Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials


ORIGINAL ARTICLE

ABSTRACT

Rationale Clinical trial design in interstitial lung diseases (ILDs) has been hampered by lack of consensus on appropriate outcome measures for reliably assessing treatment response. In the setting of connective tissue diseases (CTDs), some measures of ILD disease activity and severity may be confounded by non-pulmonary comorbidities.

Methods The Connective Tissue Disease associated Interstitial Lung Disease (CTD-ILD) working group of Outcome Measures in Rheumatology—a non-profit international organisation dedicated to consensus methodology in identification of outcome measures—conducted a series of investigations which included a Delphi process including >248 ILD medical experts as well as patient focus groups culminating in a nominal group panel of ILD experts and patients. The goal was to define and develop a consensus on the status of outcome measure candidates for use in randomised controlled trials in CTD-ILD and idiopathic pulmonary fibrosis (IPF).

Results A core set comprising specific measures in the domains of lung physiology, lung imaging, survival, dyspnoea, cough and health-related quality of life is proposed as appropriate for consideration for use in a hypothetical 1-year multicentre clinical trial for either CTD-ILD or IPF. As many widely used instruments were found to lack full validation, an agenda for future research is proposed.

Conclusion Identification of consensus preliminary domains and instruments to measure was attained and is a major advance anticipated to facilitate multicentre RCTs in the field.

BACKGROUND

The diffuse idiopathic interstitial pneumonias describe a spectrum of parenchymal lung diseases sharing clinical, physiological, radiological and pathological similarities, including varying degrees of fibrosis, inflammation and vascular injury.1 Idiopathic pulmonary fibrosis (IPF) is associated with usual interstitial pneumonia (UIP), poor survival and limited treatment options.2 Interstitial lung disease (ILD), most typically presenting as non-specific interstitial pneumonitis, is a leading cause of death in systemic sclerosis (SSc)3 and a prominent clinical feature of other connective tissue diseases (CTDs), including idiopathic inflammatory myopathy (IIM) and Sjögren syndrome. UIP is also found in rheumatoid arthritis (RA) and IIM.4 5

Current evaluations of therapies focus on patient survival or markers of chronic disease progression,
for example, change in forced vital capacity (FVC).6–8 Measures of patient function, for example, 6 min walk test (6MWT), and health-related quality of life (HRQoL) have been variably applied with inconsistent results.6 Therapeutic research has been hampered by lack of consensus on and validation of outcome measures that reliably assess the likelihood of treatment response. Furthermore, extra-pulmonary CTD manifestations may confound measures of ILD activity/severity. Patient-reported dyspnoea is demonstrated to predict time to death, yet a satisfactory dyspnoea instrument for ILD has not yet been identified.7 8 Clinically relevant, patient-reported outcome measures (PROMs) exist for obstructive lung disease and, in the absence of disease-specific measures, have been utilised in trials of ILD.

The Outcome Measures in Rheumatology (OMERACT) filter9 (see online supplement) is a dynamic and iterative process/structure through which an instrument’s performance can be evaluated under three criteria or points of examination: truth (face, content, construct and criterion validity), discrimination (reliability, sensitivity to change) and feasibility (cost, interpretability, accessibility, safety, time). The ideal instrument satisfies all three while instruments incompletely satisfying the filter may still be immediately useful but require additional study.

The Connective Tissue Disease associated Interstitial Lung Disease (CTD-ILD) working group of the OMERACT international consensus initiative convened to define outcome measures for use in randomised controlled trials (RCTs) in CTD-ILD. Given the major clinical overlap, the same process was used in parallel for IPF. We report the results of a three-component process: medical expert Delphi exercise, patient perspective investigations and a combined medical expert and patient participant nominal group technique (NGT) meeting leading to identification of preliminary core sets of domains with corresponding instruments that are clinically meaningful and feasible in the context of a 1-year multi-centre RCT for each CTD-ILD and IPF. These sets of instruments are proposed as the minimum outcome measures to be used in future RCTs and registries.

**METHODS**

**Medical expert Delphi process**

**Delphi**

International experts (n=270) were identified by authorship in peer-reviewed journals, specialty society membership and peer recommendations, and invited to participate in the web-based Delphi process.10–12 This began with an ‘item-collection’ stage called Tier 0, wherein participants nominated an unrestricted number of potential domains (qualities to measure) and instruments (specific tools for use as a measure) perceived as relevant for inclusion in a hypothetical 1-year RCT. This exercise produced a list of >6700 items—reduced only for redundancy, organised into 23 domains and 616 instruments and supplemented by expert advisory teams of pathologists and radiologists. The results of Tier 0 provided the content for sequential web-based surveys: Tiers 1, 2 and 3 which progressively reduced the number of voting items as the items with the lowest ratings were dismissed. Survey items for each CTD-ILD and IPF were aligned in parallel and rated along a nine-point Likert scale from 1 (‘not at all important’) to 9 (‘absolutely important’), with ‘insufficiently familiar’ a voting alternative. An extensive online repository of item-related journal articles was available to participants throughout the process.

**Analysis**

A cut-off of <4 (median rating) was applied to ratings from the large number of voting items in Tier 1. Cluster analyses were applied to the ratings in Tiers 2 and 3 avoiding the use of an arbitrary cut-off, thus allowing items to aggregate independently providing an unbiased analysis of agreement among raters.12 A nine-cluster analysis was initially applied and reduced to three clusters for all items during both tiers.

