



The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: Protocol for a cohort multiple randomized controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003563
Article Type:	Protocol
Date Submitted by the Author:	08-Jul-2013
Complete List of Authors:	<p>Kwakkenbos, Linda; Jewish General Hospital, Lady Davis Institute for Medical Research; McGill University, Department of Psychiatry Jewett, Lisa; Jewish General Hospital, Lady Davis Institute for Medical Research; McGill University, Educational and Counselling Psychology Baron, Murray; Jewish General Hospital, Lady Davis Institute for Medical Research; McGill University, Department of Medicine Bartlett, Susan; McGill University, Department of Medicine Furst, Daniel; Geffen School of Medicine at the University of California, Division of Rheumatology Gottesman, Karen; Scleroderma Foundation, Southern California Chapter Khanna, Dinesh; University of Michigan, Scleroderma Program Malcarne, Vanessa; San Diego State University, Psychology; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology Mayes, Maureen; University of Texas Health Science Center Houston, Division of Rheumatology and Clinical Immunogenetics Mouthon, Luc; Université Paris Descartes, Assistance Publique-Hôpitaux de Paris (AP-HP) Poiraudau, Serge; Université Paris Descartes, Assistance Publique-Hôpitaux de Paris (AP-HP) Sauve, Maureen; Scleroderma Societies of Canada and Ontario, Nielson, Warren; St. Joseph's Health Care, Beryl & Richard Ivey Rheumatology Day Programs Poole, Janet; University of New Mexico, Occupational Therapy Graduate Program Assassi, Shervin; University of Texas Health Science Center Houston, Division of Rheumatology and Clinical Immunogenetics BOUSTRON, Isabelle; INSERM, APHP, University Paris Descartes, Ells, Carolyn; McGill University, Biomedical Ethics Unit van den Ende, Cornelia; Sint Maartenskliniek, Department of Rheumatology Hudson, Marie; Jewish General Hospital, Lady Davis Institute for Medical Research; McGill University, Department of Medicine Impens, Ann; Midwestern University, Internal Medicine Körner, Annett; Jewish General Hospital, Lady Davis Institute for Medical Research Leite, Catarina; University of Minho, School of Psychology; Federation of</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	European Scleroderma Associations, Costa Maia, Angela; University of Minho, School of Psychology Mendelson, Cindy; University of New Mexico, College of Nursing Pope, Janet; The University of Western Ontario, Medicine, Division of Rheumatology Steele, Russell; Jewish General Hospital, Lady Davis Institute for Medical Research Suarez-Almazor, Maria; The University of Texas MD Anderson Cancer Center, Ahmed, Sara; McGill University, School of Physical and Occupational Therapy Coronado-Montoya, Stephanie; Jewish General Hospital, Lady Davis Institute for Medical Research Delisle, Vanessa; Jewish General Hospital, Lady Davis Institute for Medical Research Gholizadeh, Shadi; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology Jang, Yeona; McGill University, Desautels Faculty of Management Levis, Brooke; Jewish General Hospital, Lady Davis Institute for Medical Research Milette, Katherine; Jewish General Hospital, Lady Davis Institute for Medical Research; McGill University, Department of Psychiatry Mills, Sarah; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology Razykov, Ilya; Jewish General Hospital, Lady Davis Institute for Medical Research; McGill University, Department of Psychiatry Sobel, Rina; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology Thombs, Brett; McGill University, Department of Psychiatry; Jewish General Hospital, Lady Davis Institute for Medical Research
Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Research methods, Rehabilitation medicine, Mental health
Keywords:	RHEUMATOLOGY, STATISTICS & RESEARCH METHODS, REHABILITATION MEDICINE, MENTAL HEALTH



The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: Protocol for a cohort multiple randomized controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context

Linda Kwakkenbos, PhD^{1,2}; Lisa R. Jewett, MSc^{1,3}; Murray Baron, MD^{1,4}; Susan J. Bartlett, PhD⁴; Dan Furst, MD⁵; Karen Gottesman, BA⁶; Dinesh Khanna, MD, MS⁷; Vanessa L. Malcarne, PhD^{8,9}; Maureen D. Mayes, MD, MPH¹⁰; Luc Mouthon, MD, PhD^{11,12}; Serge Poiraudau, MD, PhD^{11,13,14}; Maureen Sauve, BA¹⁵; Warren R. Nielson, PhD¹⁶; Janet L. Poole, PhD, OTR/L¹⁷; Shervin Assassi, MD, MS¹⁰; Isabelle Boutron, MD, PhD^{18,19,20}; Carolyn Ells, PhD²¹; Cornelia H.M. van den Ende, PhD²²; Marie Hudson, MD, MPH^{1,4}; Ann Impens, PhD, MPH²³; Annett Körner, PhD^{1,3,24}; Catarina Leite, MSc^{25,26}; Angela Costa Maia, PhD²⁵; Cindy Mendelson, PhD, RN²⁷; Janet Pope, MD, MPH²⁸; Russell J. Steele, PhD^{1,29}; Maria E. Suarez-Almazor, MD, PhD³⁰; Sara Ahmed, PhD^{31,32}; Stephanie Coronado-Montoya, BSc¹; Vanessa C. Delisle, MSc^{1,3}; Shadi Gholizadeh, MSc⁹; Yeona Jang, PhD³³; Brooke Levis, BSc^{1,34}; Katherine Milette, MA^{1,3}; Sarah D. Mills, BA⁹; Ilya Razykov, MSc^{1,2}; Rina M. Sobel, MS⁹; Brett D. Thombs, PhD^{1-5,34,35,36§}

¹Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, Québec, Canada; ²Departments of Psychiatry; ³Educational and Counselling Psychology; and ⁴Medicine, McGill University, Montréal, Québec, Canada; ⁵Division of Rheumatology, Geffen School of Medicine at the University of California, Los Angeles, USA; ⁶Scleroderma Foundation, Southern California Chapter, USA; ⁷University of Michigan Scleroderma Program, Ann Arbor, MI; ⁸Department of Psychology, San Diego State University, San Diego, California, USA; ⁹San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California, USA; ¹⁰University of

Texas Health Science Center Houston, TX, USA; ¹¹Université Paris Descartes, Paris, France; Assistance Publique-Hôpitaux de Paris (AP-HP); ¹²Pôle de Médecine Interne, Hôpital Cochin, Paris, France; ¹³Pôle Ostéo-articulaire, Hôpital Cochin, Paris, France; ¹⁴IFR Handicap INSERM, Paris, France; ¹⁵Scleroderma Societies of Canada and Ontario, Hamilton, Ontario, Canada; ¹⁶Beryl & Richard Ivey Rheumatology Day Programs, St. Joseph's Health Care, London Ontario; ¹⁷Occupational Therapy Graduate Program, University of New Mexico, USA; ¹⁸INSERM U738, Paris France; ¹⁹University Paris Descartes, Paris, France; ²⁰Assistance Publique-Hôpitaux de Paris, Hôpital Hôtel-Dieu, Centre d'Epidémiologie Clinique, Paris, France; ²¹Biomedical Ethics Unit, McGill University, Montréal, Québec, Canada; ²²Department of Rheumatology, Sint Maartenskliniek, The Netherlands; ²³Internal Medicine, Midwestern University, Downers Grove, Illinois, USA; ²⁴Department of Oncology, McGill University, Montréal, Québec, Canada; ²⁵University of Minho, Portugal; ²⁶Federation of European Scleroderma Associations; ²⁷College of Nursing, University of New Mexico, Albuquerque, NM, USA; ²⁸University of Western Ontario, St. Joseph's Health Care, London, Ontario, Canada; ²⁹Department of Mathematics and Statistics, McGill University, Montréal, Québec, Canada; ³⁰University of Texas MD Anderson Cancer Center, Houston, Texas, USA; ³¹School of Physical and Occupational Therapy, McGill University, Montréal, Québec, Canada; ³²McGill University Health Center, Clinical Epidemiology Montréal, Québec, Canada; ³³Desautels Faculty of Management, McGill University, Canada; ³⁴Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, Québec, Canada; ³⁵Department of Psychology and ³⁶School of Nursing, McGill University, Montréal, Québec, Canada

^sCorresponding author

Brett D. Thombs, Ph.D.

Jewish General Hospital

4333 Cote Ste Catherine Road

Montreal, Quebec H3T 1E4

Telephone: (514) 340-8222 ext. 5112

Fax: (514) 340-8124

E-mail: brett.thombs@mcgill.ca

For peer review only

ARTICLE SUMMARY

Article focus

- Psychosocial and rehabilitation interventions are used to attenuate disability and improve health-related quality of life (HRQL) in many chronic diseases, but are typically not available for people with rare diseases.
- Conducting rigorous, adequately-powered trials of these interventions for patients with rare diseases is difficult.
- The Scleroderma Patient-centered Intervention Network (SPIN) is an international collaboration of patient organizations, clinicians, and researchers whose aim is to develop a research infrastructure to test accessible, low-cost, self-guided online interventions to reduce disability and improve HRQL for people living with scleroderma (systemic sclerosis).

