PROMising developments in IPF patient-reported outcome measures

Claire M. Nolan[1,2] and Surinder S. Birring[3,4]

[1] Harefield Respiratory Research Group, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, London, UK

[2] Division of Physiotherapy, Dept of Health Sciences, College of Health, Medicine and Life Sciences, Brunel University, London, UK

[3] Dept of Respiratory Medicine, King's College Hospital, London, UK

[4] Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

Corresponding author: Surinder S. Birring (surinder.birring@nhs.net)

Shareable abstract (@ERSpublications)

PROMs have an important role in the assessment of people with IPF. The studies published in this issue provide two promising instruments that, following complete psychometric evaluation, could easily be used in the clinic setting.

Idiopathic pulmonary fibrosis (IPF) is characterised by increasing severity of symptoms, including dyspnoea, cough and fatigue, functional decline and poor prognosis with a median untreated survival of 3 years from diagnosis [1]. Traditionally, IPF research and clinical management have involved objective assessments including pulmonary function tests, high-resolution computed tomography scans as well as morbidity (e.g. exacerbations, hospitalisation) and mortality endpoints. However, these measures may not capture aspects of the disease important to people living with IPF, such as symptoms and quality of life, which can be measured using patient-reported outcome measures (PROMs) [2]. In IPF, a rapidly progressive disease with a large symptom burden, the use of validated and standardised PROMs is particularly relevant, as they can highlight the impact of the disease on the person which enables consideration of their perspectives, individualised care and, in clinical trials, capture treatment effects not detected by other outcome measures [3].

Until relatively recently, PROMs used in interstitial lung disease (ILD) and IPF research had been developed for use in other chronic respiratory diseases, e.g. the St Georges' Respiratory Questionnaire (SGRQ) [4]. In the past few years, several ILD- or IPF-specific PROMs have been developed, most of which measure health-related quality of life. The King's Brief Interstitial Lung Disease (K-BILD) questionnaire is an ILD-specific measure of health-related quality of life (15 items) [5]. It has been shown to have construct validity [5, 6]; is reproducible [6]; is responsive to pulmonary rehabilitation [7], supplementary oxygen therapy [8], medical management of cough [9] and longitudinal change [10]; and is independently associated with 12-month survival in people with ILD [11] and IPF [11, 12]. It has multiple minimum clinically important difference (MCID) estimates: +5 to +8 points: longitudinal improvement [12–15]; −2.7 points: longitudinal deterioration [14]; +4 points: pulmonary rehabilitation [16]). The SGRQ-IPF (SGRQ-I) [17], a modified version of the original St Georges' Respiratory Questionnaire, has acceptable psychometric properties in terms of repeatability [17, 18] as well as concurrent [18] and construct validity [17]. It has been shown to be responsive to interventions, such as pulmonary rehabilitation [19, 20], and longitudinal change with an MCID for improvement and deterioration of +3.3 and −5.3 points respectively [14]. However, despite being shorter than the original SGRQ, it remains lengthy (34 items), which may impact its utility in the clinical setting. A Tool to Assess Quality of life in IPF (ATAQ-IPF) was developed in collaboration with people with IPF [21]. It is

reproducible and has satisfactory construct validity [21]. However, it has 74 items and there are no published data on responsiveness. Recently, ATAQ-IPF has been used to inform the development, along with other methodologies, of a new shorter instrument, Living with IPF (35 items) [22]. Initial testing demonstrated acceptable test–retest reliability as well as concurrent and discriminatory validity [22], and qualitative research demonstrated that the content of the questionnaire was relevant and important to people with other types of pulmonary fibrosis [23]. However, investigation of longitudinal validity and responsiveness in people with IPF is required, as well as full psychometric testing in individuals with other types of pulmonary fibrosis.

