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Development of Clinical Trial Assessments for the Study of Interstitial Lung Disease in Patients who have Connective Tissue Diseases—Methodological Considerations

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Abstract

This review article discusses the proposed methodology that will be utilized to develop core set items for connective tissue disease-associated interstitial lung disease (CTD-ILD). CTD-ILD remain an important enigma in clinical medicine. No consensus exists on measurement of disease activity or what constitutes a significant response to therapeutic interventions. Lack of appropriate measures inhibit effective drug development and hamper regulatory evaluation of candidate therapies.

An interdisciplinary and international Steering Committee (SC) will oversee the execution of a 3-tier Delphi exercise involving experts in CTD and ILD. In parallel to the Delphi, qualitative information will be gathered from patients with ILD using focus groups. These data will subsequently be used to construct surveys to collect quantitative response from patients with ILD. The final Delphi and Patient Perspective results are to be scrutinized by SC and specialty sub-groups (including patient advocates) for truth, discrimination and feasibility – the OMERACT filters. Through application of Nominal Group technique, a core set of outcome measures will be proposed. Subsequent exercises will evaluate the applicability of a proposed core set to the unique issues posed by individual CTDs in addition to guidelines on screening, prognostication and damage scoring.

Keywords

connective tissue disease; interstitial lung disease; OMERACT; Delphi; nominal group technique; consensus methodology; patient perspective

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Conflict of interest

Dörte Huscher, Lesley Ann Saketkoo, David Pittrow and Dinesh Khanna have nothing to declare.

Introduction

OMERACT is an international initiative to improve outcome measures in rheumatologic disease. Over the years, numerous methodological guidelines and universal disease assessment strategies have been developed under the umbrella of OMERACT. In response to a horizon hopeful with potential therapeutics in the treatment of connective tissue disease related interstitial lung disease (CTD-ILD) and in recognition of the lack of a unified approach in evaluating disease activity and therapeutic response in CTD-ILDs, the Connective Tissue Disease related Interstitial Lung Disease Special Interest Group (CTD-ILD SIG) was formed under the aegis of OMERACT to develop a core set for CTD-ILD. Our goal is to harness international expertise to provide recommendations for a provisional core set of domains and outcome measures that can be used in one-year, multi-center randomized clinical trials of therapeutics for the treatment of CTD-ILDs.

We will incorporate two well-established and formal consensus methodologies to achieve our objectives: the Delphi and Nominal Group techniques, a combination of reliable methods will be used to manage this effort (1); as well as assess and incorporate patient perspective. Our goal is to deliver a set of preliminary core set items that is immediately useful to the medical research community and later revised based on validation during use in emerging clinical trials and/or data-driven studies.

The Delphi Techniques

There is broad agreement that a formal consensus process should involve as much expertise as possible from all concerned fields (Fig. 1).

The Delphi method is an established consensus method that has been used frequently in medical and health service research.(2,3) Such methods attempt to assess the extent of agreement (consensus measurement), but also to resolve disagreement (consensus development). As opposed to the nominal group technique (face to face meeting of select experts), a Delphi exercise allows for the participation of experts without geographical limitations as well as conferring cost and time efficiency to the consensus process.(4,5) Delphi participants can offer their opinions independently and confidentially without the pressures of face-to-face meetings, in which dominant individuals may influence the discussion unduly. Thus, averting potential challenges surrounding group dynamics. In addition, participants have the flexibility and anonymity to change their ratings in subsequent rounds of the process, based on the systematic feedback from the results of the previous rounds.

In the recent years, a considerable number of *internet-based* Delphi exercises in various fields have been published and used in the formulation of guidelines.(6–14) Although web-based and traditional paper-based Delphi processes have not been formally compared, internet based Delphi exercises have been shown to be feasible, cost and time saving and better accepted by users than paper-based Delphi methods.(15) Other practical advantages include checks on completion of exercise at time of submission, avoidance of transcription errors via respondent's direct upload to database, and internal mechanisms of quality control to assess validity of response.

The CTD-ILD SIG builds on the experiences of another internet based Delphi exercise, the "Expert Panel on Outcomes measures in PAH related to Systemic Sclerosis [EPOSS]" study. (16) To ensure security and confidentiality, an email invitation with a personal log-on code was sent to participants, allowing individual access to the web site where the Delphi exercise was conducted. All information was provided via the internet, and the questionnaires were completed online by the participants. A Hypertext Preprocessor-(PHP)-based web surface

was used, and data were fed into a Structured Query Language (MySQL-) database and later transferred to SPSS 12.0 for statistical analyses. Data were backed-up on a daily basis but participants had unrestricted logons until final submission. At the end of each round of the Delphi, participants could print an overview of their responses. Members of the steering committee had no access to the primary data in order to keep the responses confidential.

