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An Interim Report of the Scleroderma Clinical Trials Consortium Working Groups

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Abstract

The Scleroderma Clinical Trials Consortium (SCTC) represents many of the clinical researchers in the world who are interested in improving the efficiency of clinical trials in Systemic Sclerosis (SSc). The SCTC has established 11 working groups (WGs) to develop and validate better ways of measuring and recording multiple aspects of this heterogeneous disease. These include groups working on arthritis, disease damage, disease activity, cardiac disease, juvenile SSc, the gastrointestinal tract, vascular component, calcinosis, scleroderma renal crisis, interstitial lung disease, and skin measurement. Members of the SCTC may join any one or more of these groups.

Some of the WGs have only recently started their work, some are nearing completion of their mandated tasks and others are in the midst of their projects.

All these projects, which are described in this paper, will help to improve clinical trials and observational studies by improving or developing better, more sensitive ways of measuring various aspects of the disease. As Lord Kelvin stated, “To measure is to know. If you cannot measure it you cannot improve it.” The SCTC is dedicated to improving the lives of patients with SSc and it is our hope that the contributions of the WGs will be one important step in this process.

The Scleroderma Clinical Trials Consortium(SCTC) represents the majority of researchers and clinicians in the world who have particular interest and expertise in the care of, and research in, systemic sclerosis (SSc, scleroderma). The mission of the SCTC is to advance knowledge about the treatment of SSc primarily by promoting efficient design, conduct, and reporting of results of clinical trials and observational studies. To this end the SCTC has assembled an assortment ofworking groups (WGs) that are tasked to investigate various aspects of scleroderma. In general, they are focused on better ways to measure various aspects of the disease. These measures are essential for the conduct of good clinical trials and observational studies.

In this report we will briefly summarize the projects of these WGs. The Table shows a summary of the WGs and the contact for the principal investigators should the reader wish to join a group.

1. Arthritis WG. PI: authors JG, PC and SJ.

Musculoskeletal disease in SSc leads to disability and poor quality of life(1). Musculoskeletal disease including arthritis and tendinopathy has been observed in24% to 97% of SSc patients at some time during the course of their illness(2). Synovitis, joint contracture, and tendon friction rubs (TFRs) are associated with early disease, disease severity, and with higher degrees of systemic inflammation(3, 4). Joint synovitis and TFRs were shown to be independent predictive factors for disease progression in early SSc(5). However, these manifestations are frequently overlooked in the context of clinical trials in part because outcome measures have not been developed for Musculoskeletal symptoms (6). This WG was formed in order to identify a core set of preliminary items considered as important for the study of arthritis and arthropathy in SSc.

In order to explore the opinions of scleroderma experts regarding utility of potential outcome measures in SSc joint disease, we conducted a two-part Delphi exercise. We utilized web-based technologies to conduct the Delphi exercise. In 2 rounds of electronic voting, experts from the SCTC email list were asked to rate various outcome measures with respect to their use in future clinical trials focused on arthritis in SSc. Individuals ranked each item 1–9 on a Likert scale with the intent to disregard any items with a mean score <3, keep items with a mean score >7 and reconsider items rated between 3 and 7.

Fifty physicians from SCTC centers participated. They were provided with a list of 29 items to consider initially, which was increased to 31 items during the second round. Consensus was achieved after 2 rounds of voting. The experts agreed that the following 7 items should be useful in an arthritis-focused SSc trial: 28 joint tenderness count, 28 joint swelling count, assessment of TFRs, assessment of contractures of small and large joints, C-reactive protein, Scleroderma Health Assessment Questionnaire-Disability Index, patient global visual analogue scale. No items on the list were ranked in the disregard category.

The two round Delphi exercise identified 7 items considered by experts as well-suited for the study of arthritis in SSc, but there was considerable ambivalence regarding the performance of these potential outcome measures for SSc arthritis. The validation of these outcome measures for use in interventional studies of SSc-arthritis is called for and is the focus of this group moving forward.

