Measures of Response in Clinical Trials of Systemic Sclerosis: The Combined Response Index for Systemic Sclerosis (CRISS) and Outcome Measures in Pulmonary Arterial Hypertension Related to Systemic Sclerosis (EPOSS)

DINESH KHANNA, OLIVER DISTLER, JEROME AVOUAC, FRANK BEHRENS, PHILIP J. CLEMENTS, CHRISTOPHER DENTON, IVAN FOELDVARI, EDWARD GIANNINI, DOERTE HUSCHER, OTYLIA KOWAL-BIELECKA, DANIEL LOVELL, MARCO MATUCCI-CERINIC, MAUREEN MAYES, PETER A. MERKEL, PETER NASH, CHRISTIAN F. OPITZ, DAVID PITTROW, LEWIS RUBIN, JAMES R. SEIBOLD, VIRGINIA STEEN, C. VIBEKE STRAND, PETER S. TUGWELL, JOHN VARGA, ANGELA ZINK, DANIEL E. FURST, for the Investigators in CRISS and EPOSS

ABSTRACT. There have been steady efforts to develop a combined response index for systemic sclerosis (CRISS). A parallel and equally successful effort has been made by an Expert Panel on Outcome Measures in PAH related to Systemic Sclerosis (EPOSS) to measure effect in treatment of pulmonary arterial hypertension of systemic sclerosis (PAH-SSc). CRISS conducted a Delphi process combined with expert review to identify 11 candidate domains for inclusion in a core set of outcomes for SSc clinical trials: soluble biomarkers, cardiac, digital ulcers, gastrointestinal, global health, health related quality of life (HRQOL) and function, musculoskeletal, pulmonary, Raynaud's, renal, and skin. Tools within domains were also agreed upon. Concentrating on one aspect of disease, PAH, EPOSS also conducted a Delphi process and judged the following domains as the most appropriate for randomized controlled trials in PAH-SSc: lung vascular/pulmonary arterial pressure, cardiac function, exercise testing; severity of dyspnea, discontinuation of treatment; quality of life/activities of daily living; global state; and survival. Possible useful tools within each domain were also agreed on. Patient derived, physician derived, and objective measures of response will be included and combined with the idea that each reflects different aspects of PAH (EPOSS) and overall disease (CRISS) although this assumption may not prove true and can be separated if statistically and clinically valid to do so. In either case, prospective studies will require measurement of all domains, and tools are required and will be developed to define appropriate combined measures of response. CRISS and EPOSS are being developed through the OMERACT process. Through Delphi process and literature review significant progress has been made for both indices, and prospective data are being collected. (J Rheumatol 2009;36:2356-61; doi:10.3899/jrheum.090372)

Key Indexing Terms:
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From the David Geffen School at University of California, Los Angeles, CA, USA; University Hospital Zurich, Zurich, Switzerland; Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris, France; Goethe University, Frankfurt, Germany; Royal Free and University College Medical School, London, UK; General Hospital Eilbek, Eilbek, Germany; Rehabilitation Institute, UCLA, Los Angeles, CA; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; German Arthritis Research Centre, Berlin, Germany; Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; Division of Medicine and Rheumatology, University of Florence, Florence, Italy. Rheumatology, University of Texas Health Science Center at Houston, Houston, TX; Boston University School of Medicine, Boston, Massachusetts, USA; University of Queensland, Queensland, Australia; Deutsches Herzzentrum Berlin, Berlin, Germany; Department of Clinical Pharmacology, Medical Faculty, Technical University of Dresden, Dresden, Germany; Department of Medicine, University of California, San Diego, USA; Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; Division of Rheumatology, Georgetown University Hospital, Washington, DC; Division of Immunology, Stanford University, Portola Valley, CA, USA; Institute of Population Health, Ottawa, ON, Canada; Feinberg School of Medicine, Northwestern School of Medicine, Chicago, IL, USA; and German Rheumatism Research Centre, Berlin, Germany. D. Khanna, MD, MSc, David Geffen School at University of California; O. Distler*, MD, University Hospital Zurich; J. Avouac, MD, Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP; F. Behrens, MD, J.W. Goethe University; P.J. Clements MD, MPH, David Geffen School at University of California; C. Denton, MD, PhD, Royal Free and University College Medical School; I. Foeldvari, MD, General Hospital Eilbek; D.E. Furst**, MD, Rehabilitation Institute, UCLA; E. Giannini, DrPH, MSc, Professor, Cincinnati Children's Hospital Medical Center; D. Huscher, Statistician, Research Associate, BS/MS in Mathematics and Statistics, German Arthritis Research Centre; O. Kowal-Bielecka, MD, Department of Rheumatology and Internal Medicine, Medical University of Bialystok; D. Lovell, MD, MPH, Professor of Pediatrics, Cincinnati Children's Hospital Medical Center;*