Delphi Content

Using established and validated methods of OMERACT and RAND/UCLA consensus methodology, the project content investigates CTD-ILD as a general entity and as the disease sub-sets of idiopathic inflammatory myositis, rheumatoid arthritis, Sjögren's syndrome and systemic sclerosis. Both in parallel and in contrast to CTD-ILD is an investigation of idiopathic pulmonary fibrosis (IPF) as a prototypic ILD unrelated to CTD (Fig. 2).

The investigation is comprised of Tract 1 and Tract 2. Tract 1 collates and analyzes medical expert opinion on CTD-ILD as a general topic and then addresses CTD sub-sets in order to capture parameters specific to these diseases. Tract 2 compiles medical expert opinion on IPF. The intention of Tract 2 is to assess what is common and discriminating between CTD-ILD and IPF. Within the Delphi survey, this will be represented by parallel voting columns for each question: one for CTD-ILD and one for IPF (Fig. 3).

Identification of Panelists

Appropriate expert panelists will be identified via an international investigation of specialist associations, study investigators of multicenter endpoint studies in parenchymal lung disease, members of respective consensus committees and task forces, dedicated to parenchymal and rheumatologic lung disease, members of disease specific groups such as The Myositis Association, Scleroderma Clinical Trials Consortium (SCTC), EULAR Scleroderma Treatment and Research Group (EUSTAR) etc as well as authors of key publications, in journals and textbooks. Patients with CTD-ILD are also included and detailed later in the Patient Perspective section.

Delphi Design

The Delphi exercise will be divided into 3 tiers with a preceding brainstorming activity called 'Tier 0' (Fig. 4). By soliciting nominations from all expert panelists during Tier 0, the entire panel of experts will build the subsequent voting survey of outcome measures. In subsequent 'Tiers' (called Tier 1, 2 and 3), participants are then asked to rate all domains and instruments on a Likert scale from 1 to 9 in Tiers 1, 2 and 3 of the Delphi exercise according to their importance and accuracy as measurements for use in one-year, multi-center randomized clinical trials of therapeutics for the treatment of CTD-ILDs. In Tiers 2 and 3, the average or median ratings for each item will be revealed to the entire group as well as their own rating of the previous round. In round 3, additional ranking of items will occur. The rankings can provide importance of each item and can be used to determine weights in development of composite index. Rating will take place in consideration of this information.

Delphi Analysis

A first approach to Delphi statistical analysis is to superimpose a pre-defined cut of the mean and/or median values before initiation of the Delphi exercise.⁽¹⁷⁾ This method may allow for expeditious analysis especially if complex statistical support is unattainable. A considerable strength of the EPOSS study, published for the first time in this context, was the application of a statistical procedure (cluster analysis) to differentiate between domains

and outcome measures of higher and lower importance.(9) This technique statistically separates groups with similar patterns, here patterns of rating. In the case of EPOSS the analysis resulted in exactly 2 groups which could be characterized as lower and higher rated items, but it might have resulted also in three or more statistically separable groups with certain rating patterns. Alternatively one can predetermine that the procedure should result in only 2 groups. That will ease the process of discarding domains and outcome measures of low importance, since a 2-group-separation will usually divide into lower and higher importance. This procedure, based on pure mathematical principles, is useful as it decreases biases of subjective cut offs. Clinical expertise from the Steering Committee will complement this statistical process.

The following analysis sequence is intended: There is no analysis of Tier 1 results, only the disclosure of ratings. At the close of Tier 2, the first analysis of ratings for domains and instruments will be conducted based on statistical cluster methods. The ideal outcome would be exactly 2 clusters that easily fall into higher and lower rated items, thus easing the decision which domains and instruments are discarded. If more than 2 clusters are built, discarding or keeping of clusters will be based on the character of the rating pattern of each cluster. If there is no obvious decision for all clusters, alternatively the clustering procedure can be forced to produce exactly two clusters. Careful evaluation of survey results are mandated by the Steering Committee before the survey is allowed to be shortened for the next round voting. For the remaining domains and tools, a second cluster analysis will be run based on respondents' rating after tier 3. Again domains and tools with low ratings will be identified for removal. Finally a core set of high consent will evolve, with resultant outcome measures that are judged by experts as being sensitive or responsive to change for use in one-year, multi-center randomized clinical trials.

