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ORIGINAL ARTICLE

Evaluation of Test Characteristics for Outcome Measures Used in Raynaud's Phenomenon Clinical Trials

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Objective. **Randomized controlled trials (RCTs) in Raynaud's phenomenon (RP) have shown conflicting efficacy data. Also, there is no consensus on the outcome measures that should be used. Our objectives were to assess the reliability of individual core set measures used in 3 RCTs, evaluate the placebo response for individual core set measures, and determine if a composite of individual core set measures will decrease the placebo response, which may improve our ability to see treatment effects in future trials.**

Methods. **We analyzed core set measures from 249 patients in the placebo-treated groups from 3 RCTs. Core set measures analyzed included the Raynaud's Condition Score (RCS); patient and physician assessment of RP; pain, numbness, and tingling during an RP attack; average number of attacks/day; and duration of attacks. Intraclass correlation coefficients (ICCs) were calculated during the run-in period to the RCTs.**

Results. **ICCs of ≥0.70 were observed for the RCS, attack symptoms, and average attacks/day. A high placebo response rate was observed for all individual core measures except the duration of attacks. For the RCS, the placebo response ranged from 56% with ≥10% improvement to 19.5% with ≥60% improvement. In contrast, placebo response rates of 10–20% were observed when several core set measures were combined to develop a composite score.**

Conclusion. **Outcome measures used in RCTs of RP are associated with marked variability. A combination of outcome measures is associated with low placebo responses. Future studies are needed to assess if a composite score will be able to differentiate placebo from an effective agent.**

INTRODUCTION

Raynaud's phenomenon (RP) is a condition where there is vasospasm of blood vessels, caused by an imbalance of vasoconstricting and vasodilating factors, resulting in decreased blood flow in the extremities, causing anoxia, paroxysmal pallor, and/or cyanosis. This recurrent ischemia can eventually result in loss of function of the fingers or toes and in extreme cases, gangrene or even amputation (1). Primary RP is generally thought to be induced (e.g., cold, emotions), whereas secondary RP tends to be associated with other diseases that have endothelial abnormalities (e.g., systemic sclerosis [SSc]), but can be exacerbated by factors known to precipitate primary RP. Although the prevalence of secondary RP is difficult to characterize, since it depends on the underlying disorder, prevalence rates of primary RP have been reported to be 11% in women and 8% in men in the US, with yearly incidence rates of 2.2% and 1.5%, respectively (2). RP is usually associated with a detrimental effect on day-to-day activities, and secondary RP is an important contributing factor for developing digital ulcers and ischemia (2).

Previous clinical trials have used different core set measures to assess efficacy and have included patient-reported frequency and duration of RP attacks, RP attack symptoms (such as pain, numbness, and tingling), the Raynaud's Condition Score (RCS), and patient and physician global assessments of RP. These studies have differed in the outcome measures used and the primary outcome measure specified. This is reminiscent of the 1980s, when rheumatoid arthritis (RA) trials were being conducted with a lack of consensus on a group of core set outcome measures to

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Significance & Innovations

- Outcome measures currently used in Raynaud's phenomenon clinical trials show marked intrarater variability and are associated with a high placebo response in an analysis of 3 large randomized controlled trials.
- A composite index of the individual outcome measures is associated with a reduction in the measurement variability and a lower placebo response.

assess efficacy. The lack of uniform outcome measures impedes drug development and hampers the meta-analysis to assess efficacy.

In this study, our objectives were to 1) assess the reliability of individual core set measures used in randomized controlled trials (RCTs) of RP, 2) evaluate the placebo response for individual core set measures in RCTs, and 3) determine if a composite of individual core set measures will decrease the placebo response. We used the placebo data from 3 large RCTs that assessed efficacy using a novel preparation of nitroglycerin in patients with primary and secondary RP.

