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ORIGINAL ARTICLE

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

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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 them was attained and is a major advance anticipated to facilitate multicentre RCTs in the field.

Key messages

Why is the key question?

- Can a core set of outcome measures that are reliable and feasible be identified by experts for use in future clinical trials in connective tissue disease associated interstitial lung disease (CTD-ILD) and idiopathic pulmonary fibrosis (IPF)?

What is the bottom line?

- Using established Delphi and nominal group techniques supplemented by patient input, a preliminary core set of outcome measures in CTD-ILD and IPF have been identified.

Why read on?

- To learn the core set of clinically meaningful and feasible measures in CTD-ILD and IPF that were identified and the gaps remaining.

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,

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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) filter[9] (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 participant[10–12] 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 IPF 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'.

Table 1 Reduction of domains and instruments in the Delphi process

Phase yielded	Analysis method	Domains CTD-ILD/IPF	Instruments CTD-ILD/IPF	Participant Dropout (%)
Tier 0	Intense review	133 nominations >>23	>6700 nominations >>616/616	0
Tier 1	<4 median cut-off	21	71/71	2
Tier 2	cluster analysis	13	58/61	<1
Tier 3	cluster analysis	5/5	18/18	0

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

Table 2 Domain results of Tier 0

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

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

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 3 Results of the Delphi Tier 3 cluster analysis of domains with median/mean reported

Five domains identified for each CTD-ILD and IPF		
Domain name	CTD-ILD (median/mean) ratings on a 9-point scale	IPF (median/mean) ratings on a 9-point scale
Dyspnoea	(8.0/7.8)	(8.0/8.1)
Health-related quality of life	(8.0/7.7)	(8.0/7.8)
Lung imaging	(9.0/8.3)	(9.0/8.3)
Lung physiology/function	(9.0/8.7)	(9.0/8.7)
Survival	(8.0/8.2)	(9.0/8.4)
Medications	(8.0/7.2)	(7.0/7.3)

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

Table 4 Results from Tier 3 of Delphi

Domain	Instrument	Acceptance in	
Dyspnoea	Borg Dyspnea Index	CTD-ILD	IPF
	MRC Breathlessness (Chronic Dyspnea) Scale or the Modified MRC Dyspnea Scale	CTD-ILD	IPF
	Borg Dyspnea Index pre and post exercise	CTD-ILD	–
HRQoL	Medical Outcomes Trust Short Form 36 health survey	CTD-ILD	IPF
	St George's Dyspnoea Respiratory Questionnaire	–	IPF
	Visual analogue scale of Patient Assessment of Disease Activity	CTD-ILD	IPF
	Ability to carry out activities of daily living	CTD-ILD	–
	Health Assessment Questionnaire Disability Index	CTD-ILD	–
Lung imaging	Extent of honeycombing on HRCT	CTD-ILD	IPF
	Extent of reticulation on HRCT	–	IPF
	Extent of ground glass opacities on HRCT	CTD-ILD	–
	Overall extent of ILD on HRCT	CTD-ILD	IPF
Lung physiology/ function	Supplemental oxygen requirement	CTD-ILD	IPF
	FVC on spirometry	CTD-ILD	IPF
	Diffusion capacity of lung for carbon monoxide	CTD-ILD	IPF
	6MWT with maximal desaturation on pulse oximetry	CTD-ILD	IPF
	6MWT for distance	–	IPF
Survival	Time to decline in FVC	CTD-ILD	IPF
	Progression-free survival	CTD-ILD	IPF
	Time to death	–	IPF
Medications	Increase or decrease in glucocorticoids	CTD-ILD	IPF
	Increase or decrease in concomitant immune suppressive agents	CTD-ILD	IPF

6MWT, 6 min walk test; CTD-ILD, connective tissue disease associated interstitial lung disease; FVC, forced vital capacity; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; HRQoL, health-related quality of life; MRC, Medical Research Council.

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,[4 7 8 18–22] although 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.[3–5 20] 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 rate of disease progression, with interval changes of FVC[20 22] more likely to represent a true change in rapidly progressive disease than in less progressive disease that crosses the same threshold. Extrapolation between two value points will provide less reliable information than continuous variables; therefore, identification of a minimal clinically important difference (MCID) would be misleading without accommodating for these non-parametric changes. Panel discussions surrounding Diffusion Capacity of Lung for Carbon Monoxide (DLCO) reflected the multiple confounders for this instrument, with ranking of FVC as being the favoured marker above DLCO. A threshold of clinically meaningful change was not determined for DLCO.