Key Messages

- SPIN will employ the cohort multiple randomized controlled trial (cmRCT) design, in which patients consent to participate in a cohort for ongoing data collection.
- The cohort framework will also be used to identify patients eligible for internet-based psychosocial and rehabilitation interventions that will be developed by SPIN investigators and to conduct feasibility and, subsequently, full-scale trials of these interventions.
- Once tested, effective interventions will be made accessible through patient organizations partnering with SPIN.

Strengths and limitations of this study

- In the context of rare diseases, the advantage of the cmRCT design to conduct multiple trials that draw participants from the same patient cohort is particularly important given the difficulty of recruiting a sufficiently large patient group for any single trial.
- Unique features of SPIN, including the use of the cmRCT design, the development of self-guided online interventions delivered using a common platform, and a robust partnership with patient organizations, may serve as a model to help facilitate research in this area for other rare diseases as well.

ABSTRACT

Introduction. Psychosocial and rehabilitation interventions are increasingly used to attenuate disability and improve health-related quality of life (HRQL) in chronic diseases, but are typically not available for patients with rare diseases. Conducting rigorous, adequately-powered trials of these interventions for patients with rare diseases is difficult. The Scleroderma Patient-centered Intervention Network (SPIN) is an international collaboration of patient organizations, clinicians, and researchers. The aim of SPIN is to develop a research infrastructure to test accessible, low-cost self-guided online interventions to reduce disability and improve HRQL for people living with the rare disease systemic sclerosis (SSc, or scleroderma). Once tested, effective interventions will be made accessible through patient organizations partnering with SPIN.

Methods and Analysis. SPIN will employ the cohort multiple randomized controlled trial (cmRCT) design, in which patients consent to participate in a cohort for ongoing data collection. The aim is to recruit 1,500-2,000 patients from centers across the world within a period of 5 years (2013-2018). Eligible participants are persons ≥ 18 years of age with a diagnosis of SSc. In addition to baseline medical data, participants will complete patient-reported outcome measures every 3 months. Upon enrolment in the cohort, patients will consent to be contacted in the future to participate in intervention research and to allow their data to be used for comparison purposes for interventions tested with other cohort participants. Once interventions are developed, patients from the cohort will be randomly selected and offered interventions as part of pragmatic RCTs. Outcomes from patients offered interventions will be compared to outcomes from trial-eligible patients who are not offered the interventions.

Ethics and Dissemination. The use of the cmRCT design, the development of self-guided online interventions, and partnerships with patient organizations will allow SPIN to develop,

rigorously test, and effectively disseminate psychosocial and rehabilitation interventions for people with SSc.

KEYWORDS

Scleroderma, Systemic; Research Design; Cohort study; Randomized Controlled Trial; Psychology, Medical. .

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Providing better patient-centered care for people living with chronic diseases is increasingly prioritized in proposals to improve health care.[1] Patient-centered care emphasizes patient empowerment through shared decision-making, the development of care plans that take into consideration patient preferences and values, and the tailoring of care to meet the specific needs of individual patients.[2-4] Comprehensive care to attenuate disability and improve health-related quality of life (HRQL) in chronic diseases involves a combination of both pharmacological and non-pharmacological interventions.[5] People with rare diseases do not, however, typically have access to disease-specific psychosocial and rehabilitation interventions that are important components of patient-centered care.

The lack of accessible, evidence-based, disease-specific interventions is an important gap in patient care. Many people with rare diseases face unique challenges that are not addressed by generic interventions or interventions developed for other chronic diseases.[6] However, there are major obstacles to developing, evaluating, and delivering psychosocial and rehabilitation interventions to meet the specific needs of people with rare diseases. An important barrier is the small number of people with a given rare disease at any single center. Furthermore, most clinical research centers are often involved in many different trials and tend to prioritize trials of primary disease treatment over non-pharmacological intervention trials to reduce disability and improve HRQL.

Illustrating the extent of this problem, we conducted a PubMed search (*"randomized controlled trial"* [publication type] NOT *"drug therapy"* [subheading]) of the 6,632 rare diseases listed by the US National Institutes of Health [7] and found only one randomized controlled trial (RCT) of a psychosocial or rehabilitation intervention with the sample size of at least 100 patients,[8] a relatively small number given typical sample size requirements to evaluate most psychosocial and rehabilitation interventions.[9, 10] Thus, for most rare

diseases, there are either no trials that have tested psychosocial and rehabilitation interventions or only very small trials that are useful to evaluate feasibility, but inadequate for assessment of treatment efficacy.[11-13]

Beyond difficulties conducting RCTs, many factors also complicate the delivery of psychosocial and rehabilitation interventions to people with rare diseases. Few centers treat enough patients with a given rare disease to sustain a disease specific psychosocial and rehabilitation intervention program. Additionally, many patients with rare diseases live far from major treatment centers. These individuals often receive care in local settings from health care providers with little or no experience treating their disease and without knowledge about the specific needs of people with the disease. Patients who live in rural areas far from specialized care are often left to cope with their illness essentially alone, may lack even relatively basic information about their disease, and, in many cases, experience substantial difficulty coping.[14, 15] Thus, finding a way to develop, test, and deliver psychosocial and rehabilitation interventions for patients with rare diseases in a cost-effective manner is an important, but unsolved problem.

Systemic sclerosis (SSc, also known as scleroderma) is a rare disease where patients have important unaddressed psychosocial and rehabilitation needs.[16, 17] SSc is an autoimmune connective tissue disease characterized by vascular injury, immune dysfunction and an abnormal fibrotic process that can affect multiple organ systems including the skin, lungs, gastrointestinal tract and cardiovascular system.[18, 19] Conditions commonly associated with SSc include Raynaud's phenomenon,[20] esophageal disease and chronic gastrointestinal symptoms (dysphagia, dyspepsia, diarrhea, chronic constipation, and malabsorption),[21] and pulmonary disease (interstitial lung disease, pulmonary vascular disease, pulmonary arterial hypertension).[18, 19] Prevalence estimates for SSc range from 7-

489 cases per million, and approximately 80% of patients diagnosed with SSc are women.[22, 23]

SSc is notable for a wide range of patient reported problems, including limitations in physical mobility and hand function, pain, fatigue, sleep disturbance, depression, sexual dysfunction, and body image distress from disfiguring changes in appearance (e.g., pigment changes, hand contractures, facial telangiectasias).[16, 24-27] There are no disease-modifying treatments for SSc and its management is predicated on identifying organ-specific disease manifestations and initiating targeted therapies (e.g., calcium channel blockers for Raynaud’s phenomenon, proton pump inhibitors for gastrointestinal reflux disease, ACE inhibitors for SSc renal crisis).[17] Because there is no cure, a primary goal of care is to reduce symptoms and disability, and to improve HRQL. However, as with many rare diseases, evidence-based psychosocial and rehabilitation interventions to meet the specific needs of patients with SSc are not available. The authors of recent guidelines for SSc management [17] noted the potential importance of psychosocial and rehabilitation interventions in disease management, but could not make recommendations for or against these types of interventions due to a general lack of evidence.

The Scleroderma Patient-centered Intervention Network (SPIN),[28] a collaboration of patient organizations, clinicians, and researchers from Canada, the USA, and Europe, was recently organized and funded by the Canadian Institutes of Health Research to address this important gap. The long-term goals of SPIN are to develop, test, and disseminate accessible interventions to complement standard medical care and improve HRQL outcomes in SSc. Once tested, effective interventions will be made accessible to patients with SSc through patient organizations around the world. SPIN currently is developing a series of interventions, including (i) general SSc self-management, (ii) support for better coping with emotional distress; (iii) support for managing body image distress; and (iv) physical and occupational

therapy for hands. Other interventions that address areas important to people with scleroderma (e.g., fatigue and energy management, sleep problems, sexual function) may be developed subsequently, depending on need and funding availability.

An important characteristic of SPIN is that all interventions will be delivered in a self-guided online format. Across medical fields, online delivery of interventions is increasingly common, and these interventions have successfully improved HRQL.[29-31] The utilization of web-based technology is particularly important in the case of rare diseases where patients typically have difficulty accessing specialized services. A recent study [32] found that 85% of Dutch patients with SSc had used the internet to search for information about SSc and that most of these patients (77-88%) perceived access to online information on physical, psychological and social consequences of the disease as important.