**Patient perspective investigation**

Patient participation is recognised as integral to development of outcome measures by OMERACT, the US Food and Drug Administration and European Medicines Agency.9 13 To investigate the patient perspective in CTD-ILD, a set of qualitative studies were conducted: focus groups (60–90 min) of 8–12 consented participants with CTD-ILD were selected by convenience sampling and asked 1) how their life has changed since the diagnosis of their lung disease? and 2) how their lung disease has changed over time? Patient perspective data in 20 English-speaking patients with IPF were previously available.14 Content was extracted from verbatim transcripts and inductive analysis was applied to minimise investigator bias.15 Following each focus group, CTD-ILD participants (study patients with IPF were not available) rated on a seven-point Likert scale the importance of the domains identified in Tier 0 of the medical expert Delphi process.

**NGT meeting**

At the 2012 OMERACT 11 conference and the 2012 American Thoracic Society (ATS) International Conference, data from the Delphi and the patient perspective investigations were reviewed by medical and patient experts. Following this, a face-to-face meeting was held to apply NGT to the overall results.

At the NGT, evaluation of each domain was led by assigned teams of medical and patient participants who presented evidence-based reviews focusing on instrument validation in accordance with the OMERACT filter.9 12 Several weeks prior to team assembly, interactive educational sessions with the patient participants examined each domain and instrument. The teams served as a resource for evidence-based information during the discussion phases.

After each team presentation, all participants engaged in a ‘round-robin’ discussion allowing equal speaking time per participant10–12 over two to three rounds examining acceptance or rejection of an item, potential clinical endpoint assignment, and determination for new instrument development within that domain. Each round of discussions was followed by group voting.

All participants were requested to register a vote for each item. With participants’ full knowledge, responses from all physicians and patients with CTD-ILD were tabulated for CTD-ILD, with only those from pulmonologists and patients with IFP for IPF. All votes were recorded. (The radiologist voting was tabulated as a pulmonologist.) A priori, acceptance was agreed upon as ≥70% affirmative votes.16 Voting addressed inclusion/exclusion of items based on the OMERACT filter and whether the patient perspective and evidence-based data warranted the need for new instrument development for that corresponding domain.

**RESULTS**

**Medical expert Delphi**

A total of 254 (137 pulmonologists, 113 rheumatologists and 4 cardiologists) engaged in the Delphi process. Seventy-four per cent reported their primary field of interest being ILD. Participation through all stages exceeded 97%. Six domains identified were: Dyspnoea, HRQoL, Lung Physiology/Function,

---

**Lung Imaging and Survival, and Medications** for each CTD-ILD and IPF. Eighteen instruments were identified for each CTD-ILD and IPF (tables 1–4).

**Focus groups**

Focus groups were conducted with patients (n=45) in IIM-ILD (n=11), RA-ILD (n=13), Ssc-ILD (n=17) and other CTD diagnoses (n=4) (table 5). Patient participants attributed importance to cough, dyspnoea, fatigue, participation (in family, social and leisure activities, work within and outside the home), physical function, self-care and sleep in the questionnaire and the focus groups. Changes in cough were perceived as reflecting potential worsening ILD. Dyspnoea largely carried descriptors different from current instruments. Patients with IPF identified cough, dyspnoea and HRQoL effects as central symptoms.14

**OMERACT 11/ATS 2012/Domain Team meetings**

Discussions and voting at the OMERACT 11/ATS 2012/Domain Team meetings resulted in the following changes based on the patient perspective data or strong evidence in recent literature (detailed in online supplement):

- **Cough** was reintroduced, discussed and voted upon at the NGT.
- To satisfy the reintroduction of **Cough**, Leicester Cough Questionnaire (LCQ) was introduced as an interim instrument to assess Cough.
- The Mahler Dyspnea Index (MDI) and University of California San Diego Shortness of Breath Questionnaire (UCSD-SBQ) were reintroduced under Dyspnoea for use in CTD-ILD and IPF, respectively, based on substantive findings in an updated literature review.
- For feasibility, **HRQoL** would capture ‘fatigue’, ‘participation’, ‘physical function’, ‘self-care’ and ‘sleep’ until disease-specific investigations into these components were conducted.
- **NGT** voting would include whether development of new instruments for Dyspnoea, Cough and HRQoL are needed.
- Owing to variability of therapies, concern regarding **Medications** as a core domain was expressed. However, being identified as important in the Delphi, a statement of clarification would be constructed at the NGT.
- ‘All-Cause Mortality’ was introduced as an assessment of ‘Survival’.

**NGT results**

The final NGT panel included 10 pulmonary experts, 12 rheumatology experts and 1 radiology expert, with 5 patient partners (tables 6–8, and see online supplement).

Table 6 displays the voting results on instruments for CTD-ILD and IPF with striking concurrence in all domains except for **HRQoL**, for which Patient Global Assessment (PtGA) was not accepted by the pulmonary experts for IPF.

Tables 7 and 8 present the content of the NGT discussions in the context of the OMERACT filter with items of special interest highlighted below.

It was agreed that ‘Medications’ (ie, the incremental increase/decrease of glucocorticoid and/or immunosuppressive therapy) should be viewed as protocol specific rather than a core domain. Depending on study design, ‘Medications’ may be either a dichotomous interpretation of treatment efficacy/failure or a reflection of changes in disease activity.

