Construct validity and reliability of the Assessment of Systemic sclerosis-associated RAynaud's Phenomenon (ASRAP) questionnaire

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Abstract

Objectives: Preliminary assessment of construct validity and reliability of a novel patient-reported outcome (PRO) instrument for assessing the severity and impact of Raynaud's phenomenon (RP) in systemic sclerosis (SSc).

Methods: An international multi-center study validation study of the 27-item Assessment of Systemic sclerosis-associated RAynaud's Phenomenon (ASRAP) and 10-item short-form (ASRAP-SF) questionnaires. The relationship between ASRAP questionnaires and demographics, clinical phenotype and legacy instruments for assessing SSc-RP severity, disability and pain was assessed. Repeatability was evaluated at 1-week. Anchor-based statements of health status were used to estimate ASRAP thresholds of meaning.

Results: Four hundred and twenty SSc subjects were enrolled. There was good correlation between ASRAP (and ASRAP-SF) with RP visual analogue scale (VAS) and Scleroderma Health Assessment Questionnaire RP VAS (rho range 0.648-0.727, $p<0.001$). Correlation with diary-based assessment of SSc-RP attack frequency and duration was lower (rho range 0.258-0.504, $p<0.001$). ASRAP questionnaires had good correlation with instruments for assessing disability, hand function, pain and global health assessment (rho range 0.427-0.575, $p<0.001$). Significantly higher ASRAP scores were identified in smokers, patients with active digital ulceration (DU), previous history of DU and calcinosis ($p<0.05$ for all comparisons). There was excellent repeatability at 1-week amongst patients with stable SSc-RP symptoms (intra-class coefficients of 0.891 and 0.848, $p<0.001$). Patient-acceptable symptom state thresholds for ASRAP and ASRAP-SF were 45.34 and 45.77 respectively. A preliminary ASRAP Minimally Important Clinical Difference threshold of 4.17 (95% CI 0.53-7.81, $p=0.029$) was estimated.

Conclusion: ASRAP and ASRAP-SF questionnaires are valid and reliable novel PRO instruments for assessing the severity and impact of SSc-RP.

Word count: 250

Key messages

What is already known on this topic:

Demonstrating treatment efficacy for interventions for Raynaud's phenomenon in systemic sclerosis using existing clinical trial endpoints has been challenging, with negative clinical trials of promising vasodilator therapies. The ASRAP questionnaire is a novel patient-reported outcome instrument for assessing the severity and impact of Raynaud's phenomenon that is grounded in the lived-experience of patients with systemic sclerosis.

What this study adds:

The present study is the largest study of Raynaud's phenomenon in systemic sclerosis undertaken to date and we have confirmed ASRAP questionnaire is feasible, repeatable, and has strong face, content and construct validity.

How this study might affect research, practice or policy:

The ASRAP questionnaire is a novel valid and reliable patient-reported outcome instrument that captures the severity and impact of Raynaud's phenomenon in people with systemic sclerosis. The ASRAP questionnaire will support the assessment of novel interventions and facilitate the capture of much needed practice-based evidence on the comparative efficacy of existing treatments for Raynaud's phenomenon in systemic sclerosis.

Introduction

Raynaud's phenomenon (RP) is a major cause of disease morbidity in systemic sclerosis (SSc), resulting in pain, numbness, tingling/burning, impaired hand function, emotional distress and reduced social participation(1, 2). SSc-RP is not easily assessed in the clinical setting, given the intrinsic relationship between RP-symptoms and cold exposure. The episodic and highly personal experience of SSc-RP has led to reliance upon patient-reported outcome (PRO) instruments to capture SSc-RP severity.

Establishing treatment efficacy has been challenging and there are currently no FDA-approved medications for SSc-RP(3). SSc-RP clinical trial endpoints have focussed on a construct of Raynaud's 'attacks', using diary-based methods to record the mean daily frequency and duration of RP symptoms(4, 5). Diary-based approaches typically incorporate a daily assessment of the overall severity and impact of RP symptoms using a single-item scale such as the Raynaud's Condition Score (RCS)(4-6). These clinician-derived instruments were developed without target patient population input and may not fully capture the patient experience of SSc-RP(6-8). Meta-analyses indicate that the benefit of existing vasodilator therapies for SSc-RP on diary-based instruments are modest at best(9, 10).

The Assessment of Systemic sclerosis-associated RAynaud's Phenomenon (ASRAP) questionnaire is a novel PRO instrument for capturing the impact and severity of SSc-RP, that is grounded in the patient experience of SSc-RP. The development, elaboration, refinement and scoring of the ASRAP questionnaire is described elsewhere (11). The present study examines the construct validity and reliability of the ASRAP questionnaire.

Methods

Patient & Public Involvement in the Development of ASRAP questionnaire

The Scleroderma Clinical Trials Consortium (SCTC) Vascular Working Group aimed to develop a novel PRO instrument that captures the severity and impact of SSc-RP, with a conceptual framework grounded in the lived-experience of SSc-RP(2). A provisional 39-item ASRAP item-bank (Supplementary Material 1) was developed with input from a patient insight partner

(JW) and SSc experts. ASRAP items were grounded in the themes/sub-themes identified in an international multicentre qualitative research study of SSc-RP (adopting wording from patient quotations were possible)(1, 2). Linguistic testing and cognitive de-briefing interviews within the target patient population examined respondent burden and ensured the ASRAP instructions and item wording achieved the intended conceptual framework in wording that was comprehensible and minimized ambiguity(11).