2. Disease Damage WG. PI: authors NF, MB, MN

The Scleroderma (SSc) Clinical Trials Consortium Damage Index (SCTC-DI) Working Group was assembled in November 2013. The mandate of this working group of 24 members, including 22 rheumatologists and 2 dermatologists from North and South America, Australia and Europe, was to develop the first disease Damage Index in SSc, an instrument to quantify organ damage in this disease. The SCTC-DI Working Group was aided by an Advisory Group of 7 non-rheumatology experts from the disciplines of cardiology, respiratory medicine, gastroenterology and nephrology, together with 3 patient partners.

The first task of the SCTC-DI Working Group was to achieve a consensus definition of ‘damage’ in SSc. This was achieved through a two-round survey of the Working Group members, and consultation with the Advisory Group and patient partners. Items for potential inclusion were generated through a systematic review of the literature (7)and items were added based on suggestions of the WG members, the Advisory Group and the patient partners. The final list of items was then presented in survey form to the members of the SCTC, who were asked to rate the appropriateness of each item, in terms of importance and feasibility, for inclusion in the SCTC-DI. In this manner, over 80 items were reduced to just over 50. Further item reduction and ‘weighting’ was achieved through regression methods relating each item with the endpoints of quality of life (‘morbidity’) measured using SF-36 and mortality, in the Australian Scleroderma Cohort Study data set of over 1500 patients followed prospectively over a median follow-up of 4 years. External validation of the SCTC-DI in the Canadian Scleroderma Research Group cohort has shown excellent performance

characteristics against similar morbidity and mortality endpoints, and steady accrual of damage over time, indicating responsiveness in an observational cohort setting. A manuscript reporting the derivation and initial validation of the SCTC-DI is currently being prepared for submission for peer review publication.

Future projects include prospective validation of the SCTC-DI in the International Systemic Sclerosis Inception Cohort (INSYNC) of patients followed from disease onset, and assessment of discriminant validity in interventional studies. Future applications of the newly derived SCTC-DI include use as an outcome measure and enrichment tool for patient selection in clinical trials, a tool to describe the course of the disease in observational studies, and an instrument to quantify disease burden for epidemiological studies and policy making.

As activity and damage lie on the same continuum, the development of the SCTC-DI has laid the foundations for the development of an Activity Index using similar methodology.

3. Disease Activity WG. PI: authors LR, MB, MN

The EUSTAR Activity Index (EScSG-AI) (8, 9) is the only previously published SSc activity index. The EScSG-AI was recently revised in 2017(9), however, it has not yet been fully validated. This remains an issue of great clinical significance as SSc continues to have the highest case-based mortality of any autoimmune connective tissue disease (10). Thus, accurate identification of high disease activity is of utmost importance in order to apply targeted therapy to lower the risk of organ damage.

The SCTC Activity WG is a collaboration of international SSc experts working towards generating a weighted, multi-system index to identify and measure SSc disease activity. Similarly to the Damage Index WG, a multidisciplinary advisory panel of non-rheumatology experts and patient partners have been assembled to provide advice and recommendations regarding aspects of disease activity relevant to their specific fields of expertise. Whilst conceptually, activity and damage are two distinct concepts, attribution of features of SSc to either disease activity or damage is not always straightforward. The complex, multi-system nature of SSc, its progressive rather than relapsing and remitting disease course, the late clinical presentation of many disease features and a lack of biomarkers all contribute to the significant difficulty researchers and clinicians have in defining and measuring SSc disease activity.

As a first step in developing an activity index, the SCTC Activity WGdevelopeda consensus, conceptual definition of disease activity in SSc. This conceptual definition of disease activity will then form the central construct of the planned SCTC Activity Index (SCTC-AI). Careful attention will be paid to the Outcome Measures in Rheumatology (OMERACT) filters of truth, discrimination and feasibility(11) in the development of the SCTC-AI.

Using a similar methodology to that employed in the development of SCTC-DI, development of items for the SCTC-AI will draw upon the expertise of the SCTC WG and systemic review of the literature. Reduction and weighting of items will be performed using data from the Australian Scleroderma Cohort Study (ASCS). Data from the Canadian

Scleroderma Research Group (CSRG) cohort study will be used for retrospective validation in an external cohort and prospective validation studies will be performed using data from the INSYNC study. In all of these validation studies, the endpoints of interest will be health-related quality of life (HRQoL), physical function, organ damage (measured by the SCTC-DI), and mortality.By ensuring that the SCTC-AI has face value, measures what is intended, and readily discriminates between high and low disease activity states, it is hoped that the SCTC-AI will overcome the criticisms faced by other outcome measures and be the first fully validated SSc disease activity outcome measure.