The lack of validated biomarkers was fully discussed. No items for bio-specimen evaluation emerged from the Delphi exercise but the importance of future biomarker research was planned for during the meeting. Consensus is required to define the minimal standards for investigation-related bio-banking and systematic access to samples by investigators.17

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Reduction of domains and instruments in the Delphi process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase yielded</td>
<td>Analysis method</td>
</tr>
<tr>
<td>Tier 0</td>
<td>Intense review</td>
</tr>
<tr>
<td>Tier 1</td>
<td>&lt;4 median cut-off</td>
</tr>
<tr>
<td>Tier 2</td>
<td>cluster analysis</td>
</tr>
<tr>
<td>Tier 3</td>
<td>cluster analysis</td>
</tr>
</tbody>
</table>

CTD-ILD, connective tissue disease associated interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Domain results of Tier 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 0 results of 23 domains</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>Mental health</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Sleep</td>
</tr>
<tr>
<td>Imaging</td>
<td>Global assessment</td>
</tr>
<tr>
<td>Lung physiology/function</td>
<td>HRQoL</td>
</tr>
<tr>
<td>Lung parenchyma</td>
<td>Physical function</td>
</tr>
<tr>
<td>Lung vascular</td>
<td>Participation</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>Employment/work productivity</td>
</tr>
<tr>
<td>Composite scores</td>
<td>Medication</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Extra-pulmonary CTD features</td>
</tr>
<tr>
<td>Cough</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Barriers to care</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

CTD, connective tissue disease; HRQoL, health-related quality of life.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Results of the Delphi Tier 3 cluster analysis of domains with median/mean reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five domains identified for each CTD-ILD and IPF</td>
<td></td>
</tr>
<tr>
<td>Domain name</td>
<td>CTD-ILD (median/mean) ratings on a 9-point scale</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>(8.0/7.8)</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>(8.0/7.7)</td>
</tr>
<tr>
<td>Lung imaging</td>
<td>(9.0/8.3)</td>
</tr>
<tr>
<td>Lung physiology/function</td>
<td>(9.0/8.7)</td>
</tr>
<tr>
<td>Survival</td>
<td>(8.0/8.2)</td>
</tr>
<tr>
<td>Medications</td>
<td>(8.0/7.2)</td>
</tr>
</tbody>
</table>

CTD-ILD, connective tissue disease associated interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

**DISCUSSION**

These comprehensive international investigations are the first to identify core sets of domains in each CTD-ILD and IPF along with a provisional consensus on a minimum cadre of feasible and clinically meaningful outcome measures/instruments. The proposed measures are intended to be a common denominator across future RCTs, longitudinal observational studies and natural history registries until work can be done that substantiates a truly durable framework. The rigorous consensus methodologies of OMERACT outline the overall status of the field. Importantly, this is the first study in ILD to incorporate patient participants in panel meetings or guidelines. From the synergy of these investigations, domains which require development of new instruments were also identified, thus providing guidance for imminent research.

Based on the current data, FVC (100% acceptance) was the measure that the group favoured most for each CTD-ILD and IPF. Again, we emphasise that the overarching construct of this exercise was limited to that of a hypothetical RCT of 1-year duration. FVC has been shown to be a consistently reliable serial variable in IPF. Declines in FVC correlate with increased risk of subsequent mortality. While no data exist demonstrating that improvement in FVC correlates with improved survival. Thus, utilising FVC as an endpoint requires consideration of the clinically meaningful magnitude of change independent of potential impact on mortality. This is particularly relevant in studies of short duration.

While changes in FVC have been shown to be reproducible in SSc-ILD, there are insufficient RCT-derived data to evaluate this in other forms of CTD-ILDs. There are confounding issues of vasculopathy, pulmonary hypertension, cardiac involvement, chest wall impairment and systemic disease activity that are often coexistent in CTD-ILDs. Nonetheless, FVC may most reliably and sensitively reflect the contribution of parenchymal disease above other endpoints.

Though a relative change from baseline predicted is preferred to absolute change from normal values, these changes are recognised as non-parametric in FVC. Thus a discrete clinically relevant threshold of minimal change was not able to be agreed upon in either IPF or CTD-ILD. Further, efforts to validate serial variables are challenged by variations in the disease above other endpoints.

While changes in FVC have been shown to be reproducible in SSc-ILD, there are insufficient RCT-derived data to evaluate this in other forms of CTD-ILDs. There are confounding issues of vasculopathy, pulmonary hypertension, cardiac involvement, chest wall impairment and systemic disease activity that are often coexistent in CTD-ILDs. Nonetheless, FVC may most reliably and sensitively reflect the contribution of parenchymal disease above other endpoints.

Though a relative change from baseline predicted is preferred to absolute change from normal values, these changes are recognised as non-parametric in FVC. Thus a discrete clinically relevant threshold of minimal change was not able to be agreed upon in either IPF or CTD-ILD. Further, efforts to validate serial variables are challenged by variations in the disease above other endpoints.

While changes in FVC have been shown to be reproducible in SSc-ILD, there are insufficient RCT-derived data to evaluate this in other forms of CTD-ILDs. There are confounding issues of vasculopathy, pulmonary hypertension, cardiac involvement, chest wall impairment and systemic disease activity that are often coexistent in CTD-ILDs. Nonetheless, FVC may most reliably and sensitively reflect the contribution of parenchymal disease above other endpoints.

Though a relative change from baseline predicted is preferred to absolute change from normal values, these changes are recognised as non-parametric in FVC. Thus a discrete clinically relevant threshold of minimal change was not able to be agreed upon in either IPF or CTD-ILD. Further, efforts to validate serial variables are challenged by variations in the disease above other endpoints.

