Patient acceptable symptom state and minimal clinically important difference for patient-reported outcomes in systemic sclerosis: A secondary analysis of a randomized controlled trial comparing personalized physical therapy to usual care

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Abstract

Background: To estimate patient acceptable symptom state (PASS) and minimal clinically important difference (MCID) for patient-reported outcomes in systemic sclerosis (SSc).

Methods: We conducted a secondary analysis of the SCLEREDUC trial, a 12-month randomized controlled trial comparing the efficacy of physical therapy to usual care in 220 SSc patients followed-up from September 2005 to October 2010. Self-rated state and change in patient health at 12 months were assessed by using 2 external anchors extracted from the Medical Outcomes Study 36-Item Short-Form. Patients who self-rated their health as "excellent", "very good" or "good" were the PASS group and those who self-rated their health change as "somewhat better" were the MCID group. Main outcomes were the estimates of PASS by using the 75th percentile method and of MCID by using the mean change in scores method for pain and activity limitation.

Results: PASS (95% confidence interval) and mean (SD) MCID estimates at 12 months were 53.75 (34.00 to 68.00) and -6.74 (32.02) for the joint-pain visual analog scale (range 0-100), 1.41 (1.13 to 1.63) and -0.21 (0.48) for the Health Assessment Questionnaire (HAQ, range 0-3), 1.27 (1.07 to 1.62) and -0.13 (0.45) for the scleroderma HAQ (range 0-3), 26.00 (17.00 to 37.00) and -3.38 (9.87) for the Cochin Hand Function Scale (range 0-90), and 19.40 (17.20 to 21.90) and -5.69 (6.79) for the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (range 0-30), respectively.

Conclusions: We provide, for the first time, the PASS and MCID estimates for pain and activity limitation in SSc.

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Key words: Systemic sclerosis; patient-reported outcomes; patient acceptable symptom state; minimal clinically important difference.

1. Introduction

Systemic sclerosis is a rare autoimmune disease involving skin, vessels, joints and internal organs such as lungs, heart, kidneys and the gastrointestinal tract [1]. Because systemic sclerosis is a chronic condition and only partially effective pharmacological treatments are available, it impairs patient functioning and health-related quality of life [2-4]. Patients' self-opinion of the efficacy of treatments is an important outcome for health care and for clinical trials. Patient-reported outcomes have been developped to capture patients' perception of their own functioning and are considered valid, reproducible and sensitive-to-change tools [5].

To determine the clinical relevance of a treatment effect, 2 treatment-response criteria have been developed on the basis of patients' perception of their functioning: the patient acceptable symptom state (PASS) [6] and the minimal clinically important difference (MCID) [7, 8]. The PASS is defined as the highest symptom level below which the patient considers the symptom state acceptable [9]. The MCID is defined as the smallest change in a score of an instrument or effect-size with which patients perceive a clinical benefit or clinicians would recommend a therapy [10]. The PASS and MCID of outcome measures are also important for calculating sample size for clinical trials and for determining whether the differences observed between 2 treatment groups are clinically relevant [11].

We aimed to estimate the PASS and MCID for 5 commonly used patient-reported outcomes, including pain and activity limitation, in clinical trials of systemic sclerosis.

2. Patients and Methods

2.1 Study design and study population.

Patients included in the present study participated in the SCLEREDUC trial, a 12-month, multicenter, randomized controlled study conducted in France from September 2005