ASRAP calibration and scoring

English-speaking SSc patients were enrolled from clinic to an international multicentre ASRAP validation study from seven UK and US scleroderma centres during 2 consecutive winters (November-March, 2019-2020). All patients were aged ≥18 years, fulfilled the American College of Rheumatology/European League Against Rheumatism classification criteria for SSc(12) and had good comprehension of written/spoken English. Pregnant people and/or subjects whose vasodilator medication had changed within 4-weeks of enrolment were excluded (background vasodilator treatment was permitted). Research ethics committee approval was obtained at each site (see statement below) and all patients provided informed written consent. The psychometric approach to refining, calibrating and scoring the ASRAP questionnaire was based on factor analysis and item response theory (IRT) and described fully elsewhere(11). The resulting 27-item long-form (ASRAP) questionnaire and fixed 10-item short form (ASRAP-SF) questionnaire are scored using IRT calibrations on the T-score scale (with a mean of 50, a SD of 10, and a scorable range between 20-80)(11).

Study procedures

Participants completed a baseline 39-item ASRAP questionnaire which includes specific instructions to respondents on which symptoms to consider when choosing their scores (Supplementary Material 1). These instructions were developed with the support of a patient research partner and underwent linguistic testing, expert review and cognitive de-briefing with patients with SSc across UK and US to ensure comprehension (11). The ASRAP instructions specifically request that respondents avoid considering symptoms caused by digital ulcers, skin involvement and/or calcinosis when choosing their scores.

Participants also completed disease-specific and legacy PRO instruments capturing patient measures of SSc-RP disease activity/impact (RP Global Severity 100mm VAS (13)), and relevant domains including pain (Present Pain Intensity Scale (14)), function (Scleroderma Health Assessment Questionnaire (SHAQ)(15) and Duruöz Hand Index (DHI)(16)), cold sensitivity (McCabe Cold Sensitivity Scale(17)) and a 100mm Global Health VAS. Baseline anchor-based assessments of overall severity/impact of SSc-RP over the previous week was collected with responses ranging from 'very mild', 'mild', 'moderate', 'moderately severe', 'severe', 'very severe' or 'unbearable'. We collected information on RP characteritsics (cold sensitivitiy and digital colour changes experienced). Patients were also asked to review 4 different 'patterns' of RP symptoms, ranging from discrete short-lived SSc-RP attacks (pattern A) to persistent digital ischaemic symptoms (pattern D) as described previously (Supplementary material 4)(18). Participants were issued paper copies of the ASRAP questionnaire and additional baseline questionnaires, which they either completed at the time of their clinic visit or returned in a pre-paid envelope.

Participants at all UK sites and two US sites (Michigan and Utah) were issued with the RCS-diary and given verbal/written instructions on its completion over the ensuing week(5, 6). From this, we calculated the mean daily frequency of SSc-RP attacks, mean daily aggregate duration of SSc-RP attacks and mean daily RCS on an 11-point numeric rating scale (0-10) as previously described(5, 6). At 1-week, these participants completed a second ASRAP questionnaire, SSc-RP global severity 100mm VAS(13), SHAQ RP 150mm VAS sub-scale(15), an repeat anchor-based assessment of present overall severity/impact of SSc-RP at week-1 and a retrospective anchor-based assessment of change in overall SSc-RP symptoms since baseline with responses ranging from 'much worse', 'somewhat worse', 'about the same', 'somewhat better', or 'much better'.

Clinical phenotyping

Patient demographics, disease duration (since RP-onset and first non-Raynaud's manifestation), autoantibodies, organ-specific manifestations, co-morbidities and prescribed classes of vasodilator drug treatment were documented using the medical record and/or clinician assessment during the corresponding clinic visit. Physician 100mm VAS for SSc-RP,

global health, and digital ulcers (DU) were completed. The presence of active DU was confirmed on physical examination.

Sample size calculations

The planned IRT calibration and scoring of ASRAP required a large sample size (target 500)(11). For the cross-sectional convergent validity analyses reported here, a sample size >109 participant was considered sufficient to detect modest correlations (0.30) at a significance level of $\alpha<0.05$ (two-tailed), with a power of 0.90. For repeatability analyses, 160 participants was sufficient to detect with 90% power correlations larger than 0.80 at $\alpha<0.05$ (two-tailed). Our target of 250 subjects allowed for considerable attrition in responses at 1-week.

Statistical analysis

Correlation between ASRAP and legacy instruments examining similar/related constructs was assessed using Pearson's rho correlation coefficients. Test-retest repeatability was assessed using intra-class correlation coefficients (ICC; optimal ≥0.8; acceptable ≥0.6). To assess Patient Acceptable Symptom State (PASS), we assigned patients who considered their Raynaud's condition as 'very mild' or 'mild' at week 1 as achieving a PASS, with a PASS cut-off point identified with the 75th percentile estimation. Minimal Clinically Important Difference (MCID) was assessed in those reporting a 1-step improvement between baseline and 1-week (e.g. "moderate" at baseline followed by "mild" at 1-week constituting 'minimal change').

Results

Study population

Four hundred and twenty SSc subjects were enrolled at UK (n=222) and US (n=198) sites and completed at least one ASRAP questionnaire. Full ASRAP questionnaire data was available on 404 subjects (96.0%), indicating excellent feasibility. The demographics and clinical phenotype of the study population conformed to expected distributions with respect to sex (79.7% female), ethnicity (86.4% white), disease subset (58.9% limited), mean age (58.9 years, SD 12.4) The mean disease duration was 15.1 years (SD 12.1), with good representation of

early and established disease (with 126/404, 31.2% enrolled within 5 years of first non-Raynaud's symptom). There was missing data on RP symptom characteristics on 13 subjects (3.2%). Of the remaining 391 subjects, 390 reported that their fingers were sensitive to cold (99.7%) and 384 of these reported digital colour changes (98.2%). The majority of subjects reported cold sensitivity with at least bi-phasic digital colour changes (330/391, 84.4%), with monophasic colour changes in 54 subjects (13.8%). Only six subjects (1.5%) reported current cold sensitivity without any digital colour changes. All subjects were, however, able to report year of Raynaud's onset and all ASRAP items included the term 'Raynaud's'.

