Systemic sclerosis: state of the art on clinical practice guidelines

Vanessa Smith,1,2 Carlo Alberto Scirè,3,4 Rosaria Talarico,5 Paolo Airo,6 Tobias Alexander,7 Yannick Allanore,8,9 Cosimo Bruni,10,11 Veronica Codullo,12,13 Virgil Dalm,14 Jeska De Vries-Bouwstra,15 Alessandra Della Rossa,5 Oliver Distler,16 Ilaria Galetti,17 David Launay,18,19 Gemma Lepri,10,11 Alex Mathian,20 Luc Mouthon,8,9 Barbara Ruaro,21 Alberto Sulli,21 Angela Tincani,6 Elisabetta Zanatta,30 Stefano Bombardieri,31 Gerd Burmester,32 Frederic Houssiau,23,24 Ulf Mueller-Ladner,36 Matthias Schneider,37 Marco Matucci-Cerinic10,11 Luc Mouthon,8,9 Barbara Ruaro,21 Alberto Sulli,21 Angela Tincani,6 Elisabetta Zanatta,30 Stefano Bombardieri,31 Gerd Burmester,32 João Eurico Fonseca,33,34 Charissa Frank,35 Eric Hachulla,18,19 Frederic Houssiau,23,24 Ulf Mueller-Ladner,36 Matthias Schneider,37 Jacob M van Laar,38 Ana Vieira,39 Maurizio Cutolo,21 Marta Mosca,40 Marco Matucci-Cerinic10,11

ABSTRACT
Systemic sclerosis (SSc) is an orphan disease characterised by autoimmunity, fibrosis of the skin and internal organs, and vasculopathy. SSc may be associated with high morbidity and mortality. In this narrative review we summarise the results of a systematic literature research, which was performed as part of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases project, aimed at evaluating existing clinical practice guidelines or recommendations. Only in the domains ‘Vascular & Ulcers’ (i.e., non-pharmacological approach to digital ulcer), ‘PAH’ (i.e., screening and treatment), ‘Treatment’ and ‘Juveniles’ (i.e., evaluation of juveniles with Raynaud’s phenomenon) evidence-based and consensus-based guidelines could be included. Hence there is a preponderance of unmet needs in SSc referring to the diagnosis and (non-)pharmacological treatment of several SSc-specific complications. Patients with SSc experience significant uncertainty concerning SSc-related taxonomy, management (both pharmacological and non-pharmacological) and education. Day-to-day impact of the disease (loss of self-esteem, fatigue, sexual dysfunction, and occupational, nutritional and relational problems) is underestimated and needs evaluation.

INTRODUCTION
The European Reference Network (ERN) on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ReCONNET) has as one of its aims to deliver high-quality and homogeneous care for the management of rare connective tissue diseases (rCTDs) across European borders through the identification and development of standard clinical guidelines and cost-effective pathways. In order to design such pathways, current existing clinical practice guidelines, more specifically recommendations or consensuses concerning management (i.e., diagnosis, monitoring and treatment), need to be identified.1 One of the rCTDs covered by the ERN ReCONNET is systemic sclerosis (SSc), an orphan disease characterised by autoimmunity, fibrosis of the skin and internal organs, and vasculopathy. SSc may be associated with high morbidity and mortality.2 3 Due to its heterogeneity, it is associated with a high uncertainty...
for the patient who does not know what complication may occur and how to treat it. Aside from this, it is a disease which may impact the quality of life. Also, for the physician SSC is challenging. Due to its rarity, it is a disease which is uncommon to non-expert rheumatologists, which may lead to late diagnosis of the disease or its complications and jeopardisation of optimal management of the patient. Also, a disease-modifying drug which tackles the natural evolution of the disease itself is yet to be discovered.

The objective of this paper is to report the state of the art on existing clinical practice guidelines and the unmet needs concerning the management of SSC, based on an in-depth systematic literature review.

METHODS
Identification of existing guidelines
We reviewed all published articles in order to identify existing clinical practice guidelines on the diagnosis, monitoring and treatment of SSC, according to the Institute of Medicine\(^1\) 2011 definition (clinical practice guidelines are statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options).