to October 2010 that compared the efficacy of a personalized physical therapy program to usual care in systemic sclerosis [12]. Overall, 220 patients were randomized (112 patients allocated to the physical therapy group and 108 patients to the usual care group) and 218 patients were included in the primary analysis. Main inclusion criteria were age ≥ 18 years, diagnosis of systemic sclerosis according to the American College of Rheumatology [13] and/or Leroy and Medsger criteria [14], Health Assessment Questionnaire (HAQ) score ≥ 0.5, self-reported reduced mouth opening, and self-reported reduced range of motion of at least 1 joint. Main exclusion criteria were disabling comorbidities, cognitive impairment, participation in a clinical trial in the previous 3 months and inclusion in a structured physical therapy program in the previous 6 months. The objectives of the personalised physical therapy were to increase muscle strength and aerobic capacity and to decrease joint impairment, mouth microstomia, skin retraction, activity limitation and participation restriction. In the SCLEREDUC trial, mean age was 52.7 (14.8) *vs* 53.1 (14.4) years, number of women was 95/110 (86.4%) *vs* 86/108 (79.6%), number of patients with diffuse systemic sclerosis was 53/110 (48.2%) *vs* 54/108 (50.9%), number of patients with limited cutaneous systemic sclerosis was 53/110 (48.2%) *vs* 50/108 (47.2%) number of patients with limited systemic sclerosis was 4/110 (3.6%) *vs* 2/108 (1.9%), mean disease duration was 6.5 (6.5) *vs* 6.7 (8.6) years and number of patients with a disease considered as severe by the treating physician was 56/110 (51.4%) *vs* 57/108 (52.8%), in the physical therapy and usual care groups, respectively. The SCLEREDUC trial showed that physical therapy had short-term benefit at 1 month for disability, pain, hand and face-specific reduction in mobility but no long-term benefits, with no significant between-group differences at 12 months, except microstomia. The study has been approved by our institutional review board (Cochin Hospital, CPP2233) and all participants have signed written informed consent. The French Ministry of Health (*Programme Hospitalier de Recherche Clinique* 2004, grant number AOM04023) provided

financial support for the conduct of the SCLEREDUC trial. The funding source was not involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. A full description of the study design and results has been previously published [12].

2.2 Patient-reported outcomes.

Patient-reported outcomes were collected at inclusion and at 12 months during face-to-face visits by using validated French versions of self-administered scales. Patient-reported outcomes included joint pain intensity assessed by a 100-mm visual analog scale (0, no pain, to 100, maximal pain), global activity limitation assessed by the HAQ (0, no limitation, to 3, maximal limitation) [15], systemic sclerosis-specific global activity limitation assessed by the scleroderma HAQ (sHAQ; 0, no limitation, to 3, maximal limitation) [4], patient-perceived activity limitation assessed by the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR; 0, no limitation, to 30, maximal limitation) [16], hand-specific activity limitation assessed by the Cochin Hand Function Scale (0, no limitation, to 90, maximal limitation) [17, 18]; and health-related quality of life assessed by the Medical Outcomes Study 36-Item Short Form (SF-36; 0, poor health-related quality of life, and 100, best health-related quality of life) [17].

2.3 Anchoring questions.

To estimate PASS and MCID of patient-reported outcomes at 12 months post-randomization, we used an external anchoring method based on patient perspectives [19, 20]. For the PASS, the anchoring question was extracted from the SF-36 (“In general, how would you say your health is?”) with a 5-class answer: “excellent”, “very good”, “good”, “fair”, and “poor”. Patients who self-rated their health as “excellent”, “very good” or “good” were

considered to have an acceptable symptom state. For the MCID, the anchoring question was also extracted from the SF-36 ("Compared to 1 year ago, how you would rate your health now?") with a 5-class answer: "much better", "somewhat better", "about the same", "somewhat worse" and "much worse" [21-23]. Patients who self-rated their health "much better" or "somewhat better" were considered as "improved"; "somewhat worse" or "much worse" as "worsened"; "somewhat better" as "minimally improved"; and "somewhat worse" as "minimally worsened".

2.4 Statistical analysis.

Post-hoc analyses were conducted by using data for participants for whom the answers to both anchoring questions were available at 12 months post-randomization. Quantitative variables were described with means (standard deviation [SD]) and qualitative variables with absolute numbers (%). For the PASS, values were estimated as the 75th percentile of the distribution of patient-reported outcome values for patients who considered their symptom state acceptable [24, 25]. The 95% confidence interval of the PASS was estimated by a normal approach using the XLSTAT version 2017.3 software. For the mean changes in scores in the "minimally improved", "minimally worsened", "improved" and "worsened" groups, we estimated bidirectional minimally important differences for patient-reported outcomes in terms of absolute (visit value – baseline value) and relative ([visit value – baseline value]/baseline value) values [26-28]. Responsiveness, describing a score's ability to detect a clinically meaningful change over time [29], was estimated with the standardized response mean and the effect-size. The standardized response mean is the mean change in a score from baseline to follow-up divided by the SD of the individual change in the score. The effect-size is the mean change in a score from baseline to follow-up divided by the SD of the score at baseline. For both approaches, 4 responsiveness ranges are described: <0.20 for poor effect;