While changes in FVC have been shown to be reproducible in SSc-ILD, there are insufficient RCT-derived data to evaluate this in other forms of CTD-ILDs. There are confounding issues of vasculopathy, pulmonary hypertension, cardiac involvement, chest wall impairment and systemic disease activity that are often coexistent in CTD-ILDs. Nonetheless, FVC may most reliably and sensitively reflect the contribution of parenchymal disease above other endpoints.

Though a relative change from baseline predicted is preferred to absolute change from normal values, these changes are recognised as non-parametric in FVC. Thus a discrete clinically relevant threshold of minimal change was not able to be agreed upon in either IPF or CTD-ILD. Further, efforts to validate serial variables are challenged by variations in the disease above other endpoints.
The importance of patient-reported dyspnoea for assessing prognosis and disease progression are well recognised. We identified the Dyspnea 12 and the Medical Research Council Dyspnea Scale as the best currently available instruments in CTD-ILD and in IPF, yet data are essentially lacking in CTD-ILD. Though the MDC has some demonstrated validity in SSc-ILD, NGT panelists allocated this interviewer-administered instrument to the research agenda for CTD-ILD, voicing concerns of poor feasibility and uncertain reliability. The UCSD-SBQ was accepted for use in studying IPF. It was agreed that development of new Dyspnea instruments is warranted to specifically reflect the restrictive lung processes of CTD-ILD and IPF.

The Short Form 36 (SF-36) was recognised as a generic HRQoL instrument as anxiety, fatigue, participation, physical function, self-care and sleep are important to patients. The St George’s Respiratory Questionnaire, although endorsed, lacked specificity in CTD-ILD and IPF. It was agreed that a new disease-specific instrument should be developed.

PtGA, previously validated across rheumatic and non-rheumatic diseases, correlates with dyspnoea in CTD-ILD and IPF, and was accepted as a measure in CTD-ILD with improvements greater than 10 mm agreed upon as an MCID. PtGA not being validated in IPF was allocated to the research agenda in IPF. PtGA may also serve as an ‘anchor’ to determine MCIDs for

Table 6 Results of nominal group proceedings with percentage for acceptance (see online supplement for expanded voting tables)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>CTD-ILD</th>
<th>IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC Chronic Dyspnea Scale</td>
<td>7/9+9/12+2/3=75%</td>
<td>10/11+1/1=92%</td>
</tr>
<tr>
<td>Dyspnea 12</td>
<td>8/10+11/12+3/3=88%</td>
<td>6/9+1/1=70%</td>
</tr>
<tr>
<td>UCSD-SBQ</td>
<td>N/A</td>
<td>7/9+1/1=80%</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leicester cough questionnaire</td>
<td>7/10+10/12+2/2=79%</td>
<td>8/10+1/1=82%</td>
</tr>
<tr>
<td>HRQoL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Form 36</td>
<td>10/10+11/11+3/1=100%</td>
<td>8/10+1/1=82%</td>
</tr>
<tr>
<td>SGRQ</td>
<td>9/10+9/11+2/2=87%</td>
<td>8/10+1/1=82%</td>
</tr>
<tr>
<td>VAS-PtGA</td>
<td>10/10+11/12+2/2=96%</td>
<td>N/A</td>
</tr>
<tr>
<td>Lung imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall extent of ILD on HRCT</td>
<td>11/11+9/11+3/1=92%</td>
<td>10/10+1/1=100%</td>
</tr>
<tr>
<td>Lung physiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td>10/10+11/11+3/3=100%</td>
<td>10/10+1/1=100%</td>
</tr>
<tr>
<td>Diffusion capacity of lung</td>
<td>10/10+8/10+3/3=91%</td>
<td>10/10+1/1=100%</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Unanimous agreement</td>
<td>Unanimous agreement</td>
</tr>
</tbody>
</table>

CTD-ILD, connective tissue disease-associated interstitial lung disease; HRCT, high-resolution CT; HRQoL, health-related quality of life; IPF, idiopathic pulmonary fibrosis; MRC, Medical Research Council; PtGA, Patient Global Assessment; PULM, pulmonary specialist; RHEUM, rheumatology specialist; SGRQ, St George’s Respiratory Questionnaire; UCSD-SBQ, University of California San Diego Shortness of Breath Questionnaire; VAS, visual analogue scale.

Table 7 Relation of CTD-ILD preliminary core set instruments to aspects of OMERACT filter in CTD-ILD

<table>
<thead>
<tr>
<th>CTD-ILD</th>
<th>Dyspnoea</th>
<th>Cough</th>
<th>HRQoL</th>
<th>Lung physiology</th>
<th>Lung imaging</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instruments</td>
<td>D-12</td>
<td>MRC</td>
<td>LCQ</td>
<td>SGRQ</td>
<td>SF-36</td>
<td>PtGA</td>
</tr>
<tr>
<td>Truth</td>
<td>Face validity</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Content validity</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Construct validity</td>
<td>Y</td>
<td>Y</td>
<td>NT</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Criterion validity</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Discrimination</td>
<td>Discriminatory</td>
<td>Y</td>
<td>Y</td>
<td>NT</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Reliable</td>
<td>Y</td>
<td>Y</td>
<td>NT</td>
<td>NT</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Reproducible</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td></td>
<td>Sensitive to change</td>
<td>Y</td>
<td>Y</td>
<td>NT</td>
<td>NT</td>
<td>Y</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Cost effective</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Interpretability</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Readily available</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Safe for patients</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Patient-derived content</td>
<td>Y</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
</tr>
</tbody>
</table>

PtGA is adopted under HRQoL, though it is an independent instrument.

