Points to Consider in the Design of Clinical Trials in Systemic Sclerosis- A Joint Project of EULAR and ACR

This project will be done as a joint project of EULAR and ACR and will be published jointly under their egis

Systemic sclerosis (Scleroderma, SSc) is one of the most fatal rheumatic diseases, and is associated with substantial morbidity\(^1\) and many detrimental effects on health-related quality of life\(^2\). Recent years have seen a revolution in the development and validation of outcome measures\(^3\) and refinement of trial methodology in SSc\(^4\). This is paralleled by an increased understanding of the pathogenesis of SSc\(^5,6\), development of targeted therapies\(^7,8\) and multiple well-conducted recent clinical trials\(^9-13\).

Our group has led a structured Delphi exercise, with participation of the Scleroderma Clinical Trial Consortium membership, to develop a provisional core set of items for clinical trials\(^14\). The Delphi exercise identified 11 domains relevant to SSc clinical trials. Our group has also led the efforts to develop a scleroderma combined response index (CRISS) and has included the pooling of data, comprising 635 diffuse SSc patients, from previously completed clinical trials of diffuse SSc to test some individual aspects of a possible combined index. We have looked at the feasibility, reliability, validity, and responsiveness of a number of commonly used outcomes measures in this data set\(^15-17\).

We feel that there is enough development in trial methodology and outcome measures in the past decade that new recommendations should be put forward in the design of future clinical trials in systemic sclerosis. The last recommendations were published by the American College of Rheumatology Committee on Design and Outcomes in Clinical Trials in Systemic Sclerosis in 1995\(^4\).

Our goal is to recommend standards when designing randomized clinical trials in SSc—both for limited SSc and diffuse SSc. **Our central hypothesis is that the recommendations regarding the design of randomized clinical trials in SSc will facilitate drug development and encourage uniform trial design.**

We have assembled a group of scleroderma international experts who have worked together over the last decade and have expertise in clinical trial design, development of response criteria, and measurement of patient-oriented outcomes. The researchers on this proposal have been Principal Investigators in multiple clinical trials in SSc, have shown a strong commitment to promote drug development in SSc, and are leaders in the assessment of outcome measures in diffuse SSc. We envision this project as a partnership between ACR and EUSTAR.

**Specific Aims**

1. **Conduct an extensive literature search and develop recommendations for designing randomized clinical trials in SSc.**
a) We will conduct an extensive literature search for literature published over the past 2 decades using the Pub Med, Cochrane, and Embase databases, hand search randomized controlled studies in SSc presented at the ACR and EUSTAR meetings, and contact authors for more details on unpublished data.

b) Develop recommendations based on best available data. The points to consider during design of clinical trial will include

i. What are the goals and rationale for the clinical trial
ii. What are the important patient characteristics for patients to be included (e.g. disease duration, ethnicity, disease activity)
iii. What outcome measures should be used (and the degree to which they are validated- e.g. skin score, forced vital capacity, scleroderma HAQ disability Index, serum creatinine)
iv. How can bias be eliminated or minimized (consideration of controls, historic or concurrent etc.)

v. What confounding variables need to be considered (e.g. comorbid conditions and concomitant medications or therapeutics, past medication use)

vi. What is the appropriate trial duration

vii. What are the statistical considerations (e.g. effect size, variability, statistical power, sample size)

viii. Employ nominal group technique to get an agreement among SSc experts from North America and Europe.

a) We will convene a nominal group meeting of key-opinion leaders to discuss the points that should be considered in design of a clinical trial.

b) We will present the best available data to support the recommendations

c) We will then ask the experts to vote whether to include or exclude these recommendations based on the current available data

d) At least an 80% agreement will be required to accept xxx to be included as a recommendation

Personnel

Senior Faculty: Daniel E. Furst  
Junior Faculty: Dinesh Khanna

Executive Committee: Daniel E. Furst, Dinesh Khanna, Marco Matucci-Cerenic  
Facilitator: Robert Landewe

Task Force

Europe

Alan Tyndall  
Doug Veale  
Frank Van den Hoogen  
Chris Denton
Methodology:
1. Extensive literature search over the past 2 decades using the Pub Med, Cochrane, and Embase databases, hand search randomized controlled studies in SSC presented at the ACR and EUSTAR meetings, and contact authors for more details on unpublished data. This will be done by Dinesh Khanna with help of a scleroderma fellow at UCLA, Dr. Jeremy Anuntiyo.
2. The EC will discuss the available data and propose recommendations regarding the following points
   i. What are the goals and rationale for the clinical trial
   ii. What are the important patient characteristics for patients to be included (e.g. disease duration, ethnicity, disease activity)
   iii. What outcome measures should be used (and the degree to which they are validated- e.g. skin score, forced vital capacity, scleroderma HAQ disability Index, serum creatinine)
   iv. How can bias be eliminated or minimized (consideration of controls, historic or concurrent etc.)
   v. What confounding variables need to be considered (e.g. comorbid conditions and concomitant medications or therapeutics, past medication use)
   vi. What is the appropriate trial duration
   vii. What are the statistical considerations (e.g. effect size, variability, statistical power, sample size)
3. The recommendations along with the summary of available data will be circulated among the Task Force panel for their input.
4. The Task Force panel will be oriented to the process and will be surveyed regarding the above domains and the tools contained therein. If the tools chosen expand the need for further literature review, this, too, will be done.
5. A nominal group meeting will be convened and each Task Force member will begin by silently rating each of the recommendations as “accepted” or “rejected.”
6. The moderator then will ask each member how he or she voted on each recommendation. If an 80% consensus is not achieved regarding the recommendation, then the recommendation will be discussed in round robin fashion and a second vote taken. If 80% consensus is still not obtained, then that recommendation will be declared "not interpretable" and not discussed further in that particular nominal group. It will be placed into a research agenda for future consideration if further data become available.
7. The co-chairs and executive committee will develop the manuscript for publication of these Points to Consider. In addition to publication, these recommendations will need to be publicized in appropriate European and North American meetings.

**Budget:** US$ 42,000; EU Euros42,000  
- Given as % because mixed currencies are being used.

- Literature review (requiring significant amount of time from three individuals) 28.2%  
- Administrative and Secretarial Staff 18.8%  
- Telephone and fax 4.7%  
- Consultants-RAND, Facilitator 4.7%  
- Travel and Taxis 18.8%  
- Meeting (three nights and two days) 18.8%  
- Overhead (5%) 4.6%  
- Publication Charges 1.4%

**Total:** 100.0%

Refs (omitted for Ex Co meeting – available from AT)