SCLERODERMA CLINICAL TRIALS CONSORTIUM, INC.

ANNUAL GENERAL MEETING 2020 – FIRST VIRTUAL MEETING VIA ZOOM
WELCOME & INTRODUCTION
LORINDA CHUNG
REMINDERS

- Please MUTE your computers and HIDE CAMERAS on your screen
- Presenters will UNMUTE and can SHOW CAMERAS while they are presenting
- PLEASE VOTE NOW
  - Amended and Restated By-Laws (summary of changes to follow)
  - Secretary and Treasurer
BY-LAWS: SUMMARY OF CHANGES

- Only full members who have paid all dues shall be permitted to vote or apply for grant funding
- At the commencement of each new President’s term the Executive can re-appoint or appoint new Committee Chairs
- The Treasurer shall be a resident of the United States for tax filing purposes
- Executive Officers may receive reimbursement of reasonable expenses for attendance at SCTC meetings
- A vote of a majority of the Full Members’ Coordinating Investigators present in person or by proxy at a meeting of the Members at which a quorum is present is required for adoption of any By-laws amendment
SECRETARY AND TREASURER

JOHN PAULING
Royal United Hospitals Bath, UK

TRACY FRECH
University of Utah, USA
131 current member institutions worldwide:

- Europe
- North America
- South America
- Asia
- Australia

NEW MEMBERS IN 2020:

- **University of Groningen**
  Groningen, Netherlands
  Udo Molder

- **University of Ulsan**
  Seoul, South Korea
  Chan Keun Lee

- **Selayang Hospital**
  Selangor, Malaysia
  Shereen Ch'ng
SCTC 2020: PRODUCTIVE AND CHALLENGING

- Industry Roundtable and Database: Murray Baron and Shervin Assassi
- Travel Awards in collaboration with WSF and Friends of WSF
- Initiation of Benedict Visiting Fellowship Program: Ariane Herrick
- White Paper: Peter Merkel and Dinesh Khanna
- Increased collaboration with EUSTAR: COVID-19 Registry
- Growth of Grants program: Working Group and Betty Benedict
- Bi-annual Newsletters: John Pauling
- Updated website: Anne Chinoy and Adara Borys
ACKNOWLEDGEMENTS

EXECUTIVE
- VICE PRESIDENT: SHERVIN ASSASSI
- TREASURER: TRACY FRECH
- SECRETARY: JOHN PAULING

ADMINISTRATIVE ASSISTANT
- ADARA BORYS

COMMITTEE CHAIRS

OUTCOME MEASURES
- PETER MERKEL, DINESH KHANNA, CHRIS DENTON

EDUCATION & TRAINING
- ARIANE HERRICK & VIRGINIA STEEN

GRANTS
- JIM SEIBOLD & LORINDA CHUNG

FINANCE
- TRACY FRECH & ROBYN DOMSIC

ROUNDTABLE & DATABASE
- MURRAY BARON & SHERVIN ASSASSI

WEBSITE
- ARIANE HERRICK
CONGRATULATIONS: JAMES SEIBOLD

2020 ACR Master Designation

Recognition as a Master of the American College of Rheumatology is one of the highest honors the College bestows. The designation of Master is conferred on ACR members, age 65 or older by October 1 of the year in which they are nominated, who have made outstanding contributions to the ACR and the field of rheumatology through scholarly achievement and/or service to their patients, students, and profession.
MEMBERSHIP DUES

“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.”

- Dues are an essential source of revenue and demonstrate the commitment of the institutions.

Institutional Members

- We have 76 institutions who have paid their dues in 2020.
- You must be a paid member to apply for “Betty Z. Benedict” and “Working Group” grants.
- Contact Adara Borys at sctcinc01@gmail.com if you are unsure of your institutional status or need to request a waiver for dues because of a financial hardship at your center.

Industry Donations

- We have 8 industry members who have paid dues in 2020.

Please pay your dues through the link on the SCTC website: https://sclerodermaclinicaltrialsconsortium.org
### Revenue

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membership-Institutions</td>
<td>$12,594</td>
</tr>
<tr>
<td>Membership-Industry</td>
<td>$125,000</td>
</tr>
<tr>
<td>Investment income*</td>
<td>$36,109</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$173,703</strong></td>
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</table>

*Year-to-Date return as of 10/15/2020 is 4.32%, and the 1 Year return is 8.08%.

### Expenses

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel Awards</td>
<td>$4,263</td>
</tr>
<tr>
<td>SCTC Grants</td>
<td></td>
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<tr>
<td>• Working Groups</td>
<td>$45,000</td>
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<tr>
<td>• Betty Benedict</td>
<td>$50,000</td>
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<tr>
<td>Administration</td>
<td></td>
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<tr>
<td>• Office administrator</td>
<td>$5,851</td>
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<tr>
<td>• Legal</td>
<td>$11,525</td>
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<td>• Accountant</td>
<td>$6,800</td>
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<td>• Website revision</td>
<td>$439</td>
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<td>• Office support software</td>
<td>$328</td>
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<tr>
<td>White Paper</td>
<td>$9,250</td>
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<td>Roundtable</td>
<td>$5,474</td>
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<td>Taxes</td>
<td>$535</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$139,465</strong></td>
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</table>
Official Journal of World Scleroderma Foundation & EUSTAR

- Launched in February 2016
- Published 3 times per year
- 2 Editors in Chief Marco Matucci-Cerinic & Masataka Kuwana
- Website: http://journals.sagepub.com/home/jso
- Web-based submission and peer-review system: www.editorialmanager.com/jsrd
- Subscription journal with SAGE Choice Open Access option to be compliant with major funding Agencies (e.g. NIH, Wellcome Trust)
JSRD Statistics

<table>
<thead>
<tr>
<th>Submissions</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020 YTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>43</td>
<td>70</td>
<td>41</td>
<td>53</td>
<td>48</td>
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<tr>
<td>Accept</td>
<td>27</td>
<td>46</td>
<td>40</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Reject</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Accept Ratio</td>
<td>73%</td>
<td>82%</td>
<td>81%</td>
<td>70%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Decision Times

- Time to First Decision
- Time to Accept

2020 YTD Submissions, by geography
PubMed Central and Impact Factor Applications

PubMed Central:
• JSRD application submitted July 2018. There is currently a large queue of journals submitted to PMC that are in the queue for evaluation.
• Feedback from PMC in July 2020 and Deferring decision on inclusion until mid-2021.

