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Scoping review protocol

DOMAINS AND OUTCOME MEASURES FOR THE ASSESSMENT OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS: A SCOPING REVIEW PROTOCOL

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DK is a consultant to Acceleron, Abbvie, Actelion, Amgen, Bayer, BMS, Boehringer Ingelheim, CSL Behring, Corbus,
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Authors' contributions: AL & MHB wrote the first draft of the manuscript. AL, MHB, WT, DR, JDP, MH, RS, FZ, DK conceived the scoping review, developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

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Abstract (286 words/300)

Introduction :

Limited cutaneous Systemic sclerosis (lcSSc) is the most frequent subset of systemic sclerosis. Despite this, lcSSc is not the major focus of clinical studies. The lack of interventional studies in lcSSc is due, in part, to a paucity of relevant outcome measures to effectively evaluate this subset. A combined response index dedicated to lcSSc would facilitate development of well-designed trials and approval of new drugs. The objective of this scoping review is to perform a broad and comprehensive identification of the outcome measures (core set items) within relevant domains, which have been used so far to assess lcSSc.

Methods and analysis :

The planned scoping review will be based on the approach proposed by Arksey et al. and further developed by Levac et al. Development and reporting will follow the Preferred Reporting Items for Systematic Reviews and MetaAnalyses—Extension for Scoping Reviews (PRISMA-ScR) checklist and guidelines. The development of the search strategy was guided by the concepts of Domains and Outcomes based on the OMERACT (Outcome Measures in Rheumatology) approach and by the different names and definitions of SSc, with a specific emphasis on their occurrence in clinical trial studies. Two databases will be searched: MEDLINE and EMBASE. Studies in English, published from the year 1988 onwards, will be included, since 1988 corresponds to the publication of LeRoy's first consensus definition of lcSSc. Data will be extracted and analyzed using a standardized charting tool.

Ethics and dissemination :

No ethical approval is required for this study. The results will be submitted to an international peer-reviewed journal and scientific conferences, informing the discussion on which items should be included in a combined response index dedicated to lcSSc (The CRISTAL project: Combined Response Index for Scleroderma Trial Assessing LcSSc).

Key words : Systemic sclerosis, scleroderma, domains, outcome measures, classification.

Strengths and limitations of this study

-The proposed scoping review will allow a broad and comprehensive identification of the outcome measures (core set items) within relevant domains, which have been used so far to assess lcSSc.

-The specific emphasis on clinical trials including patients with lcSSc will ensure the identification of relevant outcome measures used so far and their mapping within key domains, eventually highlighting gaps and main issues concerning the lack of outcome measures and/or their poor use.

-Although comprehensive, this study design has limitations regarding the number of databases, the language and search terms used, and may under-represent observational studies and basic science articles that do not explicitly mention the word "limited SSc" or "limited cutaneous SSc" in their title or abstract.

-By focusing on articles published after 1988, this scoping review may not capture the outcome measures used to assess equivalent subsets of lcSSc before this date, but this will ensure that the population included match with the contemporary definition of lcSSc.

INTRODUCTION:

Rationale

Systemic sclerosis (SSc) or scleroderma is a rare auto-immune disorder which includes a wide range of clinical manifestations, (Denton et al. 2017). SSc is characterized by the association of three main features: vasculopathy with Raynaud's phenomenon as the hallmark symptom, exuberant fibrosis of the skin and internal organs, and, immune activation with the occurrence of specific autoantibodies and inflammatory features such as synovitis and tenosynovitis (Denton et al. 2017).

SSc is further sub-classified into limited cutaneous (lcSSc), and diffuse cutaneous (dcSSc) according to 1988 Leroy & Medsger's classification (Leroy et al. 1988), revised in 2001(Leroy et al. 2001), and based on the extent of skin involvement by underlying fibrosis. LcSSc constitutes 60-70% of all SSc and is considered a milder sub-phenotype of SSc with Raynaud's phenomenon and GI involvement as common features and pulmonary arterial hypertension also observed in this subgroup. However, accumulating data from EUSTAR (European Scleroderma Trials and Research group) and other cohorts show that these and wider visceral complications occur in a significant proportion of patients with lcSSc (Frantz et al. 2020). This concept is further highlighted by the recent clinical trials targeting interstitial lung disease that recruited patients with lcSSc as well as dcSSc (SLS studies (Tashkin et al. 2006 and 2016) and SENSCIS trial (Distler et al. 2019)). Moreover, recent studies focusing on quality of life have demonstrated that patients with lcSSc experience a significant impairment in their daily quality-of-life and that patients' experiences of lcSSc have been largely overlooked (Khanna et al. 2007 ; Frantz et al. 2016).

Despite this high prevalence of lcSSc and typically earlier diagnosis of this specific subtype, there is poor validation of dedicated strategies for the management of patients with lcSSc. The lack of interventional studies in lcSSc is due, in part, to a paucity of relevant outcome measures to effectively evaluate this major subset. The range of clinical manifestations of SSc is wide, and clinical items are classified within domains, for example, outcomes related to vasculopathy such as digital ulcers, or outcomes related to interstitial lung disease such as the decline of pulmonary function measured through the annual decline of forced vital capacity (FVC) (Khanna et al. 2008 ; Boers et al. 2014). Drug development and trials have focused on dcSSc partly due to the availability of validated outcome measures, including a relevant combined response index, the ACR-CRISS index (Khanna et al. 2008 and 2016), that captures the global improvement of dcSSc. A composite index score dedicated to lcSSc that combines different aspects of the disease would similarly facilitate development of well-designed trials and approval of new drugs to treat lcSSc. Recent observational studies have highlighted the prognostic and predictive values of new imaging techniques and clinical markers such as capillaroscopy or laser doppler for vasculopathy, but the relevance of including such evaluation tools in combined index

approach is still to be determined. Identifying and defining relevant candidate outcome measures within key SSc-associated domains (Boers et al. 2014) to be included in such a combined index is the necessary first step for the construction of a future index for lcSSc.

Objective

The objective of this scoping review is to perform a broad and comprehensive identification of the core set items (and/or outcome measures) within relevant domains, which have been used so far to assess lcSSc since the endorsement of its consensual definition in 1988.

METHODS & ANALYSIS

We have chosen to conduct a scoping review to perform this literature search, based on the methodological framework proposed by Arksey and O'Malley (Arksey et al. 2005) and further developed by Levac and colleagues (Levac et al. 2010). Scoping reviews are especially effective to identify key factors/characteristics related to a concept, in our case, domains related to the assessment of lcSSc, and, to examine how research is conducted on a certain topic or field, in our case, the outcome measures within the identified domains (Munn et al. 2019). This scoping review will comprehensively identify outcomes measures in lcSSc to inform on how lcSSc has been evaluated to date and identify gaps in domains of clinical relevance. This is the first step of a project which aims to select the items that could be included in a combined response index for clinical trials assessing patients with lcSSc (The CRISTAL project : Combined Response Index for Scleroderma Trial Assessing LcSSc).

Conceptual framework and key concepts

The concepts of Domains and Outcomes are based on the OMERACT (Outcome Measures in Rheumatology) approach (Boers et al. 2019). This approach is made up of two important and sequential components: identification of **what** to measure (Domain Set), for example in the field of systemic sclerosis, measuring the impact of "vasculopathy", measuring "interstitial lung disease", or impact of pain on quality of life; and then identification of **how** to measure each of the identified domains using relevant instruments or tools (Outcome measurement Set), *i.e.* for the domain "vasculopathy" the number of new digital ulcers occurring during follow-up or for the domain "interstitial lung disease" change in FVC during the considered period or pain visual analog scale or PROMIS® items to assess the intensity of pain and pain interference.

The systematic identification of outcome measures (how to measure a manifestation / visceral involvement) and the domains they are related to (which manifestations of the disease/visceral

involvement is measured) will inform on how lcSSc has been assessed to date and to guide the discussion on which items should be included in a combined response index dedicated to lcSSc.

Publication dates and time period.

In 1988, the LeRoy's classification of SSc, built on previous 1980 criteria, crystallized the two main subsets of SSc, lcSSc and dcSSc. Prior to LeRoy's classification, the concept of limited SSc was recognised but several terms were used to describe features of this subgroup such as acrosclerosis, CREST, dermatosclerosis or acroscleroderma. These definitions were inconsistent and in contrast with those of generalized scleroderma or diffuse scleroderma, with the latter more or less matching with the definition of the diffuse cutaneous subset (Lescoat et al. 2020). The absence of a consensus classification that fully captured the concept and components of limited SSc, led to variable outcome measures and subgrouping criteria. The endorsement to define these two subsets (limited vs diffuse) of the disease within the 1988 classification criteria was based on prognostic data and defined by the extent of skin fibrosis involvement. This was a historical milestone in the nosology of SSc. Examining articles published before 1988 could lead to the inclusion of outcomes used to assess populations that would not match with the contemporary definition of lcSSc and have therefore not been included. After 1988, the term CREST/CRST syndrome persisted and overlapped with lcSSc. Based on this, articles only mentioning CREST/CRST in their title and abstract after 1988 will also be considered for full text review, and full-text assessment will confirm whether the population studies matches with the contemporary definition of lcSSc.

Scoping review questions

Main question : What are the outcome measures within relevant domains that have been used to assess lcSSc since the 1988 LeRoy's classification has been in use.

Secondary questions :

How many studies have been published by year?

What types of studies have been published?

General overview of the search strategy

As this scoping review focuses on limited cutaneous SSc/scleroderma our search terms will focus on studies with original data/original articles that explicitly mention the subtype "limited" and/or CR(E)ST in their title or abstract (**#1**). Nonetheless, when applying this strategy to milestone articles based on the reviewers' expertise (Wigley et al. 1994, Clements et al. 1995, Steen et al. 1997, Korn et al. 2004, Tashkin et al. 2006, Gliddon et al. 2007, Clements et al. 2007, Nihtvanova et al. 2008, Tashkin et al. 2016, Hachulla

et al. 2016, Cutolo et al. 2016, Denton et al. 2017, Distler et al. 2019) we identified a gap, particularly in picking up clinical trials. Indeed, many clinical trials only mention "scleroderma" in their title or abstract, without specifying limited or diffuse, although they indeed include patients with lcSSc. This is a major issue since the objective is to identify outcome measures to be included in a combined response index for clinical trials. To tackle this issue, we will include in the search terms all clinical trials mentioning scleroderma or SSc in the title or abstract (**#2**), even if the word "limited" is not mentioned in the title or abstract. For pragmatic reasons, observational studies will not be included in this **#2**, only clinical trials, in line with the overall objective of this scoping review.

Information sources :

Electronic databases: PubMed (Medline), Embase.com

Search terms (Methley et al. 2014)

Final search strategy for title/abstract evaluation = #1 and #2 as follow:

#1

Population :

Search terms :

Ovid MEDLINE SENSITIVE: exp Scleroderma, Limited/ OR (Scleroderma, Systemic/ AND limited.ti.) OR ((Systemic scleroderma.mp. OR systemic sclerodermas.mp. OR systemic sclerosis.mp. OR systemic scleroses.mp. OR SSc.mp.) ADJ3 limited.mp.) OR lcSSc.mp. OR ((Crest.ti,ab. OR CRST.ti,ab.) ADJ1 syndrome*.ti,ab.)