PATIENTS AND METHODS

Patients. We analyzed the placebo-treated groups from 3 RCTs (MediQuest Therapeutics). No patient participated in more than 1 trial. Data were collected from a total of 249 placebo-treated patients with primary or secondary RP conducted in the US during the period 2006–2008. All types of secondary RP patients were included in the 3 studies. Each patient with secondary RP was then identified by the type of primary disease; the majority of the patients had SSc.

Clinical trial descriptions. Study 05-002 (ClinicalTrials.gov identifier: NCT00266669) was a multicenter, placebo-controlled RCT enrolling 219 subjects with a clinical diagnosis of primary RP or secondary RP due to a connective tissue disease, with 108 assigned to the placebo group (3). The subjects discontinued vasodilator therapies for 2 weeks, followed by a 2-week single-blind placebo run-in phase to assess disease severity. Those with at least 5 RP attacks during a 7-day period entered the 4-week double-blinded portion of the study. The subjects were randomly assigned to receive placebo or 0.9% MQX-503, a microemulsion formulation of topical nitroglycerin for rapid local delivery with less systemic side effects, and were instructed to apply the gel immediately before or within 5 minutes of an RP event (maximum of 4 applications daily). The subjects used an electronic diary to record each gel application and/or RP event. Each day, the subjects recorded an RCS using a visual analog scale (VAS) from 0–10, where 0 = no difficulty with RP and 10 = extreme difficulty with RP, and a composite self-assessment of the severity of RP rated on a VAS from 0–10, where 0 = no attacks and 10 = severe attacks. The primary outcome was the change in the mean RCS at the target week (the treatment week that matched the run-in period in terms of ambient temperature) compared to baseline (run-in period).

Study 06-004/5 (ClinicalTrials.gov identifier: NCT004-19419) was a randomized double-blind crossover study in patients with moderate to severe primary RP or secondary RP due to a connective tissue disease that enrolled 110 patients (57 randomized to the placebo group and 53 randomized to the MQX-503 group). The subjects discontinued vasodilator therapy for 2 weeks, followed by a 2-week placebo run-in period to assess disease activity. This was followed by 6 weeks of treatment in a crossover design: 3 weeks of receiving an active drug followed by 3 weeks of receiving placebo versus 3 weeks of receiving placebo followed by 3 weeks of receiving an active drug. The subjects were then followed for 1 week after the last treatment visit. The primary outcome was to assess changes in the RCS scores. The subjects used an electronic diary to record each treatment and/or RP event. Each day, the subjects recorded the RCS and self-assessment of the RP severity.

Study 07-005 (ClinicalTrials.gov identifier: NCT005-77304) was a randomized double-blind crossover study that recruited a total of 164 patients with moderate to severe primary RP or secondary RP due to a connective tissue disease, with 84 assigned to the placebo group. The subjects were allowed to continue vasodilator therapy at a stable dose. There was a 2-week run-in period to evaluate baseline disease activity. Subjects were given pouch applicators of either the nitroglycerin preparation or placebo for use on both hands up to 5 minutes prior to an anticipated RP attack or up to 5 minutes after the beginning of an actual attack. The patients were limited to 4 applications daily, with at least 2 hours between applications. The primary outcome was the change in the RCS scores. The subjects used an electronic diary to record each gel application and/or RP event. Each day, the subjects recorded the RCS and self-assessment of the severity of RP.

Core set measures analyzed in 3 RCTs. Eight core set measures were assessed from the patients in these 3 studies, including physician assessment of RP (0–100 VAS) and the following patient-reported outcome measures: the RCS (0–10 VAS); patient assessment of RP (0–100 VAS); pain, numbness, and tingling with each attack (0–100 VAS); average number of attacks per day; and duration of attacks. Daily patient logs of RP attacks were used to compute the average number of attacks per day; the average duration of attacks; the daily averages of patient-reported pain, numbness, and tingling associated with each reported attack; and a daily RCS. Patient and physician assessments of RP were recorded weekly. Daily averages were used to compute weekly averages for the period between physician visits, and the weekly averages were averaged for the run-in period and for the treatment period. The percent improvement between the run-in and treatment periods was calculated for 8 core set measures.