Impact Factor:
• Application submitted early 2019
• Review process is extremely selective, only ~ 10% acceptance rate
• Hoping to receive a decision from Clarivate by the end of 2020
• If accepted in 2020, **JSRD would receive its first IF in July 2021**
• **Possible IF estimated in 2021 may be around 2.6-3**
January 17th, 2020
The University of Pennsylvania

Companies in Attendance:

- Corbus
- CSL Behring
- Sanofi
- MT Pharma
- Boehringer Ingelheim
- Curzion Pharma
- BMS
- Genentech
MAJOR TOPICS COVERED

**CRISS composite outcome measure**
*Is this the best we have??*

**White paper for regulatory agency**
*Objective is to identify outcomes that are ready for inclusion in SSc clinical trials.*

**What is a “good” outcome measure?**
*Invited speaker, Professor Internal Medicine George Washington University, Washington DC*
*Important re white paper project.*
MAJOR TOPICS COVERED CONT’D…

Scleroderma SCTC Damage index  
*Published and now being studied*

Scleroderma activity indices  
*SCTCWG created to develop this index*

Blood biomarkers in progressive ILD  
*Focus in ILD*

Dr. Murray Baron

Dr. Tom Leonard, BI
DATE TO BE DETERMINED:
(VIRTUAL)

TOPICS TO BE COVERED:

1. Scleroderma Trial updates
   - Review of publicly available data (post-ACR) – SCTC review

2. Revisiting scleroderma clinical trial design Phase IIb/III
   - Primary endpoint selection - Background therapy

3. Autoantibodies and clinical diversity – implications for trial design

4. Raynaud’s assessment and microvascular testing in trials

5. White Paper Update
SITE INFRASTRUCTURE DATABASE
SHERVIN ASSASSI
SCTC SITE INFRASTRUCTURE SURVEY

Number of Scleroderma Centers on our list: \(244\)

Number of Scleroderma Centers responding to the Survey: \(147\)

Overall response rate: \(147/244 = 60\%\)
Site Survey Responders (n=147 centers)
Do you participate in clinical trials in scleroderma?
What percentage of your patients have diffuse SSc?

Mean = 37.7%
What percentage of your SSc patients are on immunosuppressive agents?

Percentage of Patients on Immuno-suppressant Therapy

Mean = 51.3%
SCTC SITE INFRASTRUCTURE DATABASE

✓ Important resource on the available infrastructure in the international scleroderma community for clinical research

✓ Provides updated information on the clinical practice patterns in the Scleroderma Centers across a wide geographic area

✓ It can provide valuable information for the design and feasibility assessment when planning large-scale clinical trials
TRAVEL AWARDS & FELLOWSHIPS
ARIANE HERRICK
Travel awards 2020 World Congress

- 31 applicants
- 11 awardees (from 7 countries, 4 continents)
- Full details on SCTC website:
  https://sclerodermaclinicaltrialsconsortium.org/sctc-clinical-studies/sctc-travel-awards
TRAVEL AWARDS: WORLD CONGRESS 2020

- **Kimberly Showalter, MD** - Hospital for Special Surgery, New York, USA
  "CD34 and alpha-smooth muscle actin distinguish scleroderma gene expression subsets using a machine learning approach"

- **Sabrina Hoa, MD, MSc, FRCPc** - Centre Hospitalier de l'Université de Montréal, Canada
  "Prevention of interstitial lung disease with immunosuppressive therapy in systemic sclerosis"

- **Antonia Valenzuela, MD** - Pontificia Universidad Católica de Chile
  "Change in calcinosis over 1 year using the SCTC Radiologic Scoring System for Calcinosis of the hands in patients with Systemic Sclerosis"

- **Rebecca Ross, MD** - University of Leeds, UK
  "Biosamples from at risk SSc patients show classic pathological signs of Scleroderma: opportunity for a diagnosis of pre-clinical SSc"

- **Sandra Maximiano, MD** - Federal University of São Paulo, Brazil
  "Microparticles in systemic sclerosis: a promising biomarker of microvascular damage?"

- **Xiubo Fan, MD** - Singapore General Hospital, Singapore
  "CXCL5 ameliorates systemic sclerosis via suppressing helper T cell-mediated immune response"

- **Raluca Dumitru, MD** - Leeds Institute of Rheumatic and Musculoskeletal Medicine, UK
  "Serum cardiac biomarkers and cardiac MRI diffuse fibrosis may predict the development of cardiovascular events in systemic sclerosis patients"

- **Boyang Zheng, MD** - McGill University, Montreal, Canada
  "Systemic sclerosis auto-antibody profiles predict interstitial lung disease onset but not progression"

- **Janine Schniering, MD** - University Hospital Zurich, Switzerland
  "Computed tomography-based radiomics features for detection and staging of interstitial lung disease in Systemic Sclerosis - transferability from experimental to human lung fibrosis"

- **Melody Pei-Shien Chung, MD** - Stanford University School of Medicine, USA
  "Obstetric complications prior to systemic sclerosis diagnosis"

- **Sue-Ann Ng Pei Lun, MD** - Singapore General Hospital, Singapore
  "Evaluating use of T1-MOLLI mapping in assessing systemic sclerosis cardiac involvement"
Benedict Visiting Fellowship Programme

- Open to applications: https://sclerodermaclinicaltrialsconsortium.org/about-the-scleroderma-clinical-trials-consortium/visiting-fellowships

- Aim - to provide individuals early in their career with the opportunity to spend time in a scleroderma centre (usually for 4 weeks)

- Those eligible - clinical trainees and those within the first 5 years of completing their training /starting their first faculty position

- Travel, accommodation and subsistence costs will be covered to a maximum of 5,000 USD
Benedict Visiting Fellowship Programme:
Take home messages

• For trainees/those who have recently completed training – do apply! Remember that fellowships can be undertaken in one’s own country (may be preferable at present with Covid-19 related travel restrictions)

• For mentors - do put forward your institution as a host institution

• List of host institutions to be posted on SCTC website in near future
Goals of the SSc White Paper Project

- Identify which currently-available outcome measures in SSc will meet the FDA’s standard for validity in assessing how a patient feels, functions, or survives*

- **Comprehensively review the data for the key measures in each domain of illness in SSc and categorize each measure as:**
  
  A. Identify outcomes ready for use in trials NOW
  
  B. Identify outcomes potentially ready for use in trials SOON
     
     • Outline steps required to “get there”

  C. Identify potential outcomes for use in trials within 5 years
     
     • Outline steps required to “get there”

  D. Identify outcomes clearly not acceptable for use in trials
     
     • These outcomes may still have utility in research and/or clinical care
Specific Aim 1: Organize an extended study team of stakeholders to work through focused Task Forces to propose outcome measures suitable for use in RCTs in the main areas of disease impact in SSc.

Specific Aim 2: Hold a 2-day in-person meeting that brings together leaders of the task forces, patients, patient advocacy groups, industry representatives, FDA officials, and expert consultants to arrive at a final set of outcomes appropriate for inclusion in a White Paper describing outcomes in RCTs in SSc.

Specific Aim 3: Disseminate results and conclusions that include a manuscript of conference proceedings and presentation(s) at national and international rheumatology meetings.
SSc White Paper Organization and Plans

- Physician Investigators
- Patients & Patient Advocates
- Industry Representatives
- FDA Representatives
Thomas Fleming, PhD, Professor of Biostatistics, University of Washington is an international expert in outcome measure development and has worked as a Special Government Employee for the FDA.