Table 5 Characteristics of patients with CTD-ILD participating in the focus groups

Group	CTD type	Location	Participants	Gender	Age (years) Mean (SD)	Race
1	Various	Winnipeg, Manitoba, Canada	9 1 IIM, 2 RA, 4 SSc, 2 SLE	8 F, 1 M	53.6 (16.2)	8 C, 1 O
2	RA	Toronto, Canada	7	7 F, 0 M	64.3 (9.0)	4 C, 2 A, 1 AC
3	SSc	Baltimore, Maryland, USA	6	3 F, 3 M	58.2 (9.1)	6 C
4	IIM	Baltimore, Maryland, USA	7	4 F, 3 M	52.4 (10.5)	5 C; 2 AA
5	Various	New Orleans, Louisiana, USA	9 3 IIM, 4 RA, 1 SjS, 1 SLE	6 F; 3 M	53.8 (15.5)	4 C; 4 AA; 1 H
6	SSc	New Orleans, Louisiana, USA	7	5 F; 2 M	54.6 (5.7)	4 AA; 3 C

A, Asian; AA, African American; AC, African Caribbean; C, Caucasian; CTD-ILD, connective tissue disease associated interstitial lung disease; F, female; H, Hispanic; IIM, idiopathic inflammatory myopathy; M, male; O, other; RA, rheumatoid arthritis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus.

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

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

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.

Neither the 6MWT nor measures of oxygen desaturation survived the NGT process; although deemed feasible they were considered weak in discrimination in addition to construct and criterion validity. The need for supplemental oxygen was not accepted; changes in oxygenation, as judged partly by oxygen desaturation, are difficult to interpret since they do not correlate well with the sensation of dyspnoea or changes in disease progression in mild to moderate disease.[19 23]

The importance of patient-reported dyspnoea for assessing prognosis and disease progression are well recognised.[1 7 8] We identified the Dyspnea 12[24] and the Medical Research Council Dyspnea Scale[18 19] as the best currently available instruments in CTD-ILD and in IPF, yet data are essentially lacking in CTD-ILD. Though the MDI has some demonstrated validity in SSc-ILD[20], 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.[21] It was agreed that development of new *Dyspnoea* 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.[25] The St George's Respiratory Questionnaire, although endorsed, lacked specificity in CTD-ILD and IPF.[26 27] 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[28 29] 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 7 Relation of CTD-ILD preliminary core set instruments to aspects of OMERACT filter in CTD-ILD

CTD-ILD	Dyspnoea		Cough	HRQoL			Lung physiology		Lung imaging	Survival	
Instruments	D-12	MRC	LCQ	SGRQ	SF-36	PtGA	FVC	DLCO	HRCT—overall extent of disease	All-cause mortality	Time to decline in FVC
Truth											
Face validity	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Content validity	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Construct validity	Y	Y	NT	Y	Y	NT	Y	±	Y	Y	NT
Criterion validity	NT	NT	NT	NT	NT	NT	No	No	Y	Y	NT
Discrimination											
Discriminatory	Y	Y	NT	Y	Y	NT	±	±	Yes, except± for GGO	No	Y
Reliable	Y	Y	NT	NT	Y	NT	Y	N	Yes, except± for GGO	Y	NT
Reproducible	NT	NT	NT	NT	NT	NT	Y	±	Y	N/A	NT
Sensitive to change	Y	Y	NT	NT	Y	NT	Y	±	Yes but relatively slow	N/A	Y
Feasibility											
Cost effective	Y	Y	Y	Y	Y	Y	Y	Y	Y	No*	Y
Interpretability	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Readily available	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Safe for patients	Y	Y	Y	Y	Y	Y	Y	Y	±	Y	Y
Patient-derived content†	Y	No	No	No	No	N/A	N/A	N/A	N/A	N/A	N/A

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.[18 19]
±, 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 Dyspnea Scale; 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.

