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Considerations for a combined index for limited cutaneous systemic sclerosis to support drug development and improve outcomes

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Summary:

Systemic sclerosis (SSc; systemic scleroderma) is characterized by a heterogeneous range of clinical manifestations. SSc is classified into limited cutaneous SSc (lcSSc) and diffuse cutaneous subgroups (dcSSc) based on the extent of skin involvement. Randomized controlled trials in scleroderma have mainly focused on dcSSc partly because the measurement of skin involvement, critical for evaluating a therapeutic intervention is more dynamic in this subset. Nonetheless, lcSSc, the most common cutaneous subset (about 2/3), is also associated with significant morbidity and detrimental impact on health-related quality of life. The lack of interventional studies in lcSSc is partly due to a lack of relevant outcome measures to evaluate this subgroup. Combining several clinically meaningful outcomes selected specifically for lcSSc may improve representativeness in clinical trials and responsiveness of outcomes measured in randomized controlled trials. A composite index dedicated to lcSSc combining such relevant outcomes could advance clinical trial development for lcSSc by providing the opportunity to test and select among

candidate drugs that could act as disease-modifying treatments for this neglected subgroup of SSc. This proposed index would include items selected by expert physicians and patients with lcSSc across domains grounded in the lived experience of lcSSc. This article reviews the reasons behind the relative neglect of lcSSc, discusses the current state of outcome measures for lcSSc, identifies challenges, and proposes a roadmap for a combined lcSSc-specific treatment response index.

Keywords

Systemic sclerosis; scleroderma; limited cutaneous systemic sclerosis; classifications; combined response index; composite score; quality of life

Introduction

Systemic sclerosis (SSc; systemic scleroderma) is a disease characterized by diverse clinical manifestations (1). By broadening the previous 1980 ACR classification criteria (2), the 2013 EULAR/ACR classification criteria for SSc ensured the inclusion of patients with earlier and milder disease (3). This constitutes an important step forward for understanding SSc. The updated classification criteria of SSc have fostered translational and therapeutic research in SSc (4), and the multiple subgrouping of SSc over the past century has informed current knowledge. Leroy subclassified SSc into limited cutaneous SSc (lcSSc) and diffuse cutaneous subsets (dcSSc) based on the extent of skin involvement (5) and later revised this classification (6). This concept of lcSSc, although proposed with the publication of Leroy's classification in 1988, had previously been discussed in the literature. The abandoned nosological entities of "acrosclerosis" and CREST (Calcinosis, Raynaud's Phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia) captured this idea of a subgroup of scleroderma patients with milder skin fibrosis and marked vascular manifestations, as opposed to "diffuse" or "generalized scleroderma" with fibrotic features at the forefront (4). Although Leroy's dichotomous approach of lcSSc *versus* dcSSc has some limitations (7), it is a clear and simple subgrouping that has influenced clinical trial design and provides a meaningful clinical prognosis. The lcSSc subgroup is the most prevalent, estimated to include 57 to 77% of patients with SSc (8-14). In this article, we: a) consider the reasons why lcSSc has been largely overlooked in clinical trials, b) discuss the current state of outcome measures for lcSSc, c) identify the challenges in studying lcSSc, and d) propose a roadmap for a combined response index for lcSSc.

Limited cutaneous systemic sclerosis: an overlooked subgroup

Retained importance of "limited cutaneous systemic sclerosis" within new classification schemes

Of all rheumatic diseases, SSc has the highest case-specific mortality (1), which is largely driven by dcSSc. However, lcSSc is also associated with significant morbidity and a detrimental impact on health-related quality of life. The traditional dichotomy of SSc, distinguishing lcSSc and dcSSc, has recently been challenged as authors have highlighted there are more than two subgroups at stake and a more nuanced classification with various subgroups may more accurately reflect the heterogeneity of the disease and associated

autoimmune-driven tissue damage (15-17). Interestingly, in these attempts to develop new classification strategies, a frequent subgroup characterized by modest cutaneous evolution, a high prevalence of gastro-intestinal manifestations, low mortality rate, and a high proportion of patients positive for anticentromere antibodies, has typically emerged (18-20). These new classification approaches highlight the limitations of the binary approach to disease subsetting currently deployed (7), although a major subset of patients still responds to the “classical” and traditional image of Leroy’s lcSSc. Therefore, this traditional limited cutaneous subset still deserves attention.