Embase.com : (('limited scleroderma'/exp OR ('systemic sclerosis'/de AND limited:ti) OR ((('systemic scleroderma' OR 'systemic sclerodermas' OR 'systemic sclerosis' OR 'systemic scleroses' OR ssc) NEAR/3 limited):ti,ab) OR lcssc:ti,ab OR 'syndrome CREST'/exp OR (((crest OR crst) NEAR/1 syndrome*):ti,ab)) NOT ([animals]/lim NOT [humans]/lim)) AND ('article'/it OR 'article in press'/it)

Included

- Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well.

Excluded

- Articles only focusing on localized scleroderma / morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be excluded, articles focusing on VEDOSS (Very Early Diagnosis Of Systemic Sclerosis (Avouac et al. 2011) only and articles focusing on dcSSc only will be excluded as well.

Intervention : n/a

Comparison : n/a

Outcomes : n/a as the selection of domains and outcome measures is the aim of this scoping review

Studies:

Included articles

- Studies written in English
- Original studies including: observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, before and after studies, Meta-analyses and systematic reviews. Translational and basic sciences studies will be considered for full-text reviewing, as some of them may highlight specific biomarkers of interest.

Excluded articles

- Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded.
- Studies not concerned with human subjects or not pertaining to adult studies will be excluded
- Article published before 1988 and LeRoy's classification (official creation/endorsement of the concept of limited SSc) will be excluded

#2

Population:

Search terms :

Ovid MEDLINE SENSITIVE:
using Sensitivity/precision maximized Cochrane limit*
(Exp Scleroderma, Systemic/ OR "Systemic scleroderma".mp. OR "systemic sclerodermas".mp. OR "systemic sclerosis".mp. OR "systemic scleroses".mp.) AND

Sensitivity/precision maximized Cochrane filter
(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti.) not (exp animals/ not humans.sh.)

Included

- Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well.

Excluded

- Articles only focusing on localized scleroderma / morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded

Intervention : Randomized controlled trials and unrandomized controlled trials only
Comparison : n/a
Outcomes : n/a as the selection of domains and outcome measures is the aim of this scoping review

Studies :

Included articles

- Only studies written in English will be considered
- Only randomized controlled trials and unrandomized controlled trials will be considered for this #2

Excluded articles

- Reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded,

observational analytical cross-sectional studies, case-control studies, prospective and retrospective cohort studies will be excluded.

- Studies not concerned with human subjects or not pertaining to adults will be excluded
- Article published before 1988 and LeRoy's classification (official creation/endorsement of the concept of limited SSc) will be excluded

Synthesis of eligibility criteria (Table 1)

Inclusion criteria:

1/ Language: English

2/ Publication date: after 1988 and Leroy's classification

3/ Population:

For observational studies: Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well.

For clinical trials: Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well.

4/ Studies:

For observational studies: observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, before and after studies, Meta-analyses and systematic reviews. Translational and basic sciences studies will be considered for full-text reviewing, as some of them may highlight specific biomarkers of interest.

For clinical trials: Only randomized controlled trials and unrandomized controlled trials will be considered

Exclusion criteria:

1/ Articles only focusing on localized scleroderma/morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded

2/ The following studies will be excluded: Reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news,

newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline, articles from grey literature will be excluded.

Reporting of protocol and Study records

This study protocol follows PRISMA-ScR guidelines (Tricco et al. PRISMA Extension for scoping Reviews (PRISMA-ScR): Checklist and Explanation. Annals of Internal Medicine 2018) and PRISMA guidelines for the publication of systematic review protocols (Shamseer L et al. 2015), with specific adaptations for this scoping review protocol.

Data management will be housed through Covidence (https://www.covidence.org/home), under the supervision of DK and MHB.

DR, JP, MH, RS, AL, FZ will screen citations and review for eligibility and inclusion, based on the eligibility criteria and the article selection template (**Table1 and 2**). AL will assess all the titles (T) and abstracts (A), and the other 5 reviewers will evaluate 1/5th of T/A to ensure that all articles will be double checked. Inter-rater agreement will be evaluate using Cohen's Kappa statistics. A first test of agreement will be performed based on 50 citations. If Kappa coefficients are under 0.8, we will evaluate the disagreements and understand the reason to correct misunderstanding and ensure consistency for the rest of the review process. T and A will then be reviewed for the entire article list. Any disagreements between reviewers will be reviewed and resolved by DK and/or MHB. If uncertainty persists, the manuscript will be included for comprehensiveness. Where there is lack of data clarity pertaining to exclusion criteria in manuscripts, mentors will be contacted to discuss this issue. Agreement between pairs for overlapping citations will also be assessed using Cohen's Kappa statistics at the end of the process. After article selection, the data extraction template (**Table 3**) for full texts review will be evaluated by two reviewers on a sample of 20% of included studies to adjust its sensitivity. Once the template is finalised, one reviewer will then perform the analysis, and the second reviewer will independently check a sample of the total of 20% articles, for accuracy. Any disagreements will be reviewed and resolved by DK and/or MHB. Citation searching will be applied to identify additional studies, through checking of reference lists of primary studies.

Presentation of the results

We expect to present the main results of this scoping review, with a least one table summarizing domains and identified outcomes. For the main domains of interest their frequency in the literature will also be provided in a Table. Identified gaps and main issues concerning the lack of outcome measures

and/or their poor use will also be highlighted in a third table. In the end, a comprehensive map of the main domains and outcomes will be provided within a dedicated graphical abstract or figure.

Table 1 : Inclusion and exclusion criteria for the scoping review

Inclusion criteria	Exclusion criteria
• Language: English • Publication date: after 1988 • Population: **For observational studies:** Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. **For clinical trials:** Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well. • Studies: **For observational studies:** observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled	• Population: Articles only focusing on localized scleroderma/morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded • Studies: **For observational studies:** Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Studies not concerned with human subjects or not pertaining to adult studies will be excluded. **For clinical trials:** all non-controlled trials, *i.e.* Reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases,

ETHICS AND DISSEMINATION

This scoping review is based on the analysis of published scientific literature without involving any patient, any new clinical or fundamental research or any type of personal information. Therefore, no ethical approval is required. The results of this scoping review will be submitted for publication in an international peer-reviewed journal and will help to understand how lcSSc was assessed in the past, informing the discussion on which items should be included in a combined response index dedicated to lcSSc.

TABLES :

3 Tables

trials, before and after studies, Meta-analyses and systematic reviews. Translational and basic sciences studies will be considered for full-text reviewing, as some of them may highlight specific biomarkers of interest. **For clinical trials:** Only randomized controlled trials and non-randomized controlled trials will be considered	legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded, observational analytical cross-sectional studies, case-control studies, prospective and retrospective cohort studies will be excluded. Studies not concerned with human subjects or not pertaining to adults will be excluded

Table 2 : General template for title and abstract screening

Questions	
Is the article written in English	☐ Yes ☐ No
Is the article after 1988 (or published in 1988)	☐ Yes ☐ No
Is this an observational study based on primary data or is this a systematic review/metanalysis published as original article	☐ Yes ☐ No
• If yes, does title or abstract mention lcSSc or Sine or lSSc or CREST/CRST ?	☐ Yes ☐ No
• If no, is this a randomized controlled trial or unrandomized controlled trial which includes patients with lcSSc or Sine or lSSc or CREST/CRST ?	☐ Yes ☐ No ☐ Uncertain: needs full text reviewing

Table 3 : Preliminary charting table for data extraction

Item	Description
Journal	
First Author	
Year publication	
Patient population :	□ DcSSc and LcSSc (including lSSc, sine and CREST) □ LcSSc only (including lSSc, sine and CREST)
Number of patients evaluated (total)	
Number of patients with LcSSc (including lSSc, sine and CREST)	
Study type	□ Observational cross sectional study (pro or retrospective) □ Observational longitudinal study (pro or retrospective) □ Case control study □ Randomized Clinical trial □ Unrandomized Clinical trial □ Basic sciences (including studies only dedicated to biomarkers)
Domain 1 as explicitly mentioned in the article	
Outcome 1 (of D1) with assessment methods	
Outcome 2 (of D1) with assessment methods	
Add as many outcomes as necessary	
(…)	
Domain 2 as explicitly mentioned in the article	
Outcome 1 (of D2) with assessment methods	
Outcome 2 (of D2) with assessment methods	
Add as many outcomes as necessary	
(…)	
No domain explicitly mentioned in the article (Dn/a)	
Outcome 1 (of Dn/a) with assessment methods	
Outcome 2 (of Dn/a) with assessment methods	
Add as many outcomes as necessary	
(…)	

REFERENCES

Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005(8):19–32.

Avouac J, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis. 2011 Mar;70(3):476-81.

Boers M et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol. 2014

Boers M et al. OMERACT Filter 2.1: Elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. J Rheumatol. 2019 Aug;46(8):1021-1027

Clements P et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol. 1995 Jul;22(7):1281-5.

Clements PJ et al. Scleroderma Lung Study Group. Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. Ann Rheum Dis. 2007 Dec;66(12):1641-7.

Cutolo M et al. Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study. Arthritis Rheumatol. 2016 Oct;68(10):2527-39.

Denton CP et al. Efficacy and Safety of Selexipag in Adults With Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Randomized, Placebo Controlled, Phase II Study. Arthritis Rheumatol. 2017 Dec;69(12):2370-2379.

Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017 Oct 7;390(10103):1685-1699.

Distler O et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019 Jun 27;380(26):2518-2528.

Frantz C et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. Semin Arthritis Rheum. 2016

Frantz C et al. EUSTAR co-authors. Outcomes of limited cutaneous systemic sclerosis patients: Results on more than 12,000 patients from the EUSTAR database. Autoimmun Rev. 2020 Feb;19(2):102452.

Gliddon AE et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. Arthritis Rheum. 2007 Nov;56(11):3837-46.

Hachulla E et al. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. Ann Rheum Dis. 2016 Jun; 75(6): 1009–1015.

Khanna D, Ahmed M, Furst DE, Ginsburg SS, Park GS, Hornung R, Tsevat J. Health values of patients with systemic sclerosis. Arthritis Rheum. 2007 Feb 15;57(1):86-93.

Khanna D, et al, Development of a provisional core set of response measures for clinical trials of systemic sclerosis. Ann Rheum Dis. 2008

Khanna D et al, The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. Arthritis Rheumatol. 2016

Korn JH et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004 Dec;50(12):3985-93.

Levac D et al. Scoping studies: advancing the methodology. Implement Sci 2010;5:69.

Leroy EC et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988 Feb;15(2):202-5.

Leroy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001; 8(7):1573–6.

Lescoat et al. The nosology of systemic sclerosis: how lessons from the past offer new challenges in reframing an idiopathic rheumatological disorder. The Lancet Rheumatol, 2020 1(4):e257-e264

Methley AM et al. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res. 2014 Nov 21;14:579.

Munn Z et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 2018 Nov 19;18(1):143.

Nihtyanova SI et al. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. Ann Rheum Dis. 2008 Jan;67(1):120-3. Epub 2007 Jul 27.

Shamseer L et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;350:g7647. doi: 10.1136/bmj.g7647.

Steen VD et al. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum. 1997 Nov;40(11):1984-91.

Tashkin DP, et al, Scleroderma Lung Study Research G. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006

Tashkin DP, et al, Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016

Trico AC et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467-473.

