Patient-reported outcome instruments for assessing Raynaud's phenomenon in systemic sclerosis: A SCTC Vascular Working Group Report

John D Pauling BMedSci BMBS FRCP PhD [1,2], Tracy M Frech MD MS [3], Michael Hughes BSc (Hons) MSc MRCP [4], Jessica K Gordon MD MSc [5], Robyn T Domsic MD MPH[6], Marina E Anderson FRCP PhD [7], Francesca Ingegnoli MD PhD [8], Neil J McHugh FRCP MD[1,2], Sindhu R Johnson MD PhD[9], Marie Hudson MD MPH FRCPC [10], Francesco Boin MD [11], Voon H Ong PhD FRCP [12], Marco Matucci-Cerinic FRCP FBSRhon [13], Nezam Altorok MD [14], Marina Scolnik MD [15], Mandana Nikpour MBBS FRACP FRCPA PhD [16], Ankoor Shah MD [17], Janet E Pope MD MPH FRCPC [18], Dinesh Khanna MD MS [19] and Ariane L Herrick MD FRCP [4, 20]

[1] Royal National Hospital for Rheumatic Diseases (at Royal United Hospitals), Bath, UK

[2] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

[3] University of Utah and Salt Lake Regional Veterans Affair Medical Center, Salt Lake City, UT

[4] Centre for Musculoskeletal Research, The University of Manchester, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester.

[5] Hospital for Special Surgery, New York, NY

[6] University of Pittsburgh Medical Center, Pittsburgh, PA

[7] Institute of Ageing and Chronic Disease, Faculty of Health and Life Sciences, University of Liverpool & Aintree University Hospital

[8] Division of Rheumatology, Dept. of Clinical Sciences and Community Health, University of Milano, Milan, Italy

[9] Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital; Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

[10] Jewish General Hospital, Lady Davis Institute and McGill University, Montreal, Canada

[11] UCSF Scleroderma Center, University of California San Francisco, San Francisco, CA

[12] University College London Medical School, Royal Free Hospital, London, UK

[13] Division of Rheumatology, University of Florence, Florence, Italy

[14] University of Toledo Medical Center, Toledo, OH

[15] Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

[16] The University of Melbourne at St. Vincent's Hospital, Melbourne, Victoria, Australia

[17] Duke University Medical Center, Durham, NC

[18] Western University, London, Ontario, Canada,

[19] University of Michigan Scleroderma Program, Ann Arbor, MI

[20] NIHR Manchester Musculoskeletal Biomedical Research Centre, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, UK.

Short title: PRO instruments for assessing SSc-RP

Corresponding Author:

Dr John D Pauling BMedSci BMBS PhD FRCP

Consultant Rheumatologist & Visiting Senior Lecturer,

Royal National Hospital for Rheumatic Diseases,

Upper Borough Walls,

Bath, BA1 1RL

Tel: (0044) 1225 473 468 Fax: (0044) 1225 473 452

JohnPauling@nhs.net

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Abstract (unstructured)

The episodic nature of Raynaud's phenomenon (RP) in systemic sclerosis (SSc) has led to a reliance on patient-reported outcome (PRO) instruments such as the Raynaud's Condition Score (RCS) diary. Little is known about the utilisation in routine clinical practice and health professional attitudes towards existing PRO instruments for assessing SSc-RP. Members of the Scleroderma Clinical Trials Consortium Vascular Working Group (SCTC-VWG, n=28) were invited to participate in a survey gauging attitudes towards the RCS diary and the perceived need for novel PRO instruments for assessing SSc-RP. Nineteen SCTC-VWG members (68% response rate) from academic units based in North America (n=9), Europe (n=8), South America (n=1) and Australasia (n=1) took part in the survey. There was broad consensus that RCS diary returns could be influenced by factors including seasonal variation in weather, efforts made by patients to avoid or ameliorate attacks of RP, habituation to RP symptoms, evolution of RP symptom characteristics with progressive obliterative microangiopathy, patient coping strategies, respondent burden and placebo effect. There was consensus that limitations of the RCS diary might be a barrier to drug development (79% of respondents agree/strongly agree) and that a novel PRO instrument for assessing SSc-RP should be developed with the input of both clinicians and patients (84% agree/strongly agree). Perceived potential limitations of the RCS diary have been identified along with concerns that such factors might impede drug development programs for SSc-RP. There is support within the systemic sclerosis community for the development of a novel PRO instrument for assessing SSc-RP.