Psychometric testing

The mean baseline ASRAP was 50.0 (SD 9.9) with a mean ASRAP-SF of 49.9 (9.4). Correlation between ASRAP and ASRAP-SF was excellent (rho 0.976, p<0.001). The ASRAP and ASRAP-SF questionnaires had excellent internal consistency with Cronbach's α values of 0.918 and 0.899 respectively.

There was strong correlation with legacy retrospective single-item PRO instruments for assessing SSc-RP such as the SHAQ RP VAS and RP VAS (rho 0.648-0.727, p<0.001) (Table 2 and Figure 1). Consistent with our conceptual framework (capturing the severity *and impact* of SSc-RP), the highest correlations with ASRAP were identified with the SHAQ RP-VAS (focussing on extent to which RP interferes with activities of daily living) with rho values of 0.719 and 0.727 for ASRAP and ASRAP-SF respectively (p <0.001). Correlation was lower for diary-based collection of mean daily RCS in the week following ASRAP collection (rho 0.583 and 0.533 for ASRAP and ASRAP-SF respectively, p<0.001). The lowest correlation was identified for 'duration of RP attacks' with (rho 0.272 and 0.258 for ASRAP and ASRAP-SF respectively), with a notable floor effect evident for RP-attack duration (Figure 1). Correlation with RP-attack frequency, another diary-based approach for assessing SSc-RP, was also modest (rho 0.504 and 0.421 for ASRAP and ASRAP-SF respectively, Table 2 and Figure 1).

Correlations between ASRAP and the HAQ-DI were moderate (rho 0.438-0.490), but the higher correlation for the DHI may reflect its focus on hand function (rho values 0.499-0.528), although the DHI was also susceptible to a floor effect in this cohort (Figure1). Pain is typically

the most important physical symptoms of digital ischaemia in SSc-RP and we identified moderate correlation between ASRAP questionnaires and the pain intensity VAS (rho 0.555 and 0.575, p<0.001), which was not unexpected given other SSc organ-specific manifestations can cause pain (e.g. digital ulcers). Similarly, given the heterogeneous nature of SSc, the statistically significant but moderate correlations with the global health 100mm VAS was not unexpected (rho ~0.44, Table 2).

Association between ASRAP scales and patient demographics

Smokers reported significantly higher long-form ASRAP scores, compared to ex-smokers and non-smokers (means 55.39, 51.04 and 48.71 respectively, p=0.005). The same relationship was identified with the ASRAP-SF (means 54.57, 51.20 and 48.47, p=003) and the SHAQ RP-VAS (64.28, 56.44 and 45.79, p=0.030). In contrast, these associations were not observed with the patient global RP-VAS (55.17, 51.01 and 45.89, p=0.112). In contrast, there was no correlation between the patient global RP VAS and either RP duration (rho values of -0.038, p=0.461) or SSc disease duration (rho -0.089, p=0.084).

Association with different patterns of SSc-RP

Consistent with previous work, SSc patients were able to identify with different patterns of SSc-RP with the majority identifying with patterns A (151/404, 37.4%) and B (146/404, 36.1%) and a minority choosing patterns C (76, 18.8%) and D (14, 3.5%) respectively (Supplementary material 4). Long and short-form ASRAP scores increased significantly in magnitude across patterns A-D (p<0.001) Table 3). The same relationship was observed for patient global RP VAS, SHAQ RP VAS and RCS diary parameters, indicating that SSc patients identifying with more persistent background digital ischaemic symptoms have a higher burden of SSc-RP symptoms (Table 3).

Relationship between ASRAP and SSc disease manifestations

The ASRAP and ASRAP-SF scores were significantly higher in patients with a history of DU (52.27 vs. 47.36, p<0.001, and 52.69 vs. 47.02, p<0.001 respectively) (Table 4). A significantly higher SHAQ RP VAS and patient global RP VAS was also found in patients with a history of DU (61.47 vs 41.23, p<0.001 and 51.96 vs. 45.66, p=0.029). RP attack frequency was also

higher in patients with a history of DU (2.97 vs 2.38, p=0.03), whereas no significant differences were identified for RP attack duration or the RCS itself (Table 4). The presence of active DU (48/404, 11.9%) was associated with significantly higher long and short form ASRAP values, alongside patient global RP VAS and SHAQ RP VAS, but with no significant relationship with RCS diary parameters (including the RCS score, Table 4). The presence of digital pitting, meanwhile, was not associated with higher ASRAP or legacy instrument scores for assessing SSc-RP severity (Table 4). There was no relationship between disease subset (limited vs. diffuse) and ASRAP scores. There were significantly higher ASRAP-SF scores in patients with a history of calcinosis (51.17 (SD 9.86) vs. 48.95 (SD 9.10), p=0.045). Similarly, there was a trend for higher ASRAP scores amongst patients with a history of calcinosis (p=0.103), suggesting calcinosis is associated with SSc-RP severity (Table 4). The relationship between ASRAP scores and use of vasodilator therapies was challenging given confounding by indication (patients with more severe vascular manifestations being established on such treatments). Higher ASRAP, patient global RP, SHAQ RP VAS and RCS scores were identified amongst patients receiving phosphodiesterase inhibitors (PDEVi, 120/404 (29.7%)) compared to those not taking a PDEVi. In contrast, the frequency and duration of RP attacks did not differ between patients receiving PDEVi and those not (Table 4). There was no relationship between ASRAP and calcium channel blocker use.