John Powers, MD Professor of Clinical Medicine, George Washington University and past FDA employee with expertise in outcome measures.
SSc White Paper Organization and Plans
<table>
<thead>
<tr>
<th>Task Force Domain</th>
<th>Chair</th>
</tr>
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<tbody>
<tr>
<td>Global</td>
<td>Murray Baron</td>
</tr>
<tr>
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<td>Interstitial Lung Disease</td>
<td>Donald Tashkin</td>
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<tr>
<td>Pulmonary Arterial Hypertension</td>
<td>Stephen Mathai</td>
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<tr>
<td>Digital Ulceration</td>
<td>Ariane Herrick</td>
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<td>Biomarkers</td>
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<td>Biomarkers</td>
<td>Shervin Assisi</td>
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Each Task Force has:
- Academic investigators
- Junior investigator
- Patient
- Industry partner
- Project PIs
- Consultant
SSc White Paper Organization and Plans

- Form Leadership Team
  - Name Task Force Leaders
  - Structure Task Forces/Processes

- Task Forces Conduct Literature Searches, Review Available Data, Prepare Reports

- Draft Task Force Instructions and Templates

- Review by PIs & Consultants

- Materials for In-Person Meeting

Aim 1

Revisions
SSc White Paper “Training”

- Was required of all Task Force members

- Total of 4 hours of webinars
  - Introduction to the projects and charge to the Task Forces
  - Introduction to the major concepts: Led by nationally-recognized consultants with expertise in outcome measurement and FDA processes

- Helped get everyone to same basic level of understanding
Please complete this summary for each outcome measure evaluated. Short, bulleted lists are encouraged. Keep the answers to questions below to 1 page and complete the two tables on the following page.

Task Force: Choose an Item.

Outcome Measure: ____________________________

Brief Description of the Outcome Measure:
1. What is known about this outcome measure?

2. Has this measure been used in clinical trials of systemic sclerosis? Choose an Item.
   If YES, provide brief summary with references.

3. Does the Task Force believe this measure is a direct measure of feel, function, or survive? Choose an Item.
   If YES, move to #4 and provide justification.
   If NO, move to #4.

4. Is this outcome measure a surrogate measure? Choose an Item.
   REMEMBER: association (correlation) is not sufficient to be considered a surrogate measure.
   If YES, provide justification below and then move to #6.
   If NO, the measure may not be considered as an approvable endpoint.

5. If the Task Force anticipates the outcome measure is not ready now but could be ready in near future (Stage B or C, over next 1-5 years), outline the steps required to get there and complete Tables 1 and 2.
   If you feel the outcome measure is not appropriate as primary outcome measure in clinical trials, provide justification.

6. Is the outcome measure ready to be included as a primary outcome measure for a regulatory trial? Choose an Item.
   Provide justification and complete Tables 1 and 2.
SSc White Paper Organization and Plans

- Form Leadership Team
- Name Task Force Leaders
- Structure Task Forces/Processes

- Task Forces Conduct Literature Searches,
  Review Available Data,
  Prepare Reports

- Draft Task Force Instructions
  and Templates

- Review by PIs & Consultants

- Materials for In-Person Meeting
SSc White Paper Organization and Plans

Expert Panel
In-Person Meeting
Discuss • Vote
Final Recommendations

Draft White Paper Manuscript

Revisions

Aim 2
SSc White Paper Organization and Plans

- Finalize White Paper & Disseminate
  - Publish
  - Patient groups
  - Industry
  - Academic Meetings

Aim 3
Revised Timeline for SSc White Paper Project

- **2019-2020:**
  - TF composition decided upon
  - 3 introductory webinars recorded
  - TF members received “training”
  - TFs formed and created work streams
- **Substantial delays due to SARS-CoV2 pandemic**
- Summer-Fall 2020: TFs did a LOT of work to catch up
- Q1 2021: Anticipate initial reports from TFs
- Q1-2 2021: Revision of reports
- Q2-3 2021: Produce pre-meeting materials
- Q3 2021: Expert Panel Meeting (*In-person meeting???*)
- Q3-4 2021: Draft White Paper
- Publish & Disseminate Results
EUSTAR-SCTC Collaborations

Anna Hoffmann-Vold
EUSTAR general secretary

ACR 2020
Collaboration on COVID-19 registries

EUSTAR COVID registry
• Modul on COVID-19 and a SSc module on all patients

COVID-19 Global Rheumatology Alliance registry
• Modul on COVID-19 and a SSc module on all patients available

EULAR COVID RMD registry
• Modul on COVID-19 and a SSc module on all patients available
EUSTAR COVID registry

117 SSc patients registered in the database
- 46%dcSSc, 48%lcSSc, 6% sine scleroderma
- 38% anti-topoisomerase antibody, 28% anti.centromere antibody
- 78% organ involvement
  - 51% ILD
  - 17% PH by RHC
  - 37% DU
- Setting of care: Home Isolation 53% and Hospitalization 48%
- ICU admission: 25%
- Outcome: Death 15% and Recovery 80%

Please register your patients at: https://nettskjema.no/a/146481
## COVID-19 Global Rheumatology Alliance

<table>
<thead>
<tr>
<th>Primary Rheumatic Disease^</th>
<th>N=2543</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1,027 (40.39%)</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>435 (17.11%)</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>214 (8.42%)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>177 (6.96%)</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>162 (6.37%)</td>
</tr>
<tr>
<td>Sjogren's syndrome</td>
<td>102 (4.01%)</td>
</tr>
<tr>
<td>Other Inflammatory Arthritis</td>
<td>82 (3.22%)</td>
</tr>
<tr>
<td>Gout</td>
<td>76 (2.99%)</td>
</tr>
<tr>
<td>Inflammatory Myopathy</td>
<td>72 (2.83%)</td>
</tr>
<tr>
<td><strong>Systemic Sclerosis</strong></td>
<td><strong>66 (2.60%)</strong></td>
</tr>
</tbody>
</table>

To date: 91 SSc patients
COVID-19 Global Rheumatology Alliance

Top Comorbid Conditions  N=2543

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>898 (35.31%)</td>
</tr>
<tr>
<td>Lung Disease§</td>
<td>458 (18.01%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>409 (16.08%)</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>219 (8.61%)</td>
</tr>
<tr>
<td>Chronic Renal Insufficiency/ESRD</td>
<td>188 (7.39%)</td>
</tr>
<tr>
<td>Morbid Obesity, BMI 40+ kg/m2</td>
<td>156 (6.13%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>115 (4.52%)</td>
</tr>
</tbody>
</table>

Outcomes  N=2543

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>183 (7.20%)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>927 (36.45%)</td>
</tr>
</tbody>
</table>

Please register your patients at: https://rheum-covid.org/
Collaboration between the registries

- The project plan and statistical analysis plan has been developed
- Transfer agreements are under development
Study objectives

1. To assess SSc specific and unspecific characteristics which are associated with worse outcome in SSc patients with COVID-19

2. To characterize general and SSc specific variables and immunosuppressive treatment in SSc patients with COVID-19 infection compared to patients without infection

3. To assess SSc specific and unspecific characteristics which are predictive for a worse outcome in SSc patients with COVID-19 compared to COVID negative SSc patients
Cohort study

The included cases consist of all registered SSc patients (PCR only, or in case too few PCR or symptomatically diagnosed) from the registries.