The systematic search was performed by the ERN ReCONNET Coordinator team (RT, CAS) based on the controlled medical subject heading (MeSH) and Emtree terms for ‘systemic sclerosis’, in combination with the specification of publication type (see below).

The disease coordinators (DCs) of the ERN-ReCONNET for SSC (MM-C, VS) assigned the work on clinical practice guidelines to the healthcare providers (HCPs) involved. Moreover, in order to implement the list of guidelines provided by Medline and Embase search, the group also performed a hand search. A first screening among papers included in the final list (systematic search-hand search) based on the title and abstract selected evidence-based medicine guidelines. The electronic search was supplemented by a call to national societies and ERN ReCONNET HCPs to identify existing national guidelines, and additionally a complementary hand search to identify clinical practice guidelines through reference lists of the articles was performed by the DCs as well as by the ERN ReCONNET Coordinator team.

A general assessment of the clinical practice guidelines was performed following the Advancing Guideline Development, Reporting and Evaluation in Healthcare (AGREE II) tool checklist, not for formal appraisal but only to inform discussion. A discussion group was set for the evaluation of the existing clinical practice guidelines and to identify the unmet needs.

More specifically the following search strategy was followed:

**Medline (PubMed)**
- (“scleroderma, systemic” (MeSH Terms) OR (“scleroderma” (All Fields) AND “systemic” (All Fields)) OR “systemic scleroderma” (All Fields) OR (“systemic” (All Fields) AND “sclerosis” (All Fields)) OR “systemic sclerosis” (All Fields)) AND (“Practice Guideline” (Publication Type) OR “Practice Guidelines As Topic” (MeSH Terms) OR Practice Guideline (Publication Type) OR “Practice Guideline” (Text Word) OR “Practice Guidelines” (Text Word) OR “Guideline” (Publication Type) OR “Guidelines As Topic” (MeSH Terms) OR Guideline (Publication Type) OR “Guideline” (Text Word) OR “Guidelines” (Text Word) OR “Consensus Development Conference” (Publication Type) OR “Consensus Development Conferences As Topic” (MeSH Terms) OR “Consensus” (MeSH Terms) OR “Consensus” (Text Word) OR “Recommendation” (Text Word) OR “Recommendations” (Text Word) OR “Best Practice” (Text Word) OR “Best Practices” (Text Word)).

**Embaste**

The list with identified references was independently screened at the title and abstract levels by two SSC-DCs and the ERN ReCONNET Coordinator team. References were selected for inclusion based on predefined eligibility criteria. More specifically, evidence-based medicine guidelines, recommendations or consensuses documenting the diagnosis, monitoring or treatment of SSC (according to the 1980 American College of Rheumatology (ACR) or the 2013 ACR/European League Against Rheumatism (EULAR) criteria) were considered eligible. Subsequently, these references were classified according to SSC complications/disease manifestations, more specifically in the following domains, as decided by the SSC-DC: ‘Patients’, ‘Heart’, ‘Malignancy’, ‘Vascular & Ulcers’, ‘Gastro-intestinal (GI)’, ‘Renal’, ‘Interstitial Lung Disease (ILD)’, ‘Pulmonary Arterial Hypertension (PAH)’, ‘Diagnosis’, ‘Contribution of HCPs’, ‘Treatment’, ‘Hematopoietic Stem Cell Transplantation (HSCT)’, ‘Clinical Trials’ and ‘Juvenile’.

For preparing the state of the art of the retained full texts, the SSc-DCs sent two invitational emails to involved HCPs who had expressed their interest to participate in the guideline review. Full texts were further excluded when not meeting the inclusion criteria, as described above, in order to retain clinical practice guidelines (see table 1).

### Evaluation of existing clinical practice guidelines

The first screening and informal assessment of the methodological ‘overall’ quality of each clinical practice guideline were guided by the AGREE II instrument. A general assessment of the state of the art on clinical practice guidelines and unmet needs identification was performed by the SSc-DCs. Additionally, the levels of evidence were assessed by the SSc Junior Coordinator team (AmV, VS) using the German Association of the Scientific Medical Societies Guidance Manual and Rules for Guideline Development (see table 1). Additionally, patients’ unmet needs of the Systemic Sclerosis/Scleroderma European community have been formulated by the ERN ReCONNET European Patient Advocacy Group (ePAG), that is, IG that had carefully collected the voices and the points of view of the whole European community and had found evidence in the literature. Subsequently a synthesis of these has been described by the SSc-ePAG and SSc-DCs (see the ‘Patients’ unmet needs’ section).