In IPF, PROMs are predominantly used in research studies, rather than clinical practice. To encourage use in the clinical setting, instruments should have acceptable psychometric properties, be standardised and brief as well as simple to understand, administer, score and interpret by both people living with the disease and clinicians. Visual analogue scales (VAS) are psychometric tools that can be used to rapidly assess the severity of symptoms and other traits. The VAS consists of a horizontal or vertical line, usually 100 mm in length, with anchor descriptors such as “no breathlessness” on the left- and “worst breathlessness imaginable” on the right-hand side of the scale [24]. The person makes a mark reflecting his or her perception, and the distance from the left endpoint to the mark is measured in millimetres. An alternative to the VAS is the numerical rating scale (NRS), which is a 100 mm horizontal scale marked with 11 (most commonly used), 21 or 101 points, where the end-points are the extremes of the variable of interest, similar to the VAS [25]. The respondent marks the numeric value that best represents their experience of the symptom. These PROMs are easy to administer and score, are feasible to use across different populations as minimal use of verbal and numeric descriptors allow people with low literacy and numeracy skills to complete the assessment, and minimal language translation supports their use in different languages. Few studies have investigated the validity of VAS tools in IPF and other ILDs. A study by YATES et al. [26] reported that VAS was valid for assessing change in dyspnoea and fatigue over time in 64 people with ILD and estimated the MCID as 22.0 mm and 14.5 mm, respectively. In contrast, VAS was not valid for assessing change in cough, most likely because cough did not change significantly [26]. Furthermore, psychometric properties, including reliability and repeatability of each VAS, were not assessed [26]. In this issue of the European Respiratory Journal, two studies provide welcome insights into the validity of using VAS and NRS scales to assess symptoms and health status in IPF.

MOOR et al. [27] investigated the psychometric properties of four online VASs that measured the 1-week recall of dyspnoea (VASD), fatigue (VASF), cough (VASC), general wellbeing (VASG). Each item was represented by a 10-cm VAS (when used on a computer or tablet) with descriptors in Dutch at both ends. Participants were people with IPF enrolled in a randomised controlled trial that investigated home monitoring and included assessment of pulmonary function, K-BILD, EQ-5D and a global rating of change questionnaire at baseline, 12 and 24 weeks. Reliability was moderate to high, being strongest for fatigue and weakest for cough. The VAS scales had a weak to strong correlation with ILD and general health status (K-BILD and EQ-5D, respectively). Data for VASC were less promising: no to weak correlation with health status. This may indicate that cough should be assessed using a cough-specific instrument that captures the multiple dimensions of health impacted by cough. Another noteworthy finding was the association of VAS with health status strengthened over time. The reason for this is not clear but could be due to increasing familiarity with the tools over time. If confirmed in future

studies, this may be an important consideration for study design and data interpretation. The study by MOOR et al. [27] extends the understanding of the psychometric properties of VAS in people with IPF, but the selection of the four items included in the instrument was not described. Although the items are key traits associated with IPF, it is unclear if they reflect the experiences of participants recruited to the study [28]. Additionally, psychometric properties including internal consistency, discriminative and longitudinal validity, responsiveness and minimal important difference need to be evaluated to provide reassurance on the validity and utility of the instrument.

In another study in this issue of the European Respiratory Journal, using clinical expertise as well as focus groups and interviews of people with IPF, SCALLAN et al. [29] developed the R-Scale for Pulmonary Fibrosis (R-Scale-PF), a five-item NRS (cough, shortness of breath, fatigue, depressed mood, overall sense of wellbeing) to measure health-related quality of life in people with IPF. Each item is represented by a 13-cm NRS that ranged from 0 to 10 with 1-cm 0.5 increments and descriptors at each end (none, severe). Internal consistency was high with an acceptable floor/ceiling effect in all domains except depression (floor effect: 36%). There were moderate to strong negative correlations between R-Scale-PF and KBILD-T, EQ-5D-5L index and VAS score but, as expected, weak to moderate correlation with forced vital capacity (FVC) % predicted, diffusing capacity of the lung for carbon monoxide (DLCO) % predicted and 6-min walking distance (6MWD). R-Scale-PF scores were significantly higher in supplementary oxygen users and those with worse DLCO % predicted, GAP index and 6MWD; there was also a trend in those with worse FVC % predicted. A total of 53 participants completed the questionnaire 5–6 months following baseline assessment. The relationship between change in R-Scale-PF and change in KBILD-T, EQ-5D-5L index and VAS scores ranged from weak to strong correlation, which demonstrates concurrent validity across repeated measurements.