Outcome
1. Death (if enough outcome)
2. Hospitalization for COVID-19
3. ICU requirement
4. Combined endpoint of death and hospitalization (including ICU requirement)

Risk factors for severe outcome and SSc related risk factors will be assessed.
GRANTS
LORINDA CHUNG
SCTC Grant Review Committee:
- JIM SEIBOLD: CHAIR
- ANNA HOFFMAN-VOLD
- BRITTA MAURER
- SUSANNA PROUDMAN
- SHERVIN ASSASSI
- TRACY FRECH

SPECIAL THANKS TO:
- LUKE EVNIN & DEANN WRIGHT
  BETTY BENEDICT AWARD REVIEW AND JOINT FUNDING
"Evaluating the role of Vascular Endothelial Growth Factor (VEGF) and VEGF-induced osteoclast activity in the pathogenesis of calcinosis in systemic sclerosis"

Primary Investigators:
Antonia Valenzuela, and Claudia Huerta Calderon

“Development of SCTC Classification Criteria of Systemic Sclerosis Heart Involvement using consensus and multi-criteria decision analysis methods”

Primary Investigators:
Mandana Nikpour, Murray Baron, Alessandra Vacca and Laura Ross

"Development of preliminary classification criteria for scleroderma renal crisis"

Primary Investigators:
Marie Hudson, and Christopher Denton
TO ADVANCE OUTCOME MEASURES AND TRANSLATIONAL MEDICINE IN SYSTEMIC SCLEROSIS

In honor of our gracious donor, a former patient of Jim Seibold:

- **$100,000 over 2 years**

2019: 5 applications

- Development and Validation of a Disease Activity Index in Systemic Sclerosis
- Murray Baron, Mandana Nikpour, Laura Ross

2020: 7 applications

- Sensitivity Analysis of Thermal Imaging in Systemic Sclerosis-Related Digital Vasculopathy (SATISS)
- Andrea Murray

CONGRATULATIONS!
2019 BETTY Z. BENEDICT GRANT Awardee:
Development and Validation of a Disease Activity Index in Systemic Sclerosis

PIS: MURRAY BARON, MANDY NIKPOUR, LAURA ROSS

SCTC ANNUAL GENERAL MEETING 2020
2019 Betty Z. Benedict Grant Awardee: Development and Validation of a Disease Activity Index in Systemic Sclerosis

PIs: Murray Baron, Mandy Nikpour, Laura Ross

SCTC Annual General Meeting 2020
Objectives

• Develop and validate a multi-system activity index in SSc for use as an outcome measure in clinical trials and observational studies.
Activity Index Working Group

• Principal Investigators
  • Prof Murray Baron
  • A/Prof Mandana Nikpour
  • Dr Laura Ross

• Working Group Members
  • 31 members
    • 30 rheumatologists, 1 dermatologist
  • 4 patient partners
  • 7 interdisciplinary advisory panel members
    • Cardiology, Gastroenterology, Nephrology, Respiratory Medicine
Methodology

1. Define construct of disease activity
2. Define domains of disease to include in activity index
3. Item generation and item definition
4. Item reduction and weighting
5. Activity index validation
Define construct of disease activity

• Delphi exercise and consensus meeting to define construct of disease activity

• Disease activity in systemic sclerosis refers to aspects of disease, attributable to SSC, that are potentially reversible, or can be arrested, with time and/or effective therapy. Disease activity may be associated with morbidity and uncontrolled activity may lead to organ dysfunction and mortality.
Domains of disease activity

Delphi exercise to assess domains relevant to activity index

10 domains proposed

Subdomains and potential items suggested

Working group members invited to suggest subdomains and / or potential items

Presentation of results to working group

9 domains retained

Skin
Vascular
Musculoskeletal
Respiratory
Scleroderma renal crisis
Cardiac
Gastrointestinal
Laboratory results
 Constitutional symptoms
Item generation and definition

3 round Delphi exercise and consensus meeting

101 items suggested

28 items retained
<table>
<thead>
<tr>
<th>Activity index – consensus items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>• <strong>Change</strong> in mRSS ≥ 5 points</td>
</tr>
<tr>
<td>• New area of skin thickening within mRSS region that was not previously involved, irrespective of overall skin score</td>
</tr>
<tr>
<td>• If previous mRSS or skin assessment unavailable, patient reported worsening of skin involvement</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
</tr>
<tr>
<td>• New presentation cardiogenic shock or cardiac failure</td>
</tr>
<tr>
<td>• &gt;10% decrease of LV ejection fraction</td>
</tr>
<tr>
<td>• Myocarditis on biopsy, CMR or clinical diagnosis</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
</tr>
<tr>
<td>• Synovitis</td>
</tr>
<tr>
<td>o Extra points for higher number of swollen joints</td>
</tr>
<tr>
<td>• Tendon friction rubs</td>
</tr>
<tr>
<td>• Myositis on clinical examination, elevated biomarkers supported by MRI, EMG or biopsy findings</td>
</tr>
<tr>
<td>• New conduction defect within past 1 year</td>
</tr>
<tr>
<td>• New ventricular arrhythmia within past 1 year</td>
</tr>
<tr>
<td><strong>Pulmonary arterial hypertension</strong></td>
</tr>
<tr>
<td>• Myositis on clinical examination, elevated biomarkers supported by MRI, EMG or biopsy findings</td>
</tr>
<tr>
<td>• New diagnosis PAH diagnosed by RHC</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>• Proximal muscle weakness</td>
</tr>
<tr>
<td>• Not complete</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>• <strong>Change</strong> in FVC &gt;10% OR progression of ILD on HRCT</td>
</tr>
<tr>
<td>• <strong>Change</strong> in DLCO &gt;10%</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td>• Scleroderma renal crisis, with clinical evidence of ongoing active renal crisis</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
</tr>
<tr>
<td>• Digital tip ulcer</td>
</tr>
<tr>
<td>o Extra points for greater number of ulcers</td>
</tr>
<tr>
<td>• Critical digital ischaemia</td>
</tr>
<tr>
<td>• Patient reported worsening Raynaud’s phenomenon in past month</td>
</tr>
<tr>
<td><strong>Laboratory results</strong></td>
</tr>
<tr>
<td>• Elevated CRP</td>
</tr>
<tr>
<td><strong>Constitutional symptoms</strong></td>
</tr>
<tr>
<td>• &gt;10% unintentional weight loss in preceding 1 year</td>
</tr>
<tr>
<td><strong>Physician global scores</strong></td>
</tr>
<tr>
<td>• Organ specific physician global assessment of activity</td>
</tr>
</tbody>
</table>
Activity index – current controversies

- Can patient reported symptoms be used to assess activity in the absence of objective measures of activity?