M. Matucci-Cerinic, MD, PhD, Professor of Rheumatology and Medicine and Director of Division of Medicine and Rheumatology, University of Florence; M. Mayes, MD, MPH, Professor of Medicine, Rheumatology, University of Texas Health Science Center at Houston; P.A. Merkel, MD, MPH, Professor of Medicine, Boston University School of Medicine; P. Nash, MBBS, FRACP, University of Queensland; C.F. Opitz, MD, FESC, Deutsches Herzzentrum Berlin; D. Pittrow, MD, Associate Professor for Clinical Pharmacology, Department of Clinical Pharmacology, Medical Faculty, Technical University of Dresden; L. Rubin, MD, Professor of Medicine, Department of Medicine, University of California, San Diego; J.R. Seibold, MD, Professor, Department of Internal Medicine, University of Michigan; V. Steen, MD, Professor, Division of Rheumatology, Georgetown University Hospital; C.V. Strand, MD, Clinical Professor of Medicine, Division of Immunology, Stanford University; P.S. Tugwell, MD, Institute of Population Health; J. Varga, MD, Professor, Feinberg School of Medicine, Northwestern School of Medicine; A. Zink, PhD, German Rheumatism Research Centre.

**D. Khanna and O. Distler are co-first authors; **D.E. Furst is senior author; all other authors are listed in alphabetical order.*

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Address correspondence to Dr. D.E. Furst, Rehabilitation Institute, UCLA, Room 32-59, 1000 Veteran Ave, Los Angeles, CA, 90025, USA.

Since the last OMERACT meeting in 2006, there have been steady efforts to develop a measurement of effect for treatment of pulmonary arterial hypertension of systemic sclerosis (PAH-SSc) within the OMERACT philosophy[1]. This effort, called the Expert Panel on Outcome Measures in PAH related to Systemic Sclerosis (EPOSS), has made significant strides. A parallel effort to develop a Combined Response Index for Systemic Sclerosis (CRISS) has been ongoing and this effort is also progressing nicely.

Regarding EPOSS, there is need for a structured approach to define endpoints for PAH-SSc that take into account the methodological problems associated with possible SSc-specific confounding factors (e.g., musculoskeletal problems, joint contractures, fatigue, and deconditioning, which may affect cardiopulmonary testing).

PAH is the major debilitating complication of SSc limiting life expectancy, affecting up to 20% of patients[2]. Right heart catheterization (RHC), the gold standard for diagnosis of PAH, is underused due to limited availability, complexity, invasiveness, and the economic implications of the procedure[3]. Further, RHC-derived hemodynamic variables are useful for PAH diagnosis, but do not correlate well with either clinical outcomes or survival. Alternative endpoints are needed for clinical studies. Such endpoints will need to encompass a wide variety of domains (such as cardiac function, quality of life, lung function, soluble biomarkers) and tools [echocardiography and quality of life instruments such as the Medical Outcome Study Short Form Survey-36 (SF-36)].

Together with the CRISS effort (see below), EPOSS will work to develop a set of domains and tools specific for PAH-SSc. These activities are complementary rather than combined, although many of the same techniques and analyses are applied by both, justifying close, cooperative, and synergistic efforts.

There has been substantial progress over the past decade in the development and validation of outcome measures and refinement of trial methodology in SSc[4-6]. This progress has been paralleled by an increased understanding of the pathogenesis of SSc and development of targeted therapies[7-9]. The modified Rodnan skin score, a measure of skin thickness, has been used as the primary outcome measure in clinical trials of diffuse/diffuse cutaneous SSc (dcSSc)[10,11]. However, the complexity and heterogeneity of the disease mandates a composite response measure that will capture differing organ involvements and patient-reported outcomes. Well-validated, widely accepted combined response indices, which are more likely to be responsive to change than individual measures[12,13], will facilitate drug development and improve assessment of efficacy of therapeutic agents[12,14].

