC recordings was 3.76%, comparable to the findings of Russell et al. who reported 4.96% and better than the 8% variability found by Johannsen in weekly recordings.[43,45] It remains to be examined if asking the patient to conduct spirometry with a lower frequency (e.g. once a week), but then blowing three FVC maneuvers and selecting the best measurement, will improve accuracy. Currently home monitoring is used in an international observational study to better understand disease behavior in patients with a suspected diagnosis of IPF/ILD (NCT03261037). This includes real-time recording of FVC and of physical functional capacity through accelerometry. If having data on disease behavior during the diagnostic trajectory will facilitate diagnosis, is still subject of investigation.

Stimulating uniformity

Another important measure of pulmonary physiology is the transfer factor of the lung for carbon monoxide (TLCO) . Measurement variability hampers its use as outcome in

clinical trials. To manage this variabity and to ensure reliable, useable and reproducible results, standardization of TLCO and FVC measurements is very important and the guidelines on calibration of the equipment and test performance should be followed.[46,47] TLCO is mostly reduced in IPF patients.[48] Often IPF clinical trials use the TLCO as one of the inclusion criteria. The lower limit for inclusion varies, but is often 30% of the predicted value. For calculation of the predicted values , new reference values have been developed and published in 2017.[49] However, these new Global Lung function Initiative (GLI) reference values have not yet been adopted by all lung function laboratories which causes interlaboratory variability in trial eligibility.

In chapter 7 we describe how switching to the new GLI reference values may affect the number of patients eligible for clinical trials. Especially for severly diseased patients with a TLCO near the lower limit, using GLI reference equations may have positive implications, enabling them to participate in trials. Hopefully our research encourages lung function laboratories to adopt the GLI TLCO reference values as soon as possible, and sponsors to incorporate them in their study protocol.

Interventions aimed at improving quality of life for patients

The first parts of this thesis describe methods to measure outcomes, however, in the end the aim is to improve care and treatments for patients. The third part of this thesis describes two intervention studies that aimed to improve the quality of life of IPF and PAH/CTEPH patients. Although new pharmacological treatments have been developed in the last years, most patients with IPF and PAH/CTEPH still suffer from a progressively impaired QOL, limited exercise capacity, and high symptom burden, while their survival is still decreased. Therefore, it is important to search for opportunities other than pharmacological treatment to improve exercise capacity and QOL.

ILD and PH guidelines recommend pulmonary rehabilitation programs as add-on therapy to pharmacological treatment.[50-52] Reviews have demonstrated that PR programs have beneficial effects on exercise capacity, mostly measured with the 6MWD, and health-related QOL.[53-55] However, a major challenge is to maintain these beneficial effects by continuing the exercise regime after the program stops. Furthermore, following a PR program in an outpatient specialized rehabilitation center with 2-3 visits a week, or to stay in clinic away from family, often imposes a high burden to the patients.

Feasibility and efficacy of a home-based training program for IPF patients

To overcome the aforementioned hurdles, we wanted to offer a home-based training program with a new training modality, the walk-bike, that if well implemented in daily life could maintain potential beneficial effects of the training period. In chapter 8 we

describe a cross over pilot study to the efficacy of a home-based training program in IPF patients on QOL and exercise capacity, using this walk-bike. The results showed a tendency toward improvement in QOL as measured by SGRQ and K-BILD, and no improvement in the 6MWD. We learned that the study design was not ideal for this vulnerable patient group. On one hand, patients with reasonably preserved exercise capacity didn't want to participate, while on the other hand, patients with much more impaired exercise capacity were too dyspneic to participate or dropped out during the study due to disease progression or complications of disease. Another problem with inclusion of patients was their fear of being stigmatized. A walk-bike makes the disease visible for their surroundings. This is a similar sentiment that has been described by patients when facing the decision to start ambulatory oxygen.[56] This resulted in a study that unfortunately failed, but despite this, we learned that for some individual patients the walk-bike contributed to a better quality of life due to a an increased mobility and feeling of independency. This emphasizes the importance of personalized care, but also the difficulties faced when studying supportive measures for patients with an end-stage progressive deadly disease.

Effectiveness of a multidisciplinary outpatient program

In chapter 9 we examined the effects of a multidisciplinary PR program in an entirely outpatient setting in PAH/CTEPH patients. After 10 weeks of PR with 2 group training sessions per week in a specialized rehabilitation center, significant improvements were achieved in exercise capacity (measured by means of cycling endurance time -CET- and 6MWD), peripheral and respiratory muscle strength, CAMPHOR QOL and symptoms. The most beneficial effect was found in functional endurance measured by CET (increase of 4.8 minutes or 288 seconds). This result can be considered as a clinical meaningful effect since in a study by Laviolette et al. [57] in patients with COPD, a difference of 100-200 seconds in the CET was regarded as a clinical significant result. Although the improvement in 6MWD was statistically significant, the absolute gain was small compared to other studies.[54,55] This was most probably caused by a ceiling effect of the 6MWD in the patients studied. When patients are already treated with optimized PAH specific drug therapy like in our study, the 6MWD may be less able to detect meaningful clinical improvements.[55,58] Our patient group had, on average, a higher baseline 6MWD compared to patients in studies that demonstrated a larger effect in 6MWD. Although the 6MWD is currently often used as primary endpoint in PAH clinical trials, one should consider its limitations. Recording of daytime activity may be a more reliable and clinically valuable tool to assess the effects of a PR program. As demonstrated by Ulrich et al. a reduced daytime activity is associated with reduced survival and with severe hemodynamics.[59] Moreover, adoption of a sedentary life by PAH patients as a consequence of not being able to perform physical activities, contributes to an impaired QOL.[60] In the follow-up

study of our rehabilitation program we included measurement of daily activities by means of a move monitor, before and at the end of the PR program.

Improvement of QOL as measured in our study is also the result of the multidisciplinary approach of our PR program, including psychological counseling as well as contact with peers (reviews of patients, unpublished data). Future studies should be initiated on how to maintain daily life activities and QOL after the end of PR program. At this moment we advise patients to continue physical training under supervision of a physiotherapist. We plan to add an evaluation of daily life activities and QOL six months and one year after the end of the PR program.

In conclusion, improving daily life performance and QOL should be ultimate goals of add-on therapies like PR programs.

CONCLUSION

The past years, substantial progress has been made in acknowledging the importance of patient perspectives, by incorporating the patient's voice to assess treatment effects both in standard care as well as in research. This has taught us important lessons, but visualized the challenges of development, validation and implementation of PROMS and also the need of new PROMs. With increasing patient participation in research as well as in shared decision making in daily practice, we will be forced to further advance the field of patient-reported outcomes.[61] The importance to not only focus on prolonging survival (or its surrogate endpoint), but also putting emphasis on QOL for patients, will enhance our insights in treatments effects from the patient's perspective and will support shared decision making in choosing the best available treatment. Expanding digital solutions, new collaborations with different stakeholders (patients, researchers, pharmaceutical companies and others) and daring to incorporate new developments, will further pave the way for meaningful assessments of the patient's voice.