214 0.20 to 0.50 for small effect; 0.50 to 0.80 for moderate effect; and ≥ 0.80 for large effect.
215 High values indicate better responsiveness [29, 30]. A negative value indicates that the mean
216 score at baseline was higher than the mean score at follow-up.
217
218 **3. Results**
219 **3.1 Participants.**
220 Among the 220 patients randomized in the SCLEREDUC trial, 169/220 (76.8%)
221 completed the study. The full flow diagram of the SCLEREDUC trial has been published
222 [12]. Among these patients, 18/169 (10.7%) completed less than 50% of the questionnaires at
223 12 months. Overall, answers to both anchoring questions were available for 151/220
224 participants (68.6%) from the SCLEREDUC trial. Mean age was 52.0 years (14.4), 28/151
225 (18.5%) were men and 79/151 (52.3%) were allocated to personalized physical therapy.
226 Overall, 71/151 (47.0%) had a disease considered severe by the investigator, defined as
227 having scleroderma renal crisis and/or pulmonary arterial hypertension and/or pulmonary
228 fibrosis and/or cutaneous involvement extended to the trunk and/or a gastrointestinal tract
229 involvement of the distal gut and/or with complications (e.g. malabsorption) (Table 1).
230
231 **3.2 Health status and changes.**
232 At the time of randomization, 66/147 participants (44.9%) self-rated their health as
233 acceptable (Table 2). At 12 months, 75/151 (49.7%) participants self-rated their health as
234 acceptable, 53/151 (35.1%) improved, 35/151 (23.2%) minimally improved, 38/151 (25.2%)
235 worsened and 29/151 (19.2%) minimally worsened (Table 3) and 60/151(39.7%) unchanged.
236
237 **3.3 Patient acceptable symptom state.**

At 12 months, the PASS (95% confidence interval) estimates were 53.75 (34.00 to 68.00) for the joint-pain visual analog scale, 1.41 (1.13 to 1.63) for the HAQ, 1.27 (1.07 to 1.62) for the sHAQ, 26.00 (17.00 to 37.00) for the Cochin Hand Function Scale and 19.40 (17.20 to 21.90) for the MACTAR (Table 2).

3.4 Minimal clinically important difference for improvement and worsening.

At 12 months, mean absolute MCID for improvement and worsening scores were -6.74 (32.02) and -5.08 (31.67) for the joint-pain visual analog scale, -0.21 (0.48) and 0.04 (0.40) for the HAQ, -0.13 (0.45) and 0.14 (0.41) for the sHAQ, -3.38 (9.87) and 1.43 (13.11) for the Cochin Hand Function Scale -5.69 (6.79) and -2.63 (4.84) for the MACTAR, respectively (Table 3).

3.5 Responsiveness.

At 12 months, effect-size and standardized response mean values were -0.21 and -0.19 for the joint-pain visual analog scale, -0.31 and -0.40 for the HAQ, -0.29 and -0.32 for the sHAQ, -0.14 and -0.21 for the Cochin Hand Function Scale and -0.66 and -0.57 for the MACTAR (Table 4).

4 Discussion

Because statistical significance is not equivalent to clinical relevance, estimating the PASS and MCID for clinical outcomes is important to determine how meaningful a state or a change in functioning is to patients [8, 20]. Our study provides, for the first time, the PASS and MCID estimates for patient-reported outcomes commonly used for assessing joint pain and activity limitation in systemic sclerosis. These estimates can be useful in interpreting the clinical relevance of outcomes used in systemic sclerosis patients' care and of results from

clinical trials by shifting from the group to the individual. For clinicians, the MCID estimates can be used to assess the clinical relevance of a change in patient's health status, for a subjective patient-centered outcome such as pain, activity limitation or participation restriction, as a result of treatment effect (e.g. "does a 8 mm difference on a VAS for pain, ranging from 0 to 100 mm, has a clinical relevance justifying the change of treatment made?"). For clinicians, the PASS estimates can be used to evaluate the state of health as it is perceived by the patient and can help decision-making, for example to decide on a therapeutic intensification for a given subjective symptom, such as pain. For researchers, PASS and MCID estimates can be used as original and clinically relevant tools to dichotomize a treatment effect in "successes/failures" or patients in "responders/non responders". Using these estimates, results could be presented, for example, as the between-group comparisons of percentages of successes or responders.