### STATE OF THE ART ON CLINICAL PRACTICE GUIDELINES

#### Identification of existing guidelines

The systematic search in PubMed and Embase identified 893 references; the call to societies identified Dutch guidelines, the call to ERN-related HCPs identified no references and the hand search identified one additional reference. Of note, the Dutch guidelines were not included in the final list to be screened at the title and abstract levels since they had not yet been published in English peer-reviewed journals. Of the final list (n=894), 28 clinical practice guidelines were retained (see figure 1).

#### Evaluation of existing guidelines

Overall comments of the appraisers were mostly referring to the non-systematic review aspect of the recommendations. Evaluation of the levels of evidence showed that only five guidelines were classified as strong evidence-based and consensus-based guidelines built on a representative committee, systematic review and synthesis of evidence, and will be stipulated as such below.

<table>
<thead>
<tr>
<th>Domain (n)</th>
<th>Author and year</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (0)</td>
<td>No clinical practice guidelines were included.</td>
<td></td>
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<tr>
<td>Heart (3)</td>
<td>Avouac et al, 2014</td>
<td>S2</td>
</tr>
<tr>
<td></td>
<td>Bissell et al, 2017</td>
<td>S2</td>
</tr>
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<td></td>
<td>Mavrogeni et al, 2016</td>
<td>S2</td>
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<tr>
<td>Malignancy (1)</td>
<td>Lazzaroni et al, 2017</td>
<td>S2</td>
</tr>
<tr>
<td>Vascular and ulcers (6)</td>
<td>Baron et al, 2014</td>
<td>S2</td>
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<td></td>
<td>Fujimoto et al, 2016</td>
<td>S2</td>
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<td></td>
<td>Hughes et al, 2015</td>
<td>S2</td>
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<td></td>
<td>Pistorius et al, 2012</td>
<td>S1</td>
</tr>
<tr>
<td></td>
<td>Mavarakis et al, 2014</td>
<td>S2</td>
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<td></td>
<td>Cutolo et al, 2017</td>
<td>S1</td>
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<tr>
<td>Gastrointestinal (3)</td>
<td>Alantar et al, 2011</td>
<td>S2</td>
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<tr>
<td></td>
<td>Baron et al, 2010</td>
<td>S1</td>
</tr>
<tr>
<td></td>
<td>Hansi et al, 2014</td>
<td>S2</td>
</tr>
<tr>
<td>Renal (1)</td>
<td>Lynch et al, 2016</td>
<td>S1</td>
</tr>
<tr>
<td>Interstitial lung disease (0)</td>
<td>No clinical practice guidelines were included.</td>
<td></td>
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<tr>
<td>Pulmonary arterial hypertension (2)</td>
<td>Galib et al, 2016</td>
<td>S3</td>
</tr>
<tr>
<td></td>
<td>Khanna et al, 2013</td>
<td>S3</td>
</tr>
<tr>
<td>Diagnosis (1)</td>
<td>Knobler et al, 2017</td>
<td>S1</td>
</tr>
<tr>
<td>Contribution of healthcare providers (0)</td>
<td>No clinical practice guidelines were included.</td>
<td></td>
</tr>
<tr>
<td>Treatment (5)</td>
<td>Kowal-Bielecka et al, 2017</td>
<td>S3</td>
</tr>
<tr>
<td></td>
<td>Denton et al, 2016</td>
<td>S2</td>
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<td></td>
<td>Sampaio-Barros et al, 2013</td>
<td>S2</td>
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<td></td>
<td>Distler et al, 2011</td>
<td>S2</td>
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<td></td>
<td>Knobler et al, 2014</td>
<td>S2</td>
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<tr>
<td>Haematopoietic stem cell transplantation (3)</td>
<td>Rodrigues et al, 2013</td>
<td>S2</td>
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<td></td>
<td>Saccardi et al, 2004</td>
<td>S2</td>
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<td></td>
<td>Farge et al, 2017</td>
<td>S2</td>
</tr>
<tr>
<td>Clinical trials (2)</td>
<td>Knhanna et al, 2015</td>
<td>S3</td>
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<tr>
<td></td>
<td>Khanna et al, 2010</td>
<td>S1</td>
</tr>
<tr>
<td>Juvenile (1)</td>
<td>Pain et al, 2016</td>
<td>S3</td>
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</table>