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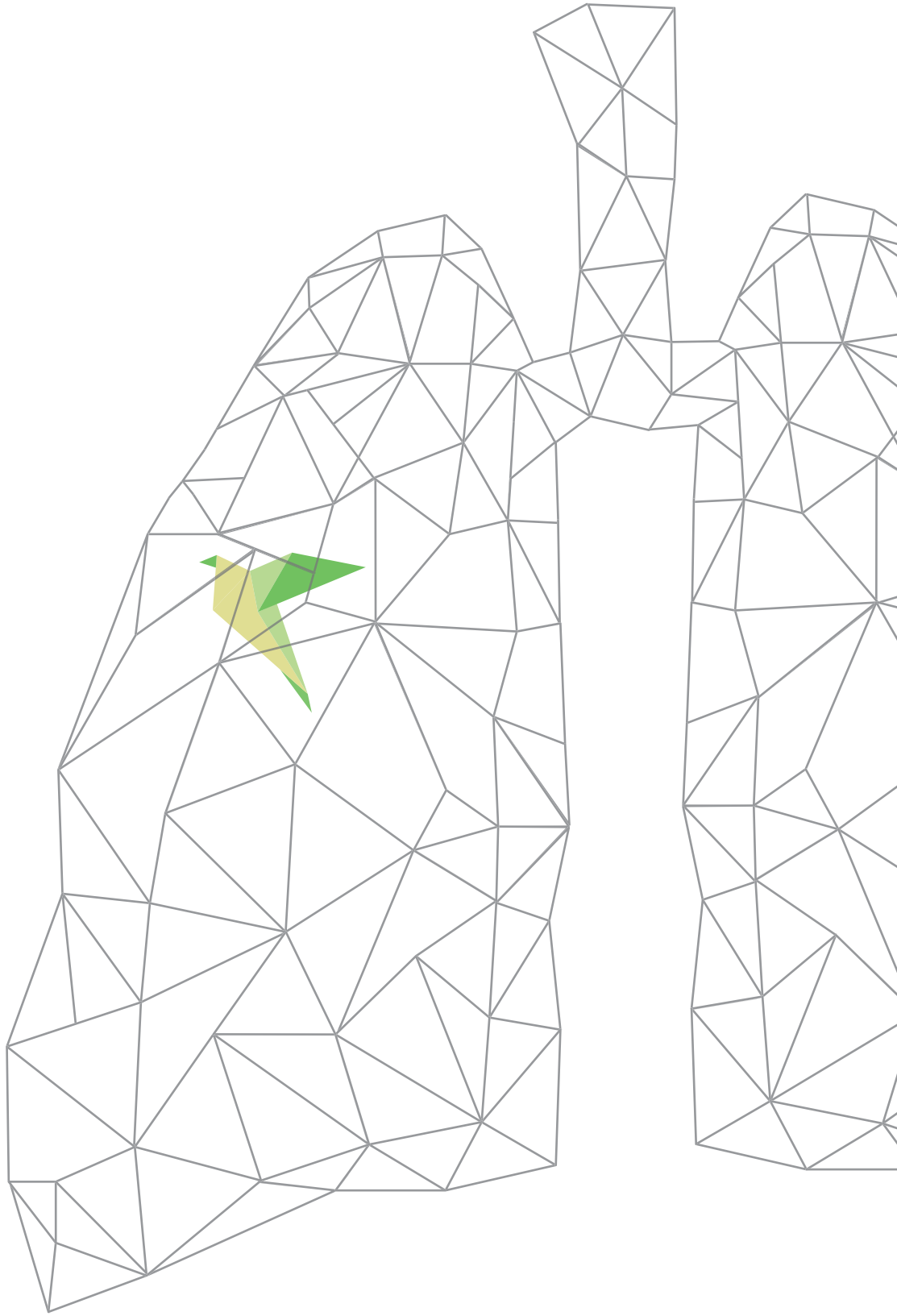
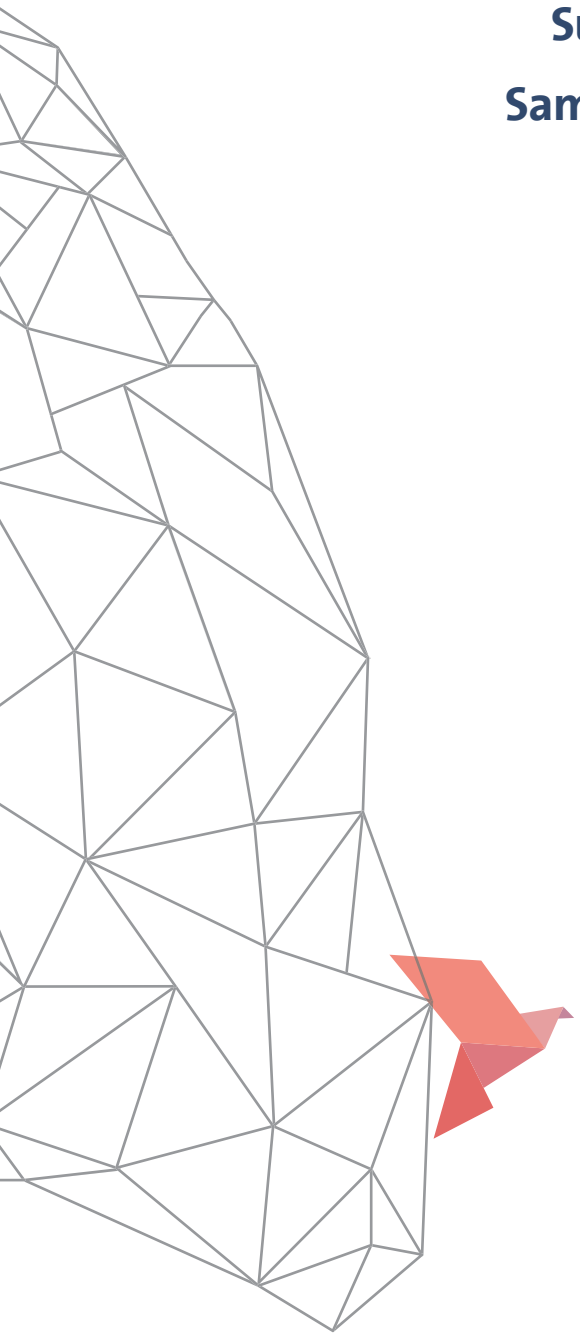


CHAPTER 11

Summary

Samenvatting



SUMMARY

Interstitial Lung Diseases (ILDs) and Pulmonary Hypertension (PH) are umbrella terms to describe two groups of chronic and debilitating lung disorders.