4. Cardiac WGPI: authors AV,LR, MB, MN

The aim of the SCTC Cardiac WG is to develop a definition of primary cardiac involvement in SSc for use in clinical trials and in observational studies. Currently, there is no consensus definition of SSc-cardiomyopathy and this is reflected in the highly variable reporting of SSc heart involvement (SCH) and its prevalence. SCH is highly heterogeneous and includes variable involvement of many cardiac structures including the myocardium, conduction system, pericardium and cardiac valves. Early definitions of SCH have included congestive cardiac failure, arrhythmias requiring therapy and symptomatic Pericarditis (12, 13). The prevalence of SCD using these criteria was 15% in a cohort of patients with diffuse SSc and these patients, particularly those with symptomatic cardiomyopathy, had poor clinical outcomes(13).

Autopsy studies have demonstrated SCH in up to 80% of patients and whilst no individual finding is pathognomonic for SCH, features of microvascular damage, myocardial fibrosis and inflammation are considered characteristic of SSc heart disease (14, 15). A definition of SCH would ideally incorporate the underlying pathophysiological processes, however routine investigations such as electrocardiography, chest radiograph and transthoracic echocardiography are known to have a low sensitivity for the detection of SCH prior to the onset of clinically overt disease(16). There is emerging evidence of a role for more sensitive diagnostic techniques such as tissue Doppler echocardiography(TDE), and cardiac magnetic resonance imaging (CMR)(17), and for biomarkers such as N-terminal pro B-type natriuretic peptide(18), and high sensitivity cardiac troponin(19, 20). However, the clinical significance of abnormalities detected by newer investigation modalities remains uncertain.

There are a significant number of other unresolved issues when considering SCH; namely, the effect of co-morbidities on the myocardium and attribution of cardiac disease to SSc, as well as appropriate screening algorithms and optimal treatment and follow-up of patients diagnosed with SCD. The lack of an accepted, standardised definition of SCH impedes progress in all of these areas.

The SCTC CardiacWG has recruited cardiologists from Europe, North America and Australia to assist in the development of a preliminary working definition of SCH. The WG will be asked to consider the scope of cardiac disease that should be included in a definition of SCH. Questions to be considered are should the definition of SCH be restricted to SSc affecting the myocardium only, and should SCH considered present only if patients are symptomatic? A scoping literature review of previously published definitions of SCH has

been performed. With these results and by drawing upon the expertise within the group, the Cardiac WG is aiming to develop a consensus, expert-opinion definition of SCH. In parallel, the Cardiac WG is also developing a research agenda to pursue the role of novel echocardiography techniques and CMR in the diagnosis of SCH and establishing cohort studies to better describe the natural history of SSc cardiac disease. There are now validated methods to non-invasively assess cardiac fibrosis with CMR, avoiding the need for endomyocardial biopsy(21). This offers SSc-researchers an opportunity to evaluate larger numbers of patients to precisely quantify the burden of myocardial fibrosis in SSc and potentially develop a feasible clinical method to diagnose SHI, prior to the onset of severe heart failure.

5. Juvenile scleroderma WG. PI: Author IF

Juvenile systemic scleroderma (jSSc) is a much rarer than the adult form. The estimated prevalence is 3 per 1 million child based on the Administrative Claims Data from the United States (Beukelman and Foeldvari et al, in press JSRD). The only published cross sectional study regarding incidence from the United Kingdom and Ireland that relied upon surveys of specialist, estimated a yearly incidence of 0.27 [0.10–0.50] per 1 million child(22).

Currently there is a proposed severity index published for jSSc(23), which is a modification of the Medsger severity index, however it is not yet validated. In the evaluation of the juvenile severity index (23) in the juvenile scleroderma inception cohort population(www.juvenile-scleroderma.com), the index appears to be unresponsive to improvement but it did correlate with the Modified Rodnan skin score(unpublished data Foeldvari et al).