Visceral involvement in patients with limited cutaneous systemic sclerosis

With regard to visceral involvement and overall disease burden, lcSSc may have been largely overlooked in most studies and may represent “an unfairly neglected subset” (12). The abandoned concept of CREST syndrome may have led to the idea that patients with lcSSc had a less severe disease phenotype, as the CREST mainly encompassed a subgroup of patients with lcSSc with anticentromere antibodies, no interstitial lung disease (ILD) and less frequent musculoskeletal manifestations. A recent analysis from the EUSTAR cohort proposed a comprehensive view on this issue (21). In this cross-sectional and longitudinal study, more than 8,000 patients with lcSSc were compared with almost 5,000 patients with dcSSc. This study highlighted that patients with lcSSc experienced multi-system involvement, as suggested by the presence of esophageal symptoms (62%), ILD (35%), digital ulcers (37 %), cardiac diastolic dysfunction (20%) and joint synovitis (13%) (Figure 1). Interestingly, 33% of patients with dcSSc and 24% of those with lcSSc were on immunosuppressive therapy (21). These findings highlight that patients with lcSSc warrant similar attention to possible visceral involvement as do patients with dcSSc, especially given the high rate of SSc-associated mortality due to ILD and cardiac involvement (22) (Figure 2). The importance of considering lcSSc-associated ILD is also supported by numerous trials in ILD that include this subgroup (23-26). Previous observational studies that evaluated pulmonary arterial hypertension (PAH) showed that the lcSSc subgroup is strikingly overrepresented in comparison with the dcSSc subgroup (27). In a meta-analysis specifically addressing the issue of PAH in SSc, more than 80% of patients with PAH had lcSSc, with no major differences in survival between the two subgroups (28).

Quality of life (QoL) in the lcSSc population may also be a neglected area of study and incorporation in clinical trials. The overall impact of dcSSc on QoL may be greater than on lcSSc, but the main clinical manifestations responsible for QoL impairment may be quite similar between the two subgroups (29). Nonetheless, the precise definitions and mapping of the domains and related outcome measures may influence these results (21). In a study addressing QoL impairment in patients with SSc, the main SSc-related manifestations that impacted daily life were Raynaud’s phenomenon, gastro-intestinal issues, and musculoskeletal manifestations (30-35), each of which are highly prevalent in lcSSc. Hand function is also compromised in lcSSc, and hand manifestations such as calcinosis and acroosteolysis are observed both in dcSSc and lcSSc (36,37). Gastrointestinal involvement may concern up to 90% of patients with SSc, and these manifestations are not associated with a specific disease subtype (38,39). Recent studies have highlighted that severe gastrointestinal dysmotility was independent from cutaneous subtype in multivariable analysis, suggesting

again that patients with lcSSc or dcSSc are equally impacted by such manifestations (40). Considering the increased frequency of lcSSc, much of the SSc-associated morbidity experienced in cohorts of patients with scleroderma is due to lcSSc. The systematic emphasis on the diffuse subgroup within clinical trial programs of SSc has inadvertently excluded over half of the patients we manage, and in doing so has restricted the therapeutic options available to this important subgroup of patients.

The lack of representativeness of limited cutaneous systemic sclerosis in clinical trials

Drug development, clinical trials and studies evaluating QoL have largely been focused on dcSSc, and/or have overrepresented the proportion of the dcSSc subgroup in comparison with lcSSc. There are, on the contrary, few studies dedicated to lcSSc, especially clinical trials (15). A recent analysis of outcomes used in scleroderma trials have highlighted that among the 97 published trials, 53 included patients with either lcSSc and dcSSc, 22 included dcSSc only, and 4 trials were specific to lcSSc (only 1 for the entire 2011-2018 period) (41). This may be justified by the greater impact of dcSSc on mortality, and the fact that a more rapid progression of some SSc-associated manifestations in dcSSc may facilitate shorter clinical trials. Moreover, many clinical trials in SSc have focused on skin involvement, using the modified Rodnan Skin Score (mRSS) as the primary outcome (42-44). It is now well established that mRSS may not be an adequate outcome measure for the assessment of skin involvement in lcSSc, especially considering its limited sensitivity to change in this subgroup (45). Although digital ulcers and pulmonary-related outcome measures may represent shared assessment tools between dcSSc and lcSSc, the lack of interventional studies specifically in lcSSc may be due, in part, to a paucity of relevant outcome measures to effectively evaluate this subgroup, such as tool assessing the impact of frequent lcSSc-associated manifestations such as calcinosis or acroosteolysis.

