Development & Testing of the Idiopathic Pulmonary Fibrosis Patient Reported Outcome Measure
UK & Ireland Multi-Centre IPF-PRoM Study

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CLINICAL RESEARCH FELLOW
International Drivers for PROM’s

- PROM’s needed
  - regulatory decision making
  - medical product development
- The quality and validity of PROMs is highly variable
- There is a need to develop and validate PROM’s to generate
  - high quality
  - relevant data
  on outcomes of importance to patients

Endpoint Model: Treatment of Symptoms Associated with IPF

**Concept**

**Indication**
Treatment of symptoms of IPF

**Supportive Concepts Secondary**
Other treatment benefit

**Endpoints**

**Primary**
Total IPF symptoms score (PRO assessment)

**Supportive Concepts Secondary**
Physical performance (PRO or non-PRO assessment)
Physical limitations of IPF (PRO assessment)
UK Drivers for PROM’s

2009 English NHS began collecting PROMs
(four elective procedures)

- Change of government in 2010
  Outcomes Framework.

- PROMs programme stalled

- Restructuring of the NHS

- PROMs programme shifted DH to NHS England

- PROMs programme rumbled along

- Millions of data points collected

- Powerful insights into how surgery improves health

- Regaining Momentum

- ?Rolling out to Chronic Conditions?

https://www.engage.england.nhs.uk/consultation/proms-programme/

Early PROM:
- Relieved
- Unrelieved
- Dead

Getting the most out of PROMs
Nancy Devlin & John Appleby
Kings Fund March 2010
https://www.kingsfund.org.uk/
UK Drivers for a PROM for IPF?

- NICE clinical guideline 2013: ‘significant variations in clinical care’
- NICE Quality Standards for IPF 2015: benchmark
- NICE technology appraisal guidance [TA282] 2013 Pirfenidone for treating idiopathic pulmonary fibrosis
- NICE technology appraisal guidance [TA379] 2016 Nintedanib for treating idiopathic pulmonary fibrosis

https://www.nice.org.uk/guidance/cg163
Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
March, 2009

The Voice of the Patient

Patient-Focused Drug Development Initiative
Idiopathic Pulmonary Fibrosis
Public Meeting: September 26, 2014
Report Date: March, 2015

The PCORI Methodology Report
PCORI Methodology Committee
November 2013 (in revision)
Patient Centred Research: IPF-PRoM Study

.............................informed by patients’ views & experiences as both participants & partners in research

▪ The study protocol reviewed by patients
▪ A Research support Group was established:
  ▪ Lead researcher
  ▪ Senior Research Nurse
  ▪ Clinical psychologist
  ▪ Patient representatives
  ▪ Care-giver representative
  ▪ Patient & Public Involvement officers

▪ Quarterly meetings
▪ Formal Terms of Reference
▪ Role descriptions agreed at outset
▪ The remit of the RSG to review study progress
▪ Have an instrumental role in analysis
▪ Participate in consensus rounds in phase one
▪ Contribute to Outputs:
  ▪ Joint publications
  ▪ International conference Presentations

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IPF PROM Methodology

- Study Configuration: Multi-centre study
- Patient Centeredness
- Literature Review
  - Qualitative: Focus groups
  - Consensus: Nominal Group of ILD experts
    - Modified NG - Expert Interdisciplinary, Patient & Carer Group
  - Survey: Delphi Method
  - Quantitative: Item reduction
    - Psychometrics – Classical Test theory
COnsensus-based Standards for the selection of health Measurement INstruments

- Literature review: 26 outcome measures in IPF studies
- 14 met the inclusion criteria
- Deconstructed
- 1212 items underwent duplicity screening
- 410 items submitted to consensus rounds

www.cosmin.nl | www.emgo.nl
Focus Group: Framework

- Brompton Hospital - London
  - n= 7 (3F) CPI > 45 No O2

- Brompton Hospital - London
  - n= 5 (2F) CPI > 45 On O2

- Pennine Acute Hospitals
  - n= 6 (2F) CPI < 45 No O2

- North Bristol Hospitals
  - n= 10 (2F) CPI < 45 No O2

http://www.natcen.ac.uk/our-expertise/methods-expertise/qualitative/framework/
FDA Claim


- Content Validity:
  - Items cover all aspects of the concept important to patients
  - Variations in severity of condition represented
  - Population characteristics represented
  - Saturation reached
  - Source of items traceable
  - An item tracking matrix

Ritchie J and Lewis J 2003 Qualitative Research Practice
Delphi*Rounds One and Two

- 305 items included in R1
- 236 items originated from focus group discussions
- Domains ranked by nominal group
- Importance of statements rated on Likert scale 1-7
- Comments & nominations of other dimensions invited
- Participants:
  - Patients diagnosed with IPF = 77
  - Relatives = 18
  - Specialist ILD physicians | nurses = 29
- Response rates ≥ 93% in all categories
- 112 items were included in R2

(16 new items identified in qualitative analysis)