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Patient Reported Outcomes, Raynaud's Phenomenon, Scleroderma, Survey, Systemic Sclerosis

Raynaud's phenomenon (RP) describes excessive vasoconstriction of the digital vessels in response to cold exposure and/or emotional stress and is a major source of morbidity in systemic sclerosis (SSc). A large patient survey ranked RP highest in the overall frequency and impact of disease-specific symptoms experienced by SSc patients (1). Due to its episodic nature and subjectivity surrounding the severity of symptoms, the assessment of RP is challenging and largely reliant upon patient reported outcome (PRO) instruments. The Raynaud's Condition Score (RCS) diary (that assesses the frequency, duration and severity/impact of RP) and the RP visual analogue scale (VAS) from the Scleroderma Health Assessment Questionnaire (SHAQ) were each developed in the 1990's and are both included in the proposed core set of response measures for clinical trials in SSc (2-5). These tools were developed primarily for clinical trials and little is known about the utilization of these instruments to evaluate the efficacy of treatments for SSc-RP in routine clinical practice. Recent research conducted in Europe and Canada has examined the frequency and choice of vasoactive medications in SSc-RP, but has not reported analyses of the comparative efficacy of different interventions in routine clinical practice because data was not available (6, 7). One explanation for this might be low utilization of PRO instruments to assess SSc-RP in routine clinical practice; possibly owing to clinician attitudes towards these tools, difficulties in interpretation, and/or respondent burden. We undertook a survey of clinicians with expertise in SSc from within the Scleroderma Clinical Trials Consortium (SCTC) Vascular Working Group (VWG) to evaluate the utilization of existing PRO instruments for assessing SSc-RP in routine clinical practice and to gauge expert's attitudes on (a) factors influencing outcomes using existing tools and (b) the possible need to develop novel instruments for assessing SSc-RP.

Methods

The SCTC-VWG is an international group of SSc experts with a focus on the assessment and management of peripheral vascular manifestations of SSc. The objectives of the SUbjective Raynaud's Phenomenon Assessment in Systemic Sclerosis (SURPASS) survey were to evaluate the utilization of existing PRO instruments for SSc-RP in routine clinical practice, critically appraise potential factors influencing outcomes using existing tools and gauge opinion regarding the need for novel PRO instruments for assessing SSc-RP. The SURPASS questionnaire was developed in an electronic format and circulated amongst SCTC-VWG members (n=28). Participation in the survey was promoted at a face-to-face SCTC-VWG meeting (ACR 2015) and working-group members received up to 2 reminder emails (November-December 2015). All respondents provided consent to participate. The UK Heath Research Authority confirmed formal ethics approval was not required for this work. The survey was reviewed and approved for dissemination by the Research & Development directorate of the Royal United Hospitals, Bath.

Results

Nineteen SCTC-VWG members (68% response rate) completed the survey. All were practicing rheumatologists with an established interest in SSc (79% seeing >15 patients with SSc per month) affiliated with academic units based in North America (n=9), Europe (n=8), South America (n=1) and Australasia (n=1). The majority of respondents (95%) had participated in clinical trials of SSc and had prior experience of SSc-RP endpoints (83% of respondents).

Most respondents (95%) enquire about RP symptom severity at most/all clinic assessments. All respondents are familiar with the SHAQ RP VAS subscale but the majority (53%) had only used this in the research/clinical trial setting. Fewer than half of respondents (42%) use the SHAQ RP VAS in routine clinical practice; only one of whom (5%) collects this outcome measure at every visit.

Utilization of the RCS diary is low; 33% have never used the instrument, 58% in a research/clinical trial setting and only 11% report using the RCS diary in clinical practice. There were mixed views from respondents regarding the extent to which the RCS diary captures its intended conceptual framework (Table 1.). There was consensus that the RCS diary returns are likely influenced by seasonal variation in weather, efforts made by patients to avoid or ameliorate attacks of RP, habituation to RP symptoms, change in RP symptom characteristics with evolution of peripheral obliterative microangiopathy, patient coping strategies, respondent burden and placebo effect (Table 1.). There was consensus that the limitations of the RCS diary might be a barrier to drug development (79% of respondents agree/strongly agree), that a novel PRO instrument for SSc-RP might aid drug development for SSc-RP (95% agree/strongly agree) and that development of a novel PRO instrument for SSc-RP should have combined input of clinicians and patients (84% agree/strongly agree).

Discussion

Existing PRO instruments for SSc-RP were primarily developed for clinical trials and this survey indicates they have not been adopted in routine clinical practice to guide treatment decisions for SSc-RP. Our survey design did not allow us to explore the reasons for the relatively limited use of instruments such as the SHAQ and RCS diary in routine clinical practice and this could form the focus of additional work. Possible explanations might include limited perceived need for quantification of clinical outcomes to guide treatment decisions in SSc and the lack of accepted “treat-to-target” approaches to management. Mistrust in the instrument, patient burden and resource implications surrounding administering and scoring the RCS diary could be factors limiting its use in routine clinical practice. In other diseases, the adoption of outcome measures developed for clinical trials into routine clinical practice (e.g. the DAS-28 informing “treat-to-target” approaches in rheumatoid arthritis) has improved outcomes (8, 9). A similar approach to routinely capturing information on SSc-