**Table 3.** Association between patient-reported symptoms and manifestations of systemic sclerosis*

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-reported Raynaud’s phenomenon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New-onset digital pitting</td>
<td>0.75 (0.60–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>1.53 (1.34–1.74)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient-reported skin worsening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening MRSS</td>
<td>2.10 (1.54–2.86)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient-reported breathlessness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% decrease in FVC</td>
<td>2.12 (1.70–2.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>15% decrease in DLco</td>
<td>1.65 (1.34–2.02)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>New-onset ILD</td>
<td>1.91 (1.40–2.61)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>New-onset PAH</td>
<td>5.08 (3.59–7.19)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* OR = odds ratio; 95% CI = 95% confidence interval; MRSS = modified Rodnan skin thickness score; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension.

Ross et al Arthritis Care Res 2020
Activity index – current controversies

**Skin**
- **Change** in mRSS ≥5 points
- New area of skin thickening within mRSS region that was not previously involved, irrespective of overall skin score
- If previous mRSS or skin assessment unavailable, patient reported worsening of skin involvement

**Musculoskeletal**
- Synovitis
  - Extra points for higher number of swollen joints
- Tendon friction rubs
- Myositis on clinical examination, elevated biomarkers supported by MRI, EMG or biopsy findings
- Proximal muscle weakness

**Respiratory**
- **Change** in FVC >10% OR progression of ILD on HRCT
- **Change** in DLCO >10%

**Vascular**
- Digital tip ulcer
  - Extra points for greater number of ulcers
- Critical digital ischaemia
- Patient reported worsening Raynaud’s phenomenon in past month

---

What is the optimal time interval to assess change in skin scores and lung function tests?

- Retrospective analysis of incident dcSSc observational cohorts
  - Michigan dcSSc cohort
  - ESOS cohort
- Primary aim:
  - Define optimal time interval to measure activity in skin and lung involvement using mRSS and FVC & DLCO
- Analysis currently underway
Activity index – current controversies

Cardiac
- New presentation cardiogenic shock or cardiac failure
- >10% decrease of LV ejection fraction
- Myocarditis on biopsy, CMR or clinical diagnosis
- Acute pericarditis
- New onset pericardial effusion
- Elevated serum troponin
- New conduction defect within past 1 year
- New ventricular arrhythmia within past 1 year

Pulmonary arterial hypertension
- New diagnosis PAH diagnosed by RHC

Gastrointestinal
- Not complete

Renal
- Scleroderma renal crisis, with clinical evidence of ongoing active renal crisis

Laboratory results
- Elevated CRP

Constitutional symptoms
- >10% unintentional weight loss in preceding 1 year

Physician global scores
- Organ specific physician global assessment of activity

Can organ specific physician assessments of skin and gastrointestinal activity be used to measure disease activity?

- Multi-centre study established
- Primary aim:
  Does physician assessed high skin and GI tract activity predict the future accrual of skin and GI damage
- Secondary aims:
  Evaluate patient assessment of GI tract activity
  Determine signs / symptoms that most significantly influence determination of skin and GI tract activity

- 49 patients recruited
  Recruitment temporarily suspended in March 2020 due to COVID-19
Methodology

1. Define construct of disease activity
2. Define domains of disease to include in activity index
3. Item generation and item definition
4. Item reduction and weighting
5. Activity index validation
Future projects - Item reduction and weighting & index validation

• Items weighted using observational data from Australian Scleroderma Cohort Study

• Internal validation in Australian Scleroderma Cohort
• External validation in Canadian Scleroderma Research Group
Ross L et al, **The challenges and controversies of measuring disease activity in systemic sclerosis** / *Scleroderma Relat Disord* 2018 3(2) 115-121

Ross L et al, **The role of inflammatory markers in assessment of disease activity in systemic sclerosis** *Clin Exp Rheumatol* 2018 Suppl 113(4) 126-134

Ross L et al, **Can patient-reported symptoms be used to measure disease activity in systemic sclerosis?** *Arthritis Care Res* 2020 72(10) 1459-1465

**Activity Index Working Group contact details:**

Murray Baron  mbaron@jgh.mcgill.ca

Mandy Nikpour  m.nikpour@unimelb.edu.au

Laura Ross  lross1@student.unimelb.edu.au
Acknowledgement and thanks

• SCTC and the Betty Benedict Grant Bequest

• Activity Index Working Group
SCTC WORKING GROUPS

- CALCINOSIS
- CARDIAC
- DAMAGE ACTIVITY INDEX
- GASTROINTESTINAL
- JUVENILE SCLERODERMA
- LUNG DISEASE
- RENAL CRISIS
- SKIN DISEASE
- VASCULAR
- DEFINITIONS OF DISEASE ONSET & ORGAN INVOLVEMENT
NEW WORKING GROUP PUBLICATIONS


**Calcinosis**


**Skin Disease**


**Vascular**

- Patient experiences of digital ulcer development and evolution in systemic sclerosis.


- What narrative devices do people with systemic sclerosis use to describe the experience of pain from digital ulcers: a multicentre focus group study at UK scleroderma centres.

WORKING GROUP PRESENTATIONS

- **CALCINOSIS**
  ANTONIA VALENZUELA

- **CARDIAC**
  MANDY NIKPOUR

- **RENAL CRISIS**
  MARIE HUDSON

- **DEFINING DISEASE & ORGAN ONSET**
  TOM MEDSGER

- **VASCULAR**
  JOHN PAULING
Calcinosis Working Group

- **Retrospective calcinosis study**\(^1\):  
  - Multi-center international cohort of 5218 SSc patients  
  - Frequency of calcinosis 25% (1290 patients)  
  - Strongly associated with **DU** and **osteoporosis**

- **Prospective calcinosis study**\(^2\):  
  - Cohort of 568 consecutive SSc patients who fulfill 2013 revised ACR/EULAR criteria at 10 centers within North America, Australia, and Mexico.