SPIN will utilize a novel research design, the cohort multiple RCT (cmRCT) design,[33] to collect longitudinal data related to problems experienced by people living with SSc and as a framework for developing, evaluating, and delivering psychosocial and rehabilitation interventions. The aim of this article is to illustrate the use of the cmRCT design in a rare disease context, which may serve as a model to help facilitate research in the area of non-pharmacological interventions for other rare diseases as well.

SPIN COHORT AIMS

The first step towards SPIN's long-term goals is the establishment of the SPIN Cohort. The specific aims of the SPIN Cohort are to:

- (1) Collect observational data at regular intervals on an ongoing basis in order to conduct research on problems identified by patients with SSc as important to them and to determine the best way to measure outcomes related to these

- problems, among other research questions that may be addressed via the cohort;
- (2) Use the cohort framework to identify patients eligible for internet-based psychosocial and rehabilitation interventions that will be developed by SPIN investigators and to conduct feasibility and, subsequently, full-scale trials of these interventions.

METHODS AND ANALYSIS

Design

The cmRCT design,[33] which SPIN will employ, was developed to take advantage of the benefits of cohort designs for longitudinal data collection and to address some important limitations to traditional RCT designs in the context of pragmatic RCTs. Pragmatic RCTs are intended to test the effectiveness of an intervention in everyday practice with relatively unselected participants and under flexible conditions, maximizing the applicability of the trial’s results to usual care settings.[34] They differ from explanatory trials in that pragmatic trials are meant to inform decisions about practice rather than explain mechanistic aspects of an intervention under ideal circumstances. In this respect, pragmatic trials are well suited to assess whether patients benefit from adding an intervention to treatment as usual, compared to treatment as usual only.

The cmRCT design involves recruitment of an observational cohort, in which patients fill out a small set of core outcomes regularly. Patients enrolled in the cohort agree to allow their longitudinal data to be used in the aggregate. They also allow their data to be used to identify them to be invited to participate in research interventions, once developed, or for comparison purposes for intervention trials that may be conducted with other patients while they are participating in the cohort. In the cmRCT design, as described to patients when they consent to participate in the cohort, only eligible patients randomly selected to be offered an

intervention, but not eligible non-selected patients, are contacted and offered treatment. Eligible patients not selected are not notified about the trial. Consent for specific trials will be obtained from those eligible patients who are invited and accept the offer to participate. Post-intervention outcomes among eligible patients who accept the offer to receive the intervention will be compared to outcomes among patients from the cohort who were identified as eligible for the intervention, but were not offered the intervention and not contacted about the intervention.

In the context of rare diseases, the advantage of the cmRCT design to conduct multiple trials that draw participants from the same patient cohort is particularly important given the difficulty of recruiting a sufficiently large patient group for any single trial. No single trial will adequately address the psychosocial and rehabilitation needs of patients with a rare disease, such as SSc. The cmRCT design will enable the implementation of multiple trials over time with different inclusion and exclusion criteria, which, together, have much greater potential in this regard.

In many areas of research, potential interventions are tested in isolation, typically including different patient groups by different research teams. The cmRCT design allows for tests of interventions that can be compared in the same overall population with similar trial methods, thus increasing the ability to compare and contrast different trial results. Furthermore, whereas the ability to collect long-term outcomes is often limited in single RCTs, core patient measures are assessed on an ongoing basis in the cmRCT model. Thus, key outcomes can be obtained over a long period post-trial for patients who participate in trials.

The cmRCT design also offers advantages in that the patient consent process more closely replicates what occurs in actual healthcare settings compared to the consent procedures typically used in traditional RCT designs. In traditional RCTs, patients are usually

told that they will be randomized to obtain the trial intervention or an alternative, which in pragmatic trials of psychosocial and rehabilitation interventions is generally usual care. In real-life health care situations, patients are only told of treatments that their healthcare provider can provide with certainty, and they are not told that the treatment they receive will be decided by chance. In the cmRCT design, patients are told about treatments that they will be able to access if they so choose.[33] As part of the initial consent process, patients are made aware that a number of trials may occur via the cohort, and that they will not likely be offered to participate in all of them and may not be offered to participate in any. It is explained that patients will only be notified about trials for which they will be offered the intervention, but that their data may be used for comparison purposes in the context of some interventions not offered to them.

Beyond increasing the ecological validity of the recruitment and consent process itself, it is possible that the cmRCT approach may increase the representativeness of trial participants, and thus the generalizability of results. Indeed, concerns about information and consent are the most common reasons for patients not participating at all in traditional RCTs.[35] These concerns likely play a role in the relatively low trial participation rates and may reduce the ecological validity of trials if patients who consent to participate comprise a small and qualitatively different group than the overall patient population who will receive the intervention in practice. Because the cmRCT design collects data on patients before they have accepted or refused the intervention, the cmRCT design also allows for collection of important information about the reasons that patients refuse an intervention and why certain patients were unable to complete the assigned intervention. This information is valuable both for assessing the validity of modeling assumptions and for predicting the success of the intervention in the general population.

In many pragmatic trials of psychosocial and rehabilitation interventions patients who consent to participate in a trial may do so because they would like the opportunity to receive the trial intervention rather than treatment as usual. Patients cannot usually be fully blinded regarding whether treatment has been offered. Therefore, patients randomised into the ‘treatment as usual’ arm, may be disappointed and some may even withdraw from the study, leading to attrition bias that might influence the results of the trial. This disappointment can also influence the perception of care and reporting of trial outcomes for patients who do not withdraw, but who are aware that they did not receive the treatment.[36] In the cmRCT design, patients will be aware when they do receive an intervention, but not when they have not been selected for an intervention trial, thus, potentially reducing the possibility of disappointment bias.

The use of the cmRCT design by SPIN to facilitate research on non-pharmacological interventions for people with SSc is feasible due to the international, multi-center nature of the network, which will facilitate the inclusion of a sufficient number of patients with SSc in the SPIN Cohort. Initially, the SPIN Cohort will be used to describe and better understand the nature of problems that have been identified by people with SSc as important [16, 28] and to determine optimal outcome measures to use in SPIN intervention trials. Once SPIN interventions are developed, patients eligible for a given trial will be identified based on trial-specific criteria using core SPIN Cohort measures (see Appendix 1), and a random selection of these eligible patients will be offered the trial intervention (Figure 1). In the SPIN Cohort, patients can participate in one SPIN intervention at the time, but may be offered to participate in more than one SPIN intervention sequentially. Core outcomes (25-30 minutes to complete) will be assessed every 6 months with brief 3-month assessments (5 minutes to complete) in between. For patients who are eligible for a SPIN intervention trial and are assigned to the intervention or control groups, the 3-months assessment will also include trial-specific

measures. Since determination of trial eligibility will be automated using routinely collected cohort measures, all patients who are eligible for an active SPIN trial at a given point in time will automatically be administered the trial-specific measures.

Study Sample

We expect to initially recruit 1,500 - 2,000 patients for the SPIN Cohort from SPIN centers in Canada, the US, France, and the Netherlands over a period of 5 years (2013-2018). Eligible participants will include patients ≥ 18 years of age who have been identified by a SPIN physician as having a diagnosis of SSc. Exclusion criteria for participation in the SPIN Cohort include having a medical disorder that compromises the ability to give informed consent, not having access to or not being able to respond to questionnaires via the internet, and not being able to respond to questionnaires in an available SPIN language (currently English, French, and Dutch).

Procedure

SSc patients treated by SPIN physicians will be recruited for the SPIN Cohort at their site, and their written informed consent will be obtained. The local participating SPIN physician, or supervised nurse coordinator, will complete a Medical Data form (see Appendix 2). This form will be submitted online to initiate patient registration in the SPIN Cohort. After completion of registration by a recruiting SPIN physician, an automated welcoming email will be sent to participants with instructions to complete the SPIN patient measures online. Two weeks prior to each 3-month follow-up, participants will receive an email reminding them to go online and complete their forms. On the date of the follow-up assessment, a second notification email will be sent to patients, reminding them to complete the questionnaires online. If one week after the assessment date the questionnaire has not yet been completed, a

SPIN investigator will contact the patient to encourage them to go online and complete the forms. If a patient has not filled out the questionnaires within two weeks after the assessment date, their data will not be collected for that assessment cycle. Patients who do not complete forms at a particular SPIN Cohort assessment are eligible to continue in the SPIN Cohort and will be contacted for subsequent assessments. If patients do not complete 4 consecutive assessments, they will be considered to have dropped out of the SPIN Cohort.