Statistical analysis. The reliability of the outcome measures between the run-in period and treatment periods was

assessed using the standard definition of intraclass correlation coefficient (ICC):

$$ICC = \frac{\sigma_{\alpha}^2}{\sigma_{\alpha}^2 + \sigma_{\varepsilon}^2}$$

where σ_{α}^2 = the between-subject variation and σ_{ε}^2 = the within-subject variation. The ICC was assessed during the run-in period before the patients were randomized to their group. Our hypothesis was that if the outcome measures are reliable, they should not differ appreciably between the run-in and treatment periods, and the ICC should be high. An ICC of ≥0.70 was considered satisfactory for group comparisons (4).

Also, for the current analysis, the pain, numbness, and tingling symptoms of RP attacks had high correlation coefficients (range 0.77–0.78), and were grouped together into attack symptoms by selecting the percent improvement of the outcome with the highest degree of improvement. This resulted in 6 individual core set measures. We also assessed preliminary definitions of improvement and required ≥X% improvement in Y of the 6 variables, where X was set at 10%, 20%, 30%, 40%, 50%, and 60% and Y was set as 2, 3, 4, 5, or 6 variables, similar to the analysis performed by Paulus et al (5).

RESULTS

Patient characteristics. A total of 249 patients receiving placebo were included in the analysis. The mean ± SD age of the subjects in the 3 RCTs was 47.5 ± 12.4 years, 92% were women, 80% were non-Hispanic whites, and 53% had secondary RP (Table 1). Baseline scores for the outcome measures are shown in Table 1. There were no baseline differences in the demographics between primary RP versus secondary RP groups. In comparing baseline scores

Table 1. Baseline characteristics of the study participants*

	All patients (n = 249)	Secondary RP (n = 132)	Primary RP (n = 117)
Age, mean ± SD years	47.5 ± 12.4	49.2 ± 11.1	45.5 ± 13.4
Female sex, no. (%)	230 (92.4)	124 (93.9)	106 (90.6)
Race, no. (%)			
White	200 (80.3)	98 (74.2)	102 (87.2)
African American	20 (8.0)	15 (11.4)	5 (4.3)
Hispanic	10 (4.0)	5 (3.8)	5 (4.3)
Asian/Pacific Islander	14 (5.6)	10 (7.6)	4 (3.4)
Other	5 (2.0)	4 (3.0)	1 (0.9)
Baseline score, %			
Patient assessment of RP (0–100 VAS)			
N	249	132	117
Mean ± SD	53.6 ± 17.6	54.1 ± 17.3	53 ± 17.9
Physician assessment of RP (0–100 VAS)			
N	249	132	117
Mean ± SD	48.2 ± 18.7	48.5 ± 19.1	47.8 ± 17.9
Attack symptoms (range 0–100)			
N	215	117	98
Mean ± SD	34.6 ± 23.0	31.4 ± 22	38.6 ± 23.4
Pain (range 0–100)†			
N	223	120	103
Mean ± SD	33.1 ± 23.3	29.4 ± 22.7	37.3 ± 23.4
Tingling (range 0–100)†			
N	223	120	103
Mean ± SD	30.9 ± 22.8	28.3 ± 21.3	33.9 ± 24.2
Numbness (range 0–100)†			
N	223	120	103
Mean ± SD	41.7 ± 24.8	38.3 ± 24.9	45.8 ± 24.1
Average attacks per day‡			
N	247	132	115
Mean ± SD	2.1 ± 1.4	2.3 ± 1.5	1.9 ± 1.3
Duration of attacks, minutes			
N	221	119	102
Mean ± SD	28.4 ± 16.0	28.1 ± 14.1	28.8 ± 18.0
RCS (range 0–10)‡			
N	247	132	115
Mean ± SD	3.6 ± 2.0	3.5 ± 2.1	3.6 ± 1.9

* $P < 0.05$ for attack symptoms, pain, tingling, and the Raynaud's Condition Score (RCS) between primary versus secondary Raynaud's phenomenon (RP). All other comparisons are not significant at $P \geq 0.05$. VAS = visual analog scale.
† Data not available for 26 patients.
‡ Data not available for 2 patients.