Relationship between ASRAP and physician-based assessment

There was a comparatively moderate relationship between ASRAP and the physician RP VAS assessment (Pearson's rho 0.395, p<0.001). This was not unexpected, given the inherently personal impact of SSc-RP on how patients 'feel' and 'function'. Unsurprisingly, the relationship between the patient and physician global RP VAS scores was also modest (rho 0.378, p<0.001). There was a weaker correlation between physician RP VAS and the traditional RCS diary parameters, with Pearson rho values for average daily frequency of attacks, average duration of attacks and the average RCS of 0.301 (p<0.001), 0.181 (p=0.015), and 0.309 (p<0.001) respectively. This suggests ASRAP may more successfully capture the experiences that influence physician-based assessment of SSc-RP than diary-based approaches to assessing SSc-RP symptom burden. There were statistically significant but comparatively modest associations between ASRAP and both the physician global health VAS

(rho 0.314, p<0.001) and physician global DU 100mm VAS (rho 0.262, p<0.001). In comparison, there was no relationship between physician global health VAS and the average number of attacks, average duration of attacks and average RCS with rho values of 0.09 (p=0.218), -0.059 (p=0.431), and 0.178 (p=0.016) respectively.

Repeatability

Adequately completed ASRAP questionnaires at week-1 were available for 180 subjects. The mean ASRAP and ASRAP-SF at 1 week was 48.64 (SD 9.45) and 48.65 (8.87) respectively, compared to 50.01 (9.87) and 49.87 (9.35) respectively at baseline. The intra-class coefficient for the long-form ASRAP was excellent at 0.884 (95% CI 0.847-0.912, p<0.001). The ASRAP-SF ICC was also excellent at 0.839 (95% CI 0.788-0.878, p<0.001). Of 223 subjects who completed the week-1 assessment anchors, 167 (74.9%) reported their SSc-RP symptoms having been stable over the preceding week, with 29 (13.0%) reporting worsening of their SSc-RP symptoms and 27 (12.1%) reporting improvement. When the ASRAP repeatability analysis was limited to patients reporting stable RP symptoms (n=135), the ICC improved to 0.891 (95% CI 0.850-0.921, p<0.001) and 0.848 (95% CI 0.792-0.891, p<0.001) for the ASRAP and ASRAP-SF respectively (Figure 2C & 2D). In contrast, repeatability for legacy instruments was surprisingly lower with ICCs of 0.673 (95% CI 0.578-0.750, p<0.001), and 0.687 (95% CI 0.596-0.762, p<0.001) for the RP patient global assessment 100mm VAS and SHAQ RP 150mm VAS respectively.

Patient acceptable symptom state (PASS)

Patients considering themselves in an acceptable state at baseline, defined as reporting their RP symptoms to be 'very mild' and/or 'mild' (n=99), had a significantly lower ASRAP than those whose RP symptoms were 'moderate' or worse (n=291) with lower mean long-form ASRAP scores (40.29 vs. 53.29, p<0.001) and short-form ASRAP scores (41.19 vs. 52.88, p<0.001). There were also significant differences between these groups (very mild/mild vs. moderate or worse) for baseline patient global RP severity 100mm VAS (16.52 vs. 59.16, p<0.001), SHAQ RP VAS (13.05 vs. 63.71, p<0.001), mean daily frequency of RP attacks (1.26 vs. 3.14, p<0.001), mean aggregate daily duration (26.38 vs. 67.61 minutes, p=0.003) and mean daily RCS score (1.24 vs. 4.02, p<0.001). The cut-off value for PASS (75th percentile of

these patients considering themselves to have an acceptable state of SSc-RP at baseline) for ASRAP and ASRAP-SF questionnaires was estimated to be 45.34 and 45.77 respectively, which are about half a standard deviation below the mean.

ASRAP responsiveness

Our study was not designed to assess sensitivity to change but a preliminary assessment of responsiveness for ASRAP was undertaken by examining the mean change in ASRAP for patients who reported a 1-step (or more) improvement in RP symptoms based on anchor-based assessments of change in RP symptoms over preceding week (presumably owing to seasonal weather variation). Amongst 18 subjects reporting a 1-step or more improvement in SSc-RP symptoms on anchor assessment between baseline and week 1, there was a statistically significant improvement in both the ASRAP score (mean difference of -5.19, 95%CI 2.51-7.87, p=0.001) and ASRAP-SF score (mean difference of -4.46, 95%CI 1.92-7.00, p=0.002). For those reporting only a 1-step improvement at follow up assessment (n=10), the preliminary MCID estimates (based on a 1-step change alone) were 4.17 (95% CI 0.53-7.81, p=0.029) and 3.76 (95%CI -0.15-7.67, p=0.058) for ASRAP and ASRAP-SF respectively, although low patient numbers limited the power for responsiveness analyses and our sample size was insufficient to run formal receiver operating characteristic curve analyses for formal MCID estimates.

Discussion

The ASRAP questionnaire is a feasible, valid and reliable novel PRO instrument for assessing the severity and impact of SSc-RP. We have confirmed good convergent validity with legacy instruments for assessing SSc-RP such as the patient global RP VAS and SHAQ RP VAS. Given the comparatively poor performance of existing instruments in demonstrating treatment efficacy in SSc-RP clinical trials, we were reassured that ASRAP had positive, but only moderate, correlation with existing diary-based methods of capturing SSc-RP 'attack' frequency and duration (and the RCS itself). Capturing Raynaud's 'attack' characteristics may still be important in SSc-RP clinical trials and ASRAP complements these existing diary-based approaches for assessing SSc-RP severity.