Potential benefits of a combined response index for patients with limited cutaneous systemic sclerosis

Phase II and III clinical trials in dcSSc have recently benefited from the creation and endorsement of a combined response index dedicated to dcSSc. This ACR-endorsed Combined Response Index for Systemic Sclerosis (CRISS) was designed to capture the global improvement of dcSSc based on the selection of domains and items in accordance with the Outcome Measure in Rheumatology (OMERACT) strategy (46). The ACR CRISS has been shown to differentiate active therapy vs. placebo in recent phase II trials (42,47) and has been utilized as an acceptable endpoint for registration trials. This combined response index is based on a two-step evaluation. The first step evaluates if there has been a new or worsening of the underlying cardiac function (ejection fraction of < 45% requiring treatment), lung function (loss of forced vital capacity (FVC) (% predicted) of at least relative 15% in documented ILD, or new onset of PAH), or the occurrence of scleroderma renal crisis during the considered period of time. If such a major event has not occurred, then a second step based on 5 variables [FVC% predicted, mRSS, patient and physician global assessments and disability (Health Assessment Questionnaire Disability Index)] is used to measure the overall probability of improvement during this same period. Although some items included in this index share relevant outcome measures between dcSSc and lcSSc [FVC%, patient and physician global assessments and disability (health assessment

questionnaire disability index), new onset of PAH], other items used in the CRISS are not equally relevant for lcSSc such as the onset of scleroderma renal crisis and mRSS. Most importantly, the CRISS was designed as an assessment tool for early dcSSc and was validated using data from randomized clinical trials of patients with dcSSc and patient profiles from longitudinal cohorts of dcSSc (48).

The ACR CRISS and its use in recent randomized clinical trials serves as proof of concept that a global assessment of SSc is possible, and potential candidates of disease-modifying drugs can be evaluated using such a tool, even in short term trials with small sample sizes (47,49). This is especially true considering that in some cases the ACR CRISS can successfully differentiate active therapy vs. placebo, when the primary outcome measure fails to do so, such as in a recent trial evaluating abatacept for dcSSc (42). An equivalent combined response index that could similarly capture the impact of therapeutic measures on lcSSc, would address this relatively under-investigated subgroup of patients. The objective of the CRISTAL project (Combined Response Index for Scleroderma Trials Assessing LcSSc) is towards the development of a combined response index for lcSSc for use in clinical trials.

Unmet needs for a combined index dedicated to lcSSc: the case for CRISTAL

The need for patient-reported outcomes tailored for limited cutaneous systemic sclerosis

Value-based health care, patient-reported outcomes (PRO) and treatment satisfaction are core values for new reference standards and therefore quality metrics in patient management and drug approval by regulatory agencies (50,51). The creation of a new assessment tool for a complex rheumatological disease, like lcSSc, requires the incorporation of the patients' perspective, especially for the identification of the most important domains for this combined response index. Comprehensive identification of outcome measures, including PRO, will therefore require highlighting the most relevant items within the domains that are considered the most bothersome by patients with lcSSc. The patient perspective of the most bothersome symptoms of lcSSc has been largely overlooked. Including specific PRO directly in candidate combined indices could help to involve the patients in the evaluation process. Most of PRO measures used to assess SSc are not specifically designed for this disease. Indeed, patients with SSc, and in particular patients with lcSSc have not been involved in the design and development activities of most of PRO measures conducted to evaluate SSc (52). Nonetheless, some exceptions exist, such as the systemic sclerosis UCLA Gastrointestinal Tract questionnaire (UCLA SCTC GIT) (53,54). Patient involvement in creating and validating PROs is now required to satisfy regulatory agencies, such as the FDA, when considering product label claims. With regards to PRO for lcSSc, the NIH PROMIS[®] initiative offers a broad range of tools; some of them, such as the NIH PROMIS[®] Gastrointestinal Symptom Scales, are relevant for (but not dedicated to) patients with SSc, some of whom were involved in the instruments' development (55). The NIH PROMIS[®] initiative also provides a large variety of formats, including short forms and computerized adaptive tests (CAT) that allows for customization of the assessment tools that are relevant

for the domains of interest, including physical health, mental health and social health domains (56,57).