Specialized Aspects of the Data Collection System

An experience, which is not solely unique to the area of CTD-ILD, is a lack of shared knowledge and inter-expert communication. This is true of both the larger arenas of the international stage and between specialties, in this case, pulmonology, rheumatology, pathology and radiology. Further within these specialties, exist fairly atomic perspective and investigation; therefore very likely exists fragmented understanding that once coalesced may bring more complete understanding to general medical community. In order to truly describe current knowledge, there is a need to transcend the isolated nature of the generic Delphi experience – which in this case mimics current expert collaboration in ILD - in order to pool and deepen current knowledge during the process. The question of how to invigorate the Delphi exercise to become one of interactive, more considered experience of shared knowledge while remaining anonymous became an important question; therefore *Inter-Expert Delphi Education* was devised.

In the EPOSS trial, after the first round of voting, median scores were revealed to the voters on the second survey. Therefore the voters were able to see how their peers had rated items and how they compared to their peers. This was an opportunity to be influenced anonymously by other voters and perhaps check one's own experience and knowledge. The CTD-ILD SIG approach will allow for a tangible opportunity for anonymous inter-expert discourse. This method will be followed by an experiential survey where panelists provide feedback on this method.

The CTD-ILD SIG, further to identifying expert consensus, is introducing an aspect to data collection which is anticipated to invigorate the Delphi experience, *Inter-Expert Delphi Education*. Within the data collection system, there is a welcoming of detailed opinion and knowledge built in (Fig. 3). This mechanism occurs during the voting rounds where items

are rated. Panelists are invited to anonymously defend or contest the presence of each item by uploading commentary, articles or images adjacent to each item on the web-site. In addition to facilitating a collaborative experience of shared knowledge and perspective, it is anticipated that the addition of this mechanism to the process will fortify evidence-driven consensus.

Patient Perspective: Another Expert Group

Patient perspective is increasingly recognized as an essential component to methodology in the development of core sets.(18) It is clear that there are issues of great concern to patients that lie outside the radar of clinical and research expertise but are intrinsic from a patient perspective for gauging disease activity. An essential component of outcome measure development of working groups operating under the aegis of OMERACT is patient perspective. OMERACT currently advocates for patient experts to be involved throughout the consensus building process including presence during the final decision making stages at face to face meetings where clinical experts meetings are finalizing disease core-sets.

Through patient focus groups and patient contribution to consensus efforts in rheumatoid arthritis, 'fatigue' was identified as one such example. Fatigue, though not considered to be central to disease activity by expert clinicians, was very clearly central to perceived disease activity in patients with rheumatoid arthritis (RA).(19,20) Since identification of this important domain through patient focus groups, fatigue has been accepted into the core set that defines disease activity in RA and has been subsequently validated as being reliable, valid, and sensitive to change over time as a disease marker in RA.(21)

This example demonstrates the power of harnessing patient perspective to identify valid, reliable measures of disease activity making them very useful in clinical investigation but without query into patient perspective, might otherwise be overlooked by clinical investigators. Thus, without consideration of patient perspective, clinical investigations are lacking important measures of disease activity and therapeutic response for use in clinical trials.

There are a number of methods and combinations of methods to assess and define patient perspective in the development of core outcome measures. Each method has its own advantages in consideration of cost, interviewer skills and available resources. Patient perspective may be aggregated by only gathering qualitative information or may proceed with a more rigorous strategy attempting to quantify the importance of qualitative findings to the generalized patient experience. The CTD-ILD SIG strategy for patient perspective will a) use qualitative methods to gather content of patient perspective b) assemble the qualitative data into a quantitative tool – the survey c) use qualitative methods again to assess the usability of the survey in regard to interpretability d) lastly, employ the survey with wide distribution to disclose aspects of patient perspective that are a priority for populations of patients, those that are generalisable and those that are specific to a particular CTD. These methodologies are well described and will be used.

The process of patient perspective is inherently fraught with the potential to unwittingly introduce bias at many junctures. Pitfalls often relate to issues of inclusion based on functional ability, computer and written word literacy, socioeconomic status, cultural background, geographic location, standardization implementation of assistance in survey completion. Protocols for patient selection, data collection and assistance language must be standardized and each participating center trained and committed to following these procedures.

The current design of enlisting patient perspective in the CTD-ILD SIG is a goal of conducting a minimum of 12 focus groups at various sites in potentially any of eleven volunteer countries. Participation will require a patient to have ILD in association with a CTD that is clearly defined by ACR or EULAR criteria. It is currently planned that there are 2 focus groups each specific to IIM-ILD, Sjögren's ILD, RA-ILD and scleroderma-ILD with 4 'mixed' disease ILD groups. The groups will be recorded and transcribed. The qualitative content of the disease specific groups will be compared against the 'mixed' group to assess for the existence of differences in experience of ILD. In addition, quantitative data from the surveys will be stratified by disease specificity with each being compared to total group response.

From this data, the survey will be assembled. Survey respondents will designate disease specificity. Surveys will be available both on line and in paper form with assistance being offered to all participants. Results from these surveys will then be incorporated into the final decision-making stages whereby patient experts will be present and encouraged to participate whether this is on-site or via remote access.