Validation of the ASRAP questionnaire

Given the importance of pain and impaired hand function in the lived experience of SSc-RP, it was encouraging to also identify good correlation between ASRAP and legacy instruments for assessing pain and disability. Reassuringly, correlations were higher between ASRAP and instruments focussing on hand function compared with overall disability (capturing themes of mobility and reach etc.). The lowest correlations between ASRAP and legacy instruments was for the diary-based assessment of SSc-RP attack frequency and duration, which together have been the most widely adopted endpoints in SSc-RP clinical trials of the last 30 years. A high correlation between ASRAP and these outcome measures might have been undesirable given our aspiration to develop a novel instrument for use in SSc-RP clinical trials and the difficulty in establishing treatment efficacy using these endpoints(3, 9, 10). There was also low correlation between physician assessment of SSc-RP and ASRAP (and legacy PRO instruments for assessing SSc-RP) highlighting the challenges in undertaking and interpreting physician-based assessments of a uniquely personal construct such as SSc-RP, that cannot be easily clinically assessed. The identification of higher ASRAP scores in smokers and those with previous DU, active DU and calcinosis (not identified using RCS diary parameters), was further evidence of strong construct validity of ASRAP; given these features are generally associated with more severe digital vasculopathy(19).

The ASRAP item-bank is grounded in the lived experience of SSc-RP with a strong focus on how patients 'feel' and 'function', which may not align strongly with diary-based approaches to assessing 'attack' characteristics. For example, a patient experiencing a solitary short-lived but severe SSc-RP attack may have a worse overall symptom burden than a patient experiencing more frequent but less intrusive SSc-RP attacks. The ASRAP questionnaires has advantages over existing diary-based approaches to assessing SSc-RP. Firstly, the instrument structure and item content, provides greater granularity on factors influencing SSc-RP severity than single-item scales such as RCS and may enable more nuanced analyses exploring the impact of therapeutic intervention on different domains of SSc-RP symptom burden (e.g. physical symptoms vs. emotional impact). Diary-based approaches do not consider the considerable efforts of patients to prevent and ameliorate SSc-RP symptoms(8, 20).

Furthermore, a focus on RP 'attacks' does not consider more persistent background digital ischaemic symptoms that could accompany progression of the obliterative microangiopathy of SSc(18, 20, 21). The statistically significant associations between ASRAP scores and distinct patterns of SSc-RP suggest evolution of SSc-RP symptoms might be important in SSc. Our analysis focused on the target patient population likely to be applied in future SSc-RP clinical trials. Whilst almost a third of our cohort had 'early' disease (within 5 years of first non-RP symptom), further work should examine the severity and burden of SSc-RP symptoms in patients fulfilling criteria for *very* early diagnosis of SSc, given the importance of RP amongst such patients (22).

The 1-week recall-period adopted for ASRAP responses may facilitate shorter clinical trials (allowing treatment efficacy to be assessed as early as 1-week), compared with prospective 2-week diary-based approaches to quantifying SSc-RP attack burden; whilst also negating the need for a 'run-in' period prior to randomisation. This will be an important mechanism for reducing the 'placebo effect' noted in many previous clinical trials of SSc-RP; many of which have enrolled patients in winter with an assessment of efficacy in spring, potentially leading to significant improvements in SSc-RP symptoms in both active and control arms(3, 23).

We have confirmed excellent repeatability at 1-week, particularly amongst patients with stable SSc-RP symptoms. We have undertaken preliminary analyses to establish thresholds-of-meaning for the ASRAP questionnaire, including estimates of PASS and MICD thresholds. In patients reporting an improvement of SSc-RP symptoms during the 1-week study, preliminary analyses suggest the ASRAP questionnaire is responsive to change, although interventional studies should examine responsiveness more fully.

The international multicentre ASRAP validation study is, to our knowledge, the largest study to focus on SSc-RP undertaken to date and benefits from a representative cohort of SSc patients enrolled from large SSc centers across diverse geographic, cultural and ethnic backgrounds. The ASRAP questionnaire is grounded in an earlier study that applied a more rigorous sampling framework to ensure representation and content validity within diverse ethnic groups(2). ASRAP has been validated within an English-speaking target patient

population, but the items have been developed to minimize ambiguity and meet accepted criteria for optimal translatability into non-English languages. Work is underway to develop and test non-English versions of the ASRAP questionnaire. We restricted enrolment of patients to winter, but longitudinal studies shall examine the relationship between seasonal variation and ASRAP scores. The responsiveness of ASRAP to therapeutic intervention and convergent validity with non-invasive methods for objectively quantifying digital perfusion shall form the focus of future work.

Conclusions

We have devised a novel PRO instrument for assessing the severity and impact of SSc-RP. Regulators increasingly seek evidence that novel interventions result in benefits to how patients 'feel' and 'function'. By developing an instrument grounded in the patient experience of SSc-RP, we have ensured ASRAP has strong content validity for capturing the impact of SSc-RP in terms of how patients 'feel' and 'function'. We have also demonstrated that ASRAP is feasible, repeatable and has important components of construct validity. In addition to incorporation of ASRAP in clinical trials, the ASRAP-SF provides clinicians and investigators with an instrument for use in clinical practice and patient registries to capture much-needed practice-based evidence on the comparative efficacy of different interventions.

CRediT Author Statement

John D Pauling: Conceptualization, Methodology, Investigation, Data Curation, Writing - Original Draft, Visualisation, Supervision and Project Administration; Lan Yu: Data Curation, statistical analysis, Writing- Reviewing and Editing; Tracy M. Frech: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing; Ariane L Herrick: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing; Laura K Hummers: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing; Ami Shah: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing; Christopher P Denton: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing; Lesley Ann Saketkoo: Conceptualization, Methodology, Investigation, Writing- Reviewing and Editing; Jane Withey; Patient Research Partner - including development and refinement of ASRAP item

bank; Dinesh Khanna: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing; Robyn T Domsic: Conceptualization, Methodology, Investigation, Data Curation, Writing- Reviewing and Editing.

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Competing Interests Statement

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Data sharing statement

De-identified data from the ASRAP study will be made available upon reasonable request to the study team.