Including quality of life and its determinants in clinical trials assessing patients with limited cutaneous systemic sclerosis

With regard to feeling, function, and QoL, an international report on the responses of patients with SSc noted that fatigue and pain were among the shared patients' priorities in all evaluated countries (58). Although this study involved patients both with dcSSc and lcSSc, it highlighted that including patients' perspective and evaluation of QoL would need to include the evaluation of general symptoms, which have been largely overlooked to date (59). This is a challenging issue as nonspecific manifestations, such as pain and fatigue, may not be directly impacted by specific therapies for SSc. Nonetheless, an effective disease-modifying drug for lcSSc may positively impact these symptoms. Moreover, some specific SSc-associated features, such as physical appearance, change with subsequent impairment of social interactions, and the risk of depression may directly impact functioning and precipitate the development of fatigue (60-62). Similarly, digital ulcers, arthritis and skin involvement could directly impact pain and the perception of pain. Deciphering the interactions between specific features of the disease and the onset of general symptoms could help to determine the most relevant items to be included in a combined response index for lcSSc. Including assessment tools based on modern psychometric and/or item response theories may help to capture important subjective feelings linked to QoL within this new index (56). Achieving the proper balance between the evaluation of lcSSc-related manifestations and the inclusion of considerations on functioning and QoL based on patient perspectives is one of the main challenges ahead. Including input from experts in SSc trials and careful evaluation of the candidate items for final selection according to the OMERACT filter 2.0 is also vital as the final goal is the creation of an index useful for specific drug evaluation (63).

A proposed roadmap for the development of the index

Figure 3 presents a possible roadmap to guide the development of a combined response index for lcSSc.

Step 1: Synthesize knowledge about the existing outcome measures in limited cutaneous systemic sclerosis and include patient input on the most bothersome symptoms

The first stage of the effort is the identification of key domains and related outcome measures to inform these domains. A cornerstone of this stage (and others) is the inclusion of patient perspectives. The first step will involve a qualitative approach based on e-focus groups, including only patients with lcSSc, to highlight the key domains they consider as the most bothersome. This e-focus group approach allows identification of items and domains without being done *a priori*, and without preconceived or pre-determined clinician-oriented query. This will ensure clinician perspectives have limited impact on patient input at the early stage of data collection. The identified domains will be informed by a systematic scoping review of the literature that will provide an overview of outcome measures previously used in the assessment of patients with lcSSc in observational and interventional

studies (41). Analyzing the frequency of use of the outcome measures and the domains identified during the literature review, may allow us to identify gaps between researcher/clinician concerns and perspectives of patients with lcSSc as identified in the e-focus groups.

Steps 2 & 3: Select domains and items to be included in data-driven approach for a study of limited cutaneous systemic sclerosis

The next steps for identifying the core set of items will be to conduct Delphi exercises for experts and patients to enrich the list of items previously identified allowing for ranking of the most relevant items from these perspectives. Based on the results of the Delphi exercises, the selection of the core set of items will be proposed through a nominal group technique (NGT), involving patients and experts, with the goal of achieving a consensus for a short list of items that will include the most relevant outcomes for randomized clinical trials according to experts (based on the OMERACT filter 2.0) and items and/or domains identified as bothersome by the patient participants. Items from the NIH PROMIS® item banks may serve as the starting point for domains that are included in PROMIS® (such pain and fatigue) but will require developing items for scleroderma specific symptoms.