The PASS is defined as a state of attainment for a patient, acceptable for a given period [6]. To estimate the PASS, we used an external anchoring question based on the SF-36 general health question: "In general, how would you say your health is?" A limitation is that this anchoring question may have been censurable. Instead of asking if the current health status is acceptable for the patient for a period of time to come, the SF-36 question, as it is formulated, implies that the current health status is acceptable right now. Therefore, we may have trespassed the concept of "staying the same over the time" of the PASS. However, the magnitude of PASS estimates remained stable at baseline and 12 months. This finding suggests that the PASS was able to capture the concept of having an acceptable state over a relevant period of time for follow-up of a chronic condition, namely 12 months, despite a potential censurable anchoring question.

To our knowledge, no data are available for the PASS in systemic sclerosis. PASS estimates, especially for the HAQ and joint-pain visual analog scale, were higher than those

reported in other musculoskeletal chronic conditions: the PASS estimate for joint-pain 100-mm visual analog scale is 36 in rheumatoid arthritis [31] and ranges from 33 to 55 in ankylosing spondylitis [32, 33]. In a recent study, the mean PASS estimates for the HAQ (0-3) were 0.60 (0.59) in rheumatoid arthritis and 0.87 (0.70) in psoriatic arthritis [34]. Patients with systemic sclerosis might have a higher tolerance of joint pain and global activity limitation. PASS estimates for patient-reported outcomes could also have been high because the study population was selected for its high level of disability at baseline. Interestingly, contrary to the MCID thresholds, the PASS thresholds are independent of the baseline score of outcomes and show little change with age, gender or disease duration [31, 33].

To estimate the MCID of patient-reported outcomes, we also used an external anchoring question based on the SF-36 question on change in health. This anchor was previously used to estimate the MCID in other studies and is considered accurate and valid [22, 23]. We estimated minimally important differences bidirectionally, which allowed for defining 4 subgroups of patients according to their perception of health changes over 12 months: “minimally improved”, “minimally worsened”, “improved” and “worsened”. Even though minimally important difference estimates for patient-reported outcomes can differ across studies because of differences in anchoring questions or in populations, our estimates were consistent with previously published data. In the D-penicillamine study, the mean MCID for improvement estimate at 12 months for the HAQ was -0.21 (0.43) [22], but changes in health status were assessed by the physician and not by the patient. In the study by Sekhon et al, mean MCID for improvement and worsening estimates were -8.00 (32.48) and 3.61 (24.52) for the joint-pain 100-mm visual analog scale and -0.0125 (0.224) and 0.042 (0.314) for the HAQ, respectively. In the Canadian Scleroderma Research Group database, mean MCID for improvement and worsening estimates were -0.037 (0.402) and 0.140 (0.387) for the HAQ, respectively [23].

Most of the patient-reported outcomes varied in the expected direction, except for the MACTAR and joint-pain visual analog scale, which had inconsistent results in the worsened and minimally worsened groups. Because the MACTAR reflects patient priorities and these can vary over time, the MACTAR score could improve even if all other patient-reported outcome scores worsen. As expected, the joint-pain visual analog scale score decreased in the minimally improved and improved groups but also in the minimally worsened subgroups. Of note, the score for joint pain at baseline and at 12-month follow-up was below the PASS score in all groups. This finding suggests that impairment such as joint pain may be less associated with perceived health status than activity limitation assessed by other patient-reported outcomes. As well, the MACTAR and joint-pain visual analog scale may be more sensitive to detecting improvement than worsening. Interestingly, at 12 months, the scores for all patient-reported outcomes were below the PASS threshold in the improved and minimally improved subgroups, but were above the PASS threshold, except for the joint-pain visual analog scale, in the worsened subgroup.

Contrary to observational cohorts, in which patient-reported outcome scores usually deteriorate over time [16, 18, 23], all our patient-reported outcomes scores improved over time. This observation may be explained by the interventional design of the SCLEREDUC trial. The responsiveness of the scores evaluated by the effect-size and standardized response mean was fair for the HAQ, sHAQ, joint-pain visual analog scale and Cochin Hand Function Scale. The most responsive instrument was the MACTAR, with moderate responsiveness (-0.66 and -0.57 for the effect-size and standardized response mean, respectively). Our results are consistent with previous studies. In the study by Nguyen et al, the effect-size and standardized response mean values were -0.38 and -0.41 for the HAQ, -0.38 and -0.41 for the MACTAR and -0.16 and -0.28 for the Cochin Hand Function Scale in patients with systemic

sclerosis [16]. The high sensitivity to change of the MACTAR may be explained by its ability to capture shifts in patient priorities over time [16].