A CRISS instrument for use in clinical trials of patients with dcSSc could facilitate interpretation of results from clinical trials, similar to the American College of Rheumatology response criteria and the Disease Activity Score definitions for rheumatoid arthritis. Rather than using numerous outcomes that vary from trial to trial, a core set of outcomes will produce a single efficacy measure.

This article outlines progress and plans for the EPOSS and CRISS initiatives.

EXPERT PANEL ON OUTCOME MEASURES IN PAH RELATED TO SYSTEMIC SCLEROSIS

Progress to date. The EPOSS group first published an article defining the need for improved outcome measures PAH-SSc[15]. Using a Delphi process, a series of domains and tools were developed that might be used as alternative endpoints to the use of RHC to define PAH-SSc, as repeated RHC are difficult to accomplish in clinical trials. The results of the EPOSS Delphi process have been published[16]: 69 PAH-SSc experts, including rheumatologists, cardiologists, and pulmonologists rated a list of domains and measurement tools in an Internet-based Delphi consensus study. A statistical cluster analysis was used to define specific domains and tools to be included in this preliminary measurement tool. A meeting of the EPOSS Steering Committee was convened to remove redundant items and inconsistencies, omit elements not feasible in clinical trials, and make other judgments on a clinical basis.

The following domains and tools were judged as most appropriate for randomized, controlled trials in PAH-SSc: lung vascular/pulmonary arterial pressure and cardiac function both measured by RHC and echocardiogram, 6-minute walk test, oxygen saturation exercise; severity of dyspnea on a visual analog scale; discontinuation of treatment as measured by serious adverse events; quality of life/activities of daily living measured by the SF-36 and Health Assessment Questionnaire Disability Index; global state assessed by physician measures and survival (Table 1).

Table 1. Final core set of physician-derived domains and measurement tools for EPOSS, defined by the Delphi survey. Modified from Distler O, et al. Arthritis Rheum 2008; 15:867-75, with permission.

Cardiac function
Right heart catheterization
Echocardiography
Dyspnea visual analog scale
Discontinuation of treatment
Adverse events
Serious adverse events
Dyspnea
Dyspnea visual analog scale
Exercise testing
6-minute Walk Test
Oxygen saturation on exercise
Global state of physician
Survival
Lung vascular
Right heart catheterization
Echocardiography
Quality of life
Short-Form-36 score
Health Assessment Questionnaire Disability Index

EPOSS: Expert Panel on Outcome Measures in PAH Related to SSc.

An additional analysis examined differences in responses between pulmonologists and cardiologists compared to rheumatologists (Huscher D, *et al*. Unpublished data). In general, it was found that rheumatologists favored patient-derived questionnaires more frequently than cardiologists/pulmonologists while the latter favored specific pulmonary related measures of response; however, combined results encompassing both groups' assessments are required for full description and measurement of PAH-SSc.

In preparation for a prospective study and/or for use of existing data to validate the domains and tools outlined above, an in-depth structured literature review was undertaken for echocardiography[16] and 6-minute walk test[17]. The structured reviews show which parts of the selected outcome measures have already been sufficiently validated in PAH-SSc based on the OMERACT filter to require no more research, and more importantly, define those measures that need further validation before their use to assess PAH-SSc.

Plans. For the EPOSS effort we are presently:

1. Completing the systematic literature review on core set outcomes defined by the Delphi study.
2. Planning to validate domains and tools as chosen through the Delphi exercise by: (a) Obtaining data from completed clinical trials that include as many chosen domains/tools as possible to corroborate and winnow the tools to be used in future clinical trials; (b) Assessing, based on results of the systematic literature review, remaining aspects of the core set measures identified as not yet fully validated, in further validation studies. Fortunately, a large number of randomized controlled trials in PAH have recently been performed. A subanalysis on PAH-SSc patients from the placebo arms of these studies will be performed and we are attempting to get these data.
3. Developing a patient Delphi exercise: From the patients' perspective, changes in functional ability may be more distressing and debilitating than changes in objective measures of disease often used by physicians. However, there is insufficient information regarding which domains may be most important to patients, because many outcome measures used in PAH-SSc report either generic HRQOL, or single domains (e.g., physical function), or are not measured (e.g., fatigue). (a) We will evaluate patient assessment of disease and symptom burden in PAH-SSc using patient-centered qualitative methods. This adds an important component to the core set defined by physicians outlined above. We will conduct focus groups and interviews of PAH-SSc patients in order to determine patients' perceptions of disease activity, disability, and HRQOL and to identify areas most distressful and concerning to patients.
4. Developing physician derived and objective measures of response separately from the patient derived measures: When completed, the 2 approaches to PAH-SSc will be examined in combination and separately to ascertain which approach is more sensitive to change in clinical trials. Each