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

IPF	Dyspnoea		Cough		HRQoL		Lung physiology		Lung imaging	Survival
Instruments	D-12	MRC	UCSD-SBQ	LCQ	SGRQ	SF-36	FVC	DLCO	HRCT—overall extent of disease	All-cause mortality
Truth										
Face validity	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Content validity	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Construct validity	Y	Y	Y	NT	Y	Y	Y	Y	Y	Y
Criterion validity	NT	NT	NT	NT	NT	NT	No	No	Y	Y
Discrimination										
Discriminatory	NT	NT	Y	NT	NT	NT	±	±	Y	No
Reliable	NT	NT	NT	NT	Y	Y	Y	N	Y	Y
Reproducible	NT	NT	NT	NT	Y	NT	Y	±	Y	N/A
Sensitive to change	NT	NT	Y	NT	Y	Y	Y	Y	Yes but relatively slow	N/A
Feasibility										
Cost effective	Y	Y	Y	Y	Y	Y	Y	Y	Y	No*
Interpretability	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Readily available	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Safe for patients	Y	Y	Y	Y	Y	Y	Y	Y	±	Y
Patient-derived content†	Y	No	No	No	No	No	N/A	N/A	N/A	N/A

*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]
±, ambiguous; D-12, Dyspnea-12; DLCO, diffusion capacity of lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; LCQ, Leicester Cough Questionnaire; MRC, Medical Research Council Dyspnea Scale; N/A, not applicable; NT, not yet tested; OMERACT, Outcome Measures in Rheumatology; SGRQ, St George's Respiratory Questionnaire; SF-36, Short Form 36; UCSD, University of San Diego Shortness of Breath Questionnaire; Y, yes.

recently developed PROMs, such as the King's Brief ILD Health Assessment Questionnaire (K-BILD).[30]

The extent of ground-glass opacities, honeycombing and/or reticulations on high-resolution CT (HRCT) scan each merited careful consideration as outcome measures. However, taken separately each was felt to incompletely capture disease progression in either CTD-ILD or IPF. The overall extent of ILD on HRCT was accepted to provisionally describe the most appropriate and feasible composite of radiological abnormalities to monitor for disease progression.[31 32] No specific assessment tool at this time was able to be confidently identified as it is not yet clear whether subjective or automated objective assessment is the more accurate approach. Though serial HRCT raises concern for patient safety, validation studies of less radio-intense methods of HRCT serial assessment[33] are underway.

Progression-free survival in IPF was agreed to have merit,[34] however the group was undecided as to the practicality of this endpoint in the context of a trial limited to 1 year's duration. Mortality was minimal or absent in two recent RCTs of SSc-ILD.[35 36] There are cogent arguments for and against survival as the primary outcome in studies of IPF.[34 37] Regardless of this unresolved debate, mortality was recognised as an essential endpoint in all treatment trials as it provides a harm signal,[34 37] with all-cause mortality identified as a valid measure of survival in CTD-ILD and IPF. The utility of other measures of progression-free survival in RCTs requires further investigation of candidate instruments before recommending their use in RCTs.

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[38] and with ILD severity in SSc.[39] In SSc-ILD, cough adversely impacted HRQoL and improved with treatment.[39] 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.

Though we recommend these proposed measures for all future research ventures, continued use of measures outside this core set, for clinical practice and research purposes, is fully expected with further research into their performance anticipated and necessary. Rather, this endeavour defines the currently available, best validated and feasible instruments while providing a much needed prioritised research agenda focus to the research community.

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 multicentre 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.

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Correction

Saketkoo LA, Mittoo S, Huscher D, *et al*. Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. *Thorax* 2014;69:428-36. doi: 10.1136/thoraxjnl-2013-204202

The following collaborator group should have been included at the end of the author list: The CTD-ILD Special Interest Group. The author list now reads: Saketkoo LA, Mittoo S, Huscher D, Khanna D, Dellaripa PF, Distler O, Flaherty KR, Frankel S, Oddis CV, Denton CP, Fischer A, Kowal-Bielecka OM, LeSage D, Merkel PA, Phillips K, Pittrow D, Swigris J, Antoniou K, Baughman RP, Castelino FV, Christmann RB, Christopher-Stine L, Collard HR, Cottin V, Danoff S, Highland KB, Hummers L, Shah AA, Kim DS, Lynch DA, Miller FW, Proudman SM, Richeldi L, Ryu JH, Sandorfi N, Sarver C, Wells AU, Strand V, Matteson EL, Brown KK, Seibold JR and the The CTD-ILD Special Interest Group.