Chosen external anchors may have affected results interpretation. A concern with using questions extracted from the SF-36 is that they ask about general health and not systemic sclerosis-specific health. Patients may not be directly thinking about their systemic sclerosis when asked how their health is. For example, a patient might think "my general health is great but my scleroderma really limits me". Therefore, the chosen anchor may not have been able to fully capture specific systemic sclerosis status. Because, it was a *post-hoc* analysis, we did not originally design the anchor question. We aim to confirm our results using more appropriate anchor questions in an online cohort. The ideal external anchor question for PASS might have been: "Think about all the ways your systemic sclerosis has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable or unacceptable to you?", as previously suggested [19]. This may be reflected in how relatively high the PASS scores were for each patient-reported outcome assessed. There are similar concerns with the external anchor used to estimate the MCID. Patients were allocated to 2 different treatment regimens. Patients receiving personalized physical therapy may have had higher expectations for treatment efficacy, which may have affected their perceived health and changes in functioning and subsequently PASS and MCID estimates.

Another limitation is that we did not adjust the MCID estimates to baseline health status and disease severity. Some studies showed that patients with the most severe symptoms at baseline have to experience a greater change in patient-reported outcomes to consider themselves improved as compared with patients with less severe symptoms [9, 33, 35]. We had baseline data from the SCLEREDUC trial, but we decided not to adjust the MCID estimates according to baseline perceived health status and disease severity tertile. First, the

MCID groups had limited sample size, therefore we had some concerns about the interpretability of the results if we had splitted these small groups into tertiles. Second, we did not prespecify these analyses in our statistical analysis plan. However, we agree that this kind of adjustment could add relevant information if performed in a larger sample.

Participants were recruited from tertiary care centers and may not have been representative of the general French population with systemic sclerosis. Some studies looked at the PASS and MCID using data from patients in different countries. In the study by Bellamy and colleagues, PASS and MCID estimates were stable in patients with osteoarthritis across 7 countries [36]. In the study by Tubach and colleagues, PASS and MCID estimates were stable across countries for similar musculoskeletal diseases and across diseases for the same country. However, patients were recruited only from hospitals [24]. The study by Sekhon and colleagues investigated MCID estimates for patients with systemic sclerosis from 2 different settings, a tertiary care center and a national registry, respectively. Patients from the tertiary care center had longer disease duration (9.2 [6.6] years in the tertiary care group *vs* 8.0 [7.5] years in the registry group) and higher baseline HAQ-DI (0.9 [0.7] *vs* 0.8 [0.7]) suggesting that populations with systemic sclerosis recruited in trials can differ according to the trial setting [23]. To our knowledge, no study has assessed the PASS estimates in patients with systemic sclerosis using data from different countries or settings.

We did not use the PASS neither the MCID estimates to perform *a posteriori* analyses of the SCLEREDUC results. Because we used the data of SCLEREDUC trial to calculate the PASS and MCID estimates, we believed that using the same population to assess the relation between the PASS or MCID estimates and the statistical results of the SCLEREDUC trial would have compromised methodological and statistical robustness. We agree however that if these estimates were prespecified and used in an independent population of patients with

systemic sclerosis, it would be interesting to know whether they would support the statistical analyses.

Both experimental and control cases of the SCLEREDUC trial were pooled during the validation process. It would be reasonable to further confirm PASS and MCID estimates in an independent cohort of patients with systemic sclerosis. This confirmatory study is ongoing. Finally, owing the *post-hoc* design of our study, outcomes reported in the present paper have not been prespecified in the original protocol of the SCLEREDUC trial.

5 Conclusions

Our study provides PASS and MCID estimates for commonly used patient-reported outcomes in systemic sclerosis. These original estimates can be useful in interpreting the clinical relevance of outcomes used in systemic sclerosis patient care and of results from clinical trials.