## Standardised Inclusion

<table>
<thead>
<tr>
<th>Statement</th>
<th>Threshold to apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely include</td>
<td>&gt;=70% of participants rate statement as &gt;=6 OR median rating of &gt;=5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Maybe include</td>
<td>&gt;=70% of participants rate statement as &gt;=5 OR median rating of &gt;=5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely exclude</td>
<td>&lt;70% of participants rate statement as &lt;=4 AND 100% participants understand statement OR median &lt;=4 AND 100% panel understand statement</td>
</tr>
<tr>
<td>Review</td>
<td>&lt;70% of panel rate statement as &gt;=6 AND &lt;100% panel understand statement</td>
</tr>
</tbody>
</table>
Delphi Results R3: 105 items

- Accessing survey: 510
- Completing survey: 281
- Completing hard copy: 20
- Partially completing survey: 72
- Not permitted to complete survey: 41
- Accessing survey preamble only: 116
- Response categories:
  - Never
  - Occasionally
  - Very often
  - Always

AGE DISTRIBUTION

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Geographical Distribution Respondents & Centres

- Complete responders male n=181 (65%)
- IP addresses were checked to detect duplication

<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK: south East</td>
<td>78</td>
<td>27.8</td>
</tr>
<tr>
<td>UK: midlands</td>
<td>61</td>
<td>21.7</td>
</tr>
<tr>
<td>UK: south West</td>
<td>32</td>
<td>11.4</td>
</tr>
<tr>
<td>UK: north West</td>
<td>24</td>
<td>8.5</td>
</tr>
<tr>
<td>UK: north East</td>
<td>20</td>
<td>7.1</td>
</tr>
<tr>
<td>Ireland</td>
<td>14</td>
<td>5.0</td>
</tr>
<tr>
<td>UK: Scotland</td>
<td>14</td>
<td>5.0</td>
</tr>
<tr>
<td>UK: Yorkshire &amp; Humber</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>UK: NI; Wales &amp; other</td>
<td>26</td>
<td>9</td>
</tr>
</tbody>
</table>
Descriptive Stats & Item Reduction

- 281 complete responses
- 72 partial responses *(test data set)*
- Questions with a ‘non relevant’ category removed (30)
  - 57 % (n=161) no experience of oxygen
  - 35% (n=98) do not have a partner
- Ambiguous items were removed (2)

### Frequency Distribution

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>281</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Strongly Agree</td>
<td>136</td>
<td>48.1%</td>
<td>48.1%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Agree</td>
<td>115</td>
<td>41.3%</td>
<td>41.3%</td>
<td>91.4%</td>
</tr>
<tr>
<td>Disagree</td>
<td>17</td>
<td>6.0%</td>
<td>6.0%</td>
<td>97.4%</td>
</tr>
<tr>
<td>Strongly Disagree</td>
<td>7</td>
<td>2.5%</td>
<td>2.5%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>281</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Factor Analysis (FA)

- FA identified 14 factors accounting for 70% of the variance
- Factors with an eigen value ≥1 were retained
- Questions with a factor loading ≥ 0.5 were retained
- Cronbach’s alpha assessed internal reliability & consistency of the scale
  - Values ≤ 0.7 were considered too low
  - Values ≥ 0.92 redundant
- Items with a communality ≤ 0.5 were removed
- Face validity was continually assessed by the research team
- Cough items: correlation co-efficient > 0.9 suggested cough was a problematic domain

KBILD-I KBILD-R - 15 items each – sharing 7 common items

KBILD-I in contrast to KBILD-R contained a cough item

The presence of a cough item did not improve the overall clinical performance of the KBILD-I

Both questionnaires equally able to detect significantly worse health status in patients with ILD and cough compared to those without cough

It is likely that cough affects a wide range of health status items that capture its impact.

The absence of a cough item did not significantly reduce the performance of the KBILD-R
12 item questionnaire

Four domains:

- Physical experience of breathlessness
- Psychological experience of breathlessness
- Emotional well-being
- Energy

Simple Scoring System

<table>
<thead>
<tr>
<th>Domain</th>
<th>Alpha Value</th>
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<tbody>
<tr>
<td>1</td>
<td>0.874</td>
</tr>
<tr>
<td>2</td>
<td>0.870</td>
</tr>
<tr>
<td>3</td>
<td>0.900</td>
</tr>
<tr>
<td>4</td>
<td>0.849</td>
</tr>
<tr>
<td>Total</td>
<td>0.920</td>
</tr>
</tbody>
</table>

Communalities ≥ 0.5
KMO & Bartletts 0.922
Test Re test Reliability

- 66 patients recruited
- 61 completed TP1 and TP2
- 14 female
- 35 electronically

<table>
<thead>
<tr>
<th>Mean Score</th>
<th>Total</th>
<th>Domain 1</th>
<th>Domain 2</th>
<th>Domain 3</th>
<th>Domain 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP1</td>
<td>28.63</td>
<td>7.18</td>
<td>7.73</td>
<td>6.33</td>
<td>7.38</td>
</tr>
<tr>
<td>TP2</td>
<td>28.52</td>
<td>7.38</td>
<td>7.52</td>
<td>6.28</td>
<td>7.33</td>
</tr>
<tr>
<td>Mean change</td>
<td>0.11</td>
<td>-0.20</td>
<td>0.23</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean absolute difference</td>
<td>2.38</td>
<td>0.87</td>
<td>0.78</td>
<td>0.95</td>
<td>0.88</td>
</tr>
</tbody>
</table>
Test Re test Reliability