Interstitial lung diseases (ILDs) comprise more than 200 different disorders, characterized by interstitial inflammation, cellular proliferation, fibrosis or a combination of these processes, which damage the lungs. Some ILDs are reversible whereas others show a progressive scarring of lung tissue with rapid decline of lung function and ultimately death. Two of the most common ILDs are Idiopathic pulmonary fibrosis (IPF) and sarcoidosis.

IPF is a fatal lung disease of unknown etiology, characterized by an irreversible decline of lung volume and gas exchange. Although the clinical course of IPF varies, overall prognosis is poor with a median survival of 2-4 year after diagnosis, if patients are not being treated. At this moment there is no curative treatment for IPF. Two antifibrotic drugs (nintedanib and pirfenidon) which have been demonstrated to slow down disease progression are currently used as standard medical care. When treatment fails, lung transplantation is the only option left, when patients are eligible. The main symptoms patients with IPF suffer from are breathlessness, chronic cough, fatigue, anxiety and depression, which often severely impair their quality of life (QOL).

Sarcoidosis is a chronic systemic inflammatory disease of unknown cause, characterized by formation of granulomas. Although sarcoidosis can affect any organ, particularly the lungs, eyes, skin, liver and lymphatic system are involved. Depending on the organs involved, patients suffer from symptoms such as dyspnea, cough, fatigue, muscle pain, weakness, fever, and lack of appetite having a negative impact on their (QOL). The majority of patients recovers from sarcoidosis spontaneously. However, a significant minority of the patients develops progressive or chronic disease.

PH is a pathophysiological disorder, characterized by narrowing of the pulmonary vessels, leading to elevated pressures in the pulmonary circulation and in the right ventricle. This will lead to progressive right ventricle dysfunction, resulting in right heart failure and ultimately death. Patients with PH experience symptoms as breathlessness, fatigue, chest pain, dizziness, and syncope. These symptoms start occurring on exertion and will eventually also occur at rest. PH is categorized in five groups. The studies described in this thesis focuses on two categories: Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary hypertension (CTEPH).

PAH is a rare and incurable condition of the pulmonary vasculature, characterized by endothelial dysfunction, muscularization of the small arteries and thickening of the adventitia. These processes lead to an elevated pulmonary vascular resistance (PVR) and increased pulmonary arterial pressures (PAP), which will ultimately lead to progressive right ventricular failure. Despite improvements in medical treatment of PAH in the last 2 decades, patients still have a poor prognosis and an impaired health-related QOL due to physical, emotional and social problems (5-years survival approx. 70%).

CTEPH is caused by thromboembolic obstruction of the pulmonary arteries and arteriopathy, which increases the PVR and the PAP. Some CTEPH patients can effectively be cured by a surgical intervention (pulmonary endarterectomy) or balloon angioplasty. For inoperable CTEPH patients, or patients with rest PAH after surgery, specific PAH medication is a therapeutic option.

Traditionally disease progression and effect of treatments in ILDs and PH are assessed by physiological outcomes measured in hospital, such as lung function and six-minute walk test. However, in both disease areas there is an increasing awareness of the importance to include patient-centered outcomes such as symptoms and quality of life, when assessing effects of treatment and other interventions. Patients can play a central role in collecting these outcome measures, by using patient-reported outcome measures (PROMs) and patient-recorded outcome measures. There is a paucity of patient-centered outcome measures and interventions aimed at improving QOL, both for patients with ILD and PH. The research described in this thesis aimed to translate and validate PROMs for ILDs and PH for Dutch patients (part 1), develop patient-recorded outcome measures (part 2) and interventions aimed at improving QOL for patients (part 3).

Part 1: Validation of patient-reported outcomes in patients with ILD and PH

In **chapter 2** we present the translation and validation of the King's Brief Interstitial Lung Disease (K-BILD) questionnaire in French, Italian, Swedish, and Dutch. No disease-specific instruments existed in Dutch, French, Italian, and Swedish to measure health status in idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs). The K-BILD questionnaire is a 15-item validated questionnaire assessing health status in patients with ILD and was originally developed in the United Kingdom (2012). The aim of this study was to translate and validate this PROM to make it available for clinical trials and clinical care in France, Italy, Sweden and the Netherlands. The French, Italian, Swedish, and Dutch versions of the K-BILD questionnaire demonstrated excellent validity, comparable to the original English K-BILD.

Chapter 3 describes the translation and validation of the King's Sarcoidosis Questionnaire (KSQ) into Dutch. The KSQ is a brief questionnaire assessing health status using five modules (General Health Status, Lung, Medication, Skin, Eyes) in patients with sarcoidosis. The KSQ originates from the UK and was developed in 2012, it contains 29 items and is adaptable to individual organ involvement. The aim of this study was to validate the KSQ in a Dutch sarcoidosis population. The Dutch translation showed to be a valid and reliable PROM to measure health status in Dutch patients with sarcoidosis.

In **chapter 4** we translated and validated The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) into Dutch. The CAMPHOR is the first disease-specific instruments for pulmonary arterial hypertension (PAH) to assess patient-perceived symptoms, activity limitations and quality of life. It has been developed in the UK. To be able to use this questionnaire in the Netherlands, the aim of the study was to translate and validate this instrument for the Dutch-speaking population. The Dutch version of the CAMPHOR showed to be a reliable and valid instrument to measure quality of life and health status in patients with PAH and CTEPH.

Part 2: Development of patient-recorded outcome measures

In **chapter 5** we evaluated early steroid treatment effects in newly treated pulmonary sarcoidosis patients using daily patient-recordings of home spirometry. Optimization of first-line prednisone therapy for sarcoidosis is urgently needed, since side effects of steroid treatment can be severe and long-term benefits are debated. Prospective data on the early response of prednisone treatment was still lacking. The aim of the study was to evaluate the early lung function response to prednisone treatment and tapering, using daily home spirometry. The results showed that in newly treated sarcoidosis patients, the greatest effect on Forced Vital Capacity, fatigue and dyspnea symptoms occurs within 2–3 weeks after initiation of prednisone therapy. These results suggest that frequent home monitoring of FVC and symptoms has the potential to help individualize prednisone therapy in pulmonary sarcoidosis patients, aiming at early dose tapering, resulting in side effect reduction and improvement of quality of life.