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ON-LINE SUPPLEMENTARY MATERIAL FOR NGT PROCEEDINGS

This supplement expands on the details and voting results of the NGT process. The voting items and results reflect end-products of an iterative process that took place over three years. The Delphi process enlisted the wide participation of the ILD medical expert community of pulmonary and rheumatology specialists, with support from an advisory panel of pathologists and radiologists to identify domains and produce a list of instruments with which to measure these domains that are acceptable to the greater community of ILD experts. **Patient Participation**: In order to proceed with the stages beyond the Delphi, patient perspective of ILD was factored into the results of the Delphi process based on focus groups with 45 patients with CTD-ILD and the results of a prior study with 20 patients with IPF (conducted by: Swigris JJ, et al. Patients' perspectives on how idiopathic pulmonary fibrosis affects the quality of their lives. Health Qual Life Outcomes. 2005).

I. NGT Participation:

Voting at the NGT was done through a pre-programmed automated response system which collected voting responses onto a computer hard drive and grouped according to participant type. Fourteen pulmonary specialists, 16 rheumatology specialists, 2 radiologists and 6 CTD-ILD patient partners and 2 IPF patient partners were invited to participate with following participants in actual attendance (of which 10 pulmonary, 12 rheumatology and 1 radiology specialist participated with ultimately a patient representing each IPF, IIM-ILD, RA-ILD and SSc-ILD participating):

Patient Research Partners: Diseases represented were IPF, RA-ILD, IIM-ILD and SSc-ILD. Several patients had clinical trial experience. All patients had the experience of oxygen dependency. Three had disease severe enough to have either received or are being considered for transplantation.

Robert Hedlund
Catherine Sarver
Karen Nichols
Pieter van den Assum
Daphne LeSage (involved in the development of the NGT proceedings but unable to attend due to inclement weather resulting in airport closure)

Pulmonary ILD Specialists:

Katerina Antoniou
Robert P. Baughman
Kevin K. Brown
Kevin Flaherty
Kristin B. Highland (Trained in Rheumatology)
Dong Soon Kim
Luca Richeldi
Jay H. Ryu
Jeffrey Swigris
Athol Wells

Rheumatology Specialists:

Paul F. Dellaripa
Oliver Distler
Aryeh Fischer
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Eric L. Matteson
Peter A. Merkel
Frederick W. Miller
Shikha Mittoo
Chester V. Oddis
Susanna Proudman
James R. Seibold
Vibeke Strand

Radiology ILD Specialist:

David Lynch (Trained in internal medicine and radiology, his votes were attributed to the Pulmonary Specialty Group, thus tabulated for both IPF and CTD-ILD)

Convener/Organiser/Methods Supervisor/Patient Educational Sessions: Lesley Ann Saketkoo **Moderation**: Peter A. Merkel, Oliver Distler

II. Domain Teams:

DYSPNEA:
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MEDICATIONS:
Chester V. Oddis
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DOMAIN TEAMS Oversight: Lesley Ann Saketkoo

III. OMERACT (Outcome Measures in Rheumatology [initially 'for Clinical Trials' though this is no longer part of the official title])

Background: OMERACT is an international non-profit organization established in 1992 dedicated to the identification and development of appropriate outcome measures in disease. OMERACT provides a home for many disease-based working groups investigating outcome measures for use in clinical trials. OMERACT has characterized validity in terms of a 'filter' that provides an organizational checklist for an instrument's ability to satisfy accepted components of validity.

Filter: The components of the filter are grouped under three main criteria: truth, discrimination and feasibility. While the ideal instrument would satisfy all three criteria completely, it is recognized that many useful instruments do not. The filter serves as a guide to identifying the degree to which instruments have demonstrated validity.

Glossary of Terms/Properties comprised in the OMERACT Filter:

Truth:

Face Validity: The instrument hypothetically or at 'face value' makes sense; usually brings the instrument into consideration for study.

Content Validity: The instrument has demonstrated ability to measure the intended concept/domain; i.e. the substance of a measure is acknowledged to reflect a concept /domain well in regards to relevant content and comprehension for a specific disease. This may be gleaned from prior studies or active presentation to and/or item collection from medical experts and/or patients.

Construct Validity: The instrument has been applied in real world setting and demonstrates confirmatory relationships with other accepted measures for that disease – whether the relations are convergent (correlative when anticipated to be so) or divergent (non-correlative when anticipated not to be so) with other accepted outcome measures in that disease. This operational step provides confirmation for further investigation of the instrument.

Criterion Validity: The values provided by the instrument correlate with or predict results of the accepted 'gold standard' for that disease.