Step 4: Select and validate items to be included in candidate indices

Once the core set of items is identified, the psychometric properties of all items will be tested in longitudinal cohorts to evaluate their clarity, feasibility, reliability and validity (including responsiveness to change). These analyses of longitudinal data will serve as the next steps by providing data for patient profiles and will help to finalize a revised set of items. A cognitive debriefing of the items will also be conducted, based on a sample of patients from longitudinal cohorts. Using a dedicated cohort could also help to include the self-reported status of the patients, as improved, stabilized or worsened. A similar rating by expert clinicians, with consensus about status among experts, would also be proposed based on patient profiles. The final selection of the items to be included in the candidate indices will be determined by evaluating their association with the identified goal (improvement/stabilization), testing their redundancy, and determining the helpfulness of the items for predicting evolution, and defining the minimal clinically important difference of candidate indices.

Step 5: Select the most efficient CRISTAL index

Based on these results, different candidate indices with the most relevant associations, as defined by a steering committee that includes various expert clinicians and patient partners, will be proposed. The last step will be the inclusion of these candidate indices as secondary endpoints in clinical trials to select the most efficient index for differentiating groups and to estimate a clinically important difference and change score for this index (48).

Limitations of the proposed development of a combined response index for limited cutaneous systemic sclerosis

Organ-by-organ outcome measures versus combined response index

It could be argued that individual organs that are most often affected in lcSSc should be the focus of outcome assessment and this should be prioritized over the creation of a combined response index. Under this argument, there is an unmet need for specific assessment tools dedicated to assessing impact on the involved organs. The development of new PRO or outcome measures for specific domains could be considered a useful complement to the creation of a combined response index. As tools that are tailored to specific domains in lcSSc are developed, they could be included with a combined index (64,65). Furthermore, inherent in the concept of studying lcSSc organ-by-organ is the supposition that these manifestations of disease stem from distinct pathophysiologies, a concept countered by the success of single therapies for other multisystem rheumatic diseases such as systemic lupus erythematosus and vasculitis (66,67). One could nonetheless argue that a treatment tailored for a manifestation such as calcinosis and another that would focus on gastrointestinal involvement would be very different and would precisely target different pathways. Thus it has been recently highlighted that a promising strategy for scleroderma trials would be the increasingly frequent evaluation of combination therapies (68), as the discovery of a single disease-modifying drug is uncertain. Combination therapies could be a viable strategy that may help to manage various SSc-associated domains, and with this in mind, a combined response index could constitute a relevant endpoint.

Sensitivity to change and disease course of limited cutaneous systemic sclerosis

LcSSc has a more prolonged disease course than dcSSc, but this very issue, in combination with the idea that organs are more often affected individually in lcSSc, supports the need for a combined index to more efficiently capture changes in disease status. This combined response index for lcSSc must be sensitive enough to capture symptoms and visceral manifestations across time that may not be present in the first years of the disease. It will also need to be responsive enough for symptoms that change over time (e.g., seasonable variability of Raynaud's phenomenon, psychological distress, or decreased oral aperture). Responsiveness to change in lcSSc may constitute specific challenges for such an index. For example, the rate of progression in lcSSc is generally slower than in dcSSc, and manifestations such as digital ulcers and PAH may occur much later in the natural history of lcSSc (21). The inclusion of items based on the time to treatment failure within candidate indices may help to tackle this issue, and the combination of multiple items in the same index may also help to increase its precision and responsiveness.

Clinical relevance, variability and overall treatment goal for limited cutaneous systemic sclerosis

The use of a combined response index could lead to increased variability with subsequent increases in the required sample size (68). The issue of overly restrictive inclusion criteria is a major concern for randomized clinical trials evaluating early dcSSc, but it would likely be a less critical barrier in lcSSc since limiting inclusion based on a maximum disease duration

may be of less importance for lcSSc than dcSSc. Another concern about a combined response index is the clinical relevance of the differences between groups. This is also true for single item primary outcomes as illustrated with the recent debate concerning the clinically-relevant decline of FVC in SSc-associated ILD (24,69). The involvement of patients at each stage of the collaboration process of a lcSSc focused combined response index would strengthen the clinical relevance of the index and ensure that this index would be adequately grounded in and responsive to the lived experience of lcSSc. This strategy would also help to properly define the minimal clinically important difference for this index. A final issue to consider when creating a useful combined response index is the question of defining the overall treatment goal. Is it improvement or stabilization? There is still an ongoing debate concerning this question in SSc in general, and this decision will greatly impact the selection of the items and domains for lcSSc. This question also highlights that this combined index will not be an activity or severity index, and it will need to be designed with the constant reminder of its relevance in clinical trials (64).

