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.

REFERENCES

1. Kreuter M, Swigris J, Pittrow D, et al. Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. *Respir Res.* 2017;18(1):139.
2. Russell AM, Ripamonti E, Vancheri C. Qualitative European survey of patients with idiopathic pulmonary fibrosis: patients' perspectives of the disease and treatment. *BMC Pulm Med.* 2016;16:10.
3. Victorson DE, Cella D, Grund H, Judson MA. A conceptual model of health-related quality of life in sarcoidosis. *Qual Life Res.* 2014;23(1):89-101.
4. Goracci A, Fagiolini A, Martinucci M, et al. Quality of life, anxiety and depression in sarcoidosis. *Gen Hosp Psychiatry.* 2008;30(5):441-445.
5. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. *Eur Respir Rev.* 2015;24(138):621-629.
6. Gu S, Hu H, Dong H. Systematic Review of Health-Related Quality of Life in Patients with Pulmonary Arterial Hypertension. *Pharmacoeconomics.* 2016;34(8):751-770.
7. Armstrong I, Billings C, Kiely DG, et al. The patient experience of pulmonary hypertension: a large cross-sectional study of UK patients. *BMC Pulmonary Medicine.* 2019;19(1):67.
8. Brown LM, Chen H, Halpern S, Taichman D, McGoon MD, Farber HW, Frost AE, Liou TG, Turner M, Feldkircher K, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest. 2011;140:19–26.
9. Raghu G, Richeldi L. Current approaches to the management of idiopathic pulmonary fibrosis. *Respir Med.* 2017;129:24-30.
10. Russell AM, Sprangers MA, Wibberley S, Snell N, Rose DM, Swigris JJ. The need for patient-centred clinical research in idiopathic pulmonary fibrosis. *BMC Med.* 2015;13:240.
11. Baughman RP, Drent M, Culver DA, et al. Endpoints for clinical trials of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2012;29(2):90-98.
12. Guidance for Industry and FDA staff: Qualification Process for Drug Development Tools (2014). US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Available from: https://www.fda.gov/media/79473/download*.
13. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res.* 2010;19(4):539-549.
14. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10(4):407-415.
15. Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. *Health and Quality of Life Outcomes.* 2006;4(1):70.
16. Ortiz-Gutierrez S, Cruz-Avelar A. Translation and Cross-Cultural Adaptation of Health Assessment Tools. *Actas Dermosifiliogr.* 2018;109(3):202-206.
17. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976).* 2000;25(24):3186-3191.
18. US Department of Health and Human Service, Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes.* 2006;4:79.
19. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med.* 1995;41(10):1403-1409.

20. Chin KM, Gomberg-Maitland M, Channick RN, et al. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results of the SYMPHONY Trial. *Chest.* 2018;154(4):848-861.
21. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol.* 2007;60(1):34-42.
22. Altman DG. *Practical statistics for medical research.* Chapman and Hall, London (1991).
23. Farin E, Heyduck K, Frye BC, Birring SS, Muller-Quernheim J, Schupp JC. Translation and psychometric properties of the King's Sarcoidosis Questionnaire (KSQ) in German language. *Health Qual Life Outcomes.* 2019;17(1):62.
24. Hannah F, Timothy T, Amit P, et al. Standardised Translation of the King's Sarcoidosis Questionnaire (KSQ) into Eleven Languages. *B104. Sarcoidosis: Clinical studies on diagnosis, prognosis and therapy*:A4759-A4759.
25. Van Manen MJ, Wapenaar M, Strookappe B, et al. Validation of the King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis.* 2016;33(1):75-82.
26. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85 Suppl B:25-31; discussion 33-27.
27. Yorke J, Jones PW, Swigris JJ. Development and validity testing of an ipf-specific version of the St George's respiratory questionnaire. *Thorax.* 2010;65(10):921-926.
28. Diamantopoulos A, Wright E, Vlahopoulou K, Cornic L, Schoof N, Maher TM. The Burden of Illness of Idiopathic Pulmonary Fibrosis: A Comprehensive Evidence Review. *Pharmacoeconomics.* 2018.
29. Aguirre-Camacho A, Stepanous J, Blanco-Donoso LM, et al. Adaptation and Validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for Use in Spain. *Rev Esp Cardiol (Engl Ed).* 2017;70(6):467-473.
30. Cima K, Twiss J, Speich R, et al. The German adaptation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). *Health Qual Life Outcomes.* 2012;10:110.
31. Coffin D, Duval K, Martel S, et al. Adaptation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) into French-Canadian and English-Canadian. *Can Respir J.* 2008;15(2):77-83.
32. Ganderton L, Jenkins S, McKenna SP, et al. Validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for the Australian and New Zealand population. *Respirology.* 2011;16(8):1235-1240.
33. Gomberg-Maitland M, Thenappan T, Rizvi K, Chandra S, Meads DM, McKenna SP. United States validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). *J Heart Lung Transplant.* 2008;27(1):124-130.
34. Malaczynska-Rajpold K, Smukowska-Gorynia A, Heaney A, et al. The Polish adaptation of the CAMbridge Pulmonary Hypertension Outcome Review (CAMPHOR). *Cardiol J.* 2018.
35. Reis A, Twiss J, Vicente M, et al. Portuguese validation of the Cambridge pulmonary hypertension outcome review (CAMPHOR) questionnaire. *Health Qual Life Outcomes.* 2016;14(1):110.
36. Selimovic N, Rundqvist B, Kjork E, Viriden J, Twiss J, McKenna SP. Adaptation and validation of the Cambridge pulmonary hypertension outcome review for Sweden. *Scand J Public Health.* 2012;40(8):777-783.
37. Wapenaar M, Twiss J, Wagenaar M, et al. Adaptation and validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for the Netherlands. *Neth Heart J.* 2016;24(6):417-424.
38. McCollister D, Shaffer S, Badesch DB, et al. Development of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT(R)) questionnaire: a new patient-reported outcome instrument for PAH. *Respir Res.* 2016;17(1):72.