List of abbreviations

HAQ: health assessment questionnaire

sHAQ: scleroderma health assessment questionnaire

MACTAR: McMaster-Toronto Arthritis Patient Preference Disability Questionnaire

MCID: Minimal Clinically Important Difference

PASS: patient acceptable symptom state

SD: standard deviation

SF-36: Medical Outcomes Study 36-Item Short Form

Declarations

- Ethics approval and consent to participate: The study has been approved by our institutional review board (Cochin Hospital, CPP2233) and all participants have signed written informed consent.
- Consent for publication: Not applicable.
- Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
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    - Drafting of the original protocol. CD, SP, CN.
    - Design of the statistical analysis plan. CD, CN.
    - Coordination of the study. FR, LM, SP.
    - Acquisition of data. CD, LM, KS, AR, VT, ÉH, PT, JC, EC, JS, CN.
    - Obtaining of funding. FR, SP.
    - Drafting of the present manuscript. CD, FR, CN.
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References

[1] Tamby MC, Chanseaud Y, Guillevin L, Mouthon L. New insights into the pathogenesis of systemic sclerosis. Autoimmunity reviews 2003;2(3):152-7.

[2] Casale R, Buonocore M, Matucci-Cerinic M. Systemic sclerosis (scleroderma): an integrated challenge in rehabilitation. Arch Phys Med Rehabil 1997;78(7):767-73.

[3] Clements PJ. Systemic sclerosis (scleroderma) and related disorders: clinical aspects. Bailliere's best practice & research Clinical rheumatology 2000;14(1):1-16.

[4] Steen VD, Medsger TA, Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis and rheumatism 1997;40(11):1984-91.

[5] Ingegnoli F, Carmona L, Castrejon I. Systematic review of systemic sclerosis-specific instruments for the EULAR Outcome Measures Library: An evolutional database model of validated patient-reported outcomes. Seminars in arthritis and rheumatism 2017;46(5):609-14.

[6] Pham T, Tubach F. Patient acceptable symptomatic state (PASS). Joint, bone, spine : revue du rhumatisme 2009;76(4):321-3.

[7] Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. Journal of clinical epidemiology 1994;47(1):81-7.

[8] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Controlled clinical trials 1989;10(4):407-15.

[9] Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Annals of the rheumatic diseases 2005;64(1):29-33.

[10] van Walraven C, Mahon JL, Moher D, Bohm C, Laupacis A. Surveying physicians to determine the minimal important difference: implications for sample-size calculation. Journal of clinical epidemiology 1999;52(8):717-23.

[11] Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). The Journal of manual & manipulative therapy 2012;20(3):160-6.

[12] Rannou F, Boutron I, Mouthon L, Sanchez K, Tiffreau V, Hachulla É, et al. Personalized Physical Therapy Versus Usual Care for Patients With Systemic Sclerosis: A Randomized Controlled Trial. Arthritis Care Res (Hoboken) 2017;69(7):1050-9.

[13] Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis and rheumatism 1980;23(5):581-90.

[14] LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. The Journal of rheumatology 2001;28(7):1573-6.

[15] Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis care and research : the official journal of the Arthritis Health Professions Association 1991;4(1):27-31.

[16] Nguyen C, Mouthon L, Mestre-Stanislas C, Rannou F, Bérezné A, Sanchez K, et al. Sensitivity to change in systemic sclerosis of the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR): shift in patient priorities over time. The Journal of rheumatology 2010;37(2):359-64.

[17] Rannou F, Poiraudeau S, Bérezné A, Baubet T, Le-Guern V, Cabane J, et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis and rheumatism 2007;57(1):94-102.

[18] Nguyen C, Bérezné A, Mestre-Stanislas C, Lefèvre-Colau MM, Rannou F, Guillevin L, et al. Changes over Time and Responsiveness of the Cochin Hand Function Scale and Mouth Handicap in Systemic Sclerosis Scale in Patients with Systemic Sclerosis: A Prospective Observational Study. American journal of physical medicine & rehabilitation 2016;95(12):e189-e97.

[19] Tubach F, Ravaud P, Beaton D, Boers M, Bombardier C, Felson DT, et al. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. The Journal of rheumatology 2007;34(5):1188-93.

[20] Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. Journal of clinical epidemiology 2003;56(5):395-407.

[21] Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992;30(6):473-83.

[22] Khanna D, Furst DE, Hays RD, Park GS, Wong WK, Seibold JR, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. Annals of the rheumatic diseases 2006;65(10):1325-9.

[23] Sekhon S, Pope J, Canadian Scleroderma Research G, Baron M. The minimally important difference in clinical practice for patient-centered outcomes including health assessment questionnaire, fatigue, pain, sleep, global visual analog scale, and SF-36 in scleroderma. The Journal of rheumatology 2010;37(3):591-8.