Table 2. Intraclass correlation coefficient analysis among the different core set measures assessed in patients in 3 clinical trials*

Core set measures†	All patients (n = 249)	Secondary RP (n = 132)	Primary RP (n = 117)
Patient assessment of RP (VAS)	0.47	0.49	0.46
Physician assessment of RP (VAS)	0.54	0.52	0.57
Attack symptoms	0.76	0.78	0.72
Pain during RP attack (VAS)	0.78	0.79	0.76
Numbness during RP attack (VAS)	0.77	0.81	0.70
Tingling during RP attack (VAS)	0.77	0.76	0.79
Average attacks/day	0.79	0.75	0.86
Duration of the attacks, minutes	0.61	0.63	0.61
Raynaud's Condition Score	0.70	0.74	0.65

* RP = Raynaud's phenomenon; VAS = visual analog scale.
† Units for each core set measure are provided in Table 1.

between primary RP versus secondary RP groups, patients with primary RP had fewer RP attacks ($P < 0.05$). In contrast, pain and numbness were significantly greater in patients with primary RP (Table 1).

ICCs. The patients had a high degree of variability in their core set measures. The ICC was acceptable for the RCS, attack symptoms, and average attacks/day (ICCs ≥0.70). Patient and physician global assessments and the duration of attacks had ICCs <0.70 (Table 2). The ICCs for the individual studies are shown in Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21858/abstract) and show variability within the 3 RCTs. For example, the ICCs ranged from 0.47–0.71 for the RCS in the 3 trials. The ICCs were similar between patients with primary and secondary RP (Table 2).

Change in individual outcome measures for a given level of improvement. We also assessed the variability in different core set measures by calculating the change in each core set measure for a given level of improvement (range from <10 to ≥60% improvement) (Table 3). There was generally a high placebo response for all individual core set measures (except duration of attacks, which ranged from 1.4–36.3%). As an example, for the RCS, the placebo response ranged from 56% with ≥10% improvement to 19.5% with ≥60% improvement. The mean placebo response for all 3 trials is shown in Figure 1 and the range of the 3 trials is shown in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21858/abstract).

Change in percent improvement in core set measures in relation to the number of outcome measures examined. Similar to the development of the criteria by Paulus et al (5), we explored if the simple arithmetic combination of percent improvement using 6 core set measures would result in a decreased placebo response. Therefore, we assessed the percent improvement relative to the number of core set measures included in the analysis (Figures 1 and 2). Of the placebo-treated patients, 92.8% showed ≥10% improvement in at least 1 core set measure (Figure 2D), with 38.5% showing ≥60% improvement in at least 1 core set measure. An increased percent improvement along with combining core set measures decreased the placebo response rate. For example, 78% of patients had an improvement in the individual core set measures by ≥30% for 1 of 6 core set measures, 53% for 2 of 6 measures, 39% for 3 of 6 measures, 26% for 4 of 6 measures, 13% for 5 of 6 measures, and 2% for 6 of 6 measures (Figure 2B). There were no significant differences between primary and secondary RP (see Supplementary Appendices C and D, available in the online version of this article at http://online

Table 3. Proportion of patients who achieved a predefined percentage of improvement for each core set measure in the 3 clinical trials*

Improvement	Patient assessment	Physician assessment	Duration of attacks	Average attacks/day	RCS	Attack symptoms
≥60%	13.9	14.7	1.4	10.3	19.5	22.3
≥50%	21.2	20.8	1.9	21.4	22.4	32.1
≥40%	29.4	31.0	4.7	31.3	29.0	41.4
≥30%	45.3	39.6	6.5	43.6	35.3	50.7
≥20%	55.5	53.5	14.4	51.4	45.6	62.3
≥10%	66.1	64.1	26.0	63.4	56.0	71.2
<10%	74.7	75.1	36.3	72.8	65.1	77.2

* Values are the percentage of patients showing the specified level of improvement for each core set measure. RCS = Raynaud's Condition Score.