Ethical approval information, institution and number(s)

The study protocol received ethics committee approval at all sites. UK-wide multicentre approval was obtained for Bath, London and Manchester (19/LO/0155, IRAS Project ID: 257368). IRB approval was obtained at US sites comprising Pittsburgh (xxx), Michigan (xxx), Johns Hopkins (xxx) and Salt Lake City (xxxx).

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Supplementary Material 1: ASRAP questionnaire (Original 39-item questionnaire)

Supplementary Material 2: The 27-item ASRAP questionnaire

Supplementary Material 3: The 10-item short-form ASRAP questionnaire

Supplementary Material 4. Raynaud's phenomenon symptom characteristics.

Table 1. Clinical phenotype of ASRAP Validation Study Cohort

Variable	All (n=404)	UK (n=216)	US (n=188)	P value
Mean age (±SD)	58.9 (12.4)	59.5 (12.8)	58.4 (11.9)	0.388
Sex				0.957
Female (n, %)	322 (79.7%)	165 (76.4%)	157 (83.5%)	
Male	62 (15.3%)	32 (14.8%)	30(16.0%)	
Not reported	20 (5.0%)	19 (8.8%)	1 (0.5%)	
Ethnicity (n, %)				0.107*
Asian	12 (3.0)	9 (4.2)	3 (1.6)	
Black	17 (4.2)	5 (2.3)	12 (6.4)	
Hispanic	2 (0.5)	2 (0.9)	0 (0.0)	
Mixed	4 (1.0)	2 (0.9)	2 (1.1)	
White	349 (86.4)	183 (84.7)	166 (88.3)	
Other	6 (1.5)	2 (0.9)	4 (2.1)	
Not reported	14 (3.5)	13 (6.0)	1 (0.5)	
Smoking status				0.288
Current	18 (4.5%)	11 (5.1%)	7 (3.7%)	
Ex-smoker	150 (37.1%)	84 (38.9%)	66 (35.1%)	
Never	222 (55.0%)	108 (50.0%)	114 (60.6%)	
Missing	14 (3.5%)	13 (6.0%)	1 (0.5%)	
Raynaud's duration				
Mean (years, SD)	15.1 (12.1)	16.0 (13.0)	14.1 (10.9)	0.111
Time since 1st non-RP symptom				
Mean (SD)	11.52 (9.6)	11.3 (9.6)	11.8 (9.6)	0.599
Disease subtype				<0.001
Limited	238 (58.9%)	145 (67.1%)	93 (49.5%)	
Diffuse	141 (34.9%)	59 (27.3%)	82 (43.6%)	
sine	15 (3.7%)	3 (1.4%)	12 (6.4%)	
Missing	10 (2.5%)	9 (4.2%)	1 (0.5%)	
History of digital ulcers				0.422
No	178 (44.1%)	95 (44.0%)	83 (44.1%)	
Yes	170 (42.1%)	98 (45.4%)	72 (38.3%)	
Missing	56 (13.9%)	23 (10.6%)	33 (17.6%)	
History of calcinosis	265 (65.6%)	132 (61.1%)	133 (70.7%)	0.030
Puffy fingers	104 (25.7%)	64 (29.6%)	40 (21.3%)	0.055
Pitting scars	118 (29.2%)	57 (26.4%)	61 (32.4%)	0.182
Telangiecetasias	295 (73.0%)	153 (70.8%)	142 (75.5%)	0.289
Abnormal nailfold	237 (58.7%)	82 (38.0%)	155 (82.4%)	<0.001
Pulmonary Hypertension	47 (11.6%)	27 (12.5%)	20 (10.6%)	0.560
Interstitial Lung Disease	106 (26.2%)	52 (24.1%)	54 (28.7%)	0.289
SSc antibody (n, %)				
Centromere	160 (39.6%)	94 (43.5%)	66 (35.1%)	0.085
Scl-70	70 (17.3%)	38 (17.6%)	32 (17.0%)	0.880
RNA Pol III	70 (17.3%)	25 (11.6%)	45 (23.9%)	0.001
U3-RNP	3 (0.7%)	2 (0.9%)	1 (0.5%)	0.645
Th/To	8 (2.0%)	4 (1.9%)	4 (2.1%)	0.843
PM/Scl	13 (3.2%)	11 (5.1%)	2 (1.1%)	0.022
U1-RNP	16 (4.0%)	8 (3.7%)	8 (4.3%)	0.777
Ro-52	17 (4.2%)	16 (7.4%)	1 (0.5%)	<0.001
Unspecified	69 (17.1%)	31 (14.4%)	38 (20.2%)	0.118
Negative	6 (1.5%)	5 (2.3%)	1 (.5%)	0.222
Vasodilators (n, %)				
CCB	156 (38.6%)	74 (34.3%)	82 (43.6%)	0.054
ARB	53 (13.1%)	37 (17.1%)	16 (8.5%)	0.010
ACEi	24 (5.9%)	13 (6.0%)	11 (5.9%)	0.943
ERA	38 (9.4%)	29 (13.4%)	9 (4.8%)	0.003
PDEVi	120 (29.7%)	79 (36.6%)	41 (21.8%)	0.001
α-antagonist	5 (1.2%)	1 (0.5%)	4 (2.1%)	0.131
SSRI	38 (9.4%)	18 (8.3%)	20 (10.6%)	0.429

Variable	All (n=404)	UK (n=216)	US (n=188)	P value
Prostanoid	38 (9.4%)	32 (14.8%)	6 (3.2%)	<0.001

All analyses are unpaired t tests or chi square analyses respectively, except * which used a Fisher's exact test given 6 cells with n<5.