*Not cost effective as a primary efficacy endpoint but highly cost effective as a secondary endpoint to detect treatment toxicity—see text for discussion on ‘survival’

†US Food and Drug Administration advocates patient-reported instruments be developed by qualitative data supplied by patients.

±, ambiguous; CTD-ILD, connective tissue disease-associated interstitial lung disease; D-12, Dyspnea-12; DLCO, diffusion capacity of lung for carbon monoxide; FVC, forced vital capacity; GGO, ground glass opacity; HRCT, high-resolution CT; LCQ, Leicester Cough Questionnaire; MRC, Medical Research Council; N/A, not applicable; NT, not yet tested; OMERACT, Outcome Measures in Rheumatology; PtGA, Patient Global Disease Activity; SGRQ, St George’s Respiratory Questionnaire; SF-36, Short Form 36; Y, yes.
Interstitial lung disease

Table 8  Relation of IPF preliminary core set instruments to aspects of OMERACT filter in IPF

<table>
<thead>
<tr>
<th>IPF</th>
<th>Dyspnoea</th>
<th>Cough</th>
<th>HRQoL</th>
<th>Lung physiology</th>
<th>Lung imaging</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D-12</td>
<td>MRC</td>
<td>UCSD-SBQ</td>
<td>LCQ</td>
<td>SGRQ</td>
<td>SF-36</td>
</tr>
<tr>
<td>Truth</td>
<td>Y Y Y Y</td>
<td>Y Y</td>
<td>Y Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Content validity</td>
<td>Y Y Y Y</td>
<td>Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Construct validity</td>
<td>Y Y Y NT</td>
<td>NT Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Criterion validity</td>
<td>NT NT NT NT</td>
<td>NT NT</td>
<td>± ±</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discrimination</td>
<td>NT NT Y NT</td>
<td>NT NT</td>
<td>± ±</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliable</td>
<td>NT NT NT NT</td>
<td>NT Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Reproducible</td>
<td>NT NT NT NT</td>
<td>NT Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Sensitive to change</td>
<td>NT NT Y NT</td>
<td>NT Y Y</td>
<td>Y Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Cost effective</td>
<td>Y Y Y Y</td>
<td>Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Interpretabililty</td>
<td>Y Y Y Y</td>
<td>Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Readily available</td>
<td>Y Y Y Y</td>
<td>Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Safe for patients</td>
<td>Y Y Y Y</td>
<td>Y Y</td>
<td>Y Y Y</td>
<td>Y Y</td>
<td>Y Y</td>
<td>Y</td>
</tr>
<tr>
<td>Patient-derived content*</td>
<td>Y No No No No No N/A N/A N/A N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not cost effective as a primary efficacy endpoint but highly cost effective as a secondary endpoint to detect treatment toxicity—see text for discussion on ‘survival’.
† US Food and Drug Administration advocates patient-reported instruments be developed by qualitative data supplied by patients.18 19

Psychological and social status declarations entail ad hoc and prospective performance analyses of these measures. While the domain of Cough did not survive the Delphi process, it was important to patient participants. Additionally, there is a correlation between cough and IPF progression and with ILD severity in SSc.19 In SSc-ILD, cough adversely impacted HRQoL and improved with treatment.19 The LCQ was selected as an interim measure as it was deemed more able to capture frequency, quality and intensity, and impact on HRQoL. It was also most feasible to administer.40 41

Primary and secondary endpoint status of the proposed measures were considered, intensely discussed and even voted upon during the NGT. However, at this preliminary stage and given the lack of full validation of the core measures, the consensus was to pursue further data. A more careful approach to endpoint status declarations entails ad hoc and prospective performance analyses of these measures.

This project applied rigorous multi-investigational processes that captured the perspectives of the international ILD expert community and the life experience of patients with ILD to identify a set of domains and measures. Participation remained robust through all tiers of the consensus process.

The importance of patient participation is supported by the incorporation of HRQoL, Participation and Fatigue in the RA core set for RCTs. From a practical perspective, qualitative data collection involved only English-speaking patients from North America, and results may be affected by cultural, environmental and resource-related effects requiring further investigations to follow up our reported findings. Nevertheless, the engagement of patients as partners in the iterative process was important in identifying and re-capturing areas of potentially meaningful measures of disease activity.

CONCLUSIONS

It is critical that valid and clinically useful instruments be developed and validated to assess the likelihood of treatment response in these disorders. Identification of consensus...
preliminary domains and instruments to measure them was attained and is a major advance anticipated to facilitate multi-centre RCTs in the field. However, none of the provisional endpoints were ultimately felt to be either ideal or fully validated. Feasible endpoints like FVC are not perfect; more rigorous endpoints like mortality, particularly in the setting of CTD-ILD, lack feasibility. Thus, selecting the best non-ideal endpoints from a larger group of non-ideal endpoints still leaves us with much work which includes further validation of existing and development of new instruments.