Wigley FM et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med. 1994 Feb 1;120(3):199-206.

AUTHORS' CONTRIBUTIONS

AL & MHB wrote the first draft of the manuscript. AL, MHB, WT, DR, JDP, MH, RS, FZ, DK conceived the scoping review, developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

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Scoping review protocol

DOMAINS AND OUTCOME MEASURES FOR THE ASSESSMENT OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS: A SCOPING REVIEW PROTOCOL

Alain Lescoat[1,2*], David Roofeh[3], Whitney Townsend[4], Michael Hughes[5], Robert D Sandler[5], François Zimmermann[2], John D Pauling[6], Maya H Buch[7,8], Dinesh Khanna[3]

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PRISMA Checklist for CRISTAL review project
Extension for Scoping Reviews (PRISMA-ScR)

Tricco, Andrea C, Lillie, Erin, Zarin, Wasifa et al. (25 more authors) (2018) PRISMA : Extension for Scoping Reviews (PRISMA-ScR) : Checklist and Explanation. Annals of Internal Medicine. pp. 467-473. ISSN 0003-4819

Table 1: PRISMA-ScR Checklist

Section	Item	PRISMA-ScR checklist item	Reported on page #
Title			
Title	1	Identify the report as a scoping review.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background, objectives, eligibility criteria, sources of evidence, charting methods, results and conclusions that relate to the review question(s) and objective(s).	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review question(s)/objective(s) lend themselves to a scoping review approach.	5 and 6
Objectives	4	Provide an explicit statement of the question(s) and objective(s) being addressed with reference to their key elements (e.g., population or participants, concepts and context), or other relevant key elements used to conceptualize the review question(s) and/or objective(s)).	6 and 7
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number.	NA it is the publication of the protocol
Eligibility criteria	6	Specify the characteristics of the sources of evidence (e.g., years considered, language, publication status) used as criteria for eligibility, and provide a rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with authors to identify additional sources) in the search, as well as the date the most recent search was executed.	8 and 10
Search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8 and 10
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening, eligibility) included in the scoping review.	8
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., piloted forms; forms that have been tested by the team before their use, whether data charting was done independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	11
Critical appraisal of individual sources of evidence	12	***If done,*** provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	8
Summary measures	13	*Not applicable for scoping reviews.*	
Synthesis of results	14	Describe the methods of handling and summarizing the data that were charted.	12
Risk of bias across studies	15	*Not applicable for scoping reviews.*	
Additional analyses	16	*Not applicable for scoping reviews.*	
Results			
Selection of sources of evidence	17	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	NA it is the publication of the protocol Results are unknown for the moment
Characteristics of sources of evidence	18	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	19	***If done***, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	20	For each included source of evidence, present the relevant data that were charted that relate to the review question(s) and objective(s).	it is the publication of the protocol Results are unknown for the moment
Synthesis of	21	Summarize and/or present the charting results as they relate to the review	

Section	Item	PRISMA-ScR checklist item	Reported on page #
results		question(s) and objective(s).	
Risk of bias across studies	22	*Not applicable for scoping reviews.*	
Additional analyses	23	*Not applicable for scoping reviews.*	
Discussion			
Summary of evidence	24	Summarize the main results (including an overview of concepts, themes, and types of evidence available), explain how they relate to the review question(s) and objectives, and consider the relevance to key groups.	NA
Limitations	25	Discuss the limitations of the scoping review process.	it is the publication of the protocol
Conclusions	26	Provide a general interpretation of the results with respect to the review question(s) and objective(s), as well as potential implications and/or next steps.	Results are unknown for the moment
Funding			
Funding	27	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2

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Scoping review protocol

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Abstract (286 words/300)

Introduction :

Limited cutaneous Systemic sclerosis (lcSSc) is the most frequent subset of systemic sclerosis. Despite this, lcSSc is not the major focus of clinical studies. The lack of interventional studies in lcSSc is due, in part, to a paucity of relevant outcome measures to effectively evaluate this subset. A combined response index dedicated to lcSSc would facilitate development of well-designed trials and approval of new drugs. The objective of this scoping review is to perform a broad and comprehensive identification of the outcome measures (core set items) within relevant domains, which have been used so far to assess lcSSc.

Methods and analysis :

The planned scoping review will be based on the approach proposed by Arksey et al. and further developed by Levac et al. Development and reporting will follow the Preferred Reporting Items for Systematic Reviews and MetaAnalyses—Extension for Scoping Reviews (PRISMA-ScR) checklist and guidelines. The development of the search strategy was guided by the concepts of Domains and Outcomes based on the OMERACT (Outcome Measures in Rheumatology) approach and by the different names and definitions of SSc, with a specific emphasis on their occurrence in clinical trial studies. Two databases will be searched: MEDLINE and EMBASE. Studies in English, published from the year 1988 onwards, will be included, since 1988 corresponds to the publication of LeRoy's first consensus definition of lcSSc. Data will be extracted and analyzed using a standardized charting tool.

Ethics and dissemination :

No ethical approval is required for this study. The results will be submitted to an international peer-reviewed journal and scientific conferences, informing the discussion on which items should be included in a combined response index dedicated to lcSSc (The CRISTAL project: Combined Response Index for Scleroderma Trial Assessing LcSSc).

Key words : Systemic sclerosis, scleroderma, domains, outcome measures, classification.

Strengths and limitations of this study

-The proposed scoping review will allow a broad and comprehensive identification of the outcome measures (core set items) within relevant domains, which have been used so far to assess lcSSc. The specific emphasis on clinical trials including patients with lcSSc will ensure the identification of relevant outcome measures used so far and their mapping within key domains, eventually highlighting gaps and main issues concerning the lack of outcome measures and/or their poor use.

-Although comprehensive, this study design has limitations regarding the number of databases, the language and search terms used, and may under-represent observational studies and basic science articles that do not explicitly mention the word "limited SSc" or "limited cutaneous SSc" in their title or abstract.

-By focusing on articles published after 1988, this scoping review may not capture the outcome measures used to assess equivalent subsets of lcSSc before this date, but this will ensure that the population included match with the contemporary definition of lcSSc.

-For this first phase of the initiative, we are seeking to identify relevant domains and outcomes as opposed to evaluate their specific properties in lcSSc. Nevertheless, the several clinical trials to be evaluated will not report results solely in lcSSc patients, which constitutes a limitation of our protocol.

-Regulatory agencies emphasize outcomes should reflect how patients feel, function and/or survive. With this in mind, as the main objective is to identify domains and outcomes that could be incorporated in a combined response index, we have not included congress databases or studies on exploratory biomarkers, or epigenetic/genetic studies. Such a selection will limit the comprehensiveness of this scoping review but will insure its coherence with the global objective of the project. Regarding this main objective, to remain consistent with the comprehensive concept of scoping review, and considering that we are not performing a systematic review or meta-analysis, we will not evaluate quality appraisal, and this could be considered as a limitation of this protocol.

INTRODUCTION:

Rationale

Systemic sclerosis (SSc) or scleroderma is a rare auto-immune disorder which includes a wide range of clinical manifestations [1]. SSc is characterized by the association of three main features: vasculopathy with Raynaud's phenomenon as the hallmark symptom, exuberant fibrosis of the skin and internal organs, and, immune activation with the occurrence of specific autoantibodies and inflammatory features such as synovitis and tenosynovitis [2].

SSc is further sub-classified into limited cutaneous (lcSSc), and diffuse cutaneous (dcSSc) according to 1988 Leroy & Medsger's classification [3], revised in 2001[4], and based on the extent of skin involvement by underlying fibrosis. LcSSc constitutes 60-70% of all SSc and is considered a milder sub-phenotype of SSc with Raynaud's phenomenon and GI involvement as common features and pulmonary arterial hypertension also observed in this subgroup. However, accumulating data from EUSTAR (European Scleroderma Trials and Research group) and other cohorts show that these and wider visceral complications occur in a significant proportion of patients with lcSSc [5]. This concept is further highlighted by the recent clinical trials targeting interstitial lung disease that recruited patients with lcSSc as well as dcSSc (SLS studies [6,7] and SENSCIS trial [8]). Moreover, recent studies focusing on quality of life have demonstrated that patients with lcSSc experience a significant impairment in their daily quality-of-life and that patients' experiences of lcSSc have been largely overlooked [9,10].

Despite this high prevalence of lcSSc and typically earlier diagnosis of this specific subtype, there is poor validation of dedicated strategies for the management of patients with lcSSc. The lack of interventional studies in lcSSc is due, in part, to a paucity of relevant outcome measures to effectively evaluate this major subset. The range of clinical manifestations of SSc is wide, and clinical items are classified within domains, for example, outcomes related to vasculopathy such as digital ulcers, or outcomes related to interstitial lung disease such as the decline of pulmonary function measured through the annual decline of forced vital capacity (FVC) [11,12]. Drug development and trials have focused on dcSSc partly due to the availability of validated outcome measures, including a relevant combined response index, the ACR-CRISS index [11,13,14], that captures the global improvement of dcSSc. A composite index score dedicated to lcSSc that combines different aspects of the disease would similarly facilitate development of well-designed trials and approval of new drugs to treat lcSSc [15]. Recent observational studies have highlighted the prognostic and predictive values of new imaging techniques and clinical markers such as capillaroscopy or laser doppler for vasculopathy, but the relevance of including such evaluation tools in combined index approach is still to be determined. Identifying and

defining relevant candidate outcome measures within key SSc-associated domains [16] to be included in such a combined index is the necessary first step for the construction of a future index for lcSSc.

Objective

The objective of this scoping review is to perform a broad and comprehensive identification of the core set items (and/or outcome measures) within relevant domains, which have been used so far to assess lcSSc since the endorsement of its consensual definition in 1988.

METHODS & ANALYSIS

We have chosen to conduct a scoping review to perform this literature search, based on the methodological framework proposed by Arksey and O'Malley [17] and further developed by Levac and colleagues [18]. Scoping reviews are especially effective to identify key factors/characteristics related to a concept, in our case, domains related to the assessment of lcSSc, and, to examine how research is conducted on a certain topic or field, in our case, the outcome measures within the identified domains [19]. This scoping review will comprehensively identify outcomes measures in lcSSc to inform on how lcSSc has been evaluated to date and identify gaps in domains of clinical relevance. This is the first step of a project which aims to select the items that could be included in a combined response index for clinical trials assessing patients with lcSSc (The CRISTAL project : Combined Response Index for Scleroderma Trial Assessing LcSSc) [15].

Conceptual framework and key concepts

The concepts of Domains and Outcomes are based on the OMERACT (Outcome Measures in Rheumatology) approach [20]. This approach is made up of two important and sequential components: identification of **what** to measure (Domain Set), for example in the field of systemic sclerosis, measuring the impact of "vasculopathy", measuring "interstitial lung disease", or impact of pain on quality of life; and then identification of **how** to measure each of the identified domains using relevant instruments or tools (Outcome measurement Set), *i.e.* for the domain "vasculopathy" the number of new digital ulcers occurring during follow-up or for the domain "interstitial lung disease" change in FVC during the considered period or pain visual analog scale or PROMIS® items to assess the intensity of pain and pain interference [21].