\(^1\)Semin Arthritis Rheum. 2016 Dec;46(3):344-349
### Table 2
Predictors of calcinosis in univariate and multivariable analysis.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.9 - 1.02)</td>
<td>0.173</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.60 (0.91 - 2.81)</td>
<td>0.101</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>1.32 (0.60 - 1.90)</td>
<td>0.127</td>
</tr>
<tr>
<td>BMI</td>
<td>0.98 (0.91 - 1.01)</td>
<td>0.178</td>
</tr>
<tr>
<td>Disease duration (10 unit increase) from first non-RP</td>
<td>1.02 (1.01 - 1.04)</td>
<td>0.005</td>
</tr>
<tr>
<td>Disease duration (10 unit increase) from first RP</td>
<td>1.16 (0.81 - 1.55)</td>
<td>0.425</td>
</tr>
<tr>
<td>Limited cutaneous subtype</td>
<td>1.00 (0.98 - 1.02)</td>
<td>0.986</td>
</tr>
<tr>
<td>Maximum modified skin Rodnan score</td>
<td>1.98 (0.77 - 5.08)</td>
<td>0.516</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>1.95 (1.37 - 2.78)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>1.21 (0.50 - 2.94)</td>
<td>0.778</td>
</tr>
<tr>
<td>Abnormal nailfold</td>
<td>0.94 (0.58 - 1.53)</td>
<td>0.810</td>
</tr>
<tr>
<td>Capillary exam</td>
<td>3.55 (1.58 - 7.97)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>1.92 (1.19 - 3.11)</td>
<td>0.007</td>
</tr>
<tr>
<td>Osteopenia or Osteoporosis</td>
<td>1.11 (0.58 - 2.13)</td>
<td>0.748</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>3.93 (1.18 - 13.10)</td>
<td>0.026</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>0.07 (0.43 - 1.09)</td>
<td>0.113</td>
</tr>
<tr>
<td>Positive Anti-cardiomy</td>
<td>1.18 (0.79 - 1.77)</td>
<td>0.4158</td>
</tr>
<tr>
<td>Positive PM-SCl</td>
<td>1.29 (0.73 - 2.31)</td>
<td>0.3887</td>
</tr>
<tr>
<td>Positive Anti-RNP</td>
<td>0.94 (0.51 - 1.73)</td>
<td>0.8055</td>
</tr>
<tr>
<td>Positive U1 KNP</td>
<td>0.85 (0.35 - 2.09)</td>
<td>0.7231</td>
</tr>
<tr>
<td>Positive ANA</td>
<td>2.09 (0.67 - 6.52)</td>
<td>0.2064</td>
</tr>
<tr>
<td>Medications</td>
<td>2.49 (1.10 - 5.57)</td>
<td>0.029</td>
</tr>
<tr>
<td>Biphosphonates</td>
<td>0.97 (0.67 - 1.39)</td>
<td>0.555</td>
</tr>
<tr>
<td>Blockers use ever</td>
<td>0.92 (0.63 - 1.36)</td>
<td>0.671</td>
</tr>
<tr>
<td>Steroid use ever</td>
<td>1.89 (1.14 - 3.15)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* Digital schema=digital ulcers, loss of digital pulp, and/or digital pitting scars.
** Other ulcers i.e over PIPs or over other extensor surfaces as elbows
OR=Odds Ratio, RR=Relative risk, HAQ-DI=Health Assessment Questionnaire disability index, GI=Gastrointestinal, VAS=visual analog scale.

### Table 4
Predictors of patient reported outcomes in multivariable analyses.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>RR (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ-DI</td>
<td>1.57 (1.12 - 2.20)</td>
<td>0.009</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>1.22 (0.87 - 1.70)</td>
<td>0.255</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.56 (1.12 - 2.18)</td>
<td>0.009</td>
</tr>
<tr>
<td>Any GI involvement</td>
<td>1.31 (0.78 - 2.11)</td>
<td>0.307</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>1.06 (0.75 - 1.51)</td>
<td>0.748</td>
</tr>
<tr>
<td>Acro-osteolysis</td>
<td>0.99 (0.58 - 1.67)</td>
<td>0.967</td>
</tr>
<tr>
<td>diffuse disease subtype</td>
<td>1.76 (1.26 - 2.47)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.52 (0.93 - 2.48)</td>
<td>0.095</td>
</tr>
<tr>
<td>Cochin Hand Functional Scale</td>
<td>1.47 (0.94 - 2.30)</td>
<td>0.096</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>1.70 (1.07 - 2.72)</td>
<td>0.025</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.56 (0.99 - 2.47)</td>
<td>0.054</td>
</tr>
<tr>
<td>Any GI involvement</td>
<td>0.94 (0.46 - 1.92)</td>
<td>0.863</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>0.82 (0.50 - 1.32)</td>
<td>0.411</td>
</tr>
<tr>
<td>Acro-osteolysis</td>
<td>0.88 (0.42 - 1.86)</td>
<td>0.738</td>
</tr>
<tr>
<td>diffuse disease subtype</td>
<td>1.88 (1.19 - 2.96)</td>
<td>0.007</td>
</tr>
<tr>
<td>VAS Pain</td>
<td>1.46 (1.08 - 1.97)</td>
<td>0.015</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>1.21 (0.91 - 1.62)</td>
<td>0.187</td>
</tr>
<tr>
<td>arthritis</td>
<td>1.47 (1.09 - 1.98)</td>
<td>0.012</td>
</tr>
<tr>
<td>Acro-osteolysis</td>
<td>1.27 (0.81 - 2.01)</td>
<td>0.298</td>
</tr>
</tbody>
</table>

RR=Relative risk, HAQ-DI=Health Assessment Questionnaire disability index, GI=Gastrointestinal, VAS=visual analog scale.
Calcinosis Working Group
Radiographic Study

Calcinosis Working Group
Radiographic Study

Distribution of change in calcinosis score over a year

# Calcification Working Group

## Patient Reported Outcomes

### Mawdsley Calcification Questionnaire

**Patient Name or Reference:**

**Current geographical location:**

**Hemisphere/season:**

**Month/Day:**

### Part A

1. a. How many calcification lesions (open or closed) do you ACTUALLY have today? ______
2. b. How many calcification do you FEEL that you have today? ______
3. a. How many digital ulcers do you have today? ______
4. b. How many of these digital ulcers do you think are related to calcification? ______

### Part B

In the past TWO WEEKS, what is the worst degree that...

1. Your Raynaud's has interfered with daily activities?

<table>
<thead>
<tr>
<th>No Limitation</th>
<th>Maximum Limitation/Worst possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Your DIGITAL ULcers interfered with daily activities?

<table>
<thead>
<tr>
<th>No Limitation</th>
<th>Maximum Limitation/Worst possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. You experienced PAIN from your calcification?

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Worst Possible Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. You felt any areas of your calcification GETTING TIGHTER or having more pressure?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. You felt any areas of your calcification GROWING under your skin?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

6. You felt any areas of your calcification THROBBING?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Your calcification has been TENDER to TOUCH?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. You felt the need to PROTECT areas of your calcification?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. You have been FEELING or WORRIED that any of your calcification areas are INFECTED?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. You have been worried that a calcification wound MIGHT NOT HEAL?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. Your calcification interfered with ability to CARE FOR SELF?