Discrimination:

Discrimination: The instrument has demonstrated ability to be responsive to changes for the intended concept/domain; while remaining sufficiently unresponsive to other like or confounding situations.

Reliability: The instrument demonstrates reproducibility and, importantly, accurate values over multiple measurements.

Sensitivity to Change: The values of the instrument demonstrate incremental results that either positively or negatively correlate with changes of the disease over time; e.g. while an instrument may have tremendous diagnostic value, it may not be useful to monitor the course of a disease.

Feasibility: Focuses on logistical and practical implementation and is often the deciding factor on the utility of an instrument.

Interpretability: Analysis/computation of results is sufficiently straightforward and undemanding so as not to introduce potential errors or hardship in implementation or interpretation of results.

Accessibility: There is little or no impediment to the instrument being commonly (or potentially) available for use; and the financial costs and time burden of obtaining, implementation and interpretation of the instrument does not impose unusual hardship.

Safety: The instrument poses little or no risk to patients or personnel implementing the measure.

IV. Post-Delphi Introduction of Items

Domain or Instrument Introduced	**Support for Post-Delphi Introduction**
Domain of *Cough*	Substantiated by Patient Perspective in both CTD-ILD and IPF (Swigris et al).
Instrument of Leicester Cough Questionnaire (LCQ) as a measure of *Cough*	Identified by comparative analysis by *Cough* domain team, discussion and Delphi voting as the most appropriate measure to supply an instrument under cough.
Instrument of Mahler Dysnea Index (MDI) as measure of *Dyspnea*	Identified by updated literature review and voted upon as having substantive findings warranting NGT discussion and voting. Exclusion of this item was collectively viewed as injurious to fair representation of post-Delphi evidence.
Instrument of University of California San Diego Shortness of Breath Questionnaire (UCSD-SBQ) as measure of *Dyspnea*	Identified by updated literature review and voted upon as having substantive findings warranting NGT discussion and voting. Exclusion of this item was collectively viewed as injurious to fair representation of post-Delphi evidence.
The concepts of *Fatigue*, *Participation*, *Physical Function*, *Self-care* and *Sleep*	These concepts were identified as important in Patient Perspective studies. It was agreed that disease-specific investigations into HRQoL would incorporate these components.
The measure of All Cause Mortality as a measure of *Survival*	Identified as an important generic identifier of death in clinical trials.

V. VOTING RESULTS:

For the following series of tables the purple shaded columns are the total responses of the groups appropriated to IPF or to CTD-ILD. While the pink shaded columns are the individual groups whose votes are appropriated to the total accepted votes. Acceptance was agreed upon a priori as ≥70% with the following tabulations: **IPF Voting**: Pulmonary Specialists + IPF Patient Partners

CTD-ILD Voting: Pulmonary Specialists + Rheumatology Specialists + CTD-ILD Patient Partners

Dyspnea IPF

Instrument		**Total for Acceptance**	Pulms	IPF Patient
Dyspnea 12		70% (7/10)	67% (6/9)	100% (1/1)
MRC		92% (11/12)	91% (10/11)	100% (1/1)
UCSD		80% (8/10)	78% (7/9)	100% (1/1)
Borg		36% (4/11)	40% (4/10)	0% (0/1)
Possible Secondary End-Point		82% (9/11)	80% (8/10)	100% (1/1)
Need New Patient Derived Instrument		73% (8/11)	70% (7/10)	100% (1/1)
Dyspnea 12 to be further evaluated	RESEARCH	100% 23/23	Show of Hands Voting from All Groups	

Dyspnea CTD-ILD

Instrument		**Total for Acceptance**	Pulms	Rheums	All Physicians	CTD ILD Patients
Dyspnea 12		88% (22/25)	80% (8/10)	92% (11/12)	86% (19/22)	100% (3/3)
MRC		75% (18/24)	78% (7/9)	75% (9/12)	76% (16/21)	66% (2/3)
Borg		32% (8/25)	30% (3/10)	33% (4/12)	32% (7/22)	33% (1/3)
MDI		58% (14/24)	40% (4/10)	67% (8/12)	55% (12/22)	100% (2/2)
MDI for SSc		54% (13/24)	50% (5/10)	55% (6/11)	52% (11/21)	66% (2/3)
Possible Secondary End-Point		96% (24/25)	90% (9/10)	100% (12/12)	95% (21/22)	100% (3/3)
Need New Patient Derived Instrument		76% (19/25)	70% (7/10)	92% (11/12)	82% (18/22)	33% (1/3)
MDI for future study	RESEARCH	91% 21/23	Show of Hands Voting from All Groups			