Author affiliations
1Louisiana State University Health Science Centers, New Orleans, Louisiana, USA
2University of Toronto, Toronto, Canada
3German Rheumatism Research Centre, Berlin, Germany
4Charité Universitätsmedizin, Berlin, Germany
5University of Michigan, Ann Arbor, Michigan, USA
6Brigham and Womens Hospital, Boston, Massachusetts, USA
7University Hospital Zurich, Zurich, Switzerland
8University of Manitoba, Manitoba, Canada
9University of Pittsburgh, Pittsburgh, Pennsylvania, USA
10Royal Free Hospital, London, UK
11National Jewish Health Denver, Colorado, USA
12Medical University of Bialystok, Bialystok, Poland
13Patient Research Partner, Office of Public Health, New Orleans, Louisiana, USA
14University of Pennsylvania, Philadelphia, Pennsylvania, USA
15University of Dresden, Dresden, Germany
16University of Crete, Heraklion, Greece
17Massachusetts General Hospital, Boston, Massachusetts, USA
18Boston University School of Medicine, Boston, Massachusetts, USA
19Johns Hopkins University, Baltimore, Maryland, USA
20University of California San Francisco, San Francisco, California, USA
21Claude Bernard University, Lyon, France
22Cleveland Clinic, Cleveland, Ohio, USA
23Asian Medical Center University of Ulsan, Ulsan, South Korea
24National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, Maryland, USA
25University of Adelaide, Adelaide, Australia
26Respiratory Biomedical Research Unit, University of Southampton, UK
27Respiratory Biomedical Research Unit, University of Southampton, UK
28Mayo Clinic College of Medicine, Rochester, Minnesota, USA
29Patient Research Partner, Maryland, USA
30Royal Brompton Hospital and National Heart and Lung Institute, London, UK
31Stanford University, Palo Alto, California, USA
32Scleroderma Research Consultants, LLC, Avon, Connecticut, USA

Correction notice This article has been corrected since it was published Online First. The author affiliation for Luca Richeldi has been updated.

Acknowledgements Acknowledgements of thanks for essential and gracious assistance: Kourtie Augustin, Louisiana State University Health Sciences Center – New Orleans, USA; Reed Barrios, Patient Expert, New Orleans, USA; Bennett deBoisblanc, Louisiana State University Health Sciences Center – New Orleans, USA; Kerri Connolly, Scleroderma Foundation, Danvers, MA, USA; Luis R Espinosa, Louisiana State University Health Sciences Center – New Orleans, USA; Daniel E and Elaine Furst, University of California – Los Angeles, CA, USA; Robert Hedlund, Patient Expert, Virginia, USA; Matthew R Lamm, Louisiana State University Health Sciences Center – New Orleans, USA; Steve Nathan, Innovia, Fairfax, Virginia, USA; Karen Nichols, Patient Expert, Virginia, USA; Frank Smart, Louisiana State University Health Sciences Center – New Orleans, USA; Virginia Steen, Georgetown University, Washington DC, USA; Valerie Thompson, DINORA; Pieter van den Assum, Patient Expert, Virginia, USA. Ms LeSage and Ms Sarver are co-investigators and have contributed their expertise as patients to key decision-making in the design, implementation as well as analysis and interpretation of data and thus listed as authors.