The systematic identification of outcome measures (how to measure a manifestation / visceral involvement) and the domains they are related to (which manifestations of the disease/visceral

involvement is measured) will inform on how lcSSc has been assessed to date and to guide the discussion on which items should be included in a combined response index dedicated to lcSSc.

Publication dates and time period.

In 1988, the LeRoy's classification of SSc, built on previous 1980 criteria, crystallized the two main subsets of SSc, lcSSc and dcSSc. Prior to LeRoy's classification, the concept of limited SSc was recognised but several terms were used to describe features of this subgroup such as acrosclerosis, CREST, dermatosclerosis or acroscleroderma. These definitions were inconsistent and in contrast with those of generalized scleroderma or diffuse scleroderma, with the latter more or less matching with the definition of the diffuse cutaneous subset [22]. The absence of a consensus classification that fully captured the concept and components of limited SSc, led to variable outcome measures and subgrouping criteria. The endorsement to define these two subsets (limited vs diffuse) of the disease within the 1988 classification criteria was based on prognostic data and defined by the extent of skin fibrosis involvement. This was a historical milestone in the nosology of SSc. Examining articles published before 1988 could lead to the inclusion of outcomes used to assess populations that would not match with the contemporary definition of lcSSc and have therefore not been included. After 1988, the term CREST/CRST syndrome persisted and overlapped with lcSSc. Based on this, articles only mentioning CREST/CRST in their title and abstract after 1988 will also be considered for full text review, and full-text assessment will confirm whether the population studies matches with the contemporary definition of lcSSc.

Scoping review questions

Main question : What are the outcome measures within relevant domains that have been used to assess lcSSc since the 1988 LeRoy's classification has been in use.

Secondary questions :

How many studies have been published by year?

What types of studies have been published?

General overview of the search strategy

As this scoping review focuses on limited cutaneous SSc/scleroderma our search terms will focus on studies with original data/original articles that explicitly mention the subtype "limited" and/or CR(E)ST in their title or abstract (**#1**). Nonetheless, when applying this strategy to milestone articles based on the reviewers' expertise [6–8,23–32], we identified a gap, particularly in picking up clinical trials. Indeed, many clinical trials only mention "scleroderma" in their title or abstract, without specifying limited or diffuse,

although they indeed include patients with lcSSc. This is a major issue since the objective is to identify outcome measures to be included in a combined response index for clinical trials. To tackle this issue, we will include in the search terms all clinical trials mentioning scleroderma or SSc in the title or abstract (**#2**), even if the word "limited" is not mentioned in the title or abstract. For pragmatic reasons, observational studies will not be included in this **#2**, only clinical trials, in line with the overall objective of this scoping review.

Information sources :

Electronic databases: PubMed (Medline), Embase.com

Search terms [33]

Final search strategy for title/abstract evaluation = #1 and #2 as follow:

#1

Population :

Search terms :

Ovid MEDLINE SENSITIVE: exp Scleroderma, Limited/ OR (Scleroderma, Systemic/ AND limited.ti.) OR ((Systemic scleroderma.mp. OR systemic sclerodermas.mp. OR systemic sclerosis.mp. OR systemic scleroses.mp. OR SSc.mp.) ADJ3 limited.mp.) OR lcSSc.mp. OR ((Crest.ti,ab. OR CRST.ti,ab.) ADJ1 syndrome*.ti,ab.)

Embase.com : (('limited scleroderma'/exp OR ('systemic sclerosis'/de AND limited:ti) OR ((('systemic scleroderma' OR 'systemic sclerodermas' OR 'systemic sclerosis' OR 'systemic scleroses' OR ssc) NEAR/3 limited):ti,ab) OR lcssc:ti,ab OR 'syndrome CREST'/exp OR (((crest OR crst) NEAR/1 syndrome*):ti,ab)) NOT ([animals]/lim NOT [humans]/lim)) AND ('article'/it OR 'article in press'/it)

Included

- Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. When the number of lcSSc patients is mentioned, only studies with 20 lcSSc patients or more will be included.

Excluded

- Articles only focusing on localized scleroderma / morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be excluded, articles focusing on VEDOSS (Very Early Diagnosis Of Systemic Sclerosis [34] only and articles focusing on dcSSc only will be excluded as well.

Intervention : n/a

Comparison : n/a

Outcomes : n/a as the selection of domains and outcome measures is the aim of this scoping review

Studies:

Included articles

- Studies written in English
- Original studies including: observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, before and after studies, Meta-analyses and systematic reviews.

Excluded articles

- Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Genetic or epigenetic studies will be excluded. Observational studies specifically evaluating the prevalence of the disease will also be excluded. Translational and basic sciences studies, including observational studies dedicated to auto-antibody testing, will not be considered for full-text review as they will not allow to identify new validated outcome measures reflecting feeling, functioning or surviving, that could be used for an acceptable combine response index.
- Studies not concerned with human subjects or not pertaining to adult studies will be excluded
- Article published before 1988 and LeRoy's classification (official creation/endorsement of the concept of limited SSc) will be excluded

#2

Population:

Search terms :

Ovid MEDLINE SENSITIVE:
using Sensitivity/precision maximized Cochrane limit*
(Exp Scleroderma, Systemic/ OR "Systemic scleroderma".mp. OR "systemic sclerodermas".mp. OR "systemic sclerosis".mp. OR "systemic scleroses".mp.) AND

Sensitivity/precision maximized Cochrane filter
(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti.) not (exp animals/ not humans.sh.)

Included

- Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well.

Excluded

- Articles only focusing on localized scleroderma / morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded

Intervention : Randomized controlled trials and unrandomized controlled trials only
Comparison : n/a
Outcomes : n/a as the selection of domains and outcome measures is the aim of this scoping review

Studies :

Included articles

- Only studies written in English will be considered
- Randomized controlled trials and unrandomized controlled trials will be especially considered for this #2. Unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trials evaluating a treatment or a therapeutic strategy will also be considered for full-text review. Meta-analysis and systematic reviews of therapeutic trials will also be included for full-text review.

Excluded articles

- Reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded, observational analytical cross-sectional studies, case-control studies, prospective and retrospective cohort studies will be excluded.
- Studies not concerned with human subjects or not pertaining to adults will be excluded
- Article published before 1988 and LeRoy's classification (official creation/endorsement of the concept of limited SSc) will be excluded

Synthesis of eligibility criteria (Table 1)

Inclusion criteria:

1/ Language: English

2/ Publication date: after 1988 and Leroy's classification

3/ Population:

For observational studies: Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. When the number of lcSSc patients is mentioned, only studies with 20 lcSSc patients or more will be included.

For clinical/therapeutic trials: Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well.

4/ Studies:

For observational studies: observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, Meta-analyses and systematic reviews.

For clinical/therapeutic trials: Randomized controlled trials and non-randomized controlled trials will be considered, unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trials evaluating a treatment or a therapeutic strategy will also be considered for full-text review. Meta-analysis and systematic reviews of clinical/therapeutic trials will also be included for full-text review.

Exclusion criteria:

1/ Population :

Articles only focusing on localized scleroderma/morphea without including systemic sclerosis /systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded. Studies not concerned with human subjects or not pertaining to adult will be excluded.

2/ Studies:

For observational studies: Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Genetic or epigenetic studies will be excluded. Observational studies specifically evaluating the prevalence of the disease will also be excluded. Translational and basic sciences studies, including observational studies dedicated to auto-antibody testing, will not be considered for full-text review as they will not allow to identify new validated outcome measures reflecting feeling, functioning or surviving, that could be used for an acceptable combine response index.

For clinical/therapeutic trials:

Narrative reviews focusing on clinical trials, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded.

For all : studies without abstract available (only title provided) will be excluded.

Reporting of protocol and Study records

This study protocol follows PRISMA-ScR guidelines [35] and PRISMA guidelines for the publication of systematic review protocols [36], with specific adaptations for this scoping review protocol.

Data management will be housed through Covidence® (https://www.covidence.org/home), under the supervision of DK and MHB.

DR, JP, MH, RS, AL, FZ will screen citations and review for eligibility and inclusion, based on the eligibility criteria and the article selection template (**Table1 and 2**). AL will assess all the titles (T) and abstracts (A), and the other 5 reviewers will evaluate 1/5th of T/A to ensure that all articles will be double checked. Inter-rater agreement will be evaluate using Cohen's Kappa statistics. A first test of agreement will be performed based on 50 citations. If Kappa coefficients are under 0.8, we will evaluate the disagreements and understand the reason to correct misunderstanding and ensure consistency for the rest of the review process. T and A will then be reviewed for the entire article list. Any disagreements between reviewers will be reviewed and resolved by DK and/or MHB. If uncertainty persists, the manuscript will be included for comprehensiveness. Where there is lack of data clarity pertaining to exclusion criteria in manuscripts, mentors will be contacted to discuss this issue. Agreement between pairs for overlapping citations will also be assessed using Cohen's Kappa statistics at the end of the process. After article selection, the data extraction template (**Table 3**) for full texts review will be evaluated by two reviewers on a sample of 20% of included studies to adjust its sensitivity. Once the template is finalized, one reviewer will then perform the analysis, and the second reviewer will independently check a sample of the total of 20% articles, for accuracy. Any disagreements will be reviewed and resolved by DK and/or MHB. Citation searching will be applied to identify additional studies, through checking of reference lists of primary studies. Although quality appraisal is typically necessary for systematic literature reviews and meta-analyses, using evaluation tools such as the Jadad scale [37], the Cochrane risk of bias tool [38] or the Newcastle-Ottawa Scale (NOS) for non-randomized studies [39] our focus is to conduct a scoping review to determine domains and outcome measures that have been studied in lcSSc. As such, quality appraisal is not planned. We intend to start Titles and Abstracts selection on Covidence ® starting January 2021.

Presentation of the results

We expect to present the main results of this scoping review, with a least one table summarizing domains and identified outcomes. For the main domains of interest their frequency in the literature will also be provided in a Table. Identified gaps and main issues concerning the lack of outcome measures

and/or their poor use will also be highlighted in a third table. In the end, a comprehensive map of the main domains and outcomes will be provided within a dedicated graphical abstract or figure.

ETHICS

This scoping review is based on the analysis of published scientific literature without involving any patient, any new clinical or fundamental research or any type of personal information. Therefore, no ethical approval is required.

PATIENT AND PUBLIC INVOLVEMENT

This scoping review plans to analyze the published scientific literature, no patients are involved for this specific analysis. The overall objective of the CRISTAL project is to develop a combined response index for lcSSc with input from the patient partners, clinicians with expertise in systemic sclerosis, and methodologists. All the steps of the project, and patient partners involvement have been published previously [15].

The results of this scoping review will be submitted for publication in a peer-reviewed journal and will provide an overview of domains and items that are captured in observational cohorts and clinical trials in lcSSc and can be utilized for a combined index.