Conclusion

As compared to dcSSc, lcSSc remains highly overlooked, specifically in terms of clinical trial programs and availability of targeted therapeutic strategies. A project to develop CRISTAL would need to properly capture relevant key domains, based on the patients' perspectives, and would include patient partners at each step of its conception in collaboration with expert clinicians. Identifying and defining the domains and relevant outcome measures to be included in such a combined response index is a necessary first step for the development of this index. Selecting standardized, patient-informed, and clinically meaningful outcome measures could lead to the design of clinical trials with a strong potential to achieve regulatory agency approval and propel much needed drug development in lcSSc.

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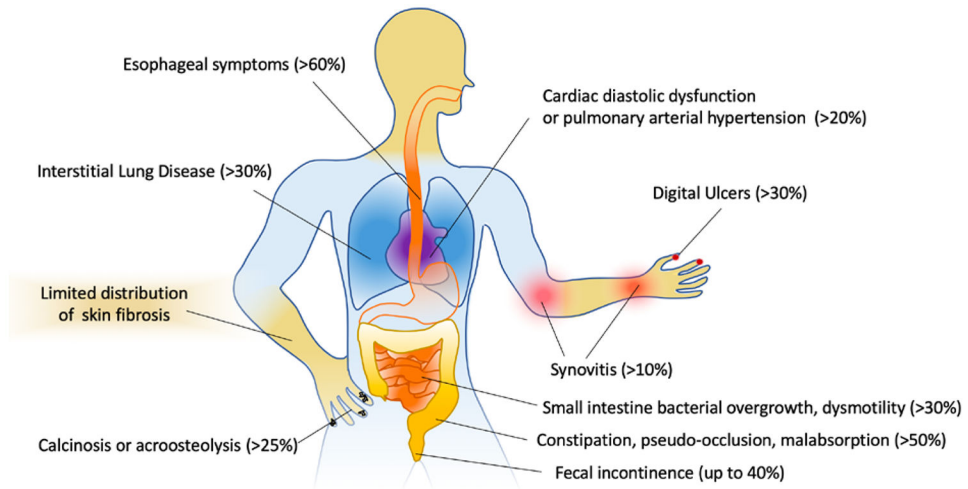


Figure 1: Major organ involvement and clinical manifestations in patients with limited cutaneous systemic sclerosis.

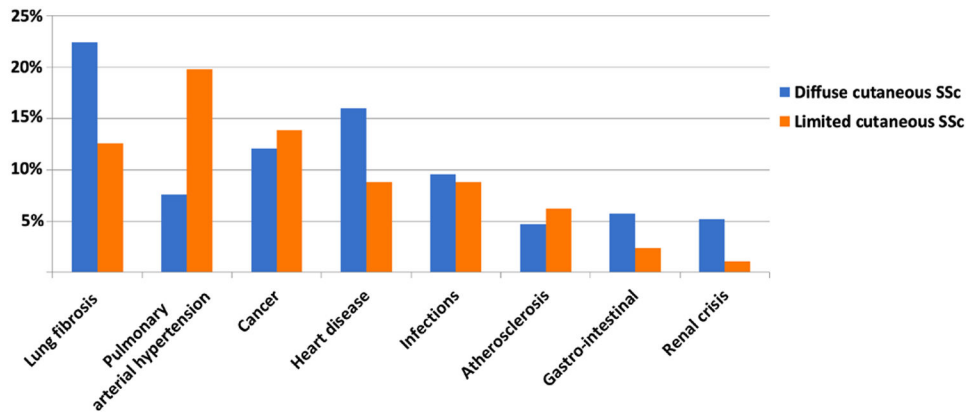


Figure 2:
Causes of death for patients with the two main forms of systemic sclerosis (SSc): diffuse cutaneous and limited cutaneous (adapted from unpublished data from (21)).