Measures

Medical information is obtained at baseline, and SPIN Cohort participants will complete a core set of 6 measures online every 6 months. The core measures include measures of overall health status and functional disability, as well as measures of patient outcomes that will be targeted by the initial set of SPIN interventions that are under development (emotional distress, body image concerns, hand function, disease self-management). Additional measures will be integrated into the SPIN Cohort periodically for the purpose of conducting measurement-related sub-studies (with a total of 25-30 minutes to complete). The core measures will determine eligibility for SPIN feasibility trials and subsequent full-scale trials, once initiated. At the 3-month interval between two core measurement occasions, a brief assessment of HRQL will be completed (5 minutes to complete). For patients who are eligible for a SPIN intervention trial (in both the intervention and control arms), this 3-months measurement will include trial-specific measures related to the trial outcomes of interest.

Medical data. At the time of enrollment, recruiting SPIN physicians will obtain and record basic demographic and medical data from patients' medical records. Medical information will be recorded on a standardized form (See Appendix 2) and will include height, weight, date of onset Raynaud's phenomenon and first non-Raynaud's symptom, date

of SSc diagnosis, disease subtype, presence of autoantibodies, skin involvement, presence of digital ulcers and pitting scars, joint involvement, organ involvement, and the presence of an overlap syndrome.

Core measures. Overall health status will be assessed with the Patient Reported Outcomes Measurement Information System-29 (PROMIS-29)[37] and functional disability from SSc with the Scleroderma Health Assessment Questionnaire (SHAQ)[38]. Depressive symptoms will be assessed with the Patient Health Questionnaire-8 (PHQ-8).[39-41] Body image concerns due to changes in appearance from SSc will be assessed with the Satisfaction with Appearance Scale (SWAP).[42-44] The Cochin Hand Function Scale [45] will be used to measure limitations in hand function. Self-efficacy for coping and disease self-management will be measured using the Self-Efficacy for Managing Chronic Disease Scale.[46] Further information on each measure is available in Appendix 1.

Analysis Plan

Sample size. We aim to recruit 1,500-2,000 patients for the SPIN Cohort. This number will be sufficient to conduct longitudinal research on problems identified by patients with SSc as important to them and to determine the best way to measure outcomes related to these problems. We also expect this to be a sufficient number to identify and recruit eligible patients to participate in future SPIN trial studies, allowing us to conduct randomized controlled trials with sufficient statistical power. Sample size calculations for SPIN trials will be determined for each SPIN trial separately, and the appropriate sample size calculations will be provided in all trial protocols.

SPIN Cohort. Initially, SPIN Cohort data will be used to gain a better understanding of problems identified by patients as important to them (e.g., body image, physical limitations, and HRQL) via observational studies and to conduct measurement studies to determine the

best way to measure outcomes related to these problems. All studies that use data from the SPIN Cohort for these purposes will be required to submit a proposal to the SPIN Data Access and Publications Committee (see below). This committee will ensure that all study designs are appropriate and that investigators adhere to a priori defined study and analysis plans.

Feasibility trials. Consistent with current best practice recommendations for intervention development and testing,[11-13] feasibility trials for all SPIN interventions will be conducted via the SPIN Cohort to ensure that trial methodology is sound, feasible, and consistent with patient expectations.[11-13] Data will be collected to review the process (e.g., feasibility of steps that need to take place in the full-scale study), required resources (e.g., time and budget), management issues (e.g., related to optimizing performance of personnel and data systems), and scientific aspects (e.g., recruitment rates of eligible patients, acceptability of intervention to patients, assessing performance of outcome measures). For each intervention, semi-structured interviews will be conducted with 15-20 randomly selected participants to assess the acceptability, utility and practicality of intervention components, and usefulness of proposed study outcome measures. Interviews will be conducted using established methods for qualitative process evaluation of trials as developed by Donovan et al.[47] We will use a topic guide to ensure consistency across participants, but with a flexible format to allow participants to generate naturalistic data related to their experience and on what they consider as important and/or successful in terms of treatment outcomes. For all SPIN interventions, feasibility study results will be used to refine the methodology and analysis plans for the full-scale RCTs.

Full-scale RCTs. In traditional RCTs, the effectiveness of an intervention may be assessed using per-protocol analysis, which includes only those patients who successfully completed the treatment originally allocated, or an intention-to-treat analysis (ITT), which

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

compares patients in the groups to which they were originally allocated after randomization, irrespective of whether or not the patient received or completed the allocated treatment. ITT is widely recommended as the preferred analysis, since it addresses the effectiveness of the intervention for all patients who agree to attempt the treatment, rather than only for patients who successfully complete it, as with per-protocol analysis. The primary analysis for SPIN trials will be ITT, comparing the outcomes of randomly selected patients who are offered the intervention, to eligible patients who were not offered the intervention.

In the cmRCT design, however, randomization occurs prior to offer of intervention, and some number of eligible patients who are randomly selected to be offered an intervention will not accept the offer. In addition to ITT analysis, it is of interest to assess the effect of an intervention among patients who accept the offer. Ideally, we would compare outcomes for patients who accept the offer of the intervention to patients who are not offered the intervention, but would have accepted if they had received an offer. This is because patients who agree to attempt an intervention may be different in important ways from patients who decline the offer of an intervention. Because we cannot actually know which patients who are not offered the intervention would have accepted if offered, we will use Complier Average Causal Effect (CACE) analysis [48, 49] to make this comparison, as a secondary analysis for SPIN trials. CACE assumes that the proportion of patients in the non-offer group who would have refused the offer is the same as for the group who were offered the intervention. Furthermore, CACE assumes that outcomes are the same among patients who refuse the intervention and patients who would have refused the intervention, if offered. On this basis, an intervention effect can be estimated that compares patients in the offer group who accepted the intervention offer to patients in the non-offer group who would have accepted the intervention if offered. See Figure 2.

All SPIN full-scale trials will be registered [50] and will be conducted and reported in accordance with standards articulated in the Consolidated Standards of Reporting Trials (CONSORT) Extension for Non-pharmacologic Trials.[51, 52] A study protocol for each full-scale trial will be published, describing the study design and content of the SPIN intervention.

ETHICS AND DISSEMINATION

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2008) and other major ethical guidelines of participating sites, including Canada's Tri-Council Policy Statement (2010). The SPIN Cohort has received ethical approval from the Research Ethics Committee of the Jewish General Hospital in Montreal, Quebec, Canada. Ethical approval for the SPIN Cohort will also be obtained from the local Institutional Review Boards of all participating sites prior to recruitment of patients from the sites.

In the cmRCT design, individuals consent to participate in a cohort for ongoing data collection and to allow their data to be used for comparison purposes with patients from the cohort who may be offered to participate in trials that are conducted within the SPIN Cohort. At the time of recruitment, written informed consent will be obtained. The local recruiting SPIN physician, or supervised nurse coordinator, will explain the nature and purpose of the Cohort and provide the participants with a copy of the consent and information sheet. Recruiting SPIN physicians will provide a description of SPIN and explain that agreeing to participate in the SPIN Cohort will involve (1) giving the physician or supervised nurse coordinator permission to complete the SPIN baseline Medical Data form, using information from the patient's medical record; (2) being contacted by email with instructions on how to complete SPIN patient measures via the internet at the time of enrolment and periodically going forward (every 3 months); (3) providing permission for their data to be used to select them for participation in trials or for comparison purposes for SPIN intervention trials that

may be conducted while they are participating in the SPIN Cohort; and (4) giving permission for SPIN investigators to contact them with an invitation to participate in SPIN interventions once developed. Patients will be informed that participation in the SPIN Cohort will not affect their usual care in any way. They will also be informed that only patients who are randomly selected to be offered an intervention will be contacted about the intervention. Finally, it is explained that patients' current consent is only for participation in the SPIN Cohort, and that separate consent will be sought for participation in a particular SPIN intervention.

Data Management and Security

All data are entered into a centralized secure electronic data management system designed, managed and located at the *Data Management Unit of the Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal Quebec, Canada*. To protect the participants' privacy, before the recruiting SPIN physician at each center enters the medical data, a unique patient identification number will automatically be assigned to each participant. Only de-identified data will be recorded in the database, with linking data available only to the SPIN Director. Only personnel authorized by the SPIN Director will be allowed to retrieve, enter or change data from the central database, and the database will be audited for any changes that are made. All data will be kept for ten years after completing the cohort study for ethical and scientific reasons.