TABLES :

3 Tables

Table 1 : Inclusion and exclusion criteria for the scoping review

Inclusion criteria	Exclusion criteria
• Language: English • Publication date: after 1988 (or in 1988) • Population: **For observational studies:** Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. When the number of lcSSc patients is mentioned, only studies with 20 lcSSc patients or more will be included. **For clinical/therapeutic trials:** Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well. • Studies: **For observational studies:** observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, Meta-analyses and systematic reviews. **For clinical/therapeutic trials:** Randomized controlled trials and non-randomized controlled trials will be considered, unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trials evaluating a treatment or a therapeutic strategy will also be considered for full-text review. Meta-analysis and systematic reviews of clinical/therapeutic trials will also be included for full-text review.	• Population: Articles only focusing on localized scleroderma/morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded. Studies not concerned with human subjects or not pertaining to adult will be excluded. • Studies: **For observational studies:** Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Genetic or epigenetic studies will be excluded. Observational studies specifically evaluating the prevalence of the disease will also be excluded. Translational and basic sciences studies, including observational studies dedicated to auto-antibody testing, will not be considered for full-text review as they will not allow to identify new validated outcome measures reflecting feeling, functioning or surviving, that could be used for an acceptable combine response index. **For clinical/therapeutic trials:** Narrative reviews focusing on clinical trials, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. **For all :** studies without abstract available (only title provided) will be excluded.

Table 2 : General template for title and abstract screening

Questions	
1/ Is the article written in English	☐ Yes ☐ No
2/ Is the article after 1988 (or published in 1988)	☐ Yes ☐ No
3/ Is this an observational study based on primary data or is this a systematic review/metanalysis published as original article, And is not a genetic or epigenetic or prevalence or basic science/biomarker study.	☐ Yes ☐ No
• If 1-2-3 fulfilled, does title or abstract mention lcSSc or Sine or lSSc or CREST/CRST ? • If yes, if the number of patients from the above mentioned subgroup is specified, is it 20 or more ?	☐ Yes ☐ No ☐ Yes ☐ No ☐ Uncertain: needs full text reviewing
If 1-2 fulfilled and if the title or abstract does not mention lcSSc or Sine or lSSc or CREST/CRST, • is this a randomized controlled trial, non-randomized controlled trial, an unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trial evaluating a treatment or a therapeutic strategy ? • Which does not exclusively concern dcSSc patients ?	☐ Yes ☐ No ☐ Uncertain: needs full text reviewing

Table 3 : Preliminary charting table for data extraction

Item	Description
Journal	
First Author	
Year publication	
Patient population :	□ DcSSc and LcSSc (including lSSc, sine and CREST) □ LcSSc only (including lSSc, sine and CREST)
Number of patients evaluated (total)	
Number of patients with LcSSc (including lSSc, sine and CREST)	
Study type	□ Observational cross sectional study (pro or retrospective) □ Observational longitudinal study (pro or retrospective) □ Case control study □ Randomized Clinical trial □ Unrandomized Clinical trial □ Basic sciences (biomarkers)
Domain 1 as explicitly mentioned in the article	
Outcome 1 (of D1) with assessment methods	
Outcome 2 (of D1) with assessment methods	
Add as many outcomes as necessary	
(…)	
Domain 2 as explicitly mentioned in the article	
Outcome 1 (of D2) with assessment methods	
Outcome 2 (of D2) with assessment methods	
Add as many outcomes as necessary	
(…)	
No domain explicitly mentioned in the article (Dn/a)	
Outcome 1 (of Dn/a) with assessment methods	
Outcome 2 (of Dn/a) with assessment methods	
Add as many outcomes as necessary	
(…)	

REFERENCES

1 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;390:1685–99. doi:10.1016/S0140-6736(17)30933-9

2 Lescoat A, Ballerie A, Belhomme N, *et al.* Synovial involvement assessed by power Doppler ultra-sonography in systemic sclerosis: results of a cross-sectional study. *Rheumatology (Oxford)* 2018;57:2012–21. doi:10.1093/rheumatology/key214

3 LeRoy EC, Black C, Fleischmajer R, *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202–5.

4 LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001;28:1573–6.

5 Frantz C, Huscher D, Avouac J, *et al.* Outcomes of limited cutaneous systemic sclerosis patients: Results on more than 12,000 patients from the EUSTAR database. *Autoimmun Rev* 2020;19:102452. doi:10.1016/j.autrev.2019.102452

6 Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655–66. doi:10.1056/NEJMoa055120

7 Tashkin DP, Roth MD, Clements PJ, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016;4:708–19. doi:10.1016/S2213-2600(16)30152-7

8 Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med* 2019;380:2518–28. doi:10.1056/NEJMoa1903076

9 Frantz C, Avouac J, Distler O, *et al.* Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. *Semin Arthritis Rheum* 2016;46:115–23. doi:10.1016/j.semarthrit.2016.02.005

10 Khanna D, Ahmed M, Furst DE, *et al.* Health values of patients with systemic sclerosis. *Arthritis Rheum* 2007;57:86–93. doi:10.1002/art.22465

11 Khanna D, Lovell DJ, Giannini E, *et al.* Development of a provisional core set of response measures for clinical trials of systemic sclerosis. *Ann Rheum Dis* 2008;67:703–9. doi:10.1136/ard.2007.078923

12 Boers M, Kirwan JR, Wells G, *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745–53. doi:10.1016/j.jclinepi.2013.11.013

13 Khanna D, Berrocal VJ, Giannini EH, *et al.* The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. *Arthritis & Rheumatology (Hoboken, NJ)* 2016;68:299–311. doi:10.1002/art.39501

14 Khanna D, Huang S, Lin CJF, *et al.* New composite endpoint in early diffuse cutaneous systemic sclerosis: revisiting the provisional American College of Rheumatology Composite Response Index in Systemic Sclerosis. *Ann Rheum Dis* Published Online First: 30 November 2020. doi:10.1136/annrheumdis-2020-219100

15 Lescoat A, Murphy SL, Roofeh D, *et al.* Considerations for a combined index for limited cutaneous systemic sclerosis to support drug development and improve outcomes. *Journal of Scleroderma and Related Disorders* 2020;:2397198320961967. doi:10.1177/2397198320961967

16 Boers M, Kirwan JR, Gossec L, *et al.* How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;41:1025–30. doi:10.3899/jrheum.131314

17 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 2005;8:19–32. doi:10.1080/1364557032000119616

18 Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:69. doi:10.1186/1748-5908-5-69

19 Munn Z, Peters MDJ, Stern C, *et al.* Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology* 2018;18:143. doi:10.1186/s12874-018-0611-x

20 Boers M, Beaton DE, Shea BJ, *et al.* OMERACT Filter 2.1: Elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. *J Rheumatol* 2019;46:1021–7. doi:10.3899/jrheum.181096

21 Khanna D, Krishnan E, Dewitt EM, *et al.* The future of measuring patient-reported outcomes in rheumatology: Patient-Reported Outcomes Measurement Information System (PROMIS). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S486-490. doi:10.1002/acr.20581

22 Lescoat A, Cavalin C, Ehrlich R, *et al.* The nosology of systemic sclerosis: how lessons from the past offer new challenges in reframing an idiopathic rheumatological disorder. *The Lancet Rheumatology* 2019;1:e257–64. doi:10.1016/S2665-9913(19)30038-4

23 Wigley FM, Wise RA, Seibold JR, *et al.* Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med* 1994;120:199–206. doi:10.7326/0003-4819-120-3-199402010-00004

24 Clements P, Lachenbruch P, Siebold J, *et al.* Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol* 1995;22:1281–5.

25 Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997;40:1984–91. doi:10.1002/art.1780401110

26 Korn JH, Mayes M, Matucci Cerinic M, *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004;50:3985–93. doi:10.1002/art.20676

27 Gliddon AE, Doré CJ, Black CM, *et al.* Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis Rheum* 2007;56:3837–46. doi:10.1002/art.22965

28 Clements PJ, Roth MD, Elashoff R, *et al.* Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. *Ann Rheum Dis* 2007;66:1641–7. doi:10.1136/ard.2007.069518

29 Nihtyanova SI, Brough GM, Black CM, *et al.* Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2008;67:120–3. doi:10.1136/ard.2007.072686

30 Hachulla E, Hatron P-Y, Carpentier P, *et al.* Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. *Ann Rheum Dis* 2016;75:1009–15. doi:10.1136/annrheumdis-2014-207001

31 Cutolo M, Herrick AL, Distler O, *et al.* Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study. *Arthritis Rheumatol* 2016;68:2527–39. doi:10.1002/art.39718

32 Denton CP, Hachulla É, Riemekasten G, *et al.* Efficacy and Safety of Selexipag in Adults With Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Randomized, Placebo-Controlled, Phase II Study. *Arthritis & Rheumatology (Hoboken, NJ)* 2017;69:2370–9. doi:10.1002/art.40242

33 Methley AM, Campbell S, Chew-Graham C, *et al.* PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014;14:579. doi:10.1186/s12913-014-0579-0

34 Avouac J, Fransen J, Walker UA, *et al.* Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. *Ann Rheum Dis* 2011;70:476–81. doi:10.1136/ard.2010.136929

35 Tricco AC, Lillie E, Zarin W, *et al.* PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467–73. doi:10.7326/M18-0850

36 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647. doi:10.1136/bmj.g7647

37 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12. doi:10.1016/0197-2456(95)00134-4

38 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898

39 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology* 2010;25:603–5.

AUTHORS' CONTRIBUTIONS

AL & MHB wrote the first draft of the manuscript. AL, MHB, WT, DR, JDP, MH, RS, FZ, DK conceived the scoping review, developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

DATA AVAILIBILIY STATEMENT

Data are available upon reasonable request to the corresponding author.

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Scoping review protocol

DOMAINS AND OUTCOME MEASURES FOR THE ASSESSMENT OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS: A SCOPING REVIEW PROTOCOL

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PRISMA Checklist for CRISTAL review project
Extension for Scoping Reviews (PRISMA-ScR)

Tricco, Andrea C, Lillie, Erin, Zarin, Wasifa et al. (25 more authors) (2018) PRISMA : Extension for Scoping Reviews (PRISMA-ScR) : Checklist and Explanation. Annals of Internal Medicine. pp. 467-473. ISSN 0003-4819

Table 1: PRISMA-ScR Checklist

Section	Item	PRISMA-ScR checklist item	Reported on page #
Title			
Title	1	Identify the report as a scoping review.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background, objectives, eligibility criteria, sources of evidence, charting methods, results and conclusions that relate to the review question(s) and objective(s).	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review question(s)/objective(s) lend themselves to a scoping review approach.	5 and 6
Objectives	4	Provide an explicit statement of the question(s) and objective(s) being addressed with reference to their key elements (e.g., population or participants, concepts and context), or other relevant key elements used to conceptualize the review question(s) and/or objective(s)).	6 and 7
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number.	NA it is the publication of the protocol
Eligibility criteria	6	Specify the characteristics of the sources of evidence (e.g., years considered, language, publication status) used as criteria for eligibility, and provide a rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with authors to identify additional sources) in the search, as well as the date the most recent search was executed.	8 and 10
Search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8 and 10
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening, eligibility) included in the scoping review.	8
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., piloted forms; forms that have been tested by the team before their use, whether data charting was done independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	11
Critical appraisal of individual sources of evidence	12	***If done,*** provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	8
Summary measures	13	*Not applicable for scoping reviews.*	
Synthesis of results	14	Describe the methods of handling and summarizing the data that were charted.	12
Risk of bias across studies	15	*Not applicable for scoping reviews.*	
Additional analyses	16	*Not applicable for scoping reviews.*	
Results			
Selection of sources of evidence	17	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	NA it is the publication of the protocol Results are unknown for the moment
Characteristics of sources of evidence	18	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	19	***If done***, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	20	For each included source of evidence, present the relevant data that were charted that relate to the review question(s) and objective(s).	it is the publication of the protocol Results are unknown for the moment
Synthesis of	21	Summarize and/or present the charting results as they relate to the review	