Chapter 6 presents our pilot study to evaluate feasibility, experiences and barriers of a home monitoring program including real-time wireless home spirometry in IPF patients. Patients with IPF often experience symptoms such as progressive dyspnea and immobility, making regular hospital visits a challenge. New eHealth technologies hold great potential for research and care by facilitating real-time, frequent data collection from home. Home monitoring experiences in IPF patients are limited, not yet real-time available nor implemented in daily care. The results showed that a home monitoring program including wireless home spirometry, is reliable, highly feasible and appreciated

by patients with IPF. It enables real-time detection of change in FVC and PROs, and in this way could facilitate personalized care. Both patients and researchers suggested relatively easy solutions for the identified potential barriers regarding real-time home monitoring in IPF, which were used to further optimize the system.

In chapter 7 we assessed the impact of adopting new TLCO reference values on clinical trial eligibility for IPF patients. IPF patients are often keen to participate in clinical trials that may give them the opportunity to improve their disease outcome. Inclusion criteria for these trials include a threshold for the diffusing capacity of the lung for carbon monoxide in percentage of the predicted value (TLCO %predicted). Screen failures are frequently based on TLCO % predicted below the lower limits permitted in the study. In 2017 the Global Lung Function Initiative (GLI) established new reference values for the TLCO. Many lung function laboratories still use older reference values. Our study aimed to assess the impact of the new TLCO reference values on inclusion in medication trials for IPF patients. Our results show that switching to the new GLI TLCO reference equations may have a small positive effect on trial inclusion for IPF patients. Physicians should be aware that the choice of a reference set can make a difference in trial inclusion for the individual patient. Urgent adoption of the globally derived and applicable GLI reference set is needed to reduce variability in trial eligibility between laboratories.

Part 3: Interventions aimed at improving quality of life in ILD and PH patients.

Chapter 8 describes a pilot study to explore feasibility and effects of a walk-bike in IPF patients. Idiopathic pulmonary fibrosis (IPF) is characterized by progressive loss of pulmonary function and exercise capacity, leading to loss of quality of life and often social isolation. A new walking aid, the walk-bike, showed an improvement in exercise performance in COPD patients. Aims of this pilot study were to evaluate the feasibility of a homebased walk-bike intervention study in IPF patients and to explore the effect of the walk-bike on quality of life and exercise capacity.

The study revealed several hurdles and it was concluded that a larger study on walk-bike training-effects in IPF patients does not seem feasible. Patient experience and satisfaction with the bike greatly varied, which seems to limit its use to a small minority of patients. The walk-bike improved action radius and showed a tendency towards improvement in QoL. No effect on exercise capacity was observed.

In **chapter 9** we evaluated the effects of a 10-week multidisciplinary pulmonary rehabilitation program in PH patients. Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance andright ventricular impairment , leading to exertional dyspnea, skeletal muscle weakness, and poor quality of life. Apart from

treatment with PAH-specific drugs, guidelines recommend pulmonary rehabilitation (PR). Clinical PR programs have shown improvement in functional capacity and quality life. However, little is known about the safety and the effectiveness of an entirely outpatient PR program. The aim of our study was to assess safety and effectiveness of a multidisciplinary outpatient PR program. This study demonstrated that a 10-wk multidisciplinary outpatient PR program is safe and has considerable beneficial effects on functional capacity, functional endurance, skeletal muscle function, and health-related quality of life for patients with PAH or CTEPH.

SAMENVATTING

Interstitiële longziekten (ILD) en pulmonale hypertensie (PH) zijn verzamelnamen om twee groepen van patiënten te beschrijven met zeldzame, meestal chronische longaandoeningen.

ILDs worden gekenmerkt door aantasting van het interstitium (de ruimte tussen longbloedvaten en longblaasjes), door ontsteking, littekenweefselvorming (fibrose), of een combinatie daarvan. Hierdoor neemt vaak zowel de longcapaciteit als de zuurstofopname af. Er zijn meer dan 200 verschillende interstitiële longaandoeningen waarvan sommige omkeerbaar zijn, terwijl andere een progressieve littekenvorming van het longweefsel laten zien met een snelle afname van de longfunctie en uiteindelijk overlijden. De onderzoeken in dit proefschrift richten zich op de twee meest voorkomende ILDs: idiopathische pulmonale fibrose (IPF) en sarcoïdose.

IPF is een fatale longziekte van onbekende oorzaak met een progressieve verlittekening van de longen (fibrose), met als gevolg achteruitgang van het longvolume en toenemende kortademigheid. Hoewel het klinische verloop van IPF varieert, is de algehele prognose slecht met een mediane overleving van 2-4 jaar na de diagnose, zonder behandeling. Op dit moment is er geen remedie voor IPF, behalve longtransplantatie. Twee anti-fibrotische geneesmiddelen (nintedanib en pirfenidone) die de progressie van de ziekte vertragen, zijn momenteel samen met ondersteunende maatregelen, de zorgstandaard.

Sarcoïdose is een chronische systeem ziekte van onbekende oorzaak, die gekenmerkt wordt door de vorming van granulomen; kleine opeenhopingen van ontstekingscellen. Hoewel deze ziekte elk orgaan kan treffen, komt sarcoïdose het meest voor in de longen, de ogen, de huid, de lever en het lymfesysteem. De klachten die patiënten ervaren zijn afhankelijk van welke organen betrokken zijn, maar kunnen ook aspecifiek zijn, zoals bijvoorbeeld moeheid. De meerderheid van de patiënten herstelt spontaan van sarcoidose, maar bij een significante minderheid wordt de ziekte chronisch en progressief.

Pulmonale hypertensie is een longaandoening waarbij door een vernauwing van de longvaten een hoge bloeddruk ontstaat in de longcirculatie. Omdat de rechter harthelft steeds harder moet werken om het bloed door de vernauwde longvaten te pompen, wordt de spierwand van het hart dikker en de rechter hartkamer groter. Op den duur werkt de pompfunctie van het hart onvoldoende en gaat de rechter hartkamer falen. Doordat de longen onvoldoende zuurstof op kunnen nemen, krijgen patiënten met pulmonale hypertensie klachten als vermoeidheid, kortademigheid, pijn op de borst,

duizeligheid en flauwvallen. Deze symptomen treden meestal op tijdens inspanning, wanneer het hart er niet in slaagt het hartminuutvolume te verhogen.

Oorzaken van pulmonale hypertensie zijn vaak onderliggende aandoeningen zoals longziekten en aandoeningen van de linker hartkamer. De Wereldgezondheidsorganisatie (WHO) heeft PH ingedeeld in vijf groepen. Dit proefschrift richt zich op twee daarvan, namelijk pulmonale arteriële hypertensie (PAH) en chronische trombo-embolische pulmonale hypertensie (CTEPH).