Nominal Group Technique

Nominal Group Technique (NGT) is a face to face structured group meeting of experts that is led by an experience moderator.(22) It is derived from social-psychological studies of decision-making conferences and that of management science. NGT, formulated in the 1960's, and like the Delphi method, originated for use in the social services, government, education and industry. In generic use of the technique, a question is generated for which a group of 5–9 panelists are convened to supply a best answer. Larger groups may be used in various formats for example, divided into several groups of 5–9 undergoing simultaneous exercises of the same question or to answer different aspects of the same question.

We will utilize NGT or a modified NGT to capture items that meet OMERACT filter criteria to select the final provisional core set of items for ILD in general and for the four CTD subsets.

OMERACT methodology

OMERACT strives to improve endpoint outcome measurement through a data driven, iterative and interactive process.

The "OMERACT Filter" scrutinizes an outcome measure by 3 criteria (23):

1. Truth: speaks to face, content, construct, and criterion validity.
2. Discrimination: evaluates for reliability, reproducibility and sensitivity to change.
3. Feasibility: often the 'Achilles heel' of an outcome measure which must pass issues related to application, interpretability, safety, cost efficiency and availability.

It is important to note influential efforts such as the International Classification of Functioning, Disability and Health (ICF) (24) who have established a framework built on a biopsychosocial model of disease that deconstructs disease based on broad components that 'should be measured' rather than 'how to be measured'; thus providing a structure upon which to base the building of disease specific core set. Other efforts have attempted to develop generic strategies to assess harm and benefit in clinical trials to permit straight forward quantitative comparisons of different treatment options.(25) These theories will be considered during the NGT component of the project.

We envision four NGT panels for idiopathic inflammatory myopathy rheumatoid arthritis, Sjögren's syndrome and systemic sclerosis with a final assembly addressing IPF and ILD in general. We acknowledge that as much as the Delphi and NGT endeavor to supply information that is data-driven, they are principally limited to expert experience informed by a limited availability of qualitative and quantitative data.

The Final Product

The final stages of a consensus project are delivering and distributing the final product. The CTD-ILD SIG has taken care to assimilate some important concepts of The Glaser State of the Art Approach to Consensus during the infant stages of development.(26) These concepts procure project visibility, acceptance and durability.

Visibility

During inception a wide base of support for the endeavor was culled by presenting the goals and potential design of the project to groups who have a vested interest in CTD-ILD. These groups will include lead members of the American College of Chest Physicians (ACCP), American College of Rheumatology (ACR), American Thoracic Society (ATS), Canadian Thoracic Society (CTS), European League Against Rheumatism (EULAR).

Acceptability

Each of these groups is represented within the hierarchy of the CTD-ILD SIG design. To ensure durability of the final product, which in this case involves outcome measures for use in clinical trials, panel involvement from the United States Food and Drug Administration (FDA) as well as the European Medical Agency (EMA) were obtained. In addition to key institutional representation, the CTD-ILD SIG is represented by over 35 countries on five continents.

Durability

This approach thus identified experts who are representative members of their profession and who are intrinsically and publically involved in CTD-ILD. We are thereby a) ensuring solidity of end product leaving little room for post-project challenge b) ensuring implementation by harnessing the expertise of those who ultimately have the power to initiate execution of resultant recommendations.

Distribution

Planned trajectory of distribution to a cache of high profile journals as well as forum at professional meetings was conceived that could conceivably carry the results of this effort to the audience most in need of receiving and utilizing this information (pulmonologists, rheumatologists). Therefore the rigor at each stage of the subsequent work would be checked for quality assurance to maintain a level of acceptance to one or more of these publications.

In summary, we have described our formal consensus methodologies (Delphi and NGT) that we will undertake to define provisional core set measures for CTD-ILD and IPF.

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Figure 1.
Road map of the CTD-ILD consensus project

Figure 2.
Overview of project content outlining relationship of CTD-ILD to IPF

Six Minute Walk Test is an outcome measure that is useful in a 1 year multi-centre clinical trial to measure response to treatment in:

CTD-ILD											IPF												
1	2	3	4	5	6	7	8	9	No opinion	1	2	3	4	5	6	7	8	9	No opinion				
☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒				
Don't use					☒	Use routinely					☒	Don't use					☒	Use routinely					☒
Upload Commentary											Upload Commentary												
Upload Commentary with Attachment											Upload Commentary with Attachment												
View Commentary / Document List											View Commentary / Document List												

Figure 3.

Example of CTD-ILD and IPF survey items displayed in parallel with Inter-Expert Education features below item

Figure 4.
Flow chart of the Delphi process for the CTD-ILD project