Several outcome measures exist for adult SSc patients including the Valentini activity index(9), the CRISS response index(24), the Medsger severity index(25) and the proposed SCTC damage index. Unfortunately, none is validated in the pediatric population.

As new therapeutics are investigated in adults with SSc, pediatric studies will be planned. It is crucial to define response index, activity index and remission in the pediatric population. A further important step for jSSc treatment studies is the decision of European Medical Agency on extrapolation of the data(26, 27), to license treatment faster for pediatric orphan diseases.

The aim of the WG is to develop, adopt and validate outcome measures for jSSc.

Three workshops took placeduring the annual meeting of the “Hamburg Symposium on Juvenile Scleroderma- Update on New Developments”, (www.juvenile-scleroderma.com) that were organised by Ivan Foeldvari, to develop a pediatric “CRIS” and other pediatric jSSc specific outcome measures. In the last workshop a preliminary pediatric CRIS was proposed (manuscript in preparation).We are also in the process of validating the proposed pediatric and adult parameters in the juvenile scleroderma inception cohort (www.juvenile-scleroderma.com),and in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) cohort.

We hope that we will have a validated instrument, regarding definition of activity, response, remission and damage, which can be applied in Phase II and III studies testing new therapy for jSSc. The indices will help clinicians in the day to day practice too.

6. Gastrointestinal Tract WG PI: authors TF, ZM, DK

Gastrointestinal (GI) tract symptoms are very common in SSc. The etiology of these symptoms is thought to be similar to other organ system pathophysiology with interrelated progressive immune dysregulation, vasculopathy, and fibrosis occurring throughout the GI tract. The study of GI symptoms in SSc must capture not only the severity of involvement, but also response of those symptoms to intervention. The ideal patient reported outcome measure should be able to provide information to guide the treating physician and inform clinical trial design while also minimizing the burden on the patient. The SCTC-GI-WG acknowledges the unmet need of a longitudinal assessment of response to therapy in SSc-associated GI tract involvement (28). Patient reported outcomes measurement system (PROMIS) questionnaires were developed to characterize GI symptoms from the esophagus to the anorectum. The GI-WG focused on assessing psychometric properties of various GI-specific patient reported outcome measures in 5 conditions—gastroesophageal reflux disease, gastroparesis, small intestinal bowel bacterial overgrowth, constipation, and fecal incontinence. Our WG comprises six international scleroderma centers from the United States and one each from Italy, Belgium and Australia. All data is entered at baseline and in follow-up into a database which was developed and is maintained at the University of Michigan.

We recently assessed the reliability, validity, and sensitivity to change of 3 PROs- the NIH PROMIS-GI Symptoms scale, the Scleroderma Clinical Trials Consortium University of California Los Angeles Gastrointestinal Tract (SCTC UCLA GIT 2.0), and the Quality of life in Reflux and Dyspepsia (29), in 116 participants with SSc and active GERD with an average age of 53.8 years and mean disease duration of 12.0 years. The UCLA GIT 2.0 Reflux scale and PROMIS Reflux scale had a significant correlation at baseline (0.61, p=<0.0001), and both instruments correlated with the QOLRAD domains (−0.56 to −0.71). Both UCLA GIT 2.0 and PROMIS Reflux scales were sensitive to change over time in patients who improved over a period of 4 weeks after an intervention.

The SCTC GI WG is now actively recruiting patients for the other SSc GI symptom domains. The next anticipated step is to better clarify the etiology of bloating and distention in an international cohort. Patient reported outcomes instruments that are applied to this cohort after a single intervention for GI symptoms can help inform clinical practice and trial design.

7. Vascular WG. PI: authors JP, RD

The aims of the SCTC Vascular WG (VWG) are to develop/improve outcome measures for SSc vascular manifestations. Challenges in establishing treatment efficacy in clinical trials of Raynaud's phenomenon (RP) led the nascent SCTC-VWG to appraise existing methods for assessing SSc-RP. The Raynaud's Condition Score (RCS) is the preferred outcome measure

for SSc-RP and is included in the provisional core set of outcome measures for SSc clinical trials (30). The RCS diary collects information on the frequency, duration and severity/ impact of RP in SSc(31). It is a clinician-derived patient-reported outcome [PRO] instrument, but there was no patient involvement in its development(32). Therefore, studies have identified poor agreement between the RCS diary and objective methods for assessing digital microvascular function (33, 34). Concerns have also been raised about the magnitude of the placebo effect in clinical trials incorporating the RCS diary (35).