PAH is een zeldzame ongeneeslijke vorm. De vernauwing in de longvaten ontstaat door een ziekteproces van de binnenlaag van bloedvaatwand, waaronder beschadiging van het oppervlak, een toename van spiervezels in de wand en verdikking van de buitenlaag van de bloedvaten. De oorzaak hiervan is niet duidelijk, mogelijk speelt erfelijkheid in een aantal gevallen een rol.

Verder is bekend dat bij een aantal auto-immuunziekten PAH vaker optreedt , zoals ook bij patienten met bepaalde aangeboren hartafwijkingen. Ondanks verbeteringen in de medische behandeling van pulmonale arteriële hypertensie in de laatste twee decennia, hebben deze patiënten met PAH een slechte prognose en een verlaagde kwaliteit van leven ten gevolge van fysieke, emotionele en sociale problemen.

CTEPH wordt veroorzaakt door obstructie van longslagaders door het optreden van chronische bloedstolsels (longembolieën). Zestig procent van deze patiënten kan tegenwoordig worden behandeld middels een operatie. Een gedeelte van de patiënten kan worden geholpen met een dotter procedure of medicamenteuze therapie.

Traditioneel wordt de ziekteprogressie en de effectiviteit van een behandeling bij ILD en PH patiënten beoordeeld aan de hand van fysiologische uitkomstmaten, zoals longfunctietesten en de 6-minuten wandeltest. Deze onderzoeken worden uitgevoerd in het ziekenhuis. Echter, er is steeds meer erkenning dat uitkomstmaten vanuit patiëntperspectief, zoals symptomen en kwaliteit van leven, belangrijk zijn en daarom beter moeten worden onderzocht. Patiënten kunnen een centrale rol vervullen bij het verzamelen van deze gegevens door gebruik te maken van door de patiënt gerapporteerde uitkomstmaten (PROMs) en door de patiënt zelf gemeten uitkomstmaten. PROMs zijn formele meetinstrumenten (meestal vragenlijsten) die, mits ze goed gevalideerd zijn, in staat zijn om subjectieve waarden als symptomen en kwaliteit van leven, op een betrouwbare manier te meten en te kwantificeren.

Patiëntgerichte uitkomstmaten én interventies die gericht zijn op het verbeteren van de kwaliteit van leven zijn schaars, zowel voor patiënten met ILD als met PH. De onderzoeken beschreven in deel 1 van dit proefschrift zijn gericht op het vertalen en valideren van ILD- en PH-specifieke PROMs, om ze beschikbaar te maken voor Nederlandse patiënten. In deel 2 van dit proefschrift beschrijven we de ontwikkeling van door de patient zelf gemeten uitkomstmaten. Deel 3 van dit proefschrift beschrijft twee interventiestudies die gericht zijn op het verbeteren van kwaliteit van leven van ILD- en PH-patiënten.

Deel 1: Validatie van PROMs voor patiënten met ILD en PH

Hoofdstuk 2 In Nederland, Frankrijk , Italië en Zweden was geen PROM beschikbaar waarmee de gezondheidstoestand van patiënten met ILD (inclusief IPF) gemeten kon worden. In 2012 werd in het Verenigd Koninkrijk de K-BILD vragenlijst ontwikkeld en gevalideerd. De K-BILD vragenlijst omvat 15 vragen waarmee de impact van de ziekte op drie domeinen (kortademigheid & activiteiten, borstklachten en psychisch) beoordeeld kan worden. Het doel van onze studie was deze vragenlijst te vertalen en te valideren zodat deze gebruikt kan worden in research en zorg in Nederland, Frankrijk, Italië en Zweden. De voor deze landen vertaalde versies van de K-BILD vragenlijst vertoonden een uitstekende validiteit, vergelijkbaar met de originele Engelse K-BILD.

In **hoofdstuk 3** beschrijven we het vertalings- en validatieproces van de King's Sarcoidose Vragenlijst (KSQ), een PROM waarmee de gezondheidstoestand van sarcoïdose patiënten gemeten kan worden. In Nederland bestond nog geen ziekte-specifieke vragenlijst voor deze patiëntengroep. De KSQ bestaat uit 29 items en 5 modules; Algemene gezondheidstoestand, Long, Huid, Ogen en Medicatie. Deze modules kunnen los gebruikt worden of gecombineerd worden, afhankelijk van de individuele orgaanbetrokkenheid. We vertaalden en valideerden de KSQ in een Nederlandse sarcoïdose populatie. De Nederlandse versie bleek een valide en betrouwbare PROM te zijn waarmee de gezondheidstoestand van Nederlandse patiënten met sarcoïdose gemeten kan worden.

In **hoofdstuk 4** presenteren we de vertaling en validering van de Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) in het Nederlands. De in 2006 ontwikkelde CAMPHOR is de eerste ziekte-specifieke PROM voor het beoordelen van de door PH patiënten waargenomen symptomen, beperkingen in activiteit en kwaliteit van leven. Het doel van ons onderzoek was deze PROM voor de Nederlandstalige PAH en CTEPH patiënten te vertalen en te valideren. De Nederlandse versie van de CAMPHOR bleek een betrouwbare en valide instrument om kwaliteit van leven en de gezondheidstoestand van PAH en CTEPH patiënten te meten.

Deel 2: Ontwikkeling van door de patiënt gemeten uitkomstmaten.
In **hoofdstuk 5** onderzochten we met behulp van thuisspirometrie, hoe snel prednison effect heeft op de longfunctie (FVC) en symptomen bij nieuwe behandelde patiënten met pulmonale sarcoïdose. Prednison is bij behandeling van pulmonale sarcoïdose het geneesmiddel van eerste keuze. Echter, de bijwerkingen van prednison kunnen ernstig zijn. We zagen dat in nieuw behandelde sarcoïdose patiënten het grootste deel van de verbetering in FVC, vermoeidheid en kortademigheid optreedt binnen 2-3 weken nadat de behandeling met prednison is gestart. Deze resultaten suggereren dat het frequent thuismonitoren van de FVC en van symptomen, de mogelijkheid biedt bij deze patiëntengroep de prednisontherapie te individualiseren, met als doel de dosering eerder af te bouwen, bijwerkingen te verminderen en kwaliteit van leven te verbeteren.

Hoofdstuk 6 beschrijft onze pilotstudie naar de haalbaarheid, ervaringen en potentiele barrières van een thuismonitoringsprogramma, inclusief real-time draadloze thuisspirometrie bij IPF-patiënten. Patiënten met IPF ervaren vaak symptomen als toenemende dyspneu en beperkt inspanningsvermogen, waardoor frequente ziekenhuisbezoeken voor de meeste patiënten een grote belasting kunnen zijn. Nieuwe eHealth-technologieën bieden de mogelijkheid, middels real-time, thuismetingen te doen en frequenter gegevens te verzamelen zowel voor zorg als onderzoek, maar ervaringen met eHealth bij IPF-patiënten zijn tot nu toe beperkt. Thuisspirometrie bleek betrouwbaar en haalbaar en werd zeer gewaardeerd door patiënten met IPF. Veranderingen in FVC, symptomen en bijwerkingen worden direct gedetecteerd, waardoor zorg op maat leveren gemakkelijker kan worden. Er werden geen grote belemmeringen voor thuismonitoring gevonden.