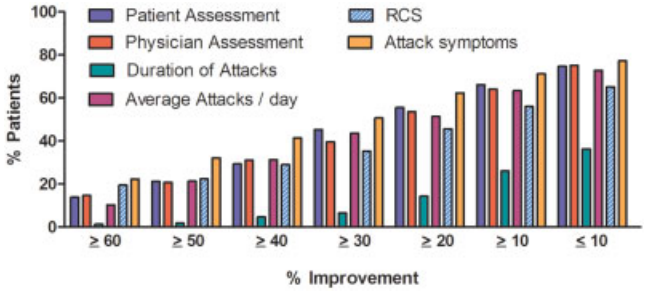

Figure 1. Percentage of patients showing improvement in the 6 core set measures. The data show the mean improvement for all 3 clinical trials. RCS = Raynaud's Condition Score.

library.wiley.com/doi/10.1002/acr.21858/abstract) (Figures 3A and B).

DISCUSSION

Current pharmacologic therapies used to treat RP have modest efficacy and include agents such as calcium-channel blockers, angiotensin II antagonists, α1-adrenergic blockers, and selective serotonin reuptake inhibitors (6). Apart from calcium-channel blockers, which are considered the first-line therapy, and prostacyclins for severe cases in patients with secondary RP, evidence for the effects of other agents is limited and side effects are common (6–8). RCTs of RP have used different outcome measures, and the results have been conflicting. This is likely due to the episodic nature of RP and lack of standardization of outcome measures. Using placebo data from 3 large RCTs, we show that outcome measures in RP have marked intrarater variability and are associated with a high placebo response. In addition, the composite index of the individual outcome measures reduces the measurement variability and placebo response.

Meta-analyses of RP trials have shown modest efficacy of current pharmacologic agents (9,10). In addition, trials have provided conflicting results. For example, in an RCT of oral iloprost in 103 patients with RP secondary to SSc (11) that evaluated the frequency of RP, daily duration of RP, severity of RP, and physician global assessment of RP as outcome measures, the duration and severity of RP showed a statistical improvement after 6 weeks of active treatment versus the placebo group. However, in another trial of 308 patients with RP secondary to SSc (12) that evaluated the average duration of RP attacks, average number of RP attacks, and RCS, there was no statistical improvement in the iloprost group versus the placebo group. More recently, tadalafil was assessed in RP in double-blind, placebo-controlled RCTs. One RCT showed improvement in the RCS and duration and frequency of attacks compared to the placebo group (13), whereas the other RCT that evaluated the RCS and frequency and duration of RP attacks failed to show a statistically significant difference compared to the placebo group in any outcome measure (14). The above data highlight the difficulty in determining whether pharmacologic interventions are efficacious, since there is no standardization of outcome measures in RCTs of RP (13,15).