probably describes somewhat different aspects of PAH-SSc; thus a combined measure could improve discriminating ability. On the other hand, combining them in all circumstances may not be appropriate if combination does not enhance discriminating ability, or if one or the other better discriminates response.

COMBINED RESPONSE INDEX FOR SYSTEMIC SCLEROSIS

Progress to date. The first step in developing a CRISS was to conduct a structured Delphi exercise with the Scleroderma Clinical Trial Consortium membership to develop a provisional core set of items for clinical trials[18]. In this exercise, 50 investigators provided 212 unique items for 11 domains in a one-year clinical trial of SSc patients. In this trial 92% of the original investigators responded in the second round and rated 177 items. Nominal group technique examined these data for consistency, redundancy, feasibility and validity, judging 31 of the items from the 11 domains to be appropriate for inclusion in a one-year multicenter clinical trial. Thereafter, in a modified third round, investigators ranked 30 of 31 items as acceptable for inclusion in the course. The final domains chosen are listed in Table 2. An additional 14 items were included in a research agenda. (Table 3).

Recruiting for the one-year prospective cohort study has begun, including obtaining data in all domains and by all tools suggested from the CRISS Delphi exercise.

Plans. Preliminary efforts to develop a CRISS have included pooling of data, comprising 635 patients with dcSSc, from previously completed clinical trials of dcSSc to test some individual aspects of a possible combined index. Unfortunately, the 635-patient dataset lacks a number of the core set items from the above Delphi exercise, making that dataset unsuitable to completely test the proposed CRISS. Therefore, we are assessing all proposed core set items in a 1-year longitudinal observational study (see above) and will then employ prospective, data-driven, consensus building techniques to develop and quantitatively evaluate candidate definitions for a CRISS that will capture different organ involvements and patient-reported outcomes.

For the CRISS effort, we are presently:

1. Performing a prospective longitudinal observational clinical study to define a reliable, valid and responsive set of dcSSc measures based on the above Delphi exercise: (a) We are collecting data specified in the above Delphi-exercise defined core set in a 1-year observational study in 200 patients with early dcSSc (defined as duration ≤ 5 yrs) at 4 academic scleroderma centers. To date about 150 patients have been recruited into the cohort. (b) We will assess the reliability, validity, and responsiveness of the core set items from the real patient data collected in the 1-year observational study. (c) We will revise and define a final core set based on results obtained from 1(b). (d) The same considerations as for EPOSS will be true for the patient-derived aspects of the CRISS, as the potential tools in the CRISS include a number of patient-derived outcomes (e.g., SF-36, HAQ-DI, pain, global evaluations, and dyspnea). These will be considered in the same manner as for EPOSS, although for the present no separate evaluation by patients is planned. Nevertheless, the multiple patient-derived measures can be examined as a separate group within the CRISS, if separat-

Table 2. Core set items selected for 11 domains for the CRISS. Modified from Khanna, et al. Ann Rheum Dis 2008; 67:703-9, with permission.

Soluble biomarkers
Acute phase reactants ESR and/or CRP
Cardiac
Cardiac echocardiogram with Doppler†
Right heart catheterization
6-Minute Walk Test*
Borg Dyspnea Instrument*
Digital ulcers
Active digital tip ulcer count on the volar surface
VAS digital ulcer (part of Scleroderma HAQ-DI)
Gastrointestinal
Body mass index
Validated GI tract VAS or other SSc-validated GI questionnaire
Global health
VAS/Likert scale for patient global severity
VAS/Likert scale for physician global severity
Scleroderma-related health transition by patient
Scleroderma-related health transition by physician**
Health-related quality of life and function
HAQ-DI
VAS pain scale from the HAQ-DI
Short Form-36 score, version 2
Musculoskeletal
Tender Joint Count
Tendon friction rubs assessed by the physician**
Serum creatinine phosphokinase, aldolase
Pulmonary
Pulmonary function testing
Validated measure of dyspnea
Breathing VAS from the Scleroderma HAQ
HRCT of the lungs: quantifiable scale*
Raynaud's phenomenon
Raynaud's condition score
VAS (part of S-HAQ)
Renal
Calculated creatinine clearance based on serum creatinine (Cockroft-Gault or MDRD formula)
Pre-defined renal crisis (presence or absence)
Skin
Modified Rodnan Skin Score (range 0–51)
VAS/Likert of patient global assessment for skin activity**
VAS/Likert of physician global assessment for skin activity**
Durometer