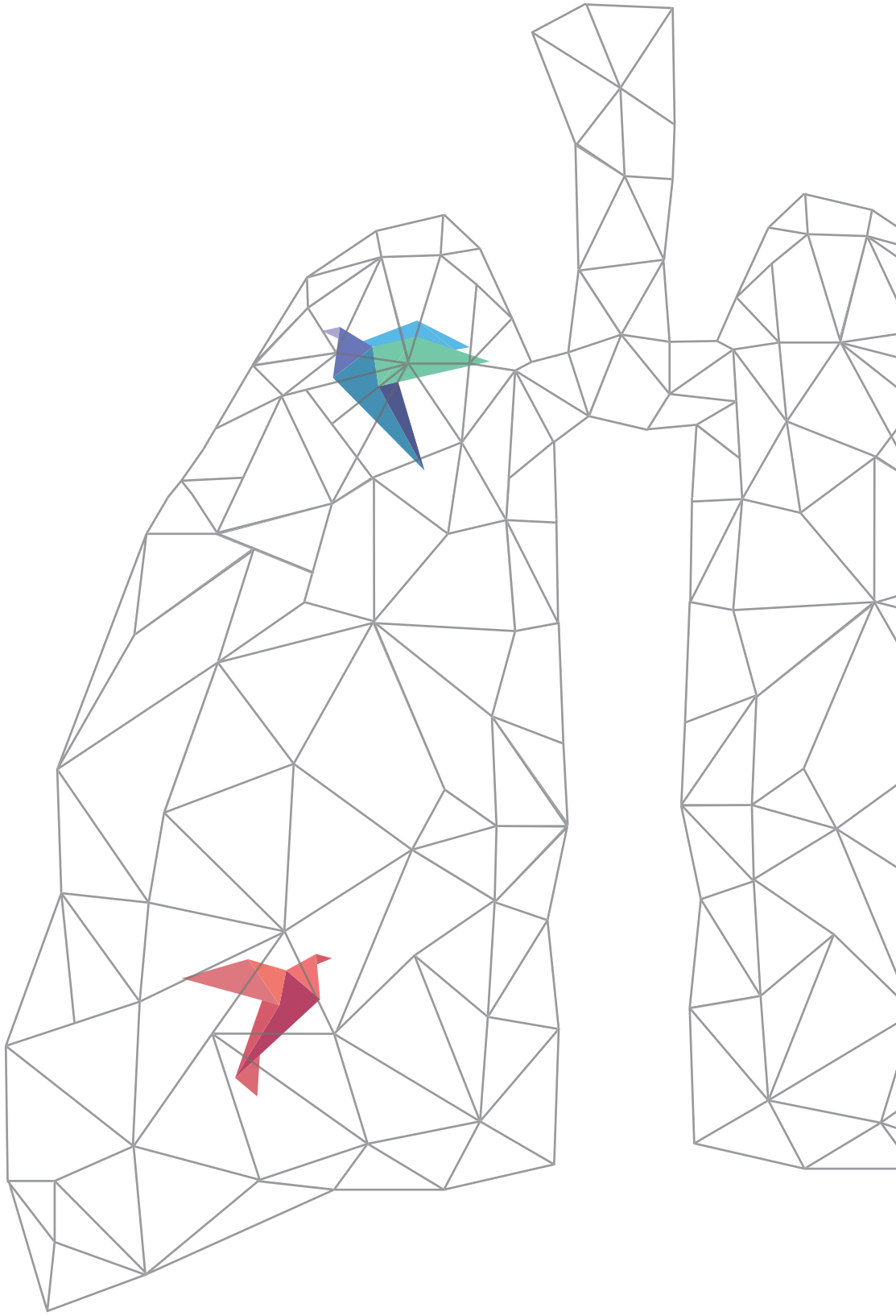
In **hoofdstuk 7** onderzochten we de impact van nieuwe longfunctiereferentiewaarden op de mogelijkheid voor deelname aan klinische studies voor patiënten met IPF. IPF-patiënten zijn vaak gemotiveerd om deel te nemen aan klinisch onderzoek dat hen een kans biedt hun vooruitzichten te verbeteren. Inclusiecriteria voor deelname aan de studie omvatten meestal een drempelwaarde voor het diffunderend vermogen van de long voor koolmonoxide, uitgedrukt in percentage van de voorspelde waarde (TLCO %voorspeld). Het niet mogen deelnemen aan een studie is vaak gebaseerd op een te lage TLCO %voorspeld en is teleurstellend voor patiënten. In 2017 heeft de Global Lung Function Initiative (GLI) werkgroep nieuwe referentiewaarden voor de TLCO vastgesteld. Veel longfunctielaboratoria gebruiken nog steeds oudere referentiewaarden. Onze studie laat zien dat het overschakelen naar de nieuwe GLI TLCO-referentievergelijkingen een aanzienlijk positief effect kan hebben voor IPF-patiënten op de mogelijkheid voor deelname aan een studie . Dit verschil kan grote gevolgen hebben voor de individuele patiënt. Niet alleen artsen moeten zich bewust zijn van deze impact, maar ook sponsors

van klinische studies bij het schrijven van het onderzoeksprotocol. Snelle en brede implementatie van de nieuwe GLI TLCO-referentiewaarden is nodig om variabiliteit in studiedeelname tussen laboratoria te verminderen.

Deel 3: Interventies gericht op het verbeteren van de kwaliteit van leven bij ILD- en PH-patiënten.

Hoofdstuk 8 beschrijft onze pilotstudie naar de haalbaarheid en effectiviteit van training met een loopfiets bij IPF-patienten. IPF wordt gekenmerkt door een progressief verlies van longfunctie en inspanningscapaciteit, leidend tot verlies van kwaliteit van leven en vaak sociaal isolement. Een nieuw loophulpmiddel, de loopfiets, liet bij COPD-patiënten een verbetering zien in mobiliteit. Het doel van onze pilotstudie was te onderzoeken of een interventiestudie met de loopfiets thuis, bij IPF-patiënten haalbaar is, en te evalueren wat het effect is van de loopfiets op kwaliteit van leven en inspanningscapaciteit. Onze bevindingen laten zien dat een groter onderzoek naar trainingseffecten van de loopfiets bij IPF-patiënten met het huidige studiedesign niet haalbaar lijkt. Ervaringen en tevredenheid van de patiënt met de loopfiets varieerden sterk, wat het gebruik ervan lijkt te beperken tot een kleine groep patiënten. Er werd geen effect op de inspanningscapaciteit waargenomen, echter de loopfiets verbeterde de actieradius en liet aanwijzingen zien voor een verbetering van kwaliteit van leven.