[24] Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. Arthritis Care Res (Hoboken) 2012;64(11):1699-707.

[25] Kviatkovsky MJ, Ramiro S, Landewe R, Dougados M, Tubach F, Bellamy N, et al. The Minimum Clinically Important Improvement and Patient-acceptable Symptom State in

the BASDAI and BASFI for Patients with Ankylosing Spondylitis. The Journal of rheumatology 2016;43(9):1680-6.

[26] Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. The Journal of rheumatology 1993;20(3):557-60.

[27] Redelmeier DA, Lorig K. Assessing the clinical importance of symptomatic improvements. An illustration in rheumatology. Archives of internal medicine 1993;153(11):1337-42.

[28] Wells G, Beaton D, Shea B, Boers M, Simon L, Strand V, et al. Minimal clinically important differences: review of methods. The Journal of rheumatology 2001;28(2):406-12.

[29] Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. Journal of chronic diseases 1987;40(2):171-8.

[30] Tuley MR, Mulrow CD, McMahan CA. Estimating and testing an index of responsiveness and the relationship of the index to power. Journal of clinical epidemiology 1991;44(4-5):417-21.

[31] Heiberg T, Kvien TK, Mowinckel P, Aletaha D, Smolen JS, Hagen KB. Identification of disease activity and health status cut-off points for the symptom state acceptable to patients with rheumatoid arthritis. Annals of the rheumatic diseases 2008;67(7):967-71.

[32] Maksymowych WP, Richardson R, Mallon C, van der Heijde D, Boonen A. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. Arthritis and rheumatism 2007;57(1):133-9.

[33] Tubach F, Pham T, Skomsvoll JF, Mikkelsen K, Bjorneboe O, Ravaud P, et al. Stability of the patient acceptable symptomatic state over time in outcome criteria in ankylosing spondylitis. Arthritis and rheumatism 2006;55(6):960-3.

[34] Puyraimond-Zemmour D, Etcheto A, Fautrel B, Balanescu A, de Wit M, Heiberg T, et al. Associations between five important domains of health and the Patient Acceptable

532 Symptom State in rheumatoid arthritis and psoriatic arthritis: A cross sectional study of 977
533 patients. Arthritis Care Res (Hoboken) 2016.
534 [35] Terwee CB, Roorda LD, Dekker J, Bierma-Zeinstra SM, Peat G, Jordan KP, et al.
535 Mind the MIC: large variation among populations and methods. Journal of clinical
536 epidemiology 2010;63(5):524-34.
537 [36] Bellamy N, Hochberg M, Tubach F, Martin-Mola E, Awada H, Bombardier C, et al.
538 Development of multinational definitions of minimal clinically important improvement and
539 patient acceptable symptomatic state in osteoarthritis. Arthritis Care Res (Hoboken)
540 2015;67(7):972-80.
541

Table 1. Demographic and systemic sclerosis characteristics of patients at inclusion.

All patients	**n=151**
Women, n (%)	123 (81.5)
Age (years), mean (SD)	52.0 (14.4)
Disease considered severe by the treating physician, n (%)	71 (47.0)
• Scleroderma renal crisis	8 (5.3)
• Pulmonary arterial hypertension[a]	12 (8.0)
• Pulmonary fibrosis	21 (13.9)
• Cutaneous involvement extended to the trunk	38 (25.2)
• Gastrointestinal tract involvement	15 (10.0)
Modified Rodnan skin score (0-51), mean (SD)	15.0 (9.3)
Microstomia (mouth opening < 40 mm), n (%)	103 (68.2)
Mouth opening (mm), mean (SD)	35.5 (8.2)[b]
Sclerodactyly, n (%)	143 (94.7)
Participants allocated to the physical therapy group, n (%)	79 (52.3)
Treatement changes during follow-up, n (%)	51 (33.8)
Patient-reported outcomes, mean (SD)	
• Joint pain visual analog scale (0-100)	37.8 (28.7)
• HAQ (0-3)	1.3 (0.6)[b]
• sHAQ (0-3)	1.2 (0.6)[c]
• Cochin Hand Function Scale (0-90)	20.5 (17.2)[c]
• MACTAR (0-30)	18.7 (6.2)

[a]confirmed by right heart catheterization; [b]n=150; [c]n=149.