The lack of reliable biomarkers or surrogate end points in RP that reliably predict efficacy has required that investigators utilize end points that can result in high placebo response rates due to the variability in these core set mea-

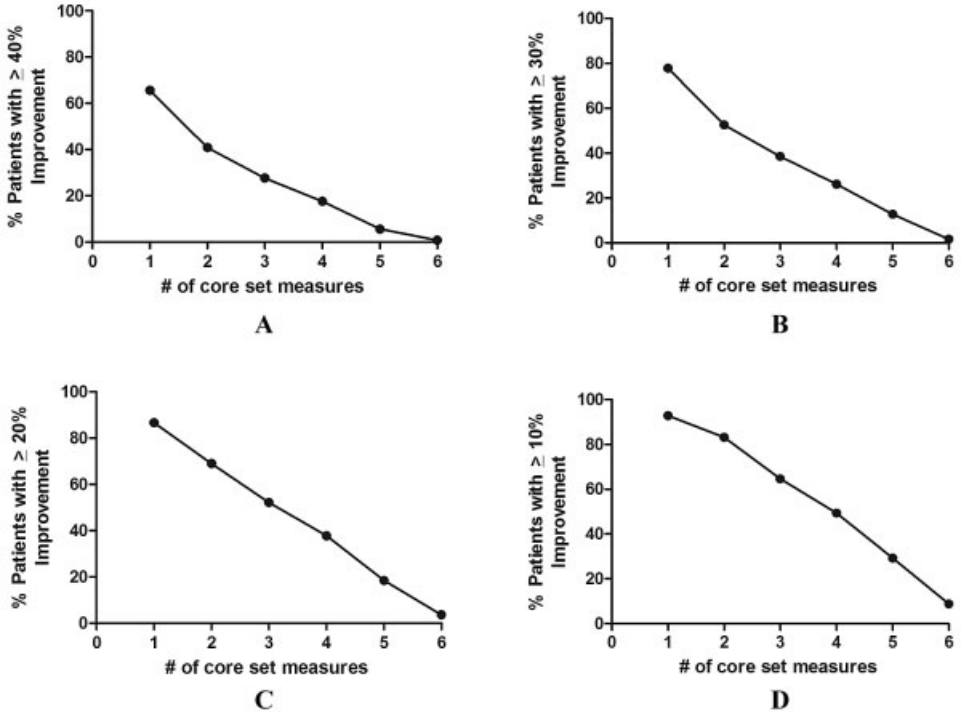

Figure 2. Percentage of patients showing improvement when assessing 1–6 core set measures. Plots show improvement over the range of ≥10% improvement to ≥40% improvement (**A–D**), as assessed against the number of core set measures included in the analyses.

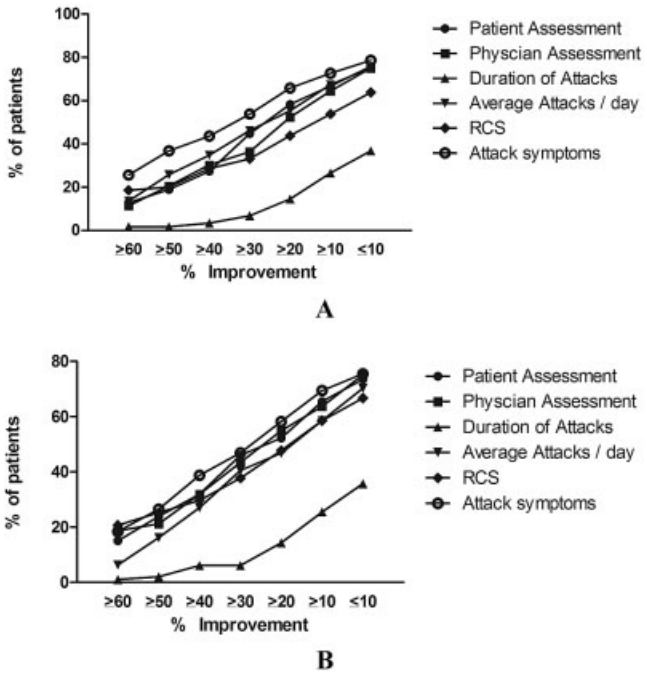

Figure 3. Percentage of patients with a given improvement in core set measures. The data show the percentage of patients with a given level of improvement for all 6 core set measures for **A,** secondary Raynaud's phenomenon (RP) patients, and **B,** primary RP patients. RCS = Raynaud's Condition Score.

sures between patients. Using varied core set measures between trials, however, makes it impossible to compare trial results, and in some cases the absence of core set measures may make investigators decide which outcome measures to report and may only report those that show significance. In addition, using a parameter insensitive to change will result in a therapy that may have otherwise showed activity being scored as ineffective. This has hampered the approval of new drugs for RP and left physicians with minimal options for treatment.