Collaborators Delphi Co-Authors: "Indicates Disease Committee Member. Rohit Aggarwal*, University of Pittsburgh School of Medicine, USA; Gillian Amslie, University of Cape Town & Groote Schuur School, South Africa; Firas Alkassab, University of North Carolina-Chapel Hill, Charlotte, USA; Yannick Allanoare*, University Paris Descartes, France; Marina E Anderson, University of Liverpool, UK; Andrew P Andonopoulos, University of Patras School of Medicine, Greece; Danielle Antin-Ozerkis, Yale University School of Medicine, USA; Ana Arboz, Cerrada de Coimbra, Portugal; Dana P Aeschliman*, University of Minnesota Miller School of Medicine, USA; Shervin Assassi, University of Texas Health Science Center at Houston, USA; Murray Baron, Jewish General Hospital, McGill University, USA; Joao M Batton*, Columbia University College of Physicians & Surgeons, USA; Juergen Behr, Ludwig-Maximilians University, Munich, Germany; Lorenzo Beretta, Reference Center for Systemic Autoimmune Diseases-Milan, Italy; Clifton O Bingham III, Johns Hopkins University, USA; Matthew Binnie, St. Michael’s Hospital, Toronto, Canada; Sun Son, University of Pittsburgh, USA; John Dering, King’s College Hospital, UK; Francesco Boin, Johns Hopkins University; USA; Tim Bongartz*, Mayo Clinic College of Medicine, USA; Arnaud Bourd, Department de Pneumologie et Addictologie INSERM U1046 - Université Montpellier; Demosthenes Bourou, Democritus University of Thrace, Greece; Richard Brasington, Washington University, St Louis, USA; Paul Bresser, Onze Lieve Vrouwe Gasthuis, Netherlands; Maya H Buch, University of Leeds, UK; P Shenwood Burge, Birmingham Heartlands Hospital, UK; Loreto Carmona, Universidad Camilo José Cela and Institute for Musculoskeletal Health, Spain; Patricia E Carreira, Hospital Universitario, Spain; Carlos RR Carvalho, University of Sao Paulo Medical School, Brasil; Luis J Catoggio, Hospital Italiano de Buenos Aires, Argentina; Kevin M Chan, University of Michigan Health Systems, USA; Jeffrey Chapman, Cleveland Clinic, USA; Soumya Chatterjee, Cleveland Clinic, USA; Felix Chua*, St. George’s Hospital NHS Trust, UK; Lorinda Chung, Stanford University School of Medicine, USA; Matthew Conron, St. Vincent’s Hospital; Australia; Tamarra Corte, University of Sidney, Australia; Gregory Cosgrove, National Jewish Health, USA; Ulrich Costabel, University of Duisburg-Essen, Germany; Gerard Cox, McMaster University, Canada; Bruno Cunliffe, Centre de Compétences Maladies Rares Pulmonaires, Paris, France; Leslie J Crough, University of Kentucky College of Medicine, USA; Mary E Cusa, Mayo College of Wisconsin, USA; Pilar de Curbelo, USA; Palma de Montevideo, Uruguay; Laszlo Czirjak, University of Pecs, Hungary; Zoë Danil, University of Thessaly, Larissa, Greece; Christine L D’Arquy, Queen’s University, Canada; Gerald S Davis, College of Medicine University of Vermont, USA; Joao A de Andrade, University of Alabama at Birmingham, USA; Paul De Vugt, Hospital Ensme, Université Libre de Bruxelles, Belgium; Owen J Dempsey, Aberdeen Royal Infirmary Foresthill, Scotland, UK; Chris T Derk, University of Pennsylvania, USA; Jong Ditler, University of Erlangen-Nuremberg, Germany; William G Dixon*, University of Manchester, UK; Gregory Downey, National Jewish Health, USA; Mitty K Doyle, Alexion Pharmaceuticals Inc, Cambridge, USA; Marjolijn Drent, Maastricht University, Maastricht, Netherlands; Lakshmi Durairaj, Carver College of Medicine, University of Iowa, USA; Paul Emery, University of Leeds, UK; Luis R Espinosa, Louisiana State University Health Sciences Center, New Orleans, USA; Dominique Farge, St. Louis Hospital, Paris, France; Maryam Fathi, Karolinska Institutet, Sweden; Charles D Fell; University of Calgary, Canada; Barry Feosler, University of Alabama at Birmingham, USA; John E Fitzgerald, University of Texas Southwestern Medical Center, USA; Ivan Foeldvari, University of Hamburg, Germany; George A Fox, Memorial University of Newfoundland, Canada; Tracy M Fuch, University of Utah, USA; Sara Freitas, Coimbra Hospital and University Centre, Portugal; Daniel E Furst*, University of California Los Angeles, USA; Armando Gabrielli, Università Politecnica delle Marche, Ancona, Italy; Rosario Garcia-Vicuña, Hospital Universitario de la Princesa, ISF, Spain; Ognian B Georgiev, University Hospital Alexandria, Sofia, Bulgaria; Anthony Gerbino, Virginia Mason Medical Center, USA; Adrian Gillisen, General Hospital Kassel, Germany; Dafna D Glademann, University of Toronto, Canada; Marilyn Glassberg, University of Miami Miller School of Medicine, USA; Bernadette R Goudsou, National Human Genome Research Institute, National Institutes of Health, USA; Ahtena Gogali, University Hospital of Ioannina, Greece; Nicole S Golth, Alfred Hospital, Melbourne, Australia; Aaram Goldberg, Hofstra North Shore LIU School of Medicine, USA; Hilary J Goldberg, Brigham and Women’s Hospital, Harvard Medical School, USA; Mark F Gourley*, National Institutes of Health, USA; Leroy Griffing, Mayo Clinic College of Medicine, USA; Jan C Grutters, University Medical Center Utrecht, Netherlands; Ragnar Gunnarsson, Oslo University Hospital, Norway; Eric Hachulla, Claude Haurie