ACEi, Angiotensin Converting Enzyme inhibitor; ARB, Angiotensin Receptor Blocker; CCB, Calcium Channel Blockers; ERA, Endothelin Receptor Antagonist; PDEVi, IQR, Interquartile Range; Phosphodiesterase V inhibitors; SD, Standard Deviation; SSRI, Selective Serotonin Reuptake Inhibitor

Table 2. Correlation between 27-item long-form and 10-item short form ASRAP questionnaire with legacy instruments for assessing SSc-RP and relevant associated domains

Domains		RP attacks		RP severity & impact global assessments			Cold sensitivity	Function		Pain	Global health
Instruments		Frequency	Duration	RCS	Scleroderma HAQ-RP VAS	RP-global severity VAS	CSS total	HAQ-DI	DHI total	Pain Intensity VAS	Global Health VAS
ASRAP	Pearson Correlation	0.504*	0.272*	0.583*	0.719*	0.663*	0.513*	0.438*	0.499*	0.555*	0.427*
	N	204	193	197	385	390	363	379	374	330	390
ASRAP-SF	Pearson Correlation	0.421*	0.258*	0.533*	0.727*	0.648*	0.490*	0.490*	0.528*	0.575*	0.444*
	N	199	188	193	365	370	344	359	356	313	370

* Correlation is significant at p<0.001 level (2-tailed)

HAQ-DI, Health Assessment Questionnaire-Disability Index; CSS, Cold Sensitivity Scale; DHI, Duruöz Hand Index; RCS, Raynaud's Condition Score; RP, Raynaud's Phenomenon; VAS, Visual Analogue Scale'

Figure 1. Correlation between ASRAP and legacy instruments for assessing SSc-RP. Scatterplots annotated with line of best fit and Pearson rho values demonstrating correlation between ASRAP (y axis on each plot) and A, RP global severity 100mm VAS; B, Duruöz Hand Index; C, Mean daily aggregate duration of RP attacks and D, Mean daily frequency of RP attacks

HAQ, Health Assessment Questionnaire; RP, Raynaud's phenomenon, VAS, Visual Analogue Scale,

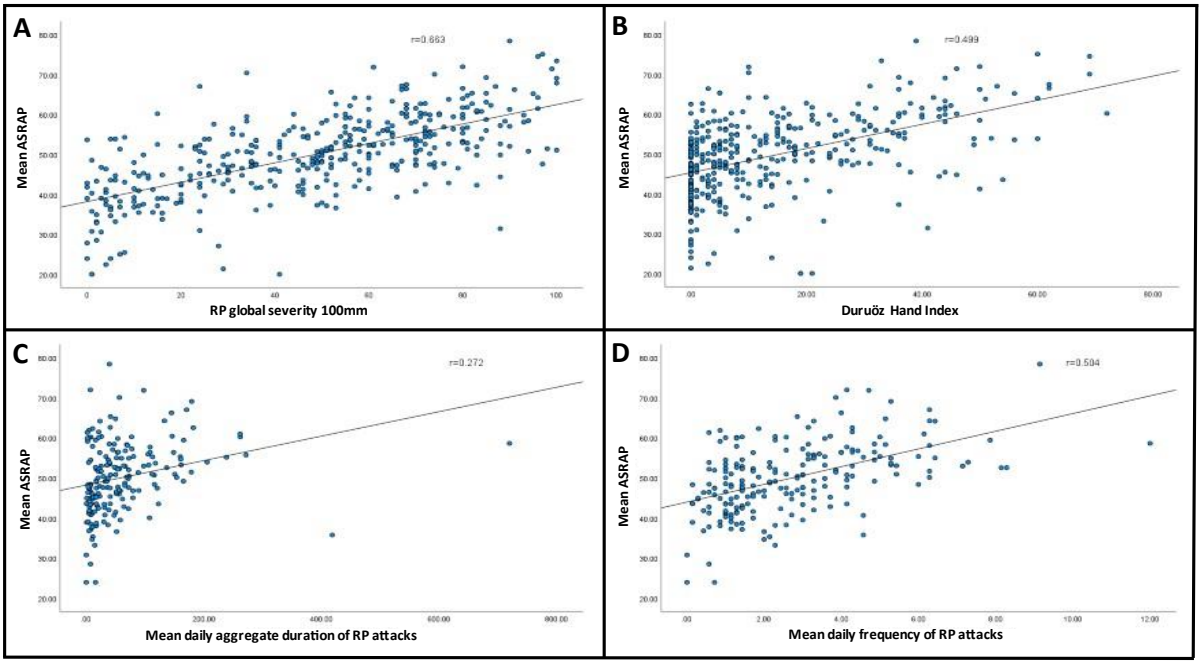

Table 3. Relationship between patterns of SSc-RP characteristics and baseline ASRAP questionnaires and legacy instruments for assessing SSc-RP impact and severity

See Supplementary Figure 4 for images depicting patterns of RP.

Pattern	**A**	**B**	**C**	**D**	**P value on ANOVA**
Description	Intermittent short-lasting attacks of Raynaud's with the circulation in the fingers always returning to normal in between attacks	Intermittent longer-lasting attacks of Raynaud's with the circulation in the fingers not always returning completely back to normal (warm and pink) in between attacks.	Intermittent attacks of acute Raynaud's but the fingers feel cold with poor blood supply the majority of the time and rarely return to feeling normal.	The fingers are cold and discoloured all of the time. It is almost impossible to appreciate distinct attacks of Raynaud's as the blood supply to the fingers appears to be permanently reduced.	Not applicable
Number (%)	151 (37.4)	146 (36.1)	76 (18.8)	14 (3.5)	
ASRAP, Mean (SD)	44.59 (8.96)	51.78 (7.88)	55.57 (8.29)*	61.45 (9.13)	<0.001
Short form ASRAP	44.7 (8.56)	51.41 (7.85)	55.44 (7.81)**	60.28 (8.80)	<0.001
Patient Global RP 100mm VAS	33.01 (23.48)	53.56† (23.36)	64.51†† (23.86)	72.86 (24.90)	<0.001
SHAQ RP 150mm VAS	25.24 (30.61)	57.05 (40.11)	78.39 ‡ (41.26)	109.14 (41.30)	<0.001
Average number of attacks	2.05 (1.54) ***	2.93 (1.69) ‡	3.72 (2.70) ^	3.84 (2.84) ¶	<0.001
Average durations of attacks	32.98 (36.97) ±	65.71 (58.89) ‡	96.19 (138.71) ^	91.20 (69.80) ¶	<0.001
Average RCS scores	2.38 (1.96) §	3.89 (2.83) ‡	4.28 (2.62) ^	5.84 (3.53)	<0.001