The SCTC-VWG undertook a survey of the attitudes of SSc experts towards the RCS diary. The SURPASS (Subjective Raynaud's phenomenon Assessment in Systemic Sclerosis) survey identified several concerns about the 2-week RCS diary including the respondent burden and an inability to control for factors that might influence the reporting of RP symptoms (36).

To this end, SCTC funding was obtained to devise a conceptual framework for a novel patient-derived PRO instrument for SSc-RP, supported by a steering committee comprising SSc patients, SSc experts and qualitative researchers.

Preliminary work included a comprehensive literature review that has highlighted the significant burden associated with SSc-RP not captured by the RCS diary(37). A multicenter qualitative research study designed to examine the patient experience of SSc-RP from a broad ethnic, geographic and cultural population of SSc patients has supported and expanded these findings (38). A purposive sampling framework ensured the enrollment of a diverse but representative group of 40 patients with SSc. We identified important experiences of SSc-RP not captured by the RCS diary including emotional distress, body image dissatisfaction, impaired social participation and relevant physical symptoms such as feeling "cold" (38). Our findings have challenged the prevailing paradigm of SSc-RP being only an episodic phenomenon with physical symptoms such as pain, numbness and loss of hand function reported in a more sustained manner and reflecting persistent digital ischemia in SSc(38). The considerable efforts taken by patients to avoid or ameliorate SSc-RP attacks were a major theme of the focus groups (38). In parallel work, SSc patients attending UK and US sites undertook2-week RCS diary collection and then completed a qualitative survey examining patient attitudes towards the instrument (39). The findings confirmed our suspicions that the RCS diary underestimates the true burden of RP symptoms and provides insight as to why the RCS diary has not performed as well as hoped in clinical trials whose primary endpoint is the frequency of SSc-RP attacks (39–41).

Work within the SCTC-VWG is currently underway on item-generation for a novel PRO instrument for SSc-RP, grounded in the patient experience of SSc-RP identified in our preliminary work.

8. Calcinosis WG PI: author LC, AV

Calcinosis cutis, the deposition of calcium in the skin and subcutaneous tissues, is a common and potentially debilitating issue affecting approximately one quarter of SSc patients(42, 43). To date, there are no effective therapies for this complication and there is a

lack of validated outcome measures to use in clinical trials(44). The SCTC Calcinosis-WG is an international collaborative effort to create new trial outcome measures and better understand the course and consequences of this complication.

Studies have shown an association between calcinosis and vascular manifestations of SSc including digital ulcers (DUs, (45–47) and acro-osteolysis(48), suggesting a role for ischemia in the pathogenesis of calcinosis. In addition, microtrauma has been implicated in the pathogenesis of calcinosis, and a prior single-center study found that the thumbs were most commonly affected, supporting this hypothesis(49).

Our group performed a retrospective analysis involving 5218 patients with SSc from 9 cohorts within the US, Australia, Canada, United Kingdom, Italy, and Mexico. In multivariate analysis, the strongest associations with calcinosis were DUs and osteoporosis(43).

Our group has developed a novel radiographic scoring system to assess the severity of calcinosis affecting the hands that accounts for area coverage, density, and anatomic location. This scoring system was found to have excellent intra- and inter-rater reliability with intra-class correlation coefficients (ICC) of .93 (.89-.97) and .89 (.86-.92), respectively(50). Similarly, we have developed a patient reported outcome measure specific to calcinosis (the Mawdsley Calcinosis Questionnaire, (51).

We have established a prospective multi-center cohort of SSc patients with and without calcinosis to better define the natural history, confirm clinical associations, and further validate these novel outcome measures. Data is being collected from 15 centers, 8 of whom are also participating in a sub-study to validate the radiographic scoring system.

We are collecting patient questionnaires at baseline and 1-year, including the Cochin Hand Functional Scale, Scleroderma Health Assessment Questionnaire, patient global assessment of calcinosis using a visual analog scale (VAS, 0–10), and the novel Mawdsley calcinosis questionnaire. In addition, physician global assessment of calcinosis VAS is being collected at baseline and 1-year, and a 5-point Likert scale at the 1-year visit for both patients and physicians to rate change in calcinosis.