In **hoofdstuk 9** onderzochten we de effectiviteit van een poliklinisch en multidisciplinaire longrevalidatieprogramma voor PH-patiënten. Van longrevalidatieprogramma's in een klinische setting is bekend dat het de functionele capaciteit en kwaliteit van leven van PH-patiënten verbeterd. Er is echter weinig onderzoek gedaan naar de effectiviteit van een longrevalidatieprogramma in een poliklinische setting. Onze studie toont aan dat een 10-weekse poliklinisch en multidisciplinair longrevalidatieprogramma veilig is en zeer gunstige effecten heeft op het uithoudingsvermogen, de skeletspierfunctie en kwaliteit van leven van PAH en CTEPH patiënten.



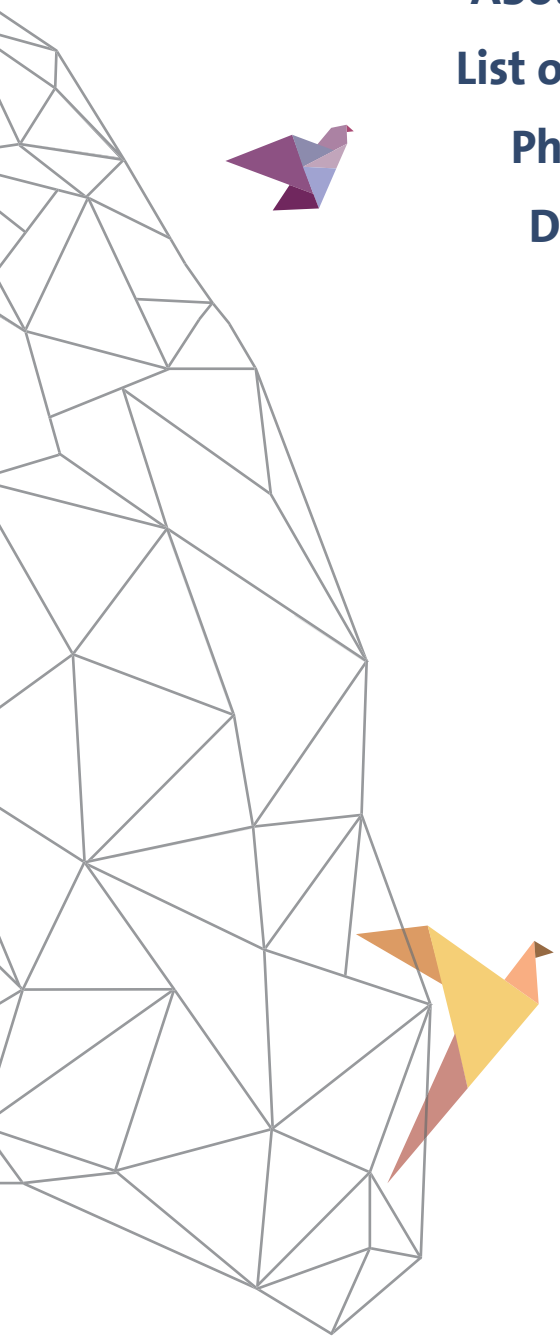
ADDENDUM

About the author

List of publications

PhD portfolio

Dankwoord



ABOUT THE AUTHOR

Monique Wapenaar (1965) was born in Vlaardingen, the Netherlands. After graduation from high school (HAVO) she started with the 3-year in-service training for pulmonary function technologist in Holy Hospital, Vlaardingen. After her graduation in 1986, she worked in various hospitals. She worked in the University Hospital Dijkzigt (Erasmus MC Rotterdam) from 1988 till 1994 as a research pulmonary function technologist (SGO-CARA trial) and as coordinator at the pulmonary function and endoscopy department in the Clara Hospital in Rotterdam from 1994 till 2000.

In 2000 Monique went on a "dream tour" for three years with her husband Gerard and travelled through the America's and New Zealand . After returning in 2003, she worked in the Sophia's Children Hospital and Dijkzigt Hospital. In 2005 her husband Gerard was offered a job in Chile and they lived in Chile for 2 ½ years. During that period Monique worked in a laboratory for propagation of plants through tissue culture technology where she set up a quality management system and functioned as an account manager for foreign customers. After returning to the Netherlands, Monique continued to work in this field at Iribov in Heerhugowaard, until 2009. Then she decided to return to the Erasmus MC and started working as a research pulmonary function technologist again. After finishing the Bachelor of Health program at the LOI Hogeschool for pulmonary function technology in 2011, she combined her work with a 2-year Master of Science in Evidence Based Practice at the University of Amsterdam. She graduated in 2014. Her master thesis formed the base for her publication in chapter 2 of this thesis. Moreover, Monique developed her educational skills and started teaching medical students at the Faculty of Medicine of the Erasmus University in 2014. Since then, Monique has been nominated 4 times for the yearly MORE education award "teacher of the year". She graduated for her BKO (University Teaching Qualification) in 2016. Monique combined her work in teaching and pulmonary function technology with clinical research under supervision of Dr. Marlies Wijsenbeek and Dr. Karin Boomars, which resulted in permission to officially start working on her PhD at the end of 2017. Monique looks forward to defend her thesis under supervision of her promotor Prof. dr. Joachim Aerts and her co-promotors Marlies and Karin, with Karin Lammering and Karen Moor as paranymphs on her side.

LIST OF PEER REVIEWED PUBLICATIONS

Van Manen MJ, **Wapenaar M**, Strookappe B, Drent M, Ellfferich M, de Vries J, Gosker HR, Birring SS, Patel AS, van den Toorn LM, van den Blink B, Boomars K, Hoitsma E, Wijsenbeek MS. Validation of the King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis.* 2016;33(1):75-82

Wapenaar M, Twiss J, Wagenaar M, Seijkens P, van den Toorn LM, Stepanous J, Heaney A, van den Bosch AE, Boomars KA. Adaptation and validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for the Netherlands. *Neth Heart J.* 2016;24(6):417-424.

Kreuter M, Birring SS, Wijsenbeek M, **Wapenaar M**, Oltmanns U, Costabel U, Bonella F. German Validation of the "King's Brief Interstitial Lung Disease (K-Bild) Health Status Questionnaire". Deutschsprachige Validierung des "King's Brief Interstitial Lung Disease (K-BILD)" Lebensqualitatsfragebogens fur interstitielle Lungenerkrankungen. *Pneumologie.* 2016;70(11):742 -746.