Level of evidence: Amendment of the ‘S-class’ classification is used to describe the degree of systematic development of guidelines and thus to identify their level of evidence, by the German Association of the Scientific Medical Societies Guidance Manual and Rules for Guideline Development. category S3: evidence-based and consensus-based guideline, based on a representative committee; systematic review and synthesis of evidence (highest level of evidence); category S2: evidence-based or consensus-based guideline, based on either a systematic review and synthesis of evidence or a representative committee; category S1: recommendations by expert groups, based on consensus development in an informal procedure (lowest level of evidence).

#### Patients

Guidelines in the domain of patients are non-existent. Nevertheless, based on exhaustive patient input (IG), guidelines covering the unmet needs of the patients are highly warranted (see the ‘Patients’ unmet needs’ section).

#### Heart

Three references were retained in the domain ‘Heart’.

First, Avouac et al proposed interim recommendations to refer patients with SSC for performing right heart...
catheterisation (RHC) for detecting PAH in SSc when suspected. Of note, these have now been encompassed in the highest level of evidence guideline, more specifically the 2015 European Society for Cardiology/European Respiratory Society (ESC/ERS) evidence-based and consensus-based guideline for the diagnosis and treatment of pulmonary hypertension (see the ‘Pulmonary arterial hypertension’ section). Second, Bissell et al\textsuperscript{19} presented, on behalf of the UK Scleroderma Study Group (UKSSG), a consensus best practice pathway for the management of cardiac disease, with a focus on primary heart disease in SSc. More specifically, approaches for early detection, standard pharmacological and device therapies have been put forward. Additionally, besides the recommendation for a multidisciplinary approach, a future research agenda has also been formulated in response to the relative lack of understanding of the natural history of primary cardiac disease. Third, Mavrogeni et al\textsuperscript{20} described possible recommendations for the use of cardiac magnetic resonance in rare connective tissue diseases (rCTDs) and in between others, also in SSc.

Malignancy
One reference was retained in the domain ‘Malignancy’. More specifically, Lazzaroni et al\textsuperscript{21} described possible recommendations for the screening for malignancies in patients with SSc with anti-RNA polymerase III. These recommendations were based on a Delphi exercise which was performed with the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) experts.

Vascular and ulcers
Six references were included in the domain ‘Vascular & Ulcers’.

First, the North American Working Group regarding the classification of digital ulcers (DUs) in SSc developed a consensus for the classification of DUs, which after training of rheumatologists with SSc expertise could be used with fair reliability to classify DUs and to measure ulcer area.\textsuperscript{22 45}

Second, Fujimoto et al\textsuperscript{23} described, on behalf of the Wound/Burn Guidelines Committee of the Japanese Dermatological Association, recommendations for the management of skin ulcers associated with CTD/vasculitis. In this way, an algorithm for SSc-related ulcers was proposed, as well as a reply to frequently asked questions in the care of SSc-related ulcers. Third, Hughes et al\textsuperscript{24} published, on behalf of the UKSSG, a best practice consensus recommendation for digital vasculopathy intended as a reference tool to inform management. In this way algorithms for the management of Raynaud’s phenomenon (RP), DUs and critical digital ischaemia in patients with SSc have been proposed.