Intersitial lung disease
Hospital, University of Lille, France; François C Hall, University of Cambridge, UK; Sergio Harari, U.O. di Pneumologia Ospedale San Giuseppe Multimedica, Milan, Italy; Ariané L Herrick, University of Manchester, UK; Erica L Herzog, Yale University School of Medicine, USA; Roger Hesselstrand, Lund University, Sweden; Nikhil Hiroi, University of Edinburgh, UK; James Hodgson, Hannover University, Germany; Lourdes Horvath, Pulmonary Center, Boston University School of Medicine, USA; Robert J Homer, Yale University School of Medicine Department of Pathology, USA; Rachel K Hoyles, Oxford Centre for Respiratory Medicine, UK; Vivien M Hu, University of Medicine and Dentistry of New Jersey, USA; Richard B Hubbard, University of Nottingham, UK; Nicole Hunzelmann, Department of Dermatology, University of Cologne, Germany; Maria Elosa Iisasi, Hospital Nicolás Monasterio, Valencia, Spain; Jonata Al-Monteverde, Emergency Department, University Hospital, Finland; Thomas J Monn, University of Lille, France; Soren Jacobsen, Rigshospitalet, Copenhagen University Hospital, Denmark; Sergio A Jimenez, Jefferson University, USA; Sindhru J Johnson, University of Toronto, Toronto, Canada; Christine H Jones, University of Vermont College of Medicine, Fletcher Allen Health Care, USA; Bashar Kakaah, University of Toledo Medical Center, USA; Ronaldo A Kairalla, Heart Institute (InCor), University of São Paulo Medical College, Brazil; Meena Kalluri, University of Alberta, Canada; Sanjay Kalra, Milton, ON, Canada; Robert J Kaner, Cornell University School of Medicine, USA; Ben J Kendrick, University of Alabama, USA; Beth K Kjeldsen, Tulane University College of Medicine, USA; Goksel Kiter, Pamukkale University, Turkey; Ross C Klingberg, Tulane University School of Medicine, USA; Maria Kokosi, Sismanoglio General Hospital, Martin RJ Kolb, McMaster University, Canada; Joanna Kur-Zalewska, Military Institute of Medicine, Warsaw, Poland; Masataka Kusama*, Keio University School of Medicine, Japan; Fiona R Lake, University of Western Australia; Edward V Lally, Brown University School of Medicine, USA; Liv vaccine, Tulane University School of Medicine, USA; M Laurindo, University of Sao Paulo, Brazil; Lawrence Abel, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India; Peter Lee, University of Toronto, Canada; Colm T Leonard, University Hospital of South Manchester NHS Foundation Trust, UK; Dale C Lien, University of Alberta, Canada; Andrew H Limper, Mayo Clinic College of Medicine, USA; Stamatios-Nik Liosis, University of Patras Medical School, Greece; Kristine M Lohr, University of Kentucky, USA; James E Loyd, Vanderbilt University, USA; Ingrid E Lundberg*, Karolinska Institute, Sweden; Yolanda N Mageto, University of Vermont, USA; Toby M Maher, Royal Brompton Hospital, UK; Tafazzul H Mahmud, Shaikh Zayed Medical complex, Lahore, Pakistan; Helena Manganas, CHUL (Notre-Dame Hospital), Canada; Isabelle Marie, Rouen University, France; Theodore K Maranas, University Health Network, Mount Sinai hospital and the University of Toronto; José Antonio Baddini Martinez, Facultad de Medicina de Ribeirão Preto, Brazil; Fernando J Martinez, University of Michigan, USA; Alessandro Mathieu, Università degli Studi di Napoli “Federico II”, Italy; Marco Maturi-Cerin*, University of Florence, Italy; Maureen D Mayes*, University of Texas Southwestern Medical Center, USA; Keith C Meyer, David Geffen School of Medicine at UCLA, USA; Ulrich A Walker, Basel University Deptartment of Rheumatology, Felix Platter-Spital, Switzerland; David A Lynch, National Jewish Hospital, Denver, Colorado, USA; Charlie Strange, Medical University of South Carolina, USA; Robert F Padera, Brigham and Women’s Hospital, USA

**Pathology Advisory Team**

Steve D Gershon, National Jewish Health, USA; Kevin O Leslie, Mayo Clinic College of Medicine, USA; Jeffery M Myers, University of Michigan, USA; Robert F Padera, Brigham and Women’s Hospital, USA

**Radiology Advisory Team**

Sujal R Desai, King’s College Hospital, London, UK; Jonathan Goldin, David Geffen School of Medicine at UCLA, USA; Ela A Kazemosnezhad, University of Michigan, Ann Arbor, USA; Jeffery S Klein, Fletcher Allen Health Care, University of Vermont, USA; David A Lynch, National Jewish Health, Denver, USA

**Analysis and coding of patient perspective transcripts**

Sophia L Cenc and Harmajwant K Grewal, Louisiana State University, New Orleans, USA; Angela M Christensen and桑ia Ferguson, Tulane University, New Orleans, USA; Malvina Tran, University of Toronto, Canada

**Additional Statistical Support**

Kevin J Keen, University of Northern British Columbia, Prince George, Canada

**Funding**

Non-profit support: These studies were supported in part by the intramural division of the National Institute of Environmental Health Sciences, National Institutes of Health; and the following non-profit organisations: Brigham and Women’s Hospital, Charlie Hospital—Berlin, German Rheumatism Research Centre, Ira J Fine Discovery Fund, Jonathan and Lisa Rye Scleroderma Research Foundation, Louisiana State University Health Sciences Center, The Nathan Jefferson Health Sciences Foundation, Mayo Clinic—Rochester, National Jewish Health Denver, Louisiana State Office of Public Health—New Orleans, OMERACT (Outcome Measures in Rheumatology), Scleroderma Foundation, Sibyl Hospital Foundation, and Sonia Roth AARC Foundation. Commercial Interest Support: Abbott Laboratories Canada, Actelion, Boehringer–Ingelheim Pharmaceuticals, Celgene, Intermune, Sigma Tau, UCB and United Therapeutics.

**Competing interests**

None.

**Ethics approval**

Louisiana State University School of Medicine Institutional Review Board for all components. Patient perspective studies also included approval from Johns Hopkins University, Massachusetts General Hospital, University of Manitoba and University of Toronto.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

We have made all data visible in the online supplement.

**Open Access**

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

**REFERENCES**


Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials


Thorax published online December 24, 2013

Updated information and services can be found at: http://thorax.bmj.com/content/early/2014/03/20/thoraxjnl-2013-20420

These include:

Supplementary Material
Supplementary material can be found at: http://thorax.bmj.com/content/suppl/2014/03/19/thoraxjnl-2013-20420.2.DC2

References
This article cites 39 articles, 12 of which you can access for free at: http://thorax.bmj.com/content/early/2014/03/20/thoraxjnl-2013-20420.2#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Errata
An erratum has been published regarding this article. Please see next page or: http://thorax.bmj.com/content/69/9/834.full.pdf

To request permissions go to: http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to: http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to: http://group.bmj.com/subscribe/
Articles on similar topics can be found in the following collections

- Open access (271)
- Interstitial lung disease (559)
Correction


Thorax 2014;69:834. doi:10.1136/thoraxjnl-2013-204202corr1