The R-Scale-PF study provides important information on the utility of a simple PROM in IPF; however, during the instrument development phase, participants identified 11 initial domains/ items but data to support saturation for new domains/items, face validity and optimal scales endorsed by participants were not analysed. IPF affects a wide range of health domains and it is therefore important that the item-generation and elimination processes for PROMs are thorough [28]. A very brief instrument may not capture all of the key items important to people with IPF; it can be challenging finding the right balance between brevity and comprehensive evaluation. Although the authors propose that the instrument assesses health-related quality of life, at least three items measure symptom severity, and although “overall sense of wellbeing” is measured, item-level interpretation may be required when used for research purposes. The length of the NRS used in this study, 13 cm, is unusual and was used to maximise the available page/screen format. These instruments are usually 10 cm long; this may impact standardisation, interpretation and comparison with similar instruments. The completion time for the R-Scale-PF was 1 min, compared to 2 min for the K-BILD, a more comprehensive measure of health-related quality of life. Despite this, a greater proportion of participants reported the K-BILD was easier to understand and complete than the R-Sale-PF. Furthermore, twice the number of participants reported the K-BILD in comparison to the R-Scale-PF accurately reflected the factors that impacted their health-related quality of life, indicating that the R-Scale-PF instrument may be too brief to measure health-related quality of life and that fewer instrument items may not always be advantageous. Nonetheless, this instrument demonstrates potential and future research should investigate repeatability, responsiveness and estimate the minimal important difference in order to fully understand its psychometric properties and utility.

In order to improve PROM development, acceptability and implementation into clinical practice, the following points are recommended. First, an important psychometric property of all outcome measures is the ability to detect a clinically important threshold which improves an instrument's utility and interpretability. Investigators usually evaluate the minimal important difference for improvement. However, due to the progressive nature of many ILDs, where the goal of medical management is to slow the decline in deterioration, improvements in quality of life and/or symptoms are often not possible. Accordingly, it may be more informative to estimate a change in PROM score that reflects clinical stability and/or deterioration [28], similar to FVC % predicted. For example, the INBUILD trial demonstrated that compared to placebo, nintedanib was associated with a slower rate of progression of FVC in individuals with fibrosing lung disease but this was not reflected by meaningful improvements in of health-related quality of life [30]. Stabilisation of health-related quality of life in people responding to nintedanib (slower FVC decline) was not investigated and should be assessed in future in studies. Second, most PROMs available for use in ILD, excluding K-BILD, have been developed for individuals with IPF. Consequently, there is a pressing need to develop new or adapt IPF-specific instruments and validate them in other ILDs to ensure parity of care and that participants' perspectives are evaluated. Third, for successful adoption into routine clinical practice, people asked to complete the instruments should be educated on the rationale for and benefit of collecting these data, which may improve completion rates. They should be collected alongside other routine tests and be available prior to clinical assessment, ideally completed using a web-based platform, as performed by MOOR et al. [27], in order to inform the consultation and management plan.

In conclusion, PROMs have an important role in the assessment of people with IPF in research and clinical practice. They can be used to understand people's experience, establish a baseline and monitor change over time as well as in response to intervention. An important evolutionary step in IPF care is the use of PROMs as part of routine clinical care. The studies published in this issue provide two promising instruments that, following complete psychometric evaluation, could easily be used in the clinic setting.

Author contributions: Concept and design: C.M. Nolan and S.S. Birring; drafting of manuscript: C.M. Nolan and S.S. Birring; revision of manuscript critically for important intellectual content: C.M. Nolan and S.S. Birring; approval of final manuscript: C.M. Nolan and S.S. Birring.

Conflict of interest: C.M. Nolan reports personal fees from Novartis, outside the submitted work. S.S. Birring reports personal fees from Boehringer Ingelheim, outside the submitted work.

References

1. 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: 788–824.
2. Russell A-M, Sprangers MA, Wibberley S, et al. The need for patient-centred clinical research in idiopathic pulmonary fibrosis. BMC Med 2015; 13: 240.
3. Swigris JJ, Fairclough D. Patient-reported outcomes in idiopathic pulmonary fibrosis research. Chest 2012; 142: 291–297.
4. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2071–2082.
5. Patel AS, Siegert RJ, Brignall K, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax 2012; 67: 804–810.