RP is desirable and might facilitate the collection of “practice-based evidence” to support future guideline development (10). The survey has identified attitudes towards existing PRO instruments for SSc-RP that might have influenced their use in routine clinical practice such as respondent burden. The survey has also captured opinions regarding a number of other factors that might influence RCS diary returns (including both factors that directly influence RP symptoms and also factors that might influence the *reporting* of RP symptoms in SSc). The potential influence of these different factors identified in this study on RCS diary returns requires further evaluation in prospective studies of SSc patients. The chief limitations of this work are the relatively small survey size and selection bias having targeted SCTC-VWG members. Nevertheless, the SCTC-VWG benefits from its composition of highly experienced clinicians affiliated to major SSc units across four continents. A broader survey of general rheumatologists would likely reveal lower utilization of SSc-RP PRO instruments and attitudes towards existing instruments could potentially be influenced by lesser experience with these tools. Nonetheless, these are significant limitations that have influenced the generalizability of our findings. Several potential limitations of existing PRO instruments for assessing SSc-RP have been highlighted and there is recognition that these factors might impede drug development programs in SSc-RP. A consensus has emerged that work towards a novel PRO for SSc-RP (developed with input from SSc clinicians and patients) is needed. A novel PRO instrument for SSc-RP that could be administered and scored easily (avoiding the need for diary monitoring if possible), and that could be applied in both clinical trials and used to guide routine clinical management decisions for SSc-RP would be desirable.

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Key Messages

- Existing PRO instruments are not routinely used to inform management of SSc-RP
- Limitations of existing PRO instruments for SSc-RP might be a barrier to drug development
- There is a need to develop novel PRO instruments for assessing SSc-RP
- Greater implementation of PROs into routine clinical practice could facilitate the emergence of valuable practice-based evidence for the management of SSc-RP

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Table 1. Summary of SURPASS survey responses.

The number indicates the number of respondents (%). The most common response for each item is highlighted in bold. RP, Raynaud's phenomenon; RCS, Raynaud's Condition Score; PRO, patient-reported outcome; SSc, systemic sclerosis

		Extent to which respondents (n, %) agreed with each statement:					
		Unable to offer opinion	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The RCS diary accurately reflects:	Frequency of RP attacks	1 (5)	1 (5)	2 (11)	6 (32)	**8 (42)**	1 (5)
	Duration of RP attacks	1 (5)	1 (5)	3 (16)	**8 (42)**	5 (26)	1 (5)
	Overall severity and impact of RP	1 (5)	1 (5)	2 (11)	6 (32)	**7 (37)**	2 (11)
The RCS diary returns are influenced by:	Difficulty recognizing attacks of RP	0 (0)	0 (0)	**7 (37)**	2 (11)	**7 (37)**	3 (16)
	Seasonal variation in weather	1 (5)	0 (0)	0 (0)	0 (0)	**9 (47)**	**9 (47)**
	Efforts made to avoid attacks of RP	1 (5)	0 (0)	0 (0)	3 (16)	**10 (53)**	5 (26)
	Efforts made to ameliorate attacks of RP	1 (5)	0 (0)	1 (5)	3 (16)	**11 (58)**	3 (16)
	Habituation to RP symptoms over time	1 (5)	0 (0)	0 (0)	0 (0)	**12 (63)**	6 (32)
	Evolution of morphological digital microvascular disease	1 (5)	0 (0)	1 (5)	4 (21)	**9 (47)**	4 (21)
	Patient coping strategies	1 (5)	0 (0)	0 (0)	1 (5)	**13 (69)**	4 (21)
	Excessive respondent burden	1 (5)	0 (0)	1 (5)	2 (11)	**9 (47)**	6 (32)
	Placebo effect	2 (11)	0 (0)	1 (5)	2 (11)	**8 (42)**	6 (32)
The RCS diary:	Might impede drug development in SSc-RP	2 (11)	0 (0)	2 (11)	0 (0)	**9 (47)**	6 (32)
	Is satisfactory and no further research is required in this area	0 (0)	7 (37)	**10 (53)**	1 (5)	0 (0)	1 (5)
A novel PRO instrument for SSc-RP:	Might aid drug development in SSc-RP	0 (0)	0 (0)	0 (0)	1 (5)	**11 (58)**	7 (37)
	Should be primarily *PATIENT*-derived	0 (0)	0 (0)	1 (5)	3 (16)	**9 (47)**	6 (32)
	Should be primarily *CLINICIAN*-derived	0 (0)	0 (0)	**9 (47)**	8 (42)	2 (11)	0 (0)
	Should be *CLINICIAN* and *PATIENT*-derived	0 (0)	0 (0)	1 (5)	2 (11)	7 (37)	**9 (47)**