Study Management

SPIN was awarded a five-year Emerging Team Grant for Rare Diseases from the Canadian Institutes of Health Research to fund the SPIN Cohort (Funding Reference Number TR3-119192; Principal Investigator, Brett D. Thombs; 2012-2017). In addition to this funding, SPIN has received institutional contributions from the Lady Davis Institute for

1
2
3 Medical Research of the Jewish General Hospital, Montreal, Canada, for database
4
5 development and from McGill University, Montreal, Canada for student training. Previously,
6
7 SPIN received funds from the Scleroderma Society of Canada, the Scleroderma Society of
8
9 Ontario, and Sclérodermie Québec for developmental work.
10

11
12 SPIN's organizational structure is depicted in Figure 3. The *SPIN Steering Committee*
13
14 is responsible for review of the SPIN project direction and coherence, including being
15
16 informed and advising on Cohort recruitment/retention and intervention development,
17
18 feasibility and full-scale testing of interventions; reviewing and approving proposals for SPIN
19
20 publications; being informed of the financial well-being of the project; and helping to resolve
21
22 administrative issues.
23

24
25 The *SPIN Advisory Board* is directed by and largely comprised of people living with
26
27 SSc, supported by expert consultants. The Advisory Board will (1) review the overall SPIN
28
29 project and individual SPIN intervention projects and (2) advise the Steering Committee so
30
31 that SPIN maximally reflects the needs of people with SSc and ensures successful knowledge
32
33 transfer within the SSc community and with the broader rare disease community.
34

35
36 Each *SPIN project team* has a leader, co-leader(s), and a multidisciplinary group of
37
38 investigators, including at least two SSc patients. Project teams, supported by the Steering
39
40 Committee and SPIN Cores (see below), will design and test SPIN interventions and work
41
42 with patient organizations to facilitate delivery of tested interventions.
43

44
45 *SPIN Cores* work closely with project teams to support high-quality investigative
46
47 work and successful knowledge transfer. SPIN Cores provide expertise in information
48
49 technology for delivering patient-centered health care services; data management; research
50
51 methods and biostatistics; measurement of patient-oriented outcomes in SSc; health
52
53 economics; knowledge transfer; and bioethics.
54
55
56
57
58
59
60

The *SPIN Data Access and Publication Policy* describes the procedures that will be used to ensure the scientific integrity of publications that emerge from SPIN. The policy ensures that responsibility and credit for SPIN publications as well as standard authorship requirements (e.g., International Committee of Medical Journal Editors) are met. Proposals to conduct analyses using SPIN data must be submitted by a SPIN investigator for review to the Data Access and Publication Committee. The Committee will ensure that proposed analyses do not overlap with existing proposals and will review the proposed methods, in consultation with the SPIN Cores. It is anticipated that, at the appropriate time, access to SPIN data will be open to other investigators, consistent with the policies of the Canadian Institute of Health Research.[53] Prior to providing access to de-identified SPIN data to non-SPIN investigators, a Data Sharing Plan describing the data sharing procedures will be written and submitted for ethics approval to the Research Ethics Committee of the Jewish General Hospital in Montreal, Quebec, Canada.

DISCUSSION

Until recently, the inability to conduct rigorous, adequately powered trials of psychosocial and rehabilitation interventions in rare diseases has been a barrier to the development of evidence-based patient-centered care for people with rare diseases. The novel cmRCT design [33] that will be utilized by SPIN is a promising approach to move forward research in this area. It will allow SPIN to both collect important observational data in a longitudinal cohort and to conduct multiple pragmatic RCTs in the same cohort.

The use of the cmRCT design in SPIN is highly feasible due to its international multi-center nature. The features of the cmRCT design make it a good option for conducting research in the context of rare chronic diseases, as well as comparing psychosocial and rehabilitation interventions to treatment as usual in pragmatic trials. There may be a number

of circumstances, however, in which the cmRCT design is less suitable.[33] These include, for instance, acute or short-term conditions, double-blinded trials with a placebo arm, and treatments for which the uptake by patients may be low. In addition, the use of relatively easy obtainable patient-reported outcomes, as in the SPIN Cohort, facilitates research using the cmRCT design, compared to more expensive and time-intensive measures such as conducting laboratory tests, which would not be feasible in the context of the cmRCT.

The end goal of SPIN is to make psychosocial and rehabilitation interventions available through patient organizations. The collaboration of investigators with patient organization partners has been crucial in the establishment of SPIN. Prior to launching SPIN, a series of projects were conducted in collaboration with patients from organizations across Canada (e.g., Scleroderma Societies of Canada and Ontario, Sclérodermie Québec, the Scleroderma Association of British Columbia), the US (US Scleroderma Foundation) and Europe (Federation of European Scleroderma Associations), which has helped to better understand important problems faced by persons living with SSc and to prioritize gaps in access to psychosocial and rehabilitation services.[16, 25, 54] Each of the proposed SPIN interventions is grounded in this work, and integrated knowledge transfer will play a major role in developing, adapting and disseminating interventions to best address the needs of persons with SSc. Patient advocacy organizations have committed to working with SPIN on an ongoing basis to ensure that the interventions developed by SPIN will be made available to patients once developed and tested.

In summary, SPIN is a unique endeavor to develop and test psychosocial and rehabilitation care interventions in SSc and to make these interventions accessible through patient organizations around the world with a low ongoing cost. Unique features of SPIN, including the use of the cmRCT design, the development of self-guided online interventions

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

delivered using a common platform, and a robust partnership with patient organizations, may
serve as a model to help facilitate research in this area for other rare diseases as well.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2013-003563 on 7 August 2013. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

REFERENCES

1. Canadian Medical Association. Health Care Transformation in Canada. 2010.
2. Stewart M. Towards a global definition of patient centred care. *BMJ* 2001;**322**:444-5.
3. Lewis S. Patient-Centered Care: An Introduction to What It Is and How to Achieve It. A Discussion Paper for the Saskatchewan Ministry of Health. 2009.
4. Ells C, Hunt MR, Evans JC. Relational autonomy as an essential component of patient-centered care. *Int J Fem Approaches Bioeth* 2011;**4**:79-101.
5. Multidisciplinary Care for Patients with Rheumatic and Musculoskeletal Diseases: The Rheumatology Health Care Team
[<http://www.rheumatology.org/practice/clinical/position/multidisciplinaryCare.pdf>]
6. Reimann A, Bend J, Dembski B. [Patient-centred care in rare diseases. A patient organisations' perspective]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007;**50**:1484-93.
7. National Institutes of Health Office of Rare Diseases Research
[<http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1>]
8. Christian BJ, D'Auria JP. Building life skills for children with cystic fibrosis: effectiveness of an intervention. *Nurs Res* 2006;**55**:300-7.
9. Coyne JC, Thombs BD, Hagedoorn M. Ain't necessarily so: review and critique of recent meta-analyses of behavioral medicine interventions in health psychology. *Health Psychol* 2010;**29**:107-16.
10. Kraemer HC, Gardner C, Brooks JO, et al. Advantages of excluding underpowered studies in meta-analysis: inclusionist versus exclusionist viewpoints. *Psychol Methods* 1998;**3**:23-31.
11. Kraemer HC, Mintz J, Noda A, et al. Caution regarding the use of pilot studies to guide power calculations for study proposals. *Arch Gen Psychiatry* 2006;**63**:484-9.

12. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;**10**:1.

13. Van Teijlingen ER, Rennie AM, Hundley V, et al. The importance of conducting and reporting pilot studies: the example of the Scottish Births Survey. *J Adv Nurs* 2001;**34**:289-95.

14. Goodridge D, Hutchinson S, Wilson D, et al. Living in a rural area with advanced chronic respiratory illness: a qualitative study. *Prim Care Respir J* 2011;**20**:54-8.

15. Weinert C, Cudney S, Comstock B, et al. Computer intervention impact on psychosocial adaptation of rural women with chronic conditions. *Nurs Res* 2011;**60**:82-91.

16. Thombs BD, van Lankveld W, Bassel M, et al. Psychological health and well-being in systemic sclerosis: State of the science and consensus research agenda. *Arthritis Care Res (Hoboken)* 2010;**62**:1181-9.

17. Kowal-Bielecka O, Landewe R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;**68**:620-8.

18. Seibold J. Scleroderma. In: Harris ED, Budd, RC, Firestein, GS, et al, eds. Kelley's textbook of rheumatology. Volume II. 7th edition. Philadelphia: Elsevier 2005:1279-1308.

19. Wigley FM, Hummers LK. Clinical features of systemic sclerosis. In Hochberg MC, Silman, AJ, Smolen, JS, et al, eds. Rheumatology. 3rd edition. Philadelphia: Mosby 2003:1463-80.

20. Merkel PA, Herlyn K, Martin RW, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002;**46**:2410-20.

21. Ntoumazios SK, Voulgari PV, Potsis K, et al. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. *Semin Arthritis Rheum* 2006;**36**:173-81.