6. Patel AS, Siegert RJ, Bajwah S, et al. Rasch analysis and impact factor methods both yield valid and comparable measures of health status in interstitial lung disease. J Clin Epidemiol 2015; 68: 1019–1027.
7. Nolan CM, Canavan JL, Jones SE, et al. Response of the King's brief interstitial lung disease questionnaire to pulmonary rehabilitation. Eur Respir J 2015; 46: Suppl. 59, PA744.
8. Visca D, Mori L, Tsipouri V, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. Lancet Respir Med 2018; 6: 759–770.
9. Birring SS, Wijsenbeek MS, Agrawal S, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. Lancet Respir Med 2017; 5: 806–815.
10. Siegert R, Bajwah S, Keir G, et al. The King's brief interstitial lung disease questionnaire; responsiveness and minimal important difference. Am J Respir Crit Care Med 2012; 185: A4580.
11. Sharp C, Baggott C, Birring S, et al. S20 Kbild scores have similar power to predict survival as pulmonaryphysiology in interstitial lung disease. Thorax 2016; 71: Suppl. 3, A13–A14.
12. Kim JW, Clark A, Birring S, et al. Psychometric properties of patient reported outcome measures in idiopathic pulmonary fibrosis. Chron Respir Dis 2021; 18: 14799731211033925.
13. Sinha A, Patel AS, Siegert R, et al. The King's brief interstitial lung disease (K-BILD) questionnaire; an updated minimal important difference. Eur Respir J 2016; 48: Suppl. 60, PA808.
14. Prior TS, Hoyer N, Hilberg O, et al. Responsiveness and minimal clinically important difference of SGRQ-I and K-BILD in idiopathic pulmonary fibrosis. Respir Res 2020; 21: 91.
15. Patel AS, Siegert RJ, Keir GJ, et al. The minimal important difference of the King's brief interstitial lung disease questionnaire (K-BILD) and forced vital capacity in interstitial lung disease. Respir Med 2013; 107: 1438–1443.
16. Barker RE, Nolan CM, Delogu V. The Kings Brief Interstitial Lung Disease questionnaire: response to pulmonary rehabilitation and minimal important difference. Am J Respir Crit Care Med 2017; 195: A2849.
17. 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: 921–926.
18. Prior TS, Hoyer N, Shaker SB, et al. Validation of the IPF-specific version of St. George's respiratory questionnaire. Respir Res 2019; 20: 199.
19. Dowman LM, McDonald CF, Hill CJ, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax 2017; 72: 610–619.
20. Gaunaurd IA, Gómez-Marín OW, Ramos CF, et al. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. Respir Care 2014; 59: 1872–1879.
21. Swigris JJ, Wilson SR, Green KE, et al. Development of the ATAQ-IPF: a tool to assess quality of life in IPF. Health Qual Life Outcomes 2010; 8: 77.
22. Swigris JJ, Andrae DA, Churney T, et al. Development and initial validation analyses of the living with idiopathic pulmonary fibrosis questionnaire. Am J Respir Crit Care Med 2020; 202: 1689–1697.
23. Swigris J, Cutts K, Male N, et al. The Living with Pulmonary Fibrosis questionnaire in progressive fibrosing interstitial lung disease. ERJ Open Res 2021; 7: 00145-2020.
24. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: myths, truths and clinical relevance. Scand J Pain 2016; 13: 67–75.
25. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs 2005; 14: 798–804.
26. Yates H, Adamali HI, Maskell N, et al. Visual analogue scales for interstitial lung disease: a prospective validation study. QJM 2018; 111: 531–539.

27. Moor CC, Mostard RLM, Grutters JC, et al. The use of online visual analogue scales in idiopathic pulmonary fibrosis. Eur Respir J 2022; 59: 2101531.
28. Aronson KI, Danoff SK, Russell A-M, et al. Patient-centered outcomes research in interstitial lung disease: an official American Thoracic Society research statement. Am J Respir Crit Care Med 2021; 204: e3–e23.
29. Scallan C, Strand L, Hayes J, et al. R-Scale for pulmonary fibrosis (PF): a simple, visual tool for the assessment of health-related quality of life. Eur Respir J 2022; 59: 2100917.
30. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381: 1718–1727.