Information on 556 patients has been entered into the central database from which 134 have completed 1-year follow-up and 60 are participating in the radiographic sub-study. Enrollment is expected to be completed in March 2018. We plan to compare patients with and without calcinosis with respect to demographic characteristics, clinical features, and autoantibodies, and to specifically assess the association between calcinosis and DU or osteoporosis, adjusting for other relevant variables. We will also determine the mean rate of change of calcinosis for the subset of patients who have baseline and 1-year hand radiographs(50). We hope to identify a subgroup of patients with rapid calcinosis progression and to determine risk factors for this severe phenotype.

9. Scleroderma Renal Crisis WG. PI: authors MH,CD

Scleroderma Renal Crisis (SRC) is characterized by acute, malignant hypertension and renal dysfunction. It is a rare complication of SSc, affecting approximately 5% of subjects. The clinical spectrum of SRC is broad, ranging from new onset accelerated arterial hypertension and rapidly progressive oliguric renal failure, to more modest elevations in blood pressure and renal dysfunction, and at times normotensive presentations. To date, two sets of criteria for SRC have been proposed and partially validated(52, 53). We wish to build on these preliminary efforts to develop classification criteria for SRC and improve systematic research in this condition.

The SCTC SRC-WG that consistsof international experts from rheumatology, nephrology and pathology was created in November 2015. A scoping review to generate evidence-based items to define SRC was performed during 2016, presented to the SCTC SRC WG in Washington, DC, in November 2016, and published in February 2017 (54). We identified 415 papers that met inclusion criteria. Forty original definitions of SRC were identified from 36 studies, 9 reviews and 2 editorials. There was significant heterogeneity in definitions. In May-October 2017, we conducted a 3-round online Delphi exercise to develop initial consensus on a core set of items to define SRC. A survey using the items identified by the scoping review was developed. An international, multidisciplinary panel of experts from the SCTC, European Scleroderma Trials and Research Group (EUSTAR), the Canadian Scleroderma Research Group (CSRG), and the Australian Scleroderma Interest Group (ASIG) were invited to participate. A Delphi exercise was performed in 3 rounds. In Round 1, participants were asked to identify omissions and clarify ambiguities. The survey was modified accordingly. In Round 2, participants were asked to rate the scientific validity and feasibility of the items using Likert-type scales ranging from 1–9 (1= very invalid/ unfeasible, 9 = very valid/feasible), and to provide comments. In Round 3, participants reviewed the results and were asked to provide final ratings. Consensus was defined as items rated highly valid and feasible (both median scores ≥7) in Round 3, and for which there was no disagreement, calculated using the RAND/UCLA Appropriateness Method formula(55). Ninety-nine experts from 17 countries participated in the Delphi exercise. Of the 31 items in the survey, consensus was achieved on items pertaining to hypertension, kidney dysfunction, proteinuria and hemolysis. Consensus was not achieved on items pertaining to hematuria, thrombocytopenia, encephalopathy, retinopathy, hyper-reninemia, cardiac dysfunction and histopathology.

In November 2017, a nominal group discussion was held in San Diego, CA, to achieve final consensus on the core set. Final consensus was achieved on items for blood pressure, acute kidney injury, microangiopathic hemolytic anemia and thrombocytopenia, target organ dysfunction (cardiac dysfunction, retinopathy and encephalopathy) and histopathology.

Two additional components of this research project are now in the planning phases. First, modeled on the *International Scleroderma Renal Crisis Survey (ISRCS*,(53), *ISRCS II* will be developed and launched to collect a new inception SRC cohort to validate the consensus criteria using data-driven methods. Second, a forced choice study using multi-criteria decision analysis methods(56), will be performed with the experts who participated in the

nominal group discussion to assign weights to the items in the criteria. Among other things, this may allow sub-classifying SRC into hypertensive and normotensive subsets.

This project will generate the first validated classification criteria for SRC. These criteria are expected to become the international standard and will be used in future randomized trials and epidemiologic research of SSc.