Cough in IPF

Instrument		**Total for Acceptance**	**Pulms**	**IPF Patient**
Leicester Cough Questionnaire as Interim Instrument		82% (9/11)	80% (8/10)	100% (1/1)
Possible Secondary End-Point		Agreement without dissension		
Need New Patient Derived Instrument		73% (8/11)	70% (7/10)	100% (1/1)

Cough in CTD ILD

Instrument		**Total for Acceptance**	**Pulms**	**Rheums**	All Physicians	**CTD ILD Patients**
Leicester Cough Questionnaire as Interim Instrument		79% (19/24)	70% (7/10)	83% (10/12)	77% (17/22)	100% (2/2)
Possible Secondary End-Point		Agreement without dissension.				
Need New Patient Derived Instrument		64% (16/25)	60% (6/10)	75% (9/12)	68% (15/22)	33% (1/3)

Patient Global Assessment of Disease Activity in IPF

Instrument		**Total for Acceptance**	**Pulms**	**IPF Patient**
Pt-GA		64% (7/11)	60% (6/10)	100% (1/1)
Possible Secondary End-Point		90% (9/10)	89% (8/9)	100% (1/1)
10mm Change is Clinically Meaningful		30% (3/10)	22% (2/9)	100% (1/1)
PtGA further evaluated as Outcome Measure	RESEARCH	100% 23/23	Show of Hands Voting from all Groups	

Patient Global Assessment of Disease Activity in CTD ILD

Instrument		**Total for Acceptance**	**Pulms**	**Rheums**	All Physicians	**CTD ILD Patients**
Pt-GA		96% (23/24)	100% (10/10)	92% (11/12)	95% (21/22)	100% (2/2)
Possible Secondary End-Point		92% (23/25)	80% (8/10)	100% (12/12)	91% (20/22)	100% (3/3)
10mm Change is Clinically Meaningful		71% (17/24)	50% (5/10)	83% (10/12)	68% (15/22)	100 (2/2)

Health Related Quality of Life in IPF

Instrument		**Total for Acceptance**	**Pulms**	**IPF Patient**
SF-36		82% (9/11)	80% (8/10)	100% (1/1)
SGRQ		82% (9/11)	80% (8/10)	100% (1/1)
Possible Secondary End-Point		100% (11/11)	100% (10/10)	100% (1/1)
Need New Patient Derived Instrument		90% (9/10)	90% (9/10)	Not Voted

Health Related Quality of Life in CTD ILD

Instrument		**Total for Acceptance**	**Pulms**	**Rheums**	All Physicians	**CTD ILD Patients**
SF-36		100% (24/24)	100% (10/10)	100% (11/11)	100% (21/21)	100% (3/3)
SGRQ		87% (20/23)	90% (9/10)	82% (9/11)	86% (18/21)	100% (2/2)
HAQ-DI		54% (13/24)	30% (3/10)	64% (7/11)	48% (10/21)	100% (3/3)
Possible Secondary End-Point		100% (24/24)	100% 10/10	100% (11/11)	100% (21/21)	100% (3/3)
Need New Patient Derived Instrument		100% (22/22)	100% (8/8)	100% (11/11)	100% (19/19)	100% (3/3)

Lung Imaging: During the NGT, it was proposed by the Lung Imaging Team and agreed upon by the assembled group, that overall extent of disease in IPF is fibrosis and honey-combing while ground glass opacities in CTD-ILD is an uncertain pattern and based on available evidence, it was therefore adopted to proceed directly with *Overall Extent of Disease of HRCT* as the single voting item. Note: regarding an end-point *for Overall Extent of Disease on HRCT* in CTD-ILD, no voting option reached the voting threshold of 70%.