22. Chiffot H, Fautrel B, Sordet C, et al. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum* 2008;**37**:223-35.
23. Bernatsky S, Joseph L, Pineau CA, et al. Scleroderma prevalence: demographic variations in a population-based sample. *Arthritis Rheum* 2009;**61**:400-4.
24. Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. *Rheum Dis Clin North Am* 2003;**29**:427-39.
25. Bassel M, Hudson M, Taillefer SS, et al. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. *Rheumatology (Oxford)* 2011;**50**:762-7.
26. Jewett LR, Haythornthwaite JA, Thombs BD. Psychosocial issues and care for patients with systemic sclerosis. In Varga J, Denton CP, Wigley FM, eds. *Scleroderma: From Pathogenesis to Comprehensive Management*. New York: Springer 2012:641-8.
27. Jewett LR, Hudson M, Thombs BD. A 38-year-old woman with elevated muscle enzymes, Raynaud's phenomenon and positive anti-topoisomerase I antibody: Is she depressed? In Silver RM, Denton CP, eds. *Case Studies in Systemic Sclerosis*. New York: Springer 2011: 273-80.
28. Thombs BD, Jewett LR, Assassi S, et al. New directions for patient-centered care in scleroderma: The Scleroderma Patient-Centered Intervention Network. *Clin Exp Rheum* 2012;**30**:23-9.
29. Cuijpers P, Donker T, Johansson R, et al. Self-guided psychological treatment for depressive symptoms: a meta-analysis. *PLoS One* 2011;**6**:e21274.
30. Griffiths KM, Farrer L, Christensen H. The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials. *Med J Aust* 2010;**192**:S4-11.

31. Donker T, Griffiths KM, Cuijpers P, et al. Psychoeducation for depression, anxiety and psychological distress: a meta-analysis. *BMC Med* 2009;**7**:79-7015-7-79.

32. van der Vaart R, Repping-Wuts H, Drossaert CH, et al. Needs for online information and support of patients with systemic sclerosis. *Arthritis Care Res (Hoboken)* 2013;**65**:594-600.

33. Relton C, Torgerson D, O'Cathain A, et al. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ* 2010;**340**:c1066.

34. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;**337**:a2390.

35. Ross S, Grant A, Counsell C, et al. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;**52**:1143-56.

36. Torgerson DJ, Torgerson CJ. *Designing randomised trials in health, education, and the social sciences: an introduction*: Palgrave Macmillan;2008.

37. Hinchcliff M, Beaumont JL, Thavarajah K, et al. Validity of two new patient-reported outcome measures in systemic sclerosis: Patient-Reported Outcomes Measurement Information System 29-item Health Profile and Functional Assessment of Chronic Illness Therapy-Dyspnea short form. *Arthritis Care Res (Hoboken)* 2011;**63**:1620-8.

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

39. Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord* 2009;**114**:163-73.

40. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry* 2010;**32**:345-59.

41. Razykov I, Hudson M, Baron M, et al. The Utility of the PHQ-9 to Assess Suicide Risk in Patients with Systemic Sclerosis. *Arthritis Care Res (Hoboken)* 2013;65:753-8.
42. Lawrence JW, Heinberg LJ, Roca R, et al. Development and Validation of the Satisfaction With Appearance Scale: Assessing Body Image Among Burn-Injured Patients. *Psychol Assess* 1998;10:64-70.
43. Jewett LR, Hudson M, Haythornthwaite JA, et al. Development and validation of the brief-satisfaction with appearance scale for systemic sclerosis. *Arthritis Care Res (Hoboken)* 2010;62:1779-86.
44. Heinberg LJ, Kudel I, White B, et al. Assessing body image in patients with systemic sclerosis (scleroderma): Validation of the Adapted Satisfaction with Appearance Scale. *Body Image* 2007;4:79-86.
45. Duruoz MT, Poiraudau S, Fermanian J, et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. *J Rheumatol* 1996;23:1167-72.
46. Lorig KR, Sobel DS, Ritter PL, et al. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract* 2001;4:256-62.
47. Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002;325:766-70.
48. Hewitt CE, Torgerson DJ, Miles JN. Is there another way to take account of noncompliance in randomized controlled trials? *CMAJ* 2006;175:347.
49. Dunn G, Maracy M, Tomenson B. Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods. *Stat Methods Med Res* 2005;14:369-95.

50. Clinical Trials Registry [<http://www.clinicaltrials.gov>]

51. Boutron I, Moher D, Altman DG, et al. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008;**148**:295-309.

52. Boutron I, Moher D, Altman DG, et al. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. *Ann Intern Med* 2008;**148**:W60-6.

53. Draft policy on access to CIHR-funded research output [<http://www.cihr-irsc.gc.ca/e/32326.html>]

54. Taillefer SS, Bernstein J, Schieir O, et al. Canadian scleroderma patient survey of health concerns and research priorities: An initiative of the Scleroderma Society of Canada and the Canadian Scleroderma Research Group. 2010.

AUTHORS' CONTRIBUTIONS

LK and LRJ participated in the design of the study and its coordination and contributed to drafting the manuscript. BDT conceived the study, participated in its design and coordination, and contributed to drafting the manuscript. MB, SJB, DF, KG, DK, VLM, MDM, LM, SP, MS, WRN, JLP, SA, IB, CE, CHME, MH, AI, AK, CL, ACM, CF, JP, RJS, MESA, SA, SCM, VCD, SG, YJ, BL, KM, SM, IR and RS participated in the design of the study and revised the manuscript critically. All authors read and approved the final manuscript.

FUNDING STATEMENT

SPIN is funded by a Canadian Institutes of Health Research (CIHR) Emerging Team Grant for Rare Diseases (PI, Thombs; TR3-119192). In addition to CIHR funding, SPIN has received institutional contributions from the Lady Davis Institute for Medical Research of the Jewish General Hospital, Montreal, Canada and from McGill University, Montreal, Canada. The initial organizational meeting for SPIN was funded by a CIHR Meetings, Planning, and Dissemination grant to B.D. Thombs (KPE-109130), Sclérodermie Québec, and the Lady Davis Institute for Medical Research of the Jewish General Hospital, Montréal, Québec. SPIN has also received operating support from the Scleroderma Society of Ontario, the Scleroderma Society of Canada, and Sclérodermie Québec. SPIN's funders did not have any role in the design, collection, analysis or interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

B.D. Thombs and M. Hudson are supported by New Investigator awards from the CIHR. M.D. Mayes and S. Assassi are supported by the NIH/NIAMS Scleroderma Center of Research Translation grant no. P50-AR054144. D. Khanna is supported by a NIH/NIAMS U01 AR057936A, the National Institutes of Health through the NIH Roadmap for Medical Research Grant (AR052177). L. Kwakkenbos is supported by a Fonds de la Recherche en

Santé Québec (FRSQ) postdoctoral fellowship. L. Jewett, V. Delisle, K. Milette, and I. Razykov are supported by a CIHR Doctoral Research award. B. Levis is supported by a FRSQ Master’s Training award.

COMPETING INTERESTS STATEMENT

D. Khanna has served as a consultant, steering committee member, or on speaker bureaus for Actelion, BMS, Bayer, DIGNA, InterMUNE, Gilead, Roche, and United Therapeutics. S. Poiraudau has served as a consultant for Pfizer, BMS and Sanofi-Aventis.

FIGURE LEGENDS

Figure 1: Outline of the cohort multiple RCT (cmRCT) design

Figure 2: Outline of Complier Average Causal Effect Analysis in the cmRCT Design

Figure3: SPIN Organizational Structure

For peer review only

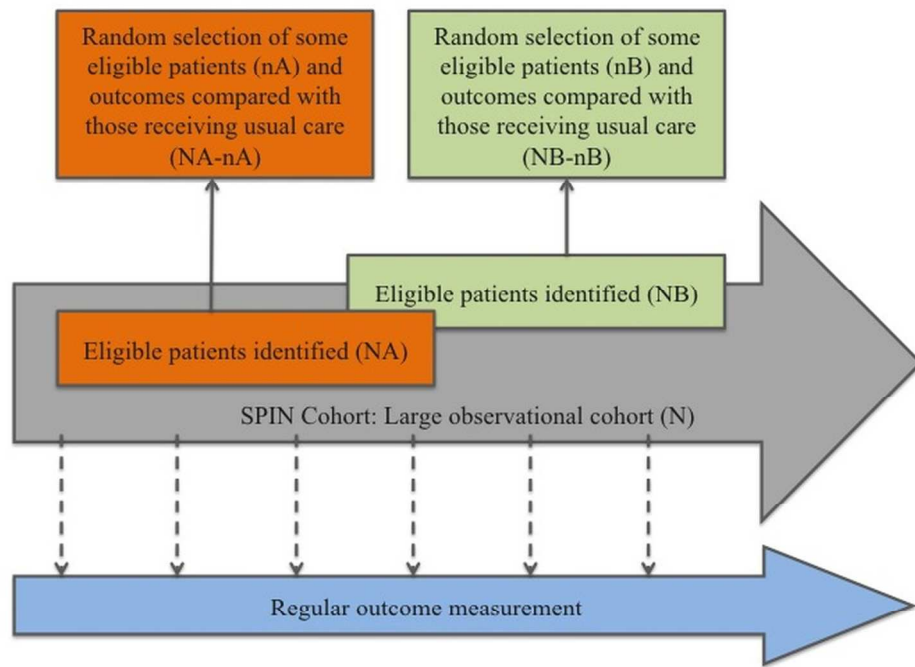
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