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Figure 1  Flow chart of the screening process. ERN ReCONNET, European Reference Network Rare and Complex Connective Tissue and Musculoskeletal Diseases; DC, disease coordinators; HCP, healthcare providers; HSCT, haematopoietic stem cell transplantation; ILD, interstitial lung disease; JC, Junior Coordinator; PAH, pulmonary arterial hypertension; SC, Senior Coordinator; SSc, systemic sclerosis.
no clinical practice guideline on 'Interstitial Lung Disease' as such, but only as part of the recommendations from the British Society for Rheumatology (BSR) on the management of patients with SSc. The criteria for early and very early diagnosis of SSc, as well as the frequently used 2013 ACR/EULAR classification criteria, had not been retained as an in verum guideline, but are nevertheless used in the treatment of patients with SSc. The diagnostic algorithm with clinical, laboratory, lung function (more specifically the role of photopheresis and anti-tumour necrosis factor in SSc, have been published.37 38

Recent evidence-based and consensus-based recommendations by the expert groups of Knobler et al, published, on behalf of the Brazilian Society of Rheumatology (BSR). The updated evidence-based and consensus-based EULAR recommendations of Kowal-Bielecka et al focus specifically on the management of Raynaud's phenomenon and include data on newer therapeutic modalities and include a research agenda. These recommendations are based on the best available evidence from the published literature. The EULAR classification criteria for the diagnosis of the Euro-Systemic Sclerosis Cooperative Group (ESSeCoG) have been passed in 2010, and the criteria for early and very early diagnosis of SSc, as well as the frequently used 2013 ACR/EULAR classification criteria, had not been retained as an in verum guideline, but are nevertheless used in the treatment of patients with SSc.

Three references were included concerning CF recommendations. Al-Attar et al.29 described the recommendations for diagnostic algorithm with the DETECT algorithm, a two-step approach for screening in the domain 'Contribution of HCPs'. Five references were retained in the domain 'Contribution of HCPs'. No references were included after title and abstract screening in the domain 'Contribution of HCPs'.

Diagnosis

The updated evidence-based and consensus-based EULAR recommendations of Kowal-Bielecka et al focus specifically on the management of Raynaud's phenomenon and include data on newer therapeutic modalities and include a research agenda. These recommendations are based on the best available evidence from the published literature. The EULAR classification criteria for the diagnosis of the Euro-Systemic Sclerosis Cooperative Group (ESSeCoG) have been passed in 2010, and the criteria for early and very early diagnosis of SSc, as well as the frequently used 2013 ACR/EULAR classification criteria, had not been retained as an in verum guideline, but are nevertheless used in the treatment of patients with SSc.

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Fourth, in the recommendations by expert groups, diagnostic algorithm with the DETECT algorithm, a two-step approach for screening in the domain 'Contribution of HCPs'. Five references were retained in the domain 'Contribution of HCPs'. No references were included after title and abstract screening in the domain 'Contribution of HCPs'.

TTE in step 2, before mandating HCC to evaluate patients with PAH at risk for PAH may be considered. However, in adults with a diagnosis of SSc, the performance of screening for PAH in patients with SSc is recommended. The criteria for early and very early diagnosis of SSc, as well as the frequently used 2013 ACR/EULAR classification criteria, had not been retained as an in verum guideline, but are nevertheless used in the treatment of patients with SSc.
Haematopoietic stem cell transplantation

Three references were retained in the domain ‘HSCT’.

In 2013 Rodrigues et al., on behalf of the Brazilian Society of Bone Marrow Transplantation, developed recommendations on the use of HSCT as a treatment for SSc.

Concerning HSCT-related cardiotoxicity, consensus-based guidelines were published in 2004 and 2017. Saccardi et al., published a consensus statement concerning cardiotoxicity during HSCT in SSc and recommendations concerning full cardiological assessment prior to HSCT. In the consensus-based guideline of Farge et al., on behalf of the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party, more recent recommendations concerning the cardiopulmonary assessment of patients with SSc prior to HSCT were developed. The latter includes, besides anamnesis and clinical examination, standard haematological, biological, urinary, immunological, cardiopulmonary and GI investigations and additionally selection criteria to use HSCT in SSc.

Clinical trials

Two references were included in the domain ‘Clinical trials’ (besides the one already mentioned above in the ‘Vascular & Ulcers’ section).

In the evidence-based and consensus-based guideline of Khanna et al., points to consider based on EULAR standards for the design of controlled clinical trials in SSc were developed.

In the recommendations by the expert groups of Khanna et al., preliminary recommendations for the design of future SSc-ILD randomised clinical trials were proposed.