Section	Item	PRISMA-ScR checklist item	Reported on page #
results		question(s) and objective(s).	
Risk of bias across studies	22	*Not applicable for scoping reviews.*	
Additional analyses	23	*Not applicable for scoping reviews.*	
Discussion			
Summary of evidence	24	Summarize the main results (including an overview of concepts, themes, and types of evidence available), explain how they relate to the review question(s) and objectives, and consider the relevance to key groups.	NA
Limitations	25	Discuss the limitations of the scoping review process.	it is the publication of the protocol
Conclusions	26	Provide a general interpretation of the results with respect to the review question(s) and objective(s), as well as potential implications and/or next steps.	Results are unknown for the moment
Funding			
Funding	27	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2

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DOMAINS AND OUTCOME MEASURES FOR THE ASSESSMENT OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS: A SCOPING REVIEW PROTOCOL

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Immunology (including allergy), Dermatology
Keywords:	IMMUNOLOGY, INTERNAL MEDICINE, Rheumatology < INTERNAL MEDICINE

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Scoping review protocol

DOMAINS AND OUTCOME MEASURES FOR THE ASSESSMENT OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS: A SCOPING REVIEW PROTOCOL

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Abstract (286 words/300)

Introduction :

Limited cutaneous Systemic sclerosis (lcSSc) is the most frequent subset of systemic sclerosis. Despite this, lcSSc is not the major focus of clinical studies. The lack of interventional studies in lcSSc is due, in part, to a paucity of relevant outcome measures to effectively evaluate this subset. A combined response index dedicated to lcSSc would facilitate development of well-designed trials and approval of new drugs. The objective of this scoping review is to perform a broad and comprehensive identification of the outcome measures (core set items) within relevant domains, which have been used so far to assess lcSSc.

Methods and analysis :

The planned scoping review will be based on the approach proposed by Arksey et al. and further developed by Levac et al. Development and reporting will follow the Preferred Reporting Items for Systematic Reviews and MetaAnalyses—Extension for Scoping Reviews (PRISMA-ScR) checklist and guidelines. The development of the search strategy was guided by the concepts of Domains and Outcomes based on the OMERACT (Outcome Measures in Rheumatology) approach and by the different names and definitions of SSc, with a specific emphasis on their occurrence in clinical trial studies. Two databases will be searched: MEDLINE and EMBASE. Studies in English, published from the year 1988 onwards, will be included, since 1988 corresponds to the publication of LeRoy's first consensus definition of lcSSc. Data will be extracted and analyzed using a standardized charting tool.

Ethics and dissemination:

No ethical approval is required for this study. The results will be submitted to an international peer-reviewed journal and scientific conferences, informing the discussion on which items should be included in a combined response index dedicated to lcSSc (The CRISTAL project: Combined Response Index for Scleroderma Trial Assessing LcSSc).

Key words : Systemic sclerosis, scleroderma, domains, outcome measures, classification.

Strengths and limitations of this study

-The proposed scoping review will allow for comprehensive identification of the outcome measures (core set items) and relevant domains, which have been incorporated in the assessment of lcSSc.

-The limitations of the scoping review include the limited number of databases, the language and search terms used.

-This scoping review may also under-represent observational studies that do not explicitly mention the words “limited SSc” or “limited cutaneous SSc” in their title or abstract.

INTRODUCTION:

Rationale

Systemic sclerosis (SSc) or scleroderma is a rare auto-immune disorder which includes a wide range of clinical manifestations [1]. SSc is characterized by the association of three main features: vasculopathy with Raynaud's phenomenon as the hallmark symptom, exuberant fibrosis of the skin and internal organs, and, immune activation with the occurrence of specific autoantibodies and inflammatory features such as synovitis and tenosynovitis [2].

SSc is further sub-classified into limited cutaneous (lcSSc), and diffuse cutaneous (dcSSc) according to 1988 Leroy & Medsger's classification [3], revised in 2001[4], and based on the extent of skin involvement by underlying fibrosis. LcSSc constitutes 60-70% of all SSc and is considered a milder sub-phenotype of SSc with Raynaud's phenomenon and GI involvement as common features and pulmonary arterial hypertension also observed in this subgroup. However, accumulating data from EUSTAR (European Scleroderma Trials and Research group) and other cohorts show that these and wider visceral complications occur in a significant proportion of patients with lcSSc [5]. This concept is further highlighted by the recent clinical trials targeting interstitial lung disease that recruited patients with lcSSc as well as dcSSc (SLS studies [6,7] and SENSCIS trial [8]). Moreover, recent studies focusing on quality of life have demonstrated that patients with lcSSc experience a significant impairment in their daily quality-of-life and that patients' experiences of lcSSc have been largely overlooked [9,10].

Despite this high prevalence of lcSSc and typically earlier diagnosis of this specific subtype, there is poor validation of dedicated strategies for the management of patients with lcSSc. The lack of interventional studies in lcSSc is due, in part, to a paucity of relevant outcome measures to effectively evaluate this major subset. The range of clinical manifestations of SSc is wide, and clinical items are classified within domains, for example, outcomes related to vasculopathy such as digital ulcers, or outcomes related to interstitial lung disease such as the decline of pulmonary function measured through the annual decline of forced vital capacity (FVC) [11,12]. Drug development and trials have focused on dcSSc partly due to the availability of validated outcome measures, including a relevant combined response index, the ACR-CRISS index [11,13,14], that captures the global improvement of dcSSc. A composite index score dedicated to lcSSc that combines different aspects of the disease would similarly facilitate development of well-designed trials and approval of new drugs to treat lcSSc [15]. Recent observational studies have highlighted the prognostic and predictive values of new imaging techniques and clinical markers such as capillaroscopy or laser doppler for vasculopathy, but the relevance of including such evaluation tools in combined index approach is still to be determined. Identifying and

defining relevant candidate outcome measures within key SSc-associated domains [16] to be included in such a combined index is the necessary first step for the construction of a future index for lcSSc.

Objective

The objective of this scoping review is to perform a broad and comprehensive identification of the core set items (and/or outcome measures) within relevant domains, which have been used so far to assess lcSSc since the endorsement of its consensual definition in 1988.

METHODS & ANALYSIS

We have chosen to conduct a scoping review to perform this literature search, based on the methodological framework proposed by Arksey and O'Malley [17] and further developed by Levac and colleagues [18]. Scoping reviews are especially effective to identify key factors/characteristics related to a concept, in our case, domains related to the assessment of lcSSc, and, to examine how research is conducted on a certain topic or field, in our case, the outcome measures within the identified domains [19]. This scoping review will comprehensively identify outcomes measures in lcSSc to inform on how lcSSc has been evaluated to date and identify gaps in domains of clinical relevance. This is the first step of a project which aims to select the items that could be included in a combined response index for clinical trials assessing patients with lcSSc (The CRISTAL project : Combined Response Index for Scleroderma Trial Assessing LcSSc) [15].

Conceptual framework and key concepts

The concepts of Domains and Outcomes are based on the OMERACT (Outcome Measures in Rheumatology) approach [20]. This approach is made up of two important and sequential components: identification of **what** to measure (Domain Set), for example in the field of systemic sclerosis, measuring the impact of "vasculopathy", measuring "interstitial lung disease", or impact of pain on quality of life; and then identification of **how** to measure each of the identified domains using relevant instruments or tools (Outcome measurement Set), *i.e.* for the domain "vasculopathy" the number of new digital ulcers occurring during follow-up or for the domain "interstitial lung disease" change in FVC during the considered period or pain visual analog scale or PROMIS® items to assess the intensity of pain and pain interference [21].

The systematic identification of outcome measures (how to measure a manifestation / visceral involvement) and the domains they are related to (which manifestations of the disease/visceral

involvement is measured) will inform on how lcSSc has been assessed to date and to guide the discussion on which items should be included in a combined response index dedicated to lcSSc.

Publication dates and time period.

In 1988, the LeRoy's classification of SSc, built on previous 1980 criteria, crystallized the two main subsets of SSc, lcSSc and dcSSc. Prior to LeRoy's classification, the concept of limited SSc was recognised but several terms were used to describe features of this subgroup such as acrosclerosis, CREST, dermatosclerosis or acroscleroderma. These definitions were inconsistent and in contrast with those of generalized scleroderma or diffuse scleroderma, with the latter more or less matching with the definition of the diffuse cutaneous subset [22]. The absence of a consensus classification that fully captured the concept and components of limited SSc, led to variable outcome measures and subgrouping criteria. The endorsement to define these two subsets (limited vs diffuse) of the disease within the 1988 classification criteria was based on prognostic data and defined by the extent of skin fibrosis involvement. This was a historical milestone in the nosology of SSc. Examining articles published before 1988 could lead to the inclusion of outcomes used to assess populations that would not match with the contemporary definition of lcSSc and have therefore not been included. After 1988, the term CREST/CRST syndrome persisted and overlapped with lcSSc. Based on this, articles only mentioning CREST/CRST in their title and abstract after 1988 will also be considered for full text review, and full-text assessment will confirm whether the population studies matches with the contemporary definition of lcSSc.

Scoping review questions

Main question : What are the outcome measures within relevant domains that have been used to assess lcSSc since the 1988 LeRoy's classification has been in use.

Secondary questions :

How many studies have been published by year?

What types of studies have been published?

General overview of the search strategy

As this scoping review focuses on limited cutaneous SSc/scleroderma our search terms will focus on studies with original data/original articles that explicitly mention the subtype "limited" and/or CR(E)ST in their title or abstract (**#1**). Nonetheless, when applying this strategy to milestone articles based on the reviewers' expertise [6–8,23–32], we identified a gap, particularly in picking up clinical trials. Indeed, many clinical trials only mention "scleroderma" in their title or abstract, without specifying limited or diffuse,

although they indeed include patients with lcSSc. This is a major issue since the objective is to identify outcome measures to be included in a combined response index for clinical trials. To tackle this issue, we will include in the search terms all clinical trials mentioning scleroderma or SSc in the title or abstract (**#2**), even if the word "limited" is not mentioned in the title or abstract. For pragmatic reasons, observational studies will not be included in this **#2**, only clinical trials, in line with the overall objective of this scoping review.

Information sources :

Electronic databases: PubMed (Medline), Embase.com

Search terms

Final search strategy for title/abstract evaluation = #1 and #2 as follow [33]**:**

#1

Population :

Search terms :

Ovid MEDLINE SENSITIVE: exp Scleroderma, Limited/ OR (Scleroderma, Systemic/ AND limited.ti.) OR ((Systemic scleroderma.mp. OR systemic sclerodermas.mp. OR systemic sclerosis.mp. OR systemic scleroses.mp. OR SSc.mp.) ADJ3 limited.mp.) OR lcSSc.mp. OR ((Crest.ti,ab. OR CRST.ti,ab.) ADJ1 syndrome*.ti,ab.)

Embase.com : (('limited scleroderma'/exp OR ('systemic sclerosis'/de AND limited:ti) OR ((('systemic scleroderma' OR 'systemic sclerodermas' OR 'systemic sclerosis' OR 'systemic scleroses' OR ssc) NEAR/3 limited):ti,ab) OR lcssc:ti,ab OR 'syndrome CREST'/exp OR (((crest OR crst) NEAR/1 syndrome*):ti,ab)) NOT ([animals]/lim NOT [humans]/lim)) AND ('article'/it OR 'article in press'/it)

Included

- Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. When the number of lcSSc patients is mentioned, only studies with 20 lcSSc patients or more will be included.