APPENDICES (ONLINE ONLY)

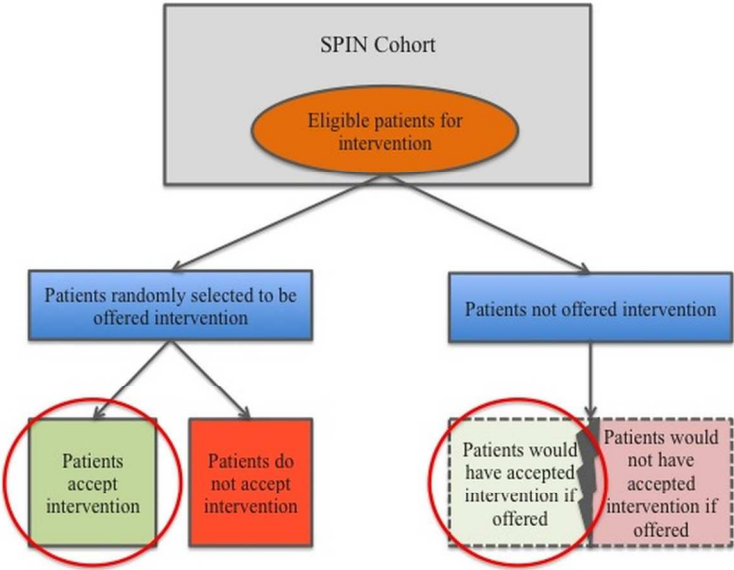
Appendix 1- SPIN Core measures

Appendix 2- SPIN Medical data form

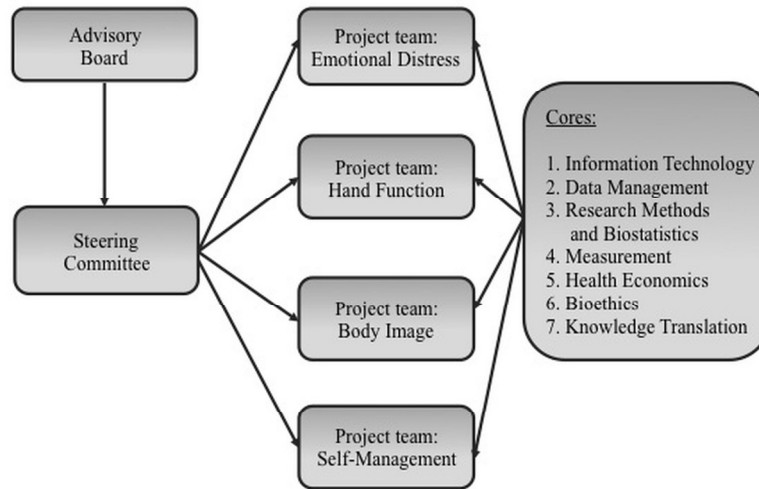
For peer review only



119x90mm (300 x 300 DPI)



119x90mm (300 x 300 DPI)



119x90mm (300 x 300 DPI)

Kwakkenbos et al.
The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

Appenndix 1: SPIN Core Measures

The Scleroderma Patient-centered Intervention Network (SPIN) Core Measures currently include six questionnaires that assess overall quality of life and function across a number of areas important to patients with systemic sclerosis (SSc).

Overall health status will be assessed with the Patient Reported Outcomes Measurement Information System-29 (PROMIS-29).[1] The PROMIS-29 measures 7 domains related to pain, fatigue, depression, anxiety, sleep, physical function, and sexual function. For each domain, 4 items are scored on a 5-point scale, and pain intensity is assessed using an 11-point rating scale. A score of 50 ± 10 represents the mean \pm SD of the general US population for each domain (except pain rating). For the anxiety, depression, fatigue, pain interference, and sleep disturbance domains, higher scores represent worse symptoms, and for physical functioning and social role, higher scores represent better functioning (thus, higher scores represent more of the domain being measured).

Functional disability from SSc will be measured using the Scleroderma Health Assessment Questionnaire (SHAQ)[2] which consists of the Health Assessment Questionnaire - Disability Index (HAQ-DI) and 6 numerical rating scales to assess functional disability due to SSc-related symptoms. The HAQ-DI is a self-report questionnaire designed to assess functional disability in patients with arthritis and is the most widely used instrument among patient-reported measures of functional status in SSc.[3] The HAQ-DI has 8 domains that inquire about hand activities, dexterity, and lower extremity function. It has found to have acceptable feasibility, reliability, and validity including sensitivity to change and predicts survival in SSc.[2, 4-6] A higher

Kwakkenbos et al.

The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

score on the HAQ-DI indicates a greater level of functional disability with a total score range of 0 (no disability) to 3 (severe disability).

The numerical rating scales assess SSc-related functional disability due to Raynaud's phenomenon, finger ulcers, breathing problems, gastrointestinal problems, pain, and overall SSc, and are anchored between "did not limit activities" to "very severe limitation". We will also assess itch using numerical rating scales, which was found to be a common symptom of SSc.[7] Transition questions are added for all symptoms (*Compared to your last assessment, how would you rate your [insert symptom]*) and are scored on a 7-point Likert scale (*very much better to very much worse*).

Depressive symptoms will be assessed with the Patient Health Questionnaire-8 (PHQ-8).[8-10] The PHQ-9 [11] is a 9-item measure of depression symptoms that has been widely used in primary care and medical populations and rates the frequency of depressive symptoms over the past 2 weeks on a 0-3 Likert-type scale (*not at all to nearly every day*). The PHQ-9 exhibits good sensitivity/specificity and has been found to be sensitive to changes in depression over time.[12] Overall, the PHQ-9 has been translated into at least 25 languages and been shown to be as accurate as longer tools for identifying major depression in a range of settings, countries, and patient populations.[13, 14] An important shortcoming of the PHQ-9, however, is that its 9th item asks about both self-harm and passive thought about "being better off dead." In medical populations, as many as 20% of patients may endorse this item, but most are responding to the passive thoughts part of the item rather than active thoughts of self-harm. Thus, increasingly, the PHQ-8 is preferred in research studies [9], including SSc.[10]

Kwakkenbos et al.
The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

Body image concerns due to changes in appearance from SSc will be assessed with the Satisfaction with Appearance Scale (SWAP)[15-17]. The 14-item SWAP [15] was developed to measure non-weight related body image dissatisfaction among burn survivors. The SWAP has been validated for SSc.[17] Respondents to the SWAP rate the degree to which they feel each item reflects their thoughts and feelings about their appearance on a 7-point scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). The SWAP has a two-factor structure, Perceived Social Impact, reflecting social discomfort, and Subjective Dissatisfaction, reflecting dissatisfaction with various body parts. High scores indicate greater body image dissatisfaction.

The Cochin Hand Function Scale (CHFS)[18] will be used to measure limitations in hand function. The CHFS is a questionnaire with 18 items concerning daily activities that require hand function and designed to assess limitations in hand function due to rheumatic disease. Each question is scored on a scale of 0 (*performed without difficulty*) to 5 (*impossible to do*). The total score is obtained by adding the scores of all items (range 0-90). The CHFS has been validated in rheumatoid arthritis,[18, 19] hand osteoarthritis,[20] and SSc.[21]

Self-efficacy for coping and disease management will be measured using the Self-Efficacy for Managing Chronic Disease Scale.[22] This scale measures the confidence individuals have in their ability to use self-management techniques to cope with the consequences of chronic disease. Various versions of this scale have been used with many different populations and disease groups.[22] The 6-item brief version was developed for use in clinical trials in order to reduce the respondent questionnaire burden. It measures confidence in one's ability to manage fatigue, pain, emotional distress and

Kwakkenbos et al.

The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

other symptoms as well as to reduce the need for medical care and reliance on medications. Each item is rated on a numerical scale ranging from 1 (*not confident at all*) to 10 (*totally confident*). The score for the scale is the mean of all items. The scale has been shown to be sensitive to change in self-management trials.[23, 24]

For peer review only

Kwakkenbos et al.
The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

REFERENCES

1. Hinchcliff M, Beaumont JL, Thavarajah K, et al. Validity of two new patient-reported outcome measures in systemic sclerosis: Patient-Reported Outcomes Measurement Information System 29-item Health Profile and Functional Assessment of Chronic Illness Therapy-Dyspnea short form. *Arthritis Care Res (Hoboken)* 2011;**63**:1620-28.