Of note, a post-hoc search of the SSc-DCs identified several recently published ‘points to consider for clinical trials’ in the following areas: ‘Health-Related Quality-of-Life’, ‘Arthritic Involvement’, ‘GI tract’, ‘Pulmonary Hypertension’, ‘Muscle Involvement’, ‘Heart’, ‘Skin Ulcers’, ‘Renal’ and ‘Interstitial Lung Disease (ILD)’. Of note, Johnson et al., highlighted in 2015 recent advances in research methodology and broadened the potential range of design and analytic considerations when planning an SSc trial.

Juvenile

One reference was retained in the domain ‘Juvenile’.

In the evidence-based and consensus-based guideline of Pain et al., on behalf of the Paediatric Rheumatology European Society Juvenile Scleroderma Working Group, recommendations for the assessment and monitoring of RP in children were proposed.

UNMET NEEDS IDENTIFICATION

This is the first clinical narrative review investigating clinical practice guidelines in the field of SSc. Of all the described domains, only in the domains ‘Vascular & Ulcers’ (ie, non-pharmacological approach to DU), ‘PAH’ (ie, screening and treatment), ‘Treatment’ and ‘Juveniles’ (ie, evaluation of juveniles with RP) evidence-based and consensus-based guidelines could be included. Hence there is a preponderance of unmet needs in SSc.

Clinicians’ unmet needs

There is a lack of (strong evidence) recommendations regarding diagnosis and (non-)pharmacological treatment of several SSc-specific complications. In particular, a contribution could be given for ulcers, GI tract involvement, renal involvement and management of calcinosis. Incentives in this field are ongoing.

Nevertheless, more intensive research should be done to provide the SSc community with high evidence-based and consensus-based guidelines to address any facet of this heterogeneous disease, which could then be dispersed to policy makers at the (inter-)national level as well as to HCP and physicians dealing with this disease.

Of note, the lack of strong evidence recommendations (ie, based on a systematic review and a representative internationally composed committee and at least one patient representative) extrapolates to cross-discipline therapies such as to the use of HSCT in patients with SSc. In this way detailed recommendations on the main clinical features of patients with SSc are an important unmet need to be addressed in the future in connection with other institutional entities such as the EBMT, EULAR and EUSTAR. Also, clinical practice guidelines stipulating the role of steroids in SSc are highly warranted.

At present, evidence-based and consensus-based guidelines for very early and early diagnosis of SSc still remain an unmet need, although the criteria for (very) early diagnosis are present in literature.

In this area, the contribution of SSc-ERN could be to raise awareness among physicians on the problem and foster the early referral of patients to tertiary centres. Moreover, the problem to be addressed by SSc-ERN could be the use of classification criteria to diagnose SSc. This highlights the absence of diagnostic criteria that are useful in practice. It is also to be noted that the dispersion (teaching and interpretation) of nailfold videocapillaroscopy (NVC) in a standardised way to early detect patients with RP who will develop SSc may be steered by both the ERN and the EULAR Study Group on Microcirculation in Rheumatic Diseases. Of note, NVC has been introduced in the ACR/EULAR criteria for SSc.

From the methodological point of view, it is interesting to notice that the ERN ReCONNET may foster awareness of standardisation of SSc-specific investigational techniques (eg, antibody assays for SSc-specific antibodies). This may help to definitely reach an agreement on the standardised evaluation of patients with SSc.
Patients’ unmet needs

Patients with SSc experience significant uncertainty concerning SSc-related taxonomy, management (both pharmacological and non-pharmacological) due to lack of (inter-)national harmonisation and standardisation and due to non-existence of overarching evidence-based and consensus-based guidelines for holistic SSc management. Access to uniform information, including knowledgeable HCPs, and management of difficult social interactions and negative emotions are key challenges.11 Patient education programmes should be promoted.