Excluded

- Articles only focusing on localized scleroderma / morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be excluded, articles focusing on VEDOSS (Very Early Diagnosis Of Systemic Sclerosis [34] only and articles focusing on dcSSc only will be excluded as well.

Intervention : n/a

Comparison : n/a

Outcomes : n/a as the selection of domains and outcome measures is the aim of this scoping review

Studies:

Included articles

- Studies written in English
- Original studies including: observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, before and after studies, Meta-analyses and systematic reviews.

Excluded articles

- Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Genetic or epigenetic studies will be excluded. Observational studies specifically evaluating the prevalence of the disease will also be excluded. Translational and basic sciences studies, including observational studies dedicated to auto-antibody testing, will not be considered for full-text review as they will not allow to identify new validated outcome measures reflecting feeling, functioning or surviving, that could be used for an acceptable combined response index.
- Studies not concerned with human subjects or not pertaining to adult studies will be excluded
- Article published before 1988 and LeRoy's classification (official creation/endorsement of the concept of limited SSc) will be excluded

#2

Population:

Search terms :

Ovid MEDLINE SENSITIVE:
using Sensitivity/precision maximized Cochrane limit*
(Exp Scleroderma, Systemic/ OR "Systemic scleroderma".mp. OR "systemic sclerodermas".mp. OR "systemic sclerosis".mp. OR "systemic scleroses".mp.) AND

Sensitivity/precision maximized Cochrane filter
(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti.) not (exp animals/ not humans.sh.)

Included

- Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well.

Excluded

- Articles only focusing on localized scleroderma / morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded

Intervention : Randomized controlled trials and unrandomized controlled trials only
Comparison : n/a
Outcomes : n/a as the selection of domains and outcome measures is the aim of this scoping review

Studies :

Included articles

- Only studies written in English will be considered
- Randomized controlled trials and unrandomized controlled trials will be especially considered for this #2. Unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trials evaluating a treatment or a therapeutic strategy will also be considered for full-text review. Meta-analysis and systematic reviews of therapeutic trials will also be included for full-text review.

Excluded articles

- Reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded, observational analytical cross-sectional studies, case-control studies, prospective and retrospective cohort studies will be excluded.
- Studies not concerned with human subjects or not pertaining to adults will be excluded
- Article published before 1988 and LeRoy's classification (official creation/endorsement of the concept of limited SSc) will be excluded

Synthesis of eligibility criteria (Table 1)

Inclusion criteria:

1/ Language: English

2/ Publication date: after 1988 and Leroy's classification

3/ Population:

For observational studies: Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. When the number of lcSSc patients is mentioned, only studies with 20 lcSSc patients or more will be included.

For clinical/therapeutic trials: Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well.

4/ Studies:

For observational studies: observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, Meta-analyses and systematic reviews.

For clinical/therapeutic trials: Randomized controlled trials and non-randomized controlled trials will be considered, unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trials evaluating a treatment or a therapeutic strategy will also be considered for full-text review. Meta-analysis and systematic reviews of clinical/therapeutic trials will also be included for full-text review.

Exclusion criteria:

1/ Population :

Articles only focusing on localized scleroderma/morphea without including systemic sclerosis /systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded. Studies not concerned with human subjects or not pertaining to adult will be excluded.

2/ Studies:

For observational studies: Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Genetic or epigenetic studies will be excluded. Observational studies specifically evaluating the prevalence of the disease will also be excluded. Translational and basic sciences studies, including observational studies dedicated to auto-antibody testing, will not be considered for full-text review as they will not allow to identify new validated outcome measures reflecting feeling, functioning or surviving, that could be used for an acceptable combined response index.

For clinical/therapeutic trials:

Narrative reviews focusing on clinical trials, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded.

For all : studies without abstract available (only title provided) will be excluded.

Reporting of protocol and Study records

This study protocol follows PRISMA-ScR guidelines [35] and PRISMA guidelines for the publication of systematic review protocols [36], with specific adaptations for this scoping review protocol.

Data management will be housed through Covidence® (https://www.covidence.org/home), under the supervision of DK and MHB.

DR, JP, MH, RS, AL, FZ will screen citations and review for eligibility and inclusion, based on the eligibility criteria and the article selection template (**Table1 and 2**). AL will assess all the titles (T) and abstracts (A), and the other 5 reviewers will evaluate 1/5th of T/A to ensure that all articles will be double checked. Inter-rater agreement will be evaluate using Cohen's Kappa statistics. A first test of agreement will be performed based on 50 citations. If Kappa coefficients are under 0.8, we will evaluate the disagreements and understand the reason to correct misunderstanding and ensure consistency for the rest of the review process. T and A will then be reviewed for the entire article list. Any disagreements between reviewers will be reviewed and resolved by DK and/or MHB. If uncertainty persists, the manuscript will be included for comprehensiveness. Where there is lack of data clarity pertaining to exclusion criteria in manuscripts, mentors will be contacted to discuss this issue. Agreement between pairs for overlapping citations will also be assessed using Cohen's Kappa statistics at the end of the process. After article selection, the data extraction template (**Table 3**) for full texts review will be evaluated by two reviewers on a sample of 20% of included studies to adjust its sensitivity. Once the template is finalized, one reviewer will then perform the analysis, and the second reviewer will independently check a sample of the total of 20% articles, for accuracy. Any disagreements will be reviewed and resolved by DK and/or MHB. Citation searching will be applied to identify additional studies, through checking of reference lists of primary studies. Although quality appraisal is typically necessary for systematic literature reviews and meta-analyses, using evaluation tools such as the Jadad scale [37], the Cochrane risk of bias tool [38] or the Newcastle-Ottawa Scale (NOS) for non-randomized studies [39] our focus is to conduct a scoping review to determine domains and outcome measures that have been studied in lcSSc. As such, quality appraisal is not planned. We intend to start Titles and Abstracts selection on Covidence ® starting January 2021.

Presentation of the results

We expect to present the main results of this scoping review, with a least one table summarizing domains and identified outcomes. For the main domains of interest their frequency in the literature will also be provided in a Table. Identified gaps and main issues concerning the lack of outcome measures

and/or their poor use will also be highlighted in a third table. In the end, a comprehensive map of the main domains and outcomes will be provided within a dedicated graphical abstract or figure.

ETHICS AND DISSEMINATION

This scoping review is based on the analysis of published scientific literature without involving any patient, any new clinical or fundamental research or any type of personal information. Therefore, no ethical approval is required. The results of this scoping review will be submitted for publication in a peer-reviewed journal and will provide an overview of domains and items that are captured in observational cohorts and clinical trials in lcSSc and can be utilized for a combined index. The results concerning these domains and items, and each step of the creation of this combined index will also be submitted for presentation in international congresses of rheumatology.

PATIENT AND PUBLIC INVOLVEMENT

This scoping review plans to analyze the published scientific literature, no patients are involved for this specific analysis. The overall objective of the CRISTAL project is to develop a combined response index for lcSSc with input from the patient partners, clinicians with expertise in systemic sclerosis, and methodologists. All the steps of the project, and patient partners involvement have been published previously [15].

STRENGTHS, LIMITATIONS AND DISCUSSION POINTS

-The proposed scoping review will allow a broad and comprehensive identification of the outcome measures (core set items) within relevant domains, which have been used so far to assess lcSSc. The specific emphasis on clinical trials including patients with lcSSc will ensure the identification of relevant outcome measures used so far and their mapping within key domains, eventually highlighting gaps and main issues concerning the lack of outcome measures and/or their poor use.

-Although comprehensive, this study design has limitations regarding the number of databases, the language and search terms used, and may under-represent observational studies that do not explicitly mention the word “limited SSc” or “limited cutaneous SSc” in their title or abstract.

-By focusing on articles published after 1988, this scoping review may not capture the outcome measures used to assess equivalent subsets of lcSSc before this date, but this will ensure that the population included match with the contemporary definition of lcSSc.

-For this first phase of the initiative, we are seeking to identify relevant domains and outcomes as opposed to evaluate their specific properties in lcSSc. Nevertheless, the several clinical trials to be evaluated will not report results solely in lcSSc patients, which constitutes a limitation of our protocol.

-Regulatory agencies emphasize outcomes should reflect how patients feel, function and/or survive. With this in mind, as the main objective is to identify domains and outcomes that could be incorporated in a combined response index, we have not included congress databases or studies on exploratory biomarkers, or epigenetic/genetic studies. Such a selection will limit the comprehensiveness of this scoping review but will insure its coherence with the global objective of the project. Regarding this main objective, to remain consistent with the comprehensive concept of scoping review, and considering that we are not performing a systematic review or meta-analysis, we will not evaluate quality appraisal, and this could be considered as a limitation of this protocol.

TABLES :

3 Tables

Table 1 : Inclusion and exclusion criteria for the scoping review

Inclusion criteria	Exclusion criteria
• Language: English • Publication date: after 1988 (or in 1988) • Population: **For observational studies:** Titles/abstract mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, limited SSc, CREST/CRST only will be kept as well. When the number of lcSSc patients is mentioned, only studies with 20 lcSSc patients or more will be included. **For clinical/therapeutic trials:** Titles/abstract that only mention Systemic sclerosis / scleroderma without specifying dcSSc or lcSSc will be kept, and articles mentioning both lcSSc and dcSSc will be kept, articles mentioning lcSSc only, SSc sine scleroderma, CREST /CRST or limited SSc will be kept as well. • Studies: **For observational studies:** observational analytical cross-sectional or longitudinal studies, case-control studies, prospective and retrospective cohort studies, randomized controlled trials, non-randomized controlled trials, Meta-analyses and systematic reviews. **For clinical/therapeutic trials:** Randomized controlled trials and non-randomized controlled trials will be considered, unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trials evaluating a treatment or a therapeutic strategy will also be considered for full-text review. Meta-analysis and systematic reviews of clinical/therapeutic trials will also be included for full-text review.	• Population: Articles only focusing on localized scleroderma/morphea without including systemic sclerosis / systemic scleroderma patients will be excluded, articles only focusing on VEDOSS only, will be excluded as well. Articles focusing on dcSSc only will be excluded. Studies not concerned with human subjects or not pertaining to adult will be excluded. • Studies: **For observational studies:** Narrative and non-systematic reviews, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. Genetic or epigenetic studies will be excluded. Observational studies specifically evaluating the prevalence of the disease will also be excluded. Translational and basic sciences studies, including observational studies dedicated to auto-antibody testing, will not be considered for full-text review as they will not allow to identify new validated outcome measures reflecting feeling, functioning or surviving, that could be used for an acceptable combined response index. **For clinical/therapeutic trials:** Narrative reviews focusing on clinical trials, conference abstracts, biography, case-report, comment, editorial, directory, festschrift, interviews, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, popular works, congresses, consensus development conference, practice guideline will be excluded. **For all :** studies without abstract available (only title provided) will be excluded.