<table>
<thead>
<tr>
<th>Domain</th>
<th>t-statistic</th>
<th>p-value</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.272</td>
<td>0.209</td>
<td>0.835</td>
</tr>
<tr>
<td>2</td>
<td>1.458</td>
<td>0.150</td>
<td>0.895</td>
</tr>
<tr>
<td>3</td>
<td>0.273</td>
<td>0.786</td>
<td>0.813</td>
</tr>
<tr>
<td>4</td>
<td>0.305</td>
<td>0.761</td>
<td>0.863</td>
</tr>
<tr>
<td>Total</td>
<td>0.275</td>
<td>0.784</td>
<td>9.24</td>
</tr>
</tbody>
</table>

No significant difference TP1 – TP2

Mean timeframe 20.69 days
Validation: 12m

The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review

Jeffrey J Swigris1, Dirk Esser2, Craig J Connett3 and Kevin K. Brown1

Abstract

Assessment of health-related quality of life (HRQoL) is particularly important in patients with progressive and incurable diseases such as idiopathic pulmonary fibrosis (IPF). The St George’s Respiratory Questionnaire (SGRQ) is frequently used to measure HRQoL in patients with IPF, but it was developed for patients with obstructive lung disease. The aim of this review was to examine published data on the psychometric performance of the SGRQ in patients with IPF. A comprehensive search was conducted to identify studies reporting data on the internal consistency, construct validity, non-responder validity, and interpretability of the SGRQ in patients with IPF, published up to August 2017. A total of 30 papers were retrieved. Internal consistency was measured for the SGRQ symptomatic subsate and reflects the reliability of the scale, and construct validity was assessed using correlation coefficients to determine whether the SGRQ was sensitive to changes in the construct of primary interest. The SGRQ was shown to be strongly related to other patient-reported outcome measures and with a measure of aerobic exercise capacity. Non-responder validity was estimated by using multiple imputation in to-datal sets. The SGRQ was found to be robust to changes in health status, and the scores of patients whose health status had improved, deteriorated or remained unchanged. Although the SGRQ was not developed specifically for use with patients with IPF, in general, its psychometric properties are adequate and suggest that it may be a useful tool to assess health-related quality of life in these patients. However, further research is needed to confirm the SGRQ's utility in this population.

Keywords: idiopathic pulmonary fibrosis, idiopathic pulmonary fibrosis-specific, HRQoL, St George’s Respiratory Questionnaire, health-related quality of life, HRQoL, Psychometrics, validity, reliability

FVC

85

…SGRQ | EQ-5D | MRC
Validation: 3m FVC + interim

Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis

Anne-Marie Russell1,2, Huzaifa Adamali3, Philip L. Molyneaux1,2, Pauline T. Lukey4, Richard P. Marshall4, Elisabetta A. Renzoni1,2, Athol U. Wells1,2, and Toby M. Maher1,2

1National Institute for Health Research Biomedical Research Unit, Royal Brompton Hospital, London, United Kingdom; 2Fibrosis Research Group, National Heart and Lung Institute, Imperial College London, London, United Kingdom; 3Bristol Interstitial Lung Disease Service, North Bristol Lung Centre, Southmead Hospital, Westbury-on-Trym, United Kingdom; and 4Fibrosis and Lung Injury DPU, GlaxoSmithKline R&D, Stevenage, Herts, United Kingdom

ORCID ID: 0000-0001-7192-9149

https://youtu.be/IqlkO1KGq90
Validation

The Idiopathic Pulmonary Fibrosis Patient Reported Outcome Measure

This questionnaire is designed to help us learn more about how Idiopathic Pulmonary Fibrosis affects your life.

The information and the answers you give will be treated with the utmost confidentiality.

There are no right or wrong answers.

Please read each item and place an ‘X’ in the box that best matches your experience over the last two weeks.

If you do not experience an item put an ‘X’ in the ‘none’ box.

Please respond to all items.

We would like to thank you very much for taking the time to answer these questions and help us with our research.

This research was supported by a research fellowship from the National Institute of Health Research, UK.

During the last two weeks how would you rate your overall quality of life?

Excellent ☐  Good ☐  Fair ☐  Poor ☐  Very poor ☐

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Research Support Group

Patient & carer co-investigators: shared experiences of a research steering group from the IPF-PRoM study
AM Russell, AM Doyle, D Ross*, C Burdett*, J Gane*, S Fleming, Z Aden, P Cullinan

Psychological distress in UK patients with IPF; Use of Emotion Thermometers interpreted within a biopsychosocial constructionist framework
A.-M. Doyle, C. Burdett*, J. Gane*, Z. Aden, A-M. Russell
Thank you

2017 ATS Abstract Scholarship