All values presented as Mean (SD) unless otherwise stated

P<0.001 for all pairwise comparisons on multiple comparisons with Bonferroni correction with the exception of:

*p=0.01 vs B and p=0.102 vs D; **p=0.006 vs B and p=0.263 vs D

† p=0.022 vs D and p=0.007 vs C; †† p=1.00 vs D;

‡ p=0.03 vs D; *** p=0.029 vs. B

¶ p>0.05 vs. A, B and C ‡ p>0.05 vs. C and D; ^ p>0.05 vs. B and D

± p=0.06 vs. B; § p=0.002 vs. B and p=0.003 vs D,

Table 4. Impact of disease manifestations on ASRAP and legacy instruments

All values expressed as mean (SD); * RCS diary data available for up to 198 subjects

		Number (%)	Long-form ASRAP	Short-form ASRAP	Pt Global RP severity 100mm VAS	SHAQ RP 150mm VAS	RP attack frequency *	RP attack duration *	RCS*
Disease subset	Limited	238 (58.9)	49.35 (9.91)	49.11 (9.21)	47.92 (27.22)	47.77 (42.82)	2.65 (1.98)	62.64 (87.52)	3.52 (2.85)
	Diffuse	141 (34.9)	51.22 (9.75)	51.37 (9.41)	49.44 (27.38)	56.50 (43.87)	2.94 (2.03)	52.47 (56.36)	3.36 (2.26)
	Sine	15 (3.7)	47.58 (10.13)	46.60 (9.54)	46.27 (25.18)	44.07 (51.37)	2.83 (1.87)	64.37 (70.87)	2.29 (1.69)
History of DU	Yes	170 (42.1)	52.27 (9.37) †	52.69 (8.92) †	51.96 ‡ (26.84)	61.47† (44.75)	2.98 (1.91) ††	64.92 (76.53)	3.76 (2.34)
	No	178 (44.1)	47.36 (9.93)	47.02 (9.14)	45.66 (26.28)	41.23 (39.31)	2.38 (1.70)	48.81 (47.57)	3.04 (2.81)
Telangiectasia	Yes	295 (73.0)	49.54 (10.17)	49.47 (9.43)	47.10 (26.93)	49.43 (43.20)	2.64 (2.01)	55.22 (76.17)	3.37 (2.69)
	No	109 (27.0)	51.29 (8.93)	50.96 (9.13)	51.74 (27.57)	54.80 (45.40)	3.06 (1.86)	69.53 (82.76)	4.00 (2.80)
Pitting scars	Yes	118 (29.2)	50.85 (10.18)	50.75 (9.74)	47.24 (28.63)	52.96 (45.75)	3.03 (2.27)	79.44 (120.05)	3.68 (2.34)
	No	286 (70.8)	49.67 (9.73)	49.52 (9.20)	48.72 (26.54)	49.90 (42.98)	2.63 (1.86)	51.05 (53.95)	3.45 (2.86)
Calcinosis	Yes	106 (26.2)	50.99 (10.92)	51.17 (9.86) †	47.66 (27.83)	55.55 (45.74)	2.85 (2.15)	51.34 (55.48)	3.72 (2.56)
	No	265 (65.6)	49.14 (9.41)	48.95 (9.10)	47.63 (26.94)	47.81 (42.01)	2.59 (1.73)	58.11 (65.09)	3.22 (2.67)
Active DU	Yes	48 (11.9)	56.29 (9.58) †	56.25 (9.45) †	59.49 ^ (25.59)	77.32 † (44.62)	3.09 (2.05)	57.39 (52.89)	4.06 (2.59)
	No	322 (79.7)	48.79 (9.72)	48.56 (9.09)	46.68 (27.05)	46.10 (41.95)	2.66 (1.85)	55.84 (63.01)	3.34 (2.64)
Treatment with PDEVi	Yes	120 (29.7)	52.75 † (10.13)	52.54† (9.39)	55.72 † (24.57)	64.92 † (45.50)	2.89 (2.30)	73.71 (112.33)	4.32 ¶ (3.11)
	No	284 (70.3)	48.86 (9.54)	48.76 (9.13)	45.14 (27.60)	44.87 (41.71)	2.68 (1.86)	53.40 (61.48)	3.24 (2.53)

† p<0.001 vs no disease manifestation/treatment; †† p=0.03 vs no disease manifestation

Validation of the ASRAP questionnaire

‡ p=0.029 vs no history of DU; ˆ p=0.003 vs no active DU; ¶ p=0.015 vs no PDEVi use

Figure 2. Relationship between ASRAP scores and patient factors and repeatability of ASRAP at 1 week.

A &B; Box -plots demonstrating distribution of ASRAP scores amongst A, smokers vs. non-smokers; B, active DU at baseline vs. no active DU;

C & D, Bland-Altman plots annotated with intra-class coefficients for assessments at baseline and 1-week for C, ASRAP questionnaire all patients; and D, ASRAP-SF questionnaire limited to those patients reporting stable RP symptoms.