Table 2 : General template for title and abstract screening

Questions	
1/ Is the article written in English	☐ Yes ☐ No
2/ Is the article after 1988 (or published in 1988)	☐ Yes ☐ No
3/ Is this an observational study based on primary data or is this a systematic review/metanalysis published as original article, And is not a genetic or epigenetic or prevalence or basic science/biomarker study.	☐ Yes ☐ No
• If 1-2-3 fulfilled, does title or abstract mention lcSSc or Sine or lSSc or CREST/CRST ? • If yes, if the number of patients from the above mentioned subgroup is specified, is it 20 or more ?	☐ Yes ☐ No ☐ Yes ☐ No ☐ Uncertain: needs full text reviewing
If 1-2 fulfilled and if the title or abstract does not mention lcSSc or Sine or lSSc or CREST/CRST, • is this a randomized controlled trial, non-randomized controlled trial, an unrandomized or uncontrolled interventional or observational studies (before and after studies in routine care) or clinical trial evaluating a treatment or a therapeutic strategy ? • Which does not exclusively concern dcSSc patients ?	☐ Yes ☐ No ☐ Uncertain: needs full text reviewing

Table 3 : Preliminary charting table for data extraction

Item	Description
Journal	
First Author	
Year publication	
Patient population :	□ DcSSc and LcSSc (including lSSc, sine and CREST) □ LcSSc only (including lSSc, sine and CREST)
Number of patients evaluated (total)	
Number of patients with LcSSc (including lSSc, sine and CREST)	
Study type	□ Observational cross sectional study (pro or retrospective) □ Observational longitudinal study (pro or retrospective) □ Case control study □ Randomized Clinical trial □ Unrandomized Clinical trial □ Basic sciences (biomarkers)
Domain 1 as explicitly mentioned in the article	
Outcome 1 (of D1) with assessment methods	
Outcome 2 (of D1) with assessment methods	
Add as many outcomes as necessary	
(…)	
Domain 2 as explicitly mentioned in the article	
Outcome 1 (of D2) with assessment methods	
Outcome 2 (of D2) with assessment methods	
Add as many outcomes as necessary	
(…)	
No domain explicitly mentioned in the article (Dn/a)	
Outcome 1 (of Dn/a) with assessment methods	
Outcome 2 (of Dn/a) with assessment methods	
Add as many outcomes as necessary	
(…)	

REFERENCES

1 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;390:1685–99. doi:10.1016/S0140-6736(17)30933-9

2 Lescoat A, Ballerie A, Belhomme N, *et al.* Synovial involvement assessed by power Doppler ultra-sonography in systemic sclerosis: results of a cross-sectional study. *Rheumatology (Oxford)* 2018;57:2012–21. doi:10.1093/rheumatology/key214

3 LeRoy EC, Black C, Fleischmajer R, *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202–5.

4 LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001;28:1573–6.

5 Frantz C, Huscher D, Avouac J, *et al.* Outcomes of limited cutaneous systemic sclerosis patients: Results on more than 12,000 patients from the EUSTAR database. *Autoimmun Rev* 2020;19:102452. doi:10.1016/j.autrev.2019.102452

6 Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655–66. doi:10.1056/NEJMoa055120

7 Tashkin DP, Roth MD, Clements PJ, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016;4:708–19. doi:10.1016/S2213-2600(16)30152-7

8 Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med* 2019;380:2518–28. doi:10.1056/NEJMoa1903076

9 Frantz C, Avouac J, Distler O, *et al.* Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. *Semin Arthritis Rheum* 2016;46:115–23. doi:10.1016/j.semarthrit.2016.02.005

10 Khanna D, Ahmed M, Furst DE, *et al.* Health values of patients with systemic sclerosis. *Arthritis Rheum* 2007;57:86–93. doi:10.1002/art.22465

11 Khanna D, Lovell DJ, Giannini E, *et al.* Development of a provisional core set of response measures for clinical trials of systemic sclerosis. *Ann Rheum Dis* 2008;67:703–9. doi:10.1136/ard.2007.078923

12 Boers M, Kirwan JR, Wells G, *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745–53. doi:10.1016/j.jclinepi.2013.11.013

13 Khanna D, Berrocal VJ, Giannini EH, *et al.* The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. *Arthritis & Rheumatology (Hoboken, NJ)* 2016;68:299–311. doi:10.1002/art.39501

14 Khanna D, Huang S, Lin CJF, *et al.* New composite endpoint in early diffuse cutaneous systemic sclerosis: revisiting the provisional American College of Rheumatology Composite Response Index in Systemic Sclerosis. *Ann Rheum Dis* Published Online First: 30 November 2020. doi:10.1136/annrheumdis-2020-219100

15 Lescoat A, Murphy SL, Roofeh D, *et al.* Considerations for a combined index for limited cutaneous systemic sclerosis to support drug development and improve outcomes. *Journal of Scleroderma and Related Disorders* 2020;:2397198320961967. doi:10.1177/2397198320961967

16 Boers M, Kirwan JR, Gossec L, *et al.* How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;41:1025–30. doi:10.3899/jrheum.131314

17 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 2005;8:19–32. doi:10.1080/1364557032000119616

18 Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:69. doi:10.1186/1748-5908-5-69

19 Munn Z, Peters MDJ, Stern C, *et al.* Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology* 2018;18:143. doi:10.1186/s12874-018-0611-x

20 Boers M, Beaton DE, Shea BJ, *et al.* OMERACT Filter 2.1: Elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. *J Rheumatol* 2019;46:1021–7. doi:10.3899/jrheum.181096

21 Khanna D, Krishnan E, Dewitt EM, *et al.* The future of measuring patient-reported outcomes in rheumatology: Patient-Reported Outcomes Measurement Information System (PROMIS). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S486-490. doi:10.1002/acr.20581

22 Lescoat A, Cavalin C, Ehrlich R, *et al.* The nosology of systemic sclerosis: how lessons from the past offer new challenges in reframing an idiopathic rheumatological disorder. *The Lancet Rheumatology* 2019;1:e257–64. doi:10.1016/S2665-9913(19)30038-4

23 Wigley FM, Wise RA, Seibold JR, *et al.* Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med* 1994;120:199–206. doi:10.7326/0003-4819-120-3-199402010-00004

24 Clements P, Lachenbruch P, Siebold J, *et al.* Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol* 1995;22:1281–5.

25 Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997;40:1984–91. doi:10.1002/art.1780401110

26 Korn JH, Mayes M, Matucci Cerinic M, *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004;50:3985–93. doi:10.1002/art.20676

27 Gliddon AE, Doré CJ, Black CM, *et al.* Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis Rheum* 2007;56:3837–46. doi:10.1002/art.22965

28 Clements PJ, Roth MD, Elashoff R, *et al.* Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. *Ann Rheum Dis* 2007;66:1641–7. doi:10.1136/ard.2007.069518

29 Nihtyanova SI, Brough GM, Black CM, *et al.* Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2008;67:120–3. doi:10.1136/ard.2007.072686

30 Hachulla E, Hatron P-Y, Carpentier P, *et al.* Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. *Ann Rheum Dis* 2016;75:1009–15. doi:10.1136/annrheumdis-2014-207001

31 Cutolo M, Herrick AL, Distler O, *et al.* Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study. *Arthritis Rheumatol* 2016;68:2527–39. doi:10.1002/art.39718

32 Denton CP, Hachulla É, Riemekasten G, *et al.* Efficacy and Safety of Selexipag in Adults With Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Randomized, Placebo-Controlled, Phase II Study. *Arthritis & Rheumatology (Hoboken, NJ)* 2017;69:2370–9. doi:10.1002/art.40242

33 Methley AM, Campbell S, Chew-Graham C, *et al.* PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014;14:579. doi:10.1186/s12913-014-0579-0

34 Avouac J, Fransen J, Walker UA, *et al.* Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. *Ann Rheum Dis* 2011;70:476–81. doi:10.1136/ard.2010.136929

35 Tricco AC, Lillie E, Zarin W, *et al.* PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467–73. doi:10.7326/M18-0850

36 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647. doi:10.1136/bmj.g7647

37 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12. doi:10.1016/0197-2456(95)00134-4

38 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898

39 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology* 2010;25:603–5.

AUTHORS' CONTRIBUTIONS

AL & MHB wrote the first draft of the manuscript. AL, MHB, WT, DR, JDP, MH, RS, FZ, DK conceived the scoping review, developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

DATA AVAILIBILIY STATEMENT

Data are available upon reasonable request to the corresponding author.

BMJ Open

Scoping review protocol

DOMAINS AND OUTCOME MEASURES FOR THE ASSESSMENT OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS: A SCOPING REVIEW PROTOCOL

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PRISMA Checklist for CRISTAL review project
Extension for Scoping Reviews (PRISMA-ScR)

Tricco, Andrea C, Lillie, Erin, Zarin, Wasifa et al. (25 more authors) (2018) PRISMA : Extension for Scoping Reviews (PRISMA-ScR) : Checklist and Explanation. Annals of Internal Medicine. pp. 467-473. ISSN 0003-4819

Table 1: PRISMA-ScR Checklist

Section	Item	PRISMA-ScR checklist item	Reported on page #
Title			
Title	1	Identify the report as a scoping review.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background, objectives, eligibility criteria, sources of evidence, charting methods, results and conclusions that relate to the review question(s) and objective(s).	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review question(s)/objective(s) lend themselves to a scoping review approach.	5 and 6
Objectives	4	Provide an explicit statement of the question(s) and objective(s) being addressed with reference to their key elements (e.g., population or participants, concepts and context), or other relevant key elements used to conceptualize the review question(s) and/or objective(s)).	6 and 7
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number.	NA it is the publication of the protocol
Eligibility criteria	6	Specify the characteristics of the sources of evidence (e.g., years considered, language, publication status) used as criteria for eligibility, and provide a rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with authors to identify additional sources) in the search, as well as the date the most recent search was executed.	8 and 10
Search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8 and 10
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening, eligibility) included in the scoping review.	8
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., piloted forms; forms that have been tested by the team before their use, whether data charting was done independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	11
Critical appraisal of individual sources of evidence	12	***If done,*** provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	8
Summary measures	13	*Not applicable for scoping reviews.*	
Synthesis of results	14	Describe the methods of handling and summarizing the data that were charted.	12
Risk of bias across studies	15	*Not applicable for scoping reviews.*	
Additional analyses	16	*Not applicable for scoping reviews.*	
Results			
Selection of sources of evidence	17	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	NA it is the publication of the protocol Results are unknown for the moment
Characteristics of sources of evidence	18	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	19	***If done***, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	20	For each included source of evidence, present the relevant data that were charted that relate to the review question(s) and objective(s).	it is the publication of the protocol Results are unknown for the moment
Synthesis of	21	Summarize and/or present the charting results as they relate to the review	

Section	Item	PRISMA-ScR checklist item	Reported on page #
results		question(s) and objective(s).	
Risk of bias across studies	22	*Not applicable for scoping reviews.*	
Additional analyses	23	*Not applicable for scoping reviews.*	
Discussion			
Summary of evidence	24	Summarize the main results (including an overview of concepts, themes, and types of evidence available), explain how they relate to the review question(s) and objectives, and consider the relevance to key groups.	NA
Limitations	25	Discuss the limitations of the scoping review process.	it is the publication of the protocol
Conclusions	26	Provide a general interpretation of the results with respect to the review question(s) and objective(s), as well as potential implications and/or next steps.	Results are unknown for the moment
Funding			
Funding	27	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2