Wapenaar M, Patel AS, Birring SS, Domburg RTV, Bakker EW, Vindigni V, Sköld CM, Cottin V, Vancheri C, Wijsenbeek MS. Translation and validation of the King's Brief Interstitial Lung Disease (K- BILD) questionnaire in French, Italian, Swedish, and Dutch. *Chron Respir Dis.* 2017;14(2):140-150.

van Manen MJG, Birring SS, Vancheri C, Vindigni V, Renzoni E, Russell AM, **Wapenaar M**, Cottin V, Wijsenbeek MS. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. *Eur Respir J.* 2017;50(4).

Moor CC, **Wapenaar M**, Miedema JR, Geelhoed JJM, Chandoesing PP, Wijsenbeek MS. A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers. *Respir Res.* 2018;19(1):105.

Broos CE, **Wapenaar M**, Looman CWN, In 't Veen JCCM, van den Toorn LM, Overbeek MJ, Grootenboers MJJH, Heller R, Mostard RL, Poell LHC, Hoogsteden HC, Kool M, Wijsenbeek MS, van den Blink B. Daily home spirometry to detect early steroid treatment effects in newly treated pulmonary sarcoidosis. *Eur Respir J.* 2018;51(1).

Broos CE, Poell LHC, Looman CWN, In 't Veen JCCM, Grootenboers MJJH, Heller R, van den Toorn LM, **Wapenaar M**, Hoogsteden HC, Kool M, Wijsenbeek MS, van den Blink B. No evidence found for an association between prednisone dose and FVC change in newly-treated pulmonary sarcoidosis. *Respir Med.* 2018;138S:S31-S37.

Kimman ML, Wijsenbeek MS, van Kuijk SMJ, Wijnsma KL, van de Kar NCAJ, Storm M, van Jaarsveld X, Dirksen CD; **PESaM Collaborating Group**.Validity of the Patient Experiences and Satisfaction with Medications (PESaM) Questionnaire. *Patient.* 2019;12(1):149-162.

Wapenaar M, Miedema JR, Lammering CJ, Mertens FW, Wijsenbeek MS. The impact of the new Global Lung Function Initiative TLCO reference values on trial inclusion for patients with idiopathic pulmonary fibrosis. *Eur Respir J. 2019 Jan 31;53(2).*

Koudstaal T*, **Wapenaar M***, van Ranst D, Beesems R, van den Toorn LM, van den Bosch AE, Chandoesing PP, Boomars KA. The effects of a 10-wk outpatient pulmonary rehabilitation program on exercise performance, muscle strength, soluble biomarkers, and quality of life in patients with pulmonary hypertension. *J Cardiopulm Rehabil Prev,*2019*,* in press . *Shared first author.

PhD PORTFOLIO

Name PhD student: M. Wapenaar	PhD period: 2017-2019
Erasmus MC Department: Pulmonary Diseases	Promotor: Prof. dr. J.G.J.V. Aerts
Research School: N.A.	Supervisors: Dr. M.S. Wijsenbeek and Dr. K.A. Boomars

	Year	Workload ECT
General courses, seminars and workshops		
- BROK® full course	2010	1.5
- CPET interpretation course ERS	2014	0.15
- BROK course re-registration	2015	0.15
- Nihes ESP65 The Practice of Epidemiologic Analysis	2015	0.7
- CPO Patient Oriented Research mini course	2015	0.3
- BKO (Full Certificate University Teaching Qualification)	2016	3.0
- Workshop Systematic Literature Retrieval in PubMed I en II	2017	0.3
- Workshop Endnote	2017	0.15
- Research integrity (25/ 9/ 2018)	2018	0.30
- Good Clinical Practice	2018	0.15
- ERS post graduate course pulmonary rehabilitation	2018	0.15
- ERS workshop CPET interpretation	2018	0.15
- ERS postgraduate course lung function testing	2018	0.15
- BROK course re-registration	2018	0.40
- Winter Interstitial Lung Disease course	2019	1
- Workshop adobe Photoshop and Illustrator	2019	0.30
- Workshop Lime survey and Gems tracker	2019	0.30
Presentation and International conferences		
- Dutch pulmonary fibrosis patient association: "Lung function and lungfibrosis"	2014	0.3
- ERS conference Munich (poster discussion)	2014	1
- WASOG conference-Kusadasi, Turkey (poster presentation and selected for oral presentation)	2014	1.5
- ERS conference, Amsterdam, the Netherlands (poster discussion)	2015	1
- ERS conference London, UK (poster presentation)	2016	1
- ERS conference, Paris, France (oral presentation) (abstract selected for "the best of international congress programme" for publication in Journal of Thoracic Diseases)	2018	1
- NVLA ERS Paris review meeting (2 oral presentations)	2019	1
- Presentation state of the art 6MWT and oxygen titration in patients with IPF, Lissabon, Portugal	2019	1
Other:		
- Reviewing article British Medical Journal (respiratory medicine)	2018	0.4
- Reviewing article Respiratory Research	2018	0.35
- Reviewing article European Respiratory Journal	2019	0.3

University teaching	2014-2019	
Lectures lung physiology and pulmonary function testing, (ventilation,diffusing capacity, breathing mechanics, ventilation-perfusion mismatch, exercise physiology and exercise testing, pulmonary function tests in Astma, COPD, ILD) to:		
- Medicine, bachelor, Erasmus University		3.5
- Minor, Internal medicine Erasmus University (interpretation pulmonary function tests)		0.5
- Life science, bachelor Erasmus University College		0.7
- Regional nursing school (Erasmus MC Zorgacademie)		1.3
- MD pulmonologists in training		2
- LOI Hogeschool bachelor pulmonary function technologist		2.4
- Pulmonary function technologists		1
Evaluation exams bachelor medical students		2.5
Supervising practicals and excursions, Tutoring	2014-2018	
- Spirometry and cases (Medicine, bachelor, Erasmus University , Clinical technology (TU/EMC) and Life science (Erasmus University College)		3.0
- Exercise physiology/testing (Medicine, bachelor, Erasmus University)		1.8
- Interpretation exercise tests (CPET) (Medicine, bachelor, Erasmus University)		2.2
Supervising Master's theses		
- 2 students	2014	4
Other		
- Nominated for the MORE education award " teacher of the year" by 1st year bachelor medical students	2015-2016-2017-2019	
Grants and funding		
- The Pender Foundation of the Dutch pulmonary fibrosis patient association supported walk-bike study	2013	
- Cosmed travel grant for visiting ERS conference	2019	
Total ECTs		**42.9**

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