Besides these, patients with SSc incur considerable costs (eg, non-reimbursement of certain therapies) and experience substantial deterioration in health-related quality of life (HRQoL).12 13 Additionally, no specific recommendations are at hand regarding non-pharmacological interventions (eg, behavioural/psychological, educational, physical/occupational therapy) to improve HRQoL. However, incentives like the ‘Scleroderma Patient centered Intervention Network’, which aims to develop, test and disseminate a set of accessible interventions designed to complement standard care to improve HRQoL, are encouraging.14

Importantly, patient participation in patient-reported outcome measures, meant to provide insight into the patient condition which is not fully captured by physician-derived assessment tools, has been non-prevalent even though this is paramount to ensure adequate capturing of those experiences most important to our patients.15

Last but not least, day-to-day impact of the disease (loss of self-esteem, fatigue, sexual dysfunction, and occupational, nutritional and relational problems) is underestimated.16 17

CONCLUSION

This indepth systematic literature review identified 28 clinical practice guidelines concerning the management of SSc. More specifically, there is an availability of evidence-based and consensus-based guidelines for screening of SSc-related PAH, treatment and points to consider in clinical trials in SSc, which are updated on a regular basis by the SSc community. Furthermore, gaps have been identified concerning patients’ needs, the role of HCPs, (very) early diagnosis of SSc, several specific organ involvements and the use of HSCT in SSc. Possible roles of the ERN ReCONNET could be to step forward to deal with patients’ unmet needs, to deal with the heterogeneity that exists in patient care throughout countries, to clearly identify at the European level the role of HCPs in the management of patients with SSc, and to step forward to the unmet need of (very) early diagnosis of the disease as well as its organ involvement, complications and management of complications, leading to a standardised, uniform holistic management of SSc.

Author affiliations

1Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
2Department of Internal Medicine, Ghent University, Ghent, Belgium
3Section of Rheumatology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
4Epidemiology Unit, Italian Society for Rheumatology (SIR), Milan, Italy
5Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
6Rheumatology and Clinical Immunology Unit, Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy
7Department of Rheumatology and Clinical Immunology Unit, Charité University Hospital Berlin, Berlin, Germany
8Service de Médecine Interne, Université Paris Descartes, Paris, France
9Centre de Référence Maladies systémiques Auto-immunes Rares d’Île de France, Assistance Publique-Hôpitaux de Paris (AP-HP), Hopital Cochin, Paris, France
10Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy
11Division of Rheumatology and Scleroderma Unit, AOI Careggi, Florence, Italy
12Department of Rheumatology, University of Pavia, Pavia, Italy
13Department of Rheumatology, IRCCS Policlinico San Matteo, Pavia, Italy
14Department of Internal Medicine and Department of Immunology, Erasmus Medical Center, Rotterdam, The Netherlands
15Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
16Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
17Federation of European Scleroderma Associations (FESCA), Brussels, Belgium
18Département de Médecine Interne et Immunologie Clinique, Université de Lille, Lille, France
19Centre de Référence des Maladies Systémiques et Auto-immunes Rares du Nord-Ouest (CERAINO), LIRIC, INSERM, CHU Lille, Lille, France
20Department of Internal Medicine, Hospital Pitié-Salpêtrière, Paris, France
21Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, IRCCS San Martino Polyclinic Hospital, University of Genoa, Genoa, Italy
22Department of Cardiology, Ghent University Hospital, Ghent, Belgium
23Department of Rheumatology, Université Catholique de Louvain, Louvain-la-Neuve, Belgium
24Department of Rheumatology, Cliniques Universitaires Saint-Luc, Louvain-la-Neuve, Belgium
25Department of Rheumatology, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands
26Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands
27Clinical Immunology & Rheumatology, Amsterdam Rheumatology & Immunology Center, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands
28Department of Rheumatology, Amsterdam UMC, Amsterdam, The Netherlands
29Amsterdam Infection & Immunity Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
30Division of Rheumatology, Department of Medicine, University of Padova, Padova, Italy
31Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Pisa, Pisa, Italy
32Department of Rheumatology and Clinical Immunology, Charité University Hospital Berlin, Berlin, Germany
33Department of Rheumatology, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal
34Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
35Flemish Patient Organization of Hereditary Collagen Disorders in Belgium, Koersel, Belgium
36Department of Rheumatology and Clinical Immunology, Kerckhoff Klinik, Justus-Liebig University of Giessen, Giessen, Germany
37Institute for Rheumatology, Hiller Research Unit for Rheumatology, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
38Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
39Núcleo Síndrome de Sjögren de Liga Portuguesa Contra as Doenças Reumáticas (LPCDR, Portuguese League Against Rheumatic Diseases), Lisbon, Portugal
40Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy

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