Table 2. Patient acceptable symptom state estimates for patient-reported outcomes at baseline and during follow-up.

	Baseline	**12 Months**
Acceptable symptom state, n/N (%)[a]	66/147 (44.90)	75/151 (49.67)
Joint-pain visual analog scale (0-100)	49.00 (45.00;63.00)[b]	53.75 (34.00;68.00)[c]
HAQ (0-3)	1.50 (1.25;1.63)[d]	1.41 (1.13;1.63)[f]
sHAQ (0-3)	1.35 (1.13;1.45)[g]	1.27 (1.07;1.62)[f]
Cochin Hand Function Scale (0-90)	28.75 (19.00;35.00)[b]	26.00 (17.00;37.00)[e]
MACTAR (0-30)	22.00 (20.60;22.80)[h]	19.40 (17.20;21.90)[i]

Data are PASS score (95% confidence interval) unless indicated.

[a]health status self-rated “excellent”, “very good” or “good” according to the anchoring question.

[b]n=64; [c]n=70; [d]n=66; [e]n=73; [f]n=75; [g]n=65; [h]n=63; [i]n=69.

Table 3. Minimal Clinically important difference estimates for patient-reported outcomes at 12 months.

	Minimally clinically improved patients **n=35/151 (23.18%)** [c]**n=16/35 (45.71%)**			**Minimally clinically worsened patients**[b] **n=29/151(19.21%)** [c]**n=13/29 (44.83%)**		
	Baseline value mean (SD)	**Absolute MID mean (SD)**	**Relative MID (% from baseline)**	**Baseline value mean (SD)**	**Absolute MID mean (SD)**	**Relative MID (% from baseline)**
Joint-pain visual analog scale (0-100)	36.06 (26.90)[d]	-6.74 (32.02)[d]	-27.65[e]	43.17 (31.14)[e]	-5.08 (31.67)[f]	-12.30[g]
HAQ (0-3)	1.10 (0.63)[h]	-0.21 (0.48)[h]	-17.70[h]	1.41 (0.63)[e]	0.04 (0.40)[e]	17.68[e]
sHAQ (0-3)	1.10 (0.63)[i]	-0.13 (0.45)[i]	-12.55[i]	1.24 (0.52)[e]	0.14 (0.41)[e]	27.72[e]
Cochin Hand Function Scale (0-90)	18.55 (17.08)[i]	-3.38 (9.87)[j]	-13.14[k]	23.17 (17.48)[e]	1.43 (13.11)[l]	21.60[l]
MACTAR (0-30)	17.67 (7.02)[d]	-5.69 (6.79)[d]	-32.94[d]	20.90 (4.78)[e]	-2.63 (4.84)[m]	-10.65[m]

[a]health status self-rated "somewhat better" as compared with 1 year ago, according to the anchoring question.

[b]health status self-rated "somewhat worse" as compared with 1 year ago, according to the anchoring question.

Overall, 60/151 participants (39.7%) self-rated their health status "unchanged" as compared with 1 year ago, according to the anchoring question.

[c]n: number of participants allocated to the usual care group.

[d]n=35; [e]n=29; [f]n=25; [g]n=21; [i]n=33; [h]n=34; [j]n=32; [k]n=31; [l]n=28; [m]n=24.

Table 4. Responsiveness of patient-reported outcomes.

	Value at baseline		Value at 12 months		Change from baseline		Effect-size	SRM
	Mean	SD	Mean	SD	Mean	SD		
Joint-pain visual analog scale (0-100)	37.77[a]	28.70	31.70[b]	30.30	-6.07	31.90	-0.21	-0.19
HAQ (0-3)	1.30[c]	0.64	1.10[c]	0.70	-0.20	0.50	-0.31	-0.40
sHAQ (0-3)	1.16[d]	0.56	1.00[a]	0.60	-0.16	0.50	-0.29	-0.32
Cochin Hand Function Scale (0-90)	20.46[d]	17.19	18.00[e]	17.00	-2.46	11.90	-0.14	-0.21
MACTAR (0-30)	18.74[a]	6.15	14.69[f]	7.63	-4.05	7.05	-0.66	-0.57

[a]n=151; [b]n=144; [c]n=150; [d]n=149; [e]n=148; [f]n=142.

SRM: standardized response mean.