In the 1980s, patients with RA also showed similar variability in individual core set measures when attempting to measure drug efficacy (16). Approximately 10 different individual core set measures had been used in an attempt to gauge the efficacy of new agents in RA. However, due to statistical chance, the possibility that any one parameter will change in response to therapy made RCTs difficult to interpret. This was first addressed by Paulus et al, who proposed a composite score based on statistical analysis to gauge the activity of disease-modifying antirheumatic drugs (DMARDs) (5). These criteria, known as the Paulus criteria, required the improvement of ≥20% in each of 4 of the following 6 core set measures: morning stiffness, erythrocyte sedimentation rate, joint pain/tenderness index, joint swelling score, patient overall assessment of current disease severity, and physician overall assessment of current disease severity. In the initial analysis, very few placebo-treated patents qualified for improvement, whereas significantly more patients treated with DMARDs improved. A consistently low placebo response is essential for any composite score to ensure that responses observed with an agent represent real improvements. The Paulus criteria were later modified to develop the American College of Rheumatology 20% improvement criteria (ACR20) (17), the gold standard for approval of drugs by regulatory agencies for RA.

Using methodology similar to the Paulus criteria, our analysis suggests a composite index for RP that can decrease the placebo response rate to an acceptable level, allowing for a better evaluation of a therapeutic efficacy with new treatments. The choice of how many core set measures should be combined and whether a certain percent improvement in the RCS and patient global assessment is required (similar to the ACR20, where 20% improvement in the swollen joint count and tender joint count is required) need to be determined in future studies. Further, some of these individual measures, although widely used, are subjective, and it is debatable whether they should be included. It also needs to be determined if a combination of individual core set variables will lead to higher discrimination between an effective drug versus placebo in RP. If predictive of efficacy, this composite index will enhance our ability to evaluate new therapies for patients with RP and should expedite approvals in this area of high medical need.

Other studies have evaluated core set measures and response measures in RP. Using data from a large RCT of oral iloprost in SSc and RP, Merkel and colleagues conducted a factor analysis and found 4 factors; of these, 2 factors assessed RP-associated disease activity and severity measures and the other 2 captured digital ulcers and mood/tension measures (18). All RP measures are included in the current study and formed the basis of this core set. In addition, we captured tingling and numbness during an acute attack of RP, since these are common symptoms in patients with RP (18). In another study, Khanna et al estimated the minimum clinically important improvement from one of the trials (19), and found that an improvement of 1.4–1.5 points in the RCS (0–10 scale) met the minimum clinically important difference criterion. However, this analysis did not address the variability of the RCS and the placebo response.

Our study has many strengths. First, we included patients from 3 large RCTs of RP where individual patient data were available. Second, uniform core set measures were incorporated in these studies, providing strength to our analysis. We have carefully evaluated the psychometric characteristics of the core set measures.

Our study is not without limitations. Lack of an effective therapeutic agent makes it difficult to assess if a composite index would be successful in discriminating an effective drug versus placebo. However, this study did not assess this, since 2 of 3 primary trials have not yet been published and the data were not available to evaluate. Future studies will evaluate this deficiency in the context of this and other trials.

In conclusion, analysis of placebo groups from 3 large RCTs shows that there is marked variability in the individual core set measures used in RP clinical trials, and that a combination of these variables reduces variability.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Paulus, Khanna.

Acquisition of data. Khanna.

Analysis and interpretation of data. Gladue, Maranian, Paulus, Khanna.

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