<table>
<thead>
<tr>
<th>No Limitation</th>
<th>Maximum Limitation/Worst possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12. Your calcification interfered with ability to USE YOUR HANDS?

<table>
<thead>
<tr>
<th>No Limitation</th>
<th>Maximum Limitation/Worst possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13. Your calcification interfered with WALKING?

<table>
<thead>
<tr>
<th>No Limitation</th>
<th>Maximum Limitation/Worst possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Test question: Your calcification interfered with your ability to USE YOUR HANDS as you WALK?

<table>
<thead>
<tr>
<th>No Limitation</th>
<th>Maximum Limitation/Worst possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Calciosis Working Group
Mawdsley Questionnaire Validation

- 750 participants with SSc-calciosis
- Online REDcap questionnaires two weeks apart
- Cochin Hand Scale, SHAQ and SF-36 for correlative comparators needed for validation
- Global Rating Of Change Scale for Minimal clinically important differences (MCID)
Calcinosis Working Group

VEGF-induced osteoclastogenesis in calcinosis

• Specific Aims: To assess whether the presence of radiographically confirmed calcinosis of the hands in patients with SSc is associated with:
  1. Increased VEGF plasma levels
  2. Increased osteoclastogenesis and osteoclast activity
  3. Increased bone resorption markers
Calcinosis Working Group

VEGF-induced osteoclastogenesis in calcinosis

Patients with SSc without calcinosis (n=10)

Patients with SSc-calcinosis (n=10)

Healthy Controls (n=10)

<table>
<thead>
<tr>
<th>ASSESSMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Concomitant medications</td>
</tr>
<tr>
<td>Physical Exam</td>
</tr>
<tr>
<td>Evaluation of calcinosis</td>
</tr>
<tr>
<td>Vital Signs</td>
</tr>
<tr>
<td>Height and Weight</td>
</tr>
<tr>
<td>Blood samples</td>
</tr>
<tr>
<td>Hand radiographs</td>
</tr>
<tr>
<td>DXA scan</td>
</tr>
<tr>
<td>SHAQ</td>
</tr>
<tr>
<td>Cochin Hand Questionnaire</td>
</tr>
<tr>
<td>Mawdsley Calcinois Questionnaire</td>
</tr>
<tr>
<td>Raynaud Severity Score</td>
</tr>
<tr>
<td>mRSS</td>
</tr>
</tbody>
</table>
Calcinosis Working Group

VEGF-induced osteoclastogenesis in calcinosis

• Methods:
  • VEGF will be measured by enzyme-linked immunosorbent assay (ELISA).
  • Osteoclasts will be identified using TRAP stain in cultures of PBMC.
  • Osteoclast activity will be assessed through pit formation assay.
  • Bone resorption markers will be determined using ELISA kits.
### Calcinosis Working Group

**VEGF-induced osteoclastogenesis in calcinosis**

<table>
<thead>
<tr>
<th>Task</th>
<th>Proposed timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifying healthy controls from Pontificia Universidad Catolica.</td>
<td>December 2020</td>
</tr>
<tr>
<td>SSc patients will come for a research visit</td>
<td>January - March 2020</td>
</tr>
<tr>
<td>Plasma levels of VEGF, OPG, RANKL and TRAP will be quantified by ELISA.</td>
<td>January - March 2020</td>
</tr>
<tr>
<td>XR radiographic score will be applied by two independent readers to determine the severity of calcinosis</td>
<td>April 2020</td>
</tr>
<tr>
<td>Statistical analyses will be performed to assess differences in VEGF plasma levels in patients with and without calcinosis and healthy controls.</td>
<td>April 2020</td>
</tr>
</tbody>
</table>
Join us

• To get involved, please contact:
  – Dr. Lorinda Chung (shauwei@stanford.edu)
  – Dr. Antonia Valenzuela (antonia.valenzuela@uc.cl)
SCTC Cardiac Working Group

SCTC Annual General Meeting 2020

Co-chairs: Murray Baron, Mandy Nikpour, Alessandra Vacca
PhD Candidate: Dr Laura Ross
Objective

• To develop classification criteria for systemic sclerosis heart involvement (SHI) for use in observational studies and clinical trials.
Team of investigators

- PIs:
  - Prof Murray Baron
  - A/Prof Mandana Nikpour
  - Dr Alessandra Vacca
  - Dr Laura Ross

- 16 rheumatologists
- 6 cardiologists
- 2 anatomical pathologists
Methodology (1)

Scoping literature review of previous definitions of SSc heart involvement (completed)
Published Ross et al Semin Arthritis Rheum 2019 48 (5) 874-997

Domains of cardiac disease to be included in classification criteria (completed)
Cardiac WG (rheumatologists & cardiologists) surveyed & results presented at working group meeting

Preliminary items defined by expert consensus (completed)
5 cardiologists, 4 rheumatologists, 2 anatomical pathologists
Preliminary results

• Initial survey of Cardiac Working Group:
  • 7 domains of heart disease presented to WG
  • Consensus to include:
    • Myocardial inflammation
    • Myocardial fibrosis
    • Arrhythmias
    • Conduction abnormalities
    • Pericardial abnormalities
  • ? Include vascular abnormalities
  • Consensus to exclude valvular abnormalities
Preliminary results

• Development of preliminary criteria
  • Developed in consultation with 5 cardiologists, 4 rheumatologists & 2 anatomical pathologists
  • Each expert presented results of WG survey
  • Cardiologists & pathologists asked to identify items to measure abnormalities in each of domains of heart disease identified by working group.
  • Experts defined 4 pathophysiological domains of heart disease and 28 items to measure SHI in each of these domains

• Item reduction by survey of cardiologists
  • 28 items reduced to 24 items
Methodology (2)

Item reduction (completed)
Survey of 12 cardiologists

Item weighting
Discrete choice experiment with multi-criteria decision analysis

Validation
Using data from *HEart Matters in Systemic Sclerosis (HEMSS)* database
HEart Matters in Systemic Sclerosis Database
HEMSS Database

• Aim: Collect cases of heart disease in SSc of ANY aetiology, including primary SSc heart involvement

• SCTC members invited to participate by submitting cases via REDCap
  • Contact Dr Laura Ross (lross1@student.unimelb.edu.au)

• Case submission requires clinical information & cardiac investigation results.
Cardiac Working Group Contact Details

Mandy Nikpour: m.nikpour@unimelb.edu.au
Murray Baron: mbaron@jgh.mcgill.ca
Alessandra Vacca: ales.vacca@tiscali.it
Laura Ross: lross1@student.unimelb.edu.au
Acknowledgement