10. Skin WG. PI: authors JG, PM, DK

Skin involvement in SSc is the most pathognomonic feature and an important manifestation of disease and a marker of severity (57, 58) , which makes its assessment a key outcome in clinical research in SSc. Skin involvement is routinely quantified using the 17-site modified Rodnan skin score (mRSS) which assesses global dermal thickness through clinical palpation of 17 body areas scored using a 4-point ordinal scale. The mRSS has high feasibility, validity (face, content, construct, and criterion), reliability, and sensitivity to change(59). The goal of this SCTC WG is to explore ways to improve the assessment of skin disease in SSc.

Although mRSS has excellent intra-rater and inter-rater reliabilities(60, 61) individual examiners approach the mRSS in different ways in clinical practice. Commonly-used techniques for a given area of the body include choosing a maximum score, a representative area, or a global average. If the examiner is consistent with his or her approach to scoring each time, the mRSS will be valid in the course of a trial. However, it is possible that maximizing the score may lead to decreased sensitivity to change of the mRSS. This WG plans to explore this controversy.

It has been observed that certain areas of the body are more sensitive to change than others. Kaldas, et al showed that hands, forearms and chest were more sensitive to change compared with other body sites in two human recombinant relaxin and oral bovine collagen clinical trials(62). Fernandez, et al showed a lower propensity for change of the fingers over the course of 3 single-center trials(63). These observations lead to the question of whether decreasing the number of body sites by exclusion of relatively static areas would further increase the sensitivity to change over time or reliability of the total MRSS. Our goal is to look at these questions in the context of studies that show more significant change as well as over a longer duration.

Further goals of this group will include investigation of complementary methods of assessing skin disease that can studied as secondary outcomes in clinical trials. Ideas include percentage change mRSS, percentage of body involvement, and possibly use of skin biopsies, ultrasound, or durometry depending on investigator interest. Importantly, the WG seeks to align its agenda with the SCTC’s efforts to standardize skin scoring and advance the science of clinical trials in SSc.

11. Lung Disease WG. PI: authors EB, SN

Interstitial lung disease (ILD) is the primary cause of death in SSc(64). Although there have been many trials for the treatment of SSc-ILD, inclusion criteria have varied widely across

studies and it remains unclear which patients to enroll to maximize the likelihood of achieving the predefined primary endpoints.

The aim of this WG is to harmonize inclusion criteria for clinical trials of SSc-ILD. We have reviewed the inclusion and exclusion criteria for 9 completed and ongoing SSc-ILD clinical trials since the year 2000(65–75).While age at time of enrollment and SSc classification criteria were fairly consistent across studies, there was considerable variability with respect to disease duration, pulmonary function test (PFT) cut points, high resolution computed tomography of the chest (HRCT) characteristics, and acceptable background therapies. While some inclusion and exclusion criteria will need to be specific to the particular drug being investigated, developing “optimal inclusion criteria” may ultimately help improve outcomes of SSc-ILD clinical trials.

At the inaugural meeting of the SCTC Lung Disease WG in 2017, an initial research agenda was defined as determining how best to define progression of SSc-ILD and whether SSc-ILD progresses in patients who have had SSc for ≥ 7 years. We will perform a nominal group technique and Delphi exercise to develop consensus among SSc experts. We will then apply the core set of inclusion and exclusion criteria to clinical trial data and observational cohort data to validate their performance. Using well-established SSc cohorts throughout the world and applying the definition of progressive SSc-ILD that we develop, we will subsequently determine whether patients with ≥ 7 years of disease have progression of their ILD.

Conclusions

The SCTC WGs are one aspect of an organization tasked with improving the efficacy of clinical trials. This interim report summarizes the work of the SCTC WGs to date.

The groupshave benefited greatly from the input and effort of the SCTC members who have attended meetings over many years. Members generously contributed their time, effort and wide-ranging expertise on subjects as diverse as the disease that we are studying. Members’ involvement has ensured that the WGs reports will reflect a wide range of perspectives and skills. Leaders of the groups are grateful for the tireless input of all those who have been involved in these many exercises.