39. Yorke J, Corris P, Gaine S, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *European Respiratory Journal.* 2014;43(4):1106-1113.
40. Mellema JJ, O'Connor CM, Overbeek CL, Hageman MG, Ring D. The effect of feedback regarding coping strategies and illness behavior on hand surgery patient satisfaction and communication: a randomized controlled trial. *Hand (N Y).* 2015;10(3):503-511.
41. Keulen MHF, Teunis T, Vagner GA, Ring D, Reichel LM. The Effect of the Content of Patient-Reported Outcome Measures on Patient Perceived Empathy and Satisfaction: A Randomized Controlled Trial. *J Hand Surg Am.* 2018;43(12):1141 e1141-1141 e1149.
42. Smith AB, Hanbury A, Retzler J. Item banking and computer-adaptive testing in clinical trials: Standing in sight of the PROMISed land. *Contemp Clin Trials Commun.* 2019;13:005-005.
43. Russell AM, Adamali H, Molyneaux PL, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2016;194(8):989-997.
44. Johannson KA, Vittinghoff E, Morisset J, Lee JS, Balmes JR, Collard HR. Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis. *Eur Respir J.* 2017;50(1).
45. 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.
46. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J.* 2005;26(4):720-735.
47. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J.* 2017;49(1).
48. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: Diagnosis, epidemiology and natural history. *Respirology.* 2016;21(3):427-437.
49. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J.* 2017;50(3).
50. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* 2013;188(8):e13-64.
51. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J.* 2015;46(4):903-975.
52. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183(6):788-824.
53. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev.* 2014(10):CD006322.
54. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev.* 2017;1:CD011285.
55. Grunig E, Eichstaedt C, Barbera JA, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J.* 2018.
56. Wijsenbeek MS, Holland AE, Swigris JJ, Renzoni EA. Comprehensive Supportive Care for Patients with Fibrosing Interstitial Lung Disease. *Am J Respir Crit Care Med.* 2019.

57. Laviolette L, Bourbeau J, Bernard S, et al. Assessing the impact of pulmonary rehabilitation on functional status in COPD. *Thorax.* 2008;63(2):115-121.
58. Peacock AJ, Naeije R, Galiè N, Rubin L. End-points and clinical trial design in pulmonary arterial hypertension: have we made progress? *European Respiratory Journal.* 2009;34(1):231-242.
59. Ulrich S, Fischler M, Speich R, Bloch KE. Wrist actigraphy predicts outcome in patients with pulmonary hypertension. *Respiration.* 2013;86(1):45-51.
60. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest.* 2012;142(6):1391-1398.
61. Concannon TW. Can patient centered outcomes research improve healthcare? *BMJ : British Medical Journal.* 2015;351:h3859.