SCTC Working Group Grants

NHMRC and Musculoskeletal Australia
Definition of Scleroderma Renal Crisis

Scoping Review
Hoa et al. Autoimmun Rev 2017

Delphi 1 Delphi 2 Delphi 3

NGT meeting

Consensus on a core set
Butler et al. A and R 2019

International Scleroderma Renal Crisis Survey II

Consensus methods

Data-driven methods
A successful start for the International Scleroderma Renal Crisis Study II
Marie Hudson & Christopher Denton
Co-chairs of the SCTC SRC working group

The International Scleroderma Renal Crisis Study II (ISRCSII) started recruiting in January 2020. We have had a great response from 106 collaborators from 95 institutions around the world, including 28 countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Egypt, France, Germany, Hungary, Iran, Israel, Italy, Japan, Mexico, The Netherlands, Norway, Pakistan, Poland, Portugal, Romania, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom, USA.
Controls

Development of classification criteria for Scleroderma Renal Crisis (SRC): controls with thrombotic microangiopathy

Thank you for taking the time to complete the International Scleroderma Renal Crisis Survey II for control cases.
Acknowledgements

**WG Steering committee**
- Christopher Denton
- Dinesh Khanna
- Murray Baron
- Tracy Frech
- Sindhu Johnson
- Luc Mouthon
- Mandy Nikpour
- Susanna Proudman
- Virginia Steen
- John Varga

**Nephrologists**
- Edward Stern
- Cybele Ghossein
- Sharon Nessim

**Pathologist**
- Agnes Fogo

**Delphi Participants (N=99)**

**NGT Participants (N=11)**
- Dinesh Khanna (moderator)

**Trainees**
- Sabrina Hoa
- Emily-Ann Butler

**ISRCS II participants (N=106)**
DEFINING TIME OF ONSET OF SSc and ITS INDIVIDUAL ORGAN SYSTEM INVOLVEMENTS

Tom Medsger and Marie Hudson

Purpose: To recommend guidelines for use in SSc clinical trials (especially in dcSSc) and observational studies

Organ System Leaders: Skin, Peripheral Vascular (John Pauling); Skeletal Muscle (Julie Paik, Ami Shah); Joint/Tendon, Heart (Tatiana Rodriguez); Interstitial Lung Disease (Francesco Boin); Pulmonary Hypertension (Wendy Stevens); Gastrointestinal Tract (Tracy Frech); Kidney (Luc Mouthon)
EXAMPLE OF ORGAN SYSTEM INVOLVEMENT
DEFINITION AND ONSET DATE: SKELETAL MUSCLE

Elements: muscle pain (Hx), muscle weakness (Hx, PE); CPK; EMG; Bx; MRI

- Definition: (1) proximal muscle weakness on PE or CPK 2 or greater times upper limit of normal
  OR
(2) any one of: (a) EMG: myopathic changes; (b) muscle biopsy: inflammation, necrosis or fibrosis or (c) MRI: muscle edema

- Onset Date: Month/Year of first patient reported proximal muscle weakness, provided one of the above criteria is satisfied or Month/Year of documentation of (2) above, whichever is first.

- Notes: (1) Proximal muscle weakness is defined as: ..........  
  (2) EMG, Bx, MRI as recorded by physician interpreting studies

- References: (maximum 3-5) ............
Delphi exercise – To achieve consensus on standardized definitions for time of onset of SSc and individual organ systems

Online Delphi Exercise

• Round 1 - consider preliminary definitions, to identify omissions and ambiguities; modify accordingly

• Round 2 - Provide ratings of agreement with the definitions using Likert-type scales (1 = strongly disagree, 5 = neutral, 9 = strongly agree)

• Round 3 - Review results of Round 2 and provide final ratings of agreement

• Agreement defined as scores ≥7 in Round 3 (with no disagreement) based on RAND/UCLA methods
SCTC Vascular Working Group: Optimise methods for assessing peripheral vascular dysfunction in SSc

**Assessment of Scleroderma-associated RAynaud’s Phenomenon (ASRAP) questionnaire**

- 39 item self-administered questionnaire (anticipated redundancy) grounded in patient experience of SSc-RP

- Enrolled 442 patients attending English-speaking SSc units in Bath, London, Manchester, Pittsburgh, Ann Arbor, Johns Hopkins and Salt Lake City

- Data cleaning and analysis underway
- IRT to establish scoring methods, remove redundant items and undertake preliminary psychometric testing
- ASRAP being included as exploratory endpoint in forthcoming early phase clinical trials
Exploring the patient experience of Digital Ulcers in SSc

Comprehensive scoping review and focus groups held in Bath, London and Manchester

- Patient experiences of digital ulcer development and evolution in systemic sclerosis.
- What narrative devices do people with systemic sclerosis use to describe the experience of pain from digital ulcers: a multicentre focus group study at UK scleroderma centres.
Systemic Sclerosis impact of Digital Ulcers (SSiDU) Questionnaire

Stage 1: Define the patient experience of SSc-RP

Stage 2: Item development & refinement for novel PRO

Stage 3: Test and validate novel PRO (n=100)

SCTC Vascular Working Group: Optimise methods for assessing peripheral vascular dysfunction in SSc
SCTC/ WSF certification for the modified Rodnan skin score

Dinesh Khanna and Christopher Denton
Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis

Dinesh Khanna¹, Daniel E. Furst², Philip J. Clements³, Yannick Allanore³, Murray Baron⁴, Lazlo Czirjak⁵, Oliver Distler⁶, Ivan Foeldvari⁷, Masataka Kuwana⁸, Marco Matucci-Cerinic⁹, Maureen Mayes¹⁰, Thomas Medsger¹¹, Peter A. Merkel¹², Janet E. Pope¹³, James R. Seibold¹⁴, Virginia Steen¹⁵, Wendy Stevens¹⁶, Christopher P. Denton¹⁷, on behalf of the Scleroderma Clinical Trials Consortium and the World Scleroderma Foundation

◆ In-depth expert consensus on mRSS
  – Recommendations on assessment in Phase 2 and Phase 3 trials
  – Discussion on practical aspects and caveats
Certification

- Certification at the completion of the training.
- Information is kept in the SCTC database.
- Future sponsors can request this information for their trials.
- Certification every 2-3 years.
Progress so far

- Trained 300+ individuals in following countries
  - Australia
  - Canada
  - European Union
  - Japan
  - Singapore
  - South Korea
  - USA

- Identified teachers in different countries to accomplish this
Covid-19 impact

- SCTC certification program is on hold to protect the patients and the clinicians.
- Modifications to be considered for ongoing trials.
  1. SCTC certification in the past 2-3 years—can be considered as an assessor.
  2. Exceptions for those who are not certified but have expertise in SSc- regularly perform mRSS and have participated in recent trials.
  3. In-Person mRSS Training by Selected Senior PI (locally or regional)—will be not considered for the SCTC certification
- Plan to launch the training program next year
SPECIAL PRESENTATIONS:

Q & A PERIOD
THANK YOU!

ANNUAL GENERAL MEETING 2020 – FIRST VIRTUAL MEETING VIA ZOOM