

Scientific Summary

Recent randomised controlled trials (RCTs) have failed to reach their primary endpoint and demonstrate efficacy of much-needed novel therapies for systemic sclerosis (SSc). The lack of fully validated outcome measures to assess overall disease status has contributed to the failure of recent RCTs.¹ Analysis of the use of the both the patient global assessment (PGA) and physician global assessment (PhyGA) shows there is inconsistent application of these commonly used outcome measures and high variability of constructs assessed by both instruments. In contrast to multi-question patient-reported outcomes measuring individual organ manifestations or health-related quality of life, global assessments are presented as a single question and ask respondents to rate global disease status, either via a visual analogue, numeric rating or Likert scale. Newer multi-system outcome measures for use in SSc RCTs such as the American College of Rheumatology (ACR) Composite Response Index for Systemic Sclerosis (CRISS) include both patient and physician global assessments as part of a composite measure of response to treatment.²

Despite the long-recognised importance of measuring a global assessments in clinical studies, there are no standardised, SSc-specific global assessment instruments. There has never been any patient or broad physician input into the development of either instrument. Therefore, as they are currently applied, both the PGA and PhyGA in SSc have uncertain face and content validity and unproven construct validity. The Scleroderma Clinical Trials Consortium Global Assessment Working Group was convened in 2022 to address this issue.

Overall Project Aim:

The overarching aim of this project is to develop a SSc-specific patient global assessment (PGA) and physician global assessment (PhyGA) for use in randomised controlled trials.

Progress towards aims specific to this funding opportunity

1. Completion of systematic literature review

Successful publication of a review of the psychometric properties of both the patient and physician global assessment instruments as they are current used in *Arthritis Care & Research* (appendix 1).

2. Establish a SCTC Global Assessment Working Group & project steering committee

We have established a working group to address the need to develop a SSc specific patient global assessment instrument. The working group comprises of members from North America, Europe, the UK and Australia.

In addition to the 10 rheumatology members of the working group, a qualitative researcher Ms Hana Sabanovic (University of Melbourne, Australia) and two patient research partners, Mr Martin Retscko

(Australia) and Ms Amanda Feagans (US) have been recruited to the project steering committee. These 13 members comprise the project steering committee.

Upon establishment of the working group, the need for the development of a physician global assessment instrument, in addition to a patient global instrument was recognised. Therefore, the working group has accepted as its aims to develop in parallel, both:

1. A patient global assessment instrument
2. A physician global assessment instrument.

The working group elected to proceed with the development of the physician global assessment first in order to refine the methods of development of a disease specific global assessment prior to commencing the development of the patient global assessment instrument.

3. Retrospective evaluation of global assessments in the Australian Scleroderma Cohort Study

Two retrospective analyses of the data from the Australian Scleroderma Cohort Study have been performed evaluating the performance of the physician global instrument. I have examined the concordance three different physician global assessments that are simultaneously applied at each study visit in the Australian Scleroderma Cohort Study to examine the effect of the various wordings of global assessments on outcomes measured by each instrument. Additionally, again using Australian Scleroderma Cohort Study data, I have evaluated whether including a physician global assessment as part of a composite outcome measure improves the sensitivity and specificity of each measure to predict clinically important disease outcomes. These projects have resulted in two manuscripts.

4. Development of a physician global assessment instrument using qualitative research methods

We have performed 13 semi-structured interviews of 20 physicians and 1 patient research partner to investigate the physician and patient perspective of the physician global assessment instrument and explore the construct that should be assessed by this instrument in systemic sclerosis RCTs. These interviews have provided 15 hours of interview transcript that has undergone content and discourse analysis. This study has resulted in one manuscript currently in preparation and these results will form the basis of the futures steps of this project.

5. Development of a project protocol using qualitative research methods to develop a patient global assessment instrument

A project protocol to develop a patient global assessment instrument has been developed, drawing upon the expertise of the working group and qualitative research experience of Ms Sabanovic. Development and finalisation of this protocol was delayed by the late recruitment of Ms Sabanovic to the project steering committee. Initial methodological input was provided by the qualitative research team at the University of Bristol. However, due to conflicting work schedules, the Bristol qualitative research team were unable to

continue to provide methodological support to this project. There were delays in finding a suitably qualified qualitative researcher with capacity to take on this project and assist in the ongoing development and then implementation of the project. The final protocol for the development of a patient global instrument has been developed and submitted for Human Research Ethics approval.

Research outputs supported by this grant:

1. Ross et al, Patient and Physician Global Assessments of Disease Status in Systemic Sclerosis *Arthritis Care Res* 2023 75(7) 1443-1451
2. Ross et al, A Comparison of Three Physician Global Assessment Instruments in Systemic Sclerosis 2024 manuscript under review at *Arthritis Care Res*
3. Ross et al, Does the physician global instrument improve the performance of existing systemic sclerosis composite outcome measures? *Manuscript in preparation*
4. Sabanovic H, Pauling J & Ross L, A multinational qualitative research study exploring the physician global assessment in systemic sclerosis *Manuscript in preparation*