† Standardized central reading mechanism strongly encouraged; * if relevant to the study; ** Items were based on Steering Committee and SCTC consensus despite lack of full validation. CRISS: Combined Response Index for SSc; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; VAS: visual analog scale; HRCT: high resolution computed tomography; MDRD: modification of diet in renal disease.

Table 3. Proposed items for future research. Modified from Khanna, et al. Ann Rheum Dis 2008;67:703-9, with permission.

Research Agenda
Biomarkers
Markers of the collagen breakdown e.g., soluble IL-2 receptor levels, procollagen I and III aminopropeptide, CTGF levels, serum collagen I carboxyterminal telopeptide, urinary pyridinoline cross-link compounds of collagen, etc.
Cardiac
Serum probrain natriuretic peptide (Pro-BNP) or NT-Pro-BNP
Noninvasive measures of cardiac function e.g., cardiac MRI, tissue Doppler
Digital ulcers
Development of digital ulcer condition score that captures activity, severity, and impact
Gastrointestinal
Scleroderma-gastrointestinal 1.0 questionnaire
Gastric emptying time and/or 24-h small bowel transit time
Global Health
Medsger Severity Index
Health-related Quality of Life and Function
Measure of health utility e.g., SF-6D, EuroQol, Quality of Well Being Scale, time trade-off standard gamble
Measure of fatigue e.g., Functional assessment of chronic illness therapy (FACIT)-Fatigue
Measure of depression/anxiety e.g., Beck Depression Inventory, Center for Epidemiologic-Depression Scale
Musculoskeletal
Large joint contracture
Michigan Hand Questionnaire
Skin
Measure of telangiectasia
VAS/Likert patient global assessment for pruritus

IL-2: interleukin 2; CTGF: connective tissue growth factor; SF-6D: Medical Outcome Study Short Form 6D; FACIT: Functional assessment of chronic illness therapy; VAS: visual analog scale.

ing those aspects from their underlying instruments is statistically and clinically valid.

2. Employing prospective, data-driven, consensus building techniques to develop and quantitatively evaluate candidate definitions for a SSc-CRI for dcSSc. (a) We will create paper-patient profiles from data gathered as part of 1(c), above, from diffuse SSc patients over a 1-year period. (b) Using consensus formation techniques (nominal group technique) we will have key opinion leaders in the field rate paper-patient profiles to estimate validity characteristics of each candidate definition for a CRISS. We are planning a sample size of 200 patients to be able to select patient profiles plus anticipated dropouts. (c) We will use ratings of key opinion leaders as a gold standard to estimate validity characteristics, such as sensitivity and specificity, and compare each using area under the curve and receiver operating characteristics analyses. (d) We will select a definition of CRISS for use in clinical trials in dcSSc that has high statistical discriminatory power and is most credible (highest face validity).

In SSc, the multiple organ system involvements can be either reversible or irreversible and the measures to separate these 2 aspects of SSc are not available. Rather the process of choosing the tools within the domains will be utilized to choose tools that are most sensitive to change. This, by implication, assumes those tools reflect reversible aspects of SSc, although this is clearly an empiric rather than physiologic or pathologically based decision.

By grouping patient derived measures, it may also be possible to find a patient oriented portion of the CRISS that can be used separately or within the complete CRISS. However, if patient derived measures prove to be an integral and required portion of the CRISS when considering sensitivity to change and clinical relevance (as seen in ACR criteria for rheumatoid arthritis and juvenile idiopathic arthritis), such a determination would be specifically addressed when the final version of the CRISS has been completed.

CONCLUSION

An overall combined measure of response in systemic sclerosis (CRISS) and a combined measure of response for PAH-SSc (EPOSS) are being developed through the OMERACT process. Significant progress has been made using the Delphi process and literature review for both indices, and prospective data are being collected.

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