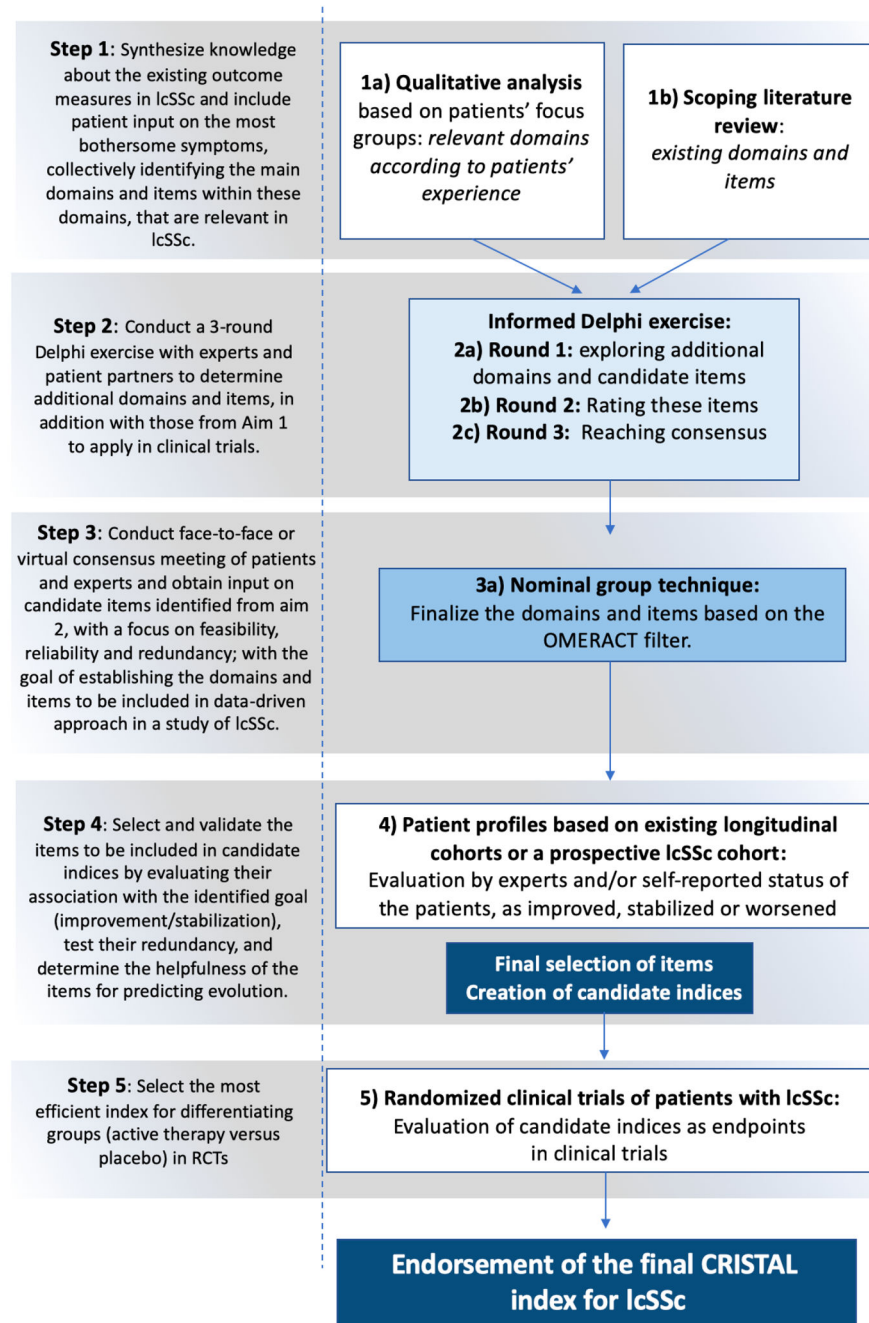


Figure 3:

A proposed roadmap for the creation of the CRISTAL index (Combined Response Index for Scleroderma Trials Assessing Limited cutaneous SSs).
lcSSc=limited cutaneous systemic sclerosis ; OMERACT= Outcome Measures in Rheumatology
 RCTs=Randomized Clinical Trials