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.

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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

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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
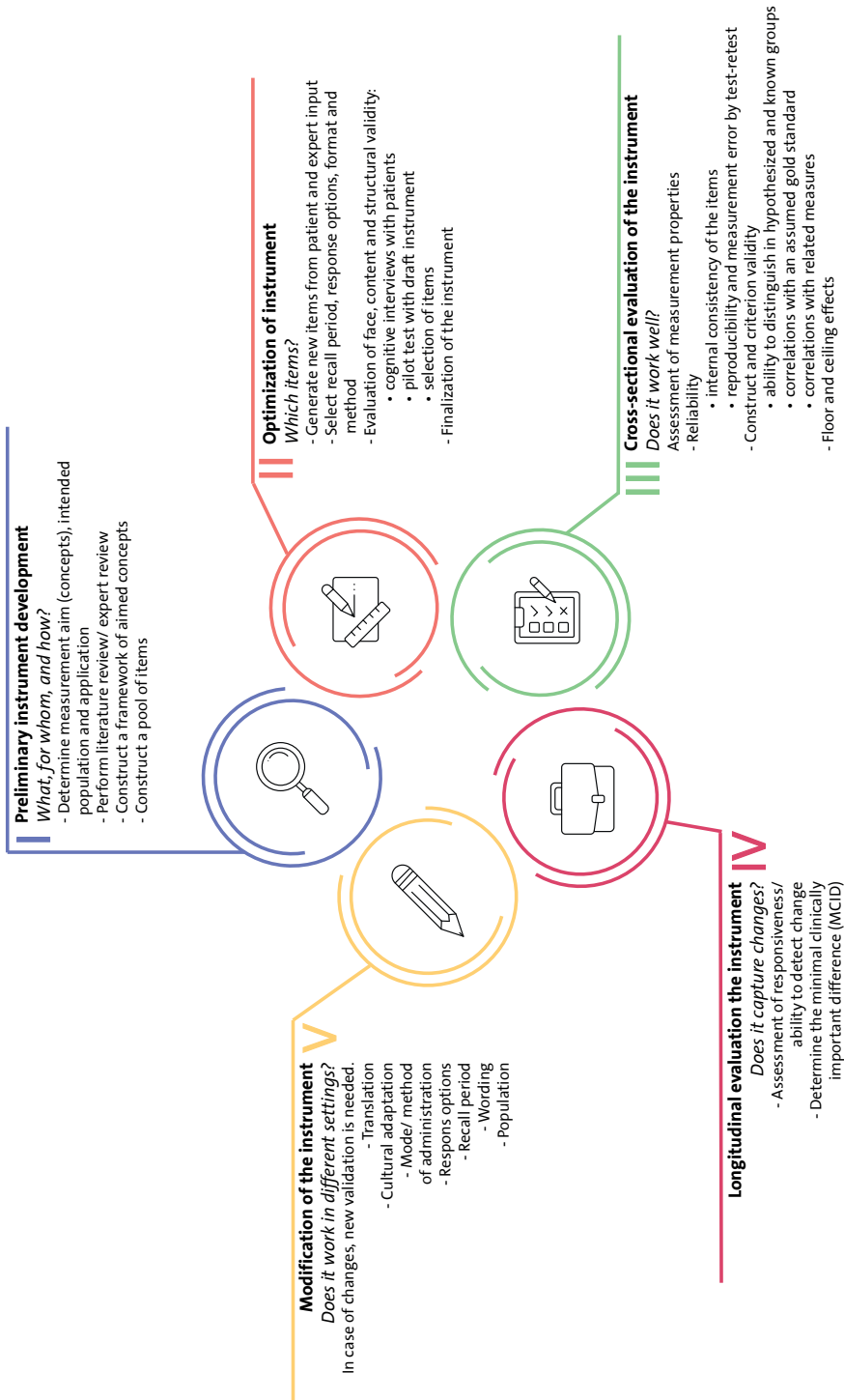
Preliminary instrument development
What, for whom, and how?
- Determine measurement aim (concepts), intended population and application
- Perform literature review/ expert review
- Construct a framework of aimed concepts
- Construct a pool of items

Optimization of instrument
Which items?
- Generate new items from patient and expert input
- Select recall period, response options, format and method
- Evaluation of face, content and structural validity:
  • cognitive interviews with patients
  • pilot test with draft instrument
  • selection of items
- Finalization of the instrument

Cross-sectional evaluation of the instrument
Does it work well?
Assessment of measurement properties
- Reliability
  • internal consistency of the items
  • reproducibility and measurement error by test-retest
- Construct and criterion validity
  • ability to distinguish in hypothesized and known groups
  • correlations with an assumed gold standard
  • correlations with related measures
- Floor and ceiling effects

Modification of the instrument
Does it work in different settings?
In case of changes, new validation is needed.
- Translation
- Cultural adaptation
- Mode/ method of administration
- Respons options
- Recall period
- Wording
- Population

Longitudinal evaluation the instrument
Does it capture changes?
- Assessment of responsiveness/ ability to detect change
- Determine the minimal clinically important difference (MCID)

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

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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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