Lung Imaging in IPF

Instrument		**Total for Acceptance**	**Pulms**	**IPF Patient**
Overall Extent of Lung Disease on HRCT		100% (1/11)	100% (10/10)	100% (1/1)
Possible Primary End-Point		8% (1/12)	9% (1/11)	0% (0/1)
Possible Secondary End-Point		33% (4/12)	27% (3/11)	100% (1/1)
Endpoint Perceived as Difficult to Assign At This Time		58% (7/12)	64% (7/11)	0% (0/1)
End-Point		NONE		

Lung Imaging in CTD ILD

Instrument		**Total for Acceptance**	**Pulms**	**Rheums**	All Physicians	**CTD ILD Patients**
Overall Extent of Lung Disease on HRCT		92% (23/25)	100% (11/11)	82% (9/11)	91% (20/22)	100% (3/3)
Possible Primary Endpoint		0% (0/23)	0% (0/11)	0% (0/10)	0% (0/21)	0% (0/2)
Possible Secondary Endpoint		65% (15/23)	45% (5/11)	80% (8/10)	62% (13/21)	100% (2/2)
Endpoint Perceived as Difficult to Assign At This Time		35% (8/23)	55% (6/11)	20% (2/10)	38% (8/21)	0% (0/2)
End Point		NONE				

Lung Physiology / Function in IPF

Instrument		**Total for Acceptance**	**Pulms**	**IPF Patient**
FVC		100% (11/11)	100% (10/10)	100% (1/1)
FVC as Possible Primary Endpoint		82% (9/11)	80% (8/10)	100% (1/1)
DLCO		100% (11/11)	100% (10/10)	100% (1/1)
DLCO as Possible Secondary Endpoint		91% (10/11)	90% (9/10)	100% (1/1)
Supplemental O2		0% (0/11)	0% (0/10)	0% (0/1)
6MWT Max Desat		45% (5/11)	40% (4/10)	100% (1/1)
6MWT Distance		45% (5/11)	40% (4/10)	100% (1/1)

Lung Physiology / Function in CTD-ILD

Instrument		**Total for Acceptance**	**Pulms**	**Rheums**	All Physicians	**CTD-ILD Patients**
FVC		100% (24/24)	100% (10/10)	100% (11/11)	100% (21/21)	100% (3/3)
FVCas Possible Primary Endpoint		88% (21/24)	80% (8/10)	100% (11/11)	90% (19/21)	67% (2/3)
DLCO		100% (21/23)	100% (10/10)	80% (8/10)	90% (18/20)	100% (3/3)
DLCO as Possible Secondary Endpoint		87% (20/23)	89% (8/9)	91% (10/11)	90% (18/20)	67% (2/3)
Supplemental O2		4% (1/23)	0% (0/10)	10% (1/10)	5% (1/20)	0% (0/3)
6MWT Max Desat		42% (10/24)	40% (4/10)	36% (4/11)	38% (8/21)	67% (2/3)

Survival: During the NGT, it was proposed by the Survival Team and agreed upon by the assembled group, that *Time to Death* and *Progression Free Survival* in both IPF and CTD-ILD should immediately be tabled to *Research Agenda*, there was no dissension to this. The group opted to proceed, upon advisement of the Survival Team, directly to *All Cause Mortality* and *FVC as a Surrogate Endpoint for Survival* as the voting items.

Survival in IPF

Instrument		**Total for Acceptance**	**Pulms**	**IPF Patient**
All Cause Mortality as a Secondary Endpoint		92% (11/12)	100% (11/11)	0% (0/1)
All Cause Mortality as a Possible Primary Endpoint		25% (3/12)	18% (2/11)	100% (1/1)
FVC as Surrogate Endpoint for Survival		45% (5/11)	40% (4/10)	100% (1/1)
Time to Death	RESEARCH			
Progression Free Survival	RESEARCH			

Survival in CTD ILD

Instrument		**Total for Acceptance**	**Pulms**	**Rheums**	All Physicians	**CTD ILD Patients**
All Cause Mortality as a Secondary Endpoint		92% (23/25)	100% (11/11)	91% (10/11)	95% (21/22)	67% (2/3)
All-Cause Mortality as a Possible Primary Endpoint		0% (0/25) ()1/1	0% (0/11)	0% (0/11)	0% (0/22)	0% (0/3)
FVC as a Surrogate End-Point for Survival		33% (8/24)	30% (3/10)	27% (3/11)	29% (6/21)	67% (2/3)
Progression Free Survival	RESEARCH AGENDA					

Additional questions posed at the NGT Meeting:

Do you think that the CTD-ILD OMERACT group should recommend the collection of bio-samples (according to published guidelines such as the EULAR-EUSTAR biomarker guidelines) in any multicentre RCT in IPF and CTD-ILD? 23/23 Yes by Vote of Hands From All Groups.

The Instruments accepted by the NGT are approved as research agenda items. 23/23 Yes by Vote of Hands From All Groups.

VI. Further References

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