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Table:

Summary of Working Groups

Working Group	Contact Email Addresses for PIs	Objectives	Work to Date	Future Plans
Arthritis	GordonJ@HSS.EDU, PClements@mednet.ucla.edu Sindhu.Johnson@uhn.on.ca	Identify preliminary core set of items important for the study of arthritis and arthropathy in SSc	Delphi exercise determined items useful in arthritis-focused SSc trial	Validation of items
Disease damage	m.nikpour@unimelb.edu.au mbaron@rhu.jgh.mcgill.ca	Develop the first disease Damage Index in SSc	Damage Index completed and validate in one other cohort	Validation in inception cohort and assessment of discriminant validity in interventional studies
Disease Activity	m.nikpour@unimelb.edu.au mbaron@rhu.jgh.mcgill.ca laurajross109@gmail.com	Develop a new Damage Activity Index in SSc	Developed by consensus a conceptual definition of disease activity in SSc	Systemic review of the literature; further Delphi exercises; data driven choices for and weighting of items, validation
Cardiac	ales.vacca@tiscali.it m.nikpour@unimelb.edu.au mbaron@rhu.jgh.mcgill.ca laurajross09@gmail.com	Develop a definition of primary cardiac involvement in SSc for use in clinical trials and observational studies	Scoping literature review	Develop a consensus, expert-opinion definition of SSc cardiac disease
Juvenile scleroderma	foeldvari@t-online.de	Develop, adopt and validate outcome measures for jSSc	Developed a preliminary combined response index	Validation of preliminary index
Gastrointestinal Tract	tracy.frech@hsc.utah.edu khannad@umich.edu zmcmaha1@jhmi.edu	Assess properties of several PROs in SSc	Assessemnts of the reliability, validity, and sensitivity to change of NIH PROMIS-GI Symptoms scale, the Scleroderma Clinical Trials Consortium University of California Los Angeles Gastrointestinal Tract Scale and the Quality of life in Reflux and Dyspepsia Scale for use in SSc.	Recruit patients for the study of other SSc GI symptom domains; clarify the etiology of bloating and distention
Vascular	johnpauling@nhs.net rtd4@pitt.edu	Develop/improve outcome measures for SSc vascular manifestations	Completed survey of the attitudes of SSc experts towards the RCS diary; comprehensive literature review; multicenter qualitative research study to examine the patient experience of SSc-RP	Item-generation for a novel PRO instrument for SSc-RP
Calcinosis	shauwei@stanford.edu antoniav@stanford.edu	Create new trial outcome measures and better understand the	Retrospective analysis involving 5218 patients with SSc from 9 cohorts; developed a novel	Validate radiographic scoring and PRO; identify a subgroup of

Working Group	Contact Email Addresses for PIs	Objectives	Work to Date	Future Plans
		course and consequences of calcinosis	radiographic scoring system; established a prospective multi-center cohort of SSc patients with and without calcinosis; developed PRO for calcinosis	patients with rapid calcinosis progression and to determine risk factors for this severe phenotype
Scleroderma Renal Crisis	Marie.hudson@mcgill.ca c.denton@ucl.ac.uk	Develop classification criteria for SRC	Scoping literature review; Delphi exercise; nominal group discussion	New International Scleroderma Renal Crisis Survey to create a new inception SRC cohort to validate the consensus criteria using data-driven methods; a forced choice study to develop weights for items
Skin	GordonJ@HSS.EDU pmerkel@upenn.edu khannad@umich.edu	Determine whether decreasing the number of body sites in the mRSS by exclusion of relatively static areas would increase the sensitivity to change over time; investigate complementary methods of assessing skin disease for use as secondary outcomes	This is a newly formed group with no work performed as yet	
Lung Disease	ejb2153@cumc.columbia.edu snarain@northwell.edu	Harmonize inclusion criteria for clinical trials of SSc-ILD; determine how best to define progression of SSc-ILD and whether SSc-ILD progresses in patients who have had SSc for ≥ 7 years	Reviewed inclusion and exclusion criteria for 9 completed and ongoing SSc-ILD clinical trials	Nominal group technique and Delphi exercise

Abbreviations: PI: principal investigator; PRO: Patient reported outcome; SRC: Scleroderma renal crisis; mRSS : modified Rodnan skin score; ILD: interstitial lung disease; RP Raynaud's phenomenon; GI: gastrointestinal