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

3. Clements PJ, Wong WK, Hurwitz EL, et al. Correlates of the disability index of the health assessment questionnaire: a measure of functional impairment in systemic sclerosis. *Arthritis Rheum* 1999;**42**:2372-80.

4. Poole JL. Grasp pattern variations seen in the scleroderma hand. *Am J Occup Ther* 1994, **48**:46-54.

5. Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. *Arthritis Care Res* 1991;**4**:27-31.

6. Khanna D, Furst DE, Clements PJ, et al. Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. *J Rheumatol* 2005; **32**:832-40.

7. Razykov I, Thombs BD, Hudson M, et al. Prevalence and clinical correlates of pruritus in patients with systemic sclerosis. *Arthritis Rheum* 2009, **61**:1765-70.

8. Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord* 2009, **114**:163-73.

Kwakkenbos et al.

The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

9. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry* 2010;**32**:345-59.
10. Razykov I, Hudson M, Baron M, et al. The Utility of the PHQ-9 to Assess Suicide Risk in Patients with Systemic Sclerosis. *Arthritis Care Res (Hoboken)* 2013;**65**:753-8.
11. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;**16**:606-13.
12. Lowe B, Unutzer J, Callahan CM, et al. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care* 2004;**42**:1194-1201.
13. Gilbody S, Richards D, Brealey S, et al. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J Gen Intern Med* 2007;**22**:1596-1602.
14. Wittkamp KA, Naeije L, Schene AH, et al. Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review. *Gen Hosp Psychiatry* 2007;**29**:388-95.
15. Lawrence JW, Heinberg LJ, Roca R, et al. Development and Validation of the Satisfaction With Appearance Scale: Assessing Body Image Among Burn-Injured Patients. *Psychol Assess* 1998;**10**:64-70.
16. Jewett LR, Hudson M, Haythornthwaite JA, et al. Development and validation of the brief-satisfaction with appearance scale for systemic sclerosis. *Arthritis Care Res (Hoboken)* 2010;**62**:1779-86.

Kwakkenbos et al.
The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

17. Heinberg LJ, Kudel I, White B, et al. Assessing body image in patients with systemic sclerosis (scleroderma): Validation of the Adapted Satisfaction with Appearance Scale. *Body Image* 2007, **4**:79-86.

18. Duruoz MT, Poiraudau S, Fermanian J, et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. *J Rheumatol* 1996;**23**:1167-72.

19. Poiraudau S, Lefevre-Colau MM, Fermanian J, et al. The ability of the Cochin rheumatoid arthritis hand functional scale to detect change during the course of disease. *Arthritis Care Res* 2000;**13**:296-303.

20. Poiraudau S, Chevalier X, Conrozier T, et al. Reliability, validity, and sensitivity to change of the Cochin hand functional disability scale in hand osteoarthritis. *Osteoarthritis Cartilage* 2001;**9**:570-7.

21. Rannou F, Poiraudau S, Berezne A, et al. Assessing disability and quality of life in systemic sclerosis: Construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. *Arthritis Rheum* 2007;**57**:94-102.

22. Lorig KR, Sobel DS, Ritter PL, et al. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract* 2001;**4**:256-62.

23. Osborne RH, Wilson T, Lorig KR, et al. Does self-management lead to sustainable health benefits in people with arthritis? A 2-year transition study of 452 Australians. *J Rheumatol* 2007, **34**:e-publication.

Kwakkenbos et al.

The Scleroderma Patient-centered Intervention Network (SPIN) Cohort

24. Foster G, Taylor SJ, Eldridge SE, et al. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* 2007;(4):CD005108.

For peer review only

Kwakkenbos et al.
Scleroderma Patient-centered Intervention Network (SPIN)

Additional File 2: SPIN Medical Data Form

1. Patient ID

2. Date

/

/

(dd/mm/yyyy)

3. Sex

Male

Female

4. Date of Birth

/

/

(dd/mm/yyyy)

5. Height

cm

Not available

6. Weight

kg

Not available

7. Raynauds

Yes

No

Not available

8. Date of onset of Raynaud's

(if exact date is not known, provide best approximate estimate)

/

/

(dd/mm/yyyy)

Not available

9. Date of onset of first non-Raynaud's disease manifestation

(if exact date is not known, provide best approximate estimate)

/

/

(dd/mm/yyyy)

Not available

10. Date of SSc diagnosis

(if exact date is not known, provide best approximate estimate)

/

/

(dd/mm/yyyy)

Not available

11. Disease Subset

Diffuse – skin sclerosis involving the limbs proximal to the elbows and knees and/or the chest and/or trunk, at any time

Limited – skin sclerosis confined to the limbs distal to the elbows and knees and/or face

Limited

Diffuse

Sine

Not available

12. Autoantibodies

a. Antinuclear Antibody (ANA)

By Indirect immunofluorescence (IIF)

Positive

Negative

Not done

If ANA positive, titre > 1:160

Kwakkenbos et al.

Scleroderma Patient-centered Intervention Network (SPIN)

☐ **Yes** ☐ **No**

b. Anti-centromere

By IIF or other antigen-based methods

☐ **Positive** ☐ **Negative** ☐ **Not done**

c. Anti-topoisomerase I (also called Scl-70)

☐ **Positive** ☐ **Negative** ☐ **Not done**

d. Anti-RNA polymerase III

☐ **Positive** ☐ **Negative** ☐ **Not done**

13. Modified Rodnan Skin Score (MRSS, range 0-51)

Score ☐ **Not done**

14. Puffy fingers

Enlarged/swollen fingers, which may be pitting or non-pitting

☐ **Yes** ☐ **No** ☐ **Not available**

15. Sclerodactyly

Symmetric thickening and non-pitting induration of the skin of the digits (at any time, now or in the past)

☐ **Yes** ☐ **No** ☐ **Not available**

16. Sclerodermatous skin involvement proximal to the metacarpophalangeal joints (MCPs)

☐ **Yes** ☐ **No** ☐ **Not available**

17. Digital pitting scars

Depressed areas at tips of digits or loss of digital pad tissue as a result of digital ischemia rather than trauma or exogenous causes (at any time, now or in the past)

☐ **Yes** ☐ **No** ☐ **Not available**

18. Digital ulcers

Areas of de-epithelialization that can vary from focal infarcts to extensive gangrene of the fingers, and that are substituted by scars when healed, regardless of etiology (ischemia, calcinosis, trauma), at any time, now or in the past.

a. Digital pulp (volar), distal to distal interphalangeal joints (DIPs)

Kwakkenbos et al.
Scleroderma Patient-centered Intervention Network (SPIN)

☐ **Yes** ☐ **No** ☐ **Not available**

b. Dorsal finger, distal to DIPs

☐ **Yes** ☐ **No** ☐ **Not available**

c. Between the MCPs and DIPs, volar or dorsal

☐ **Yes** ☐ **No** ☐ **Not available**

19. Telangiectasias

Visible macular dilatation of superficial cutaneous blood vessels that collapse upon pressure and fill slowly when pressure is released (do not include spider angiomas [point-like, dilated arterioles] or linear superficial dilated vessels that are found in sun-exposed areas or in areas of venous dependency, mostly the legs)

a. Any

☐ **Yes** ☐ **No** ☐ **Not available**

b. On the face

☐ **Yes** ☐ **No** ☐ **Not available**

20. Abnormal nailfold capillaries

☐ **Yes** ☐ **No**

Specify method of detection:

- ☐ **Naked eye**
- ☐ **Dermatoscope**
- ☐ **Ophthalmoscope**
- ☐ **Widefield microscopy**
- ☐ **Videocapillaroscopy**
- ☐ **Other**

21. Abnormal skin pigmentation

Hyperpigmentation, often but not necessarily containing areas of punctuate or patchy hypopigmentation or depigmentation (“pepper and salt”), thought to be related to SSc

a. Any

☐ **Yes** ☐ **No** ☐ **Not available**

b. On the face

☐ **Yes** ☐ **No** ☐ **Not available**

22. Tendon friction rubs

Kwakkenbos et al.

Scleroderma Patient-centered Intervention Network (SPIN)

Palpable crepitus over flexor or extensor tendons, particularly common over the wrists, fingers, knees and ankles

- ☐ **Currently, with or without past**
☐ **In the past, but not currently**
☐ **Never**
☐ **Not available**

23. Joint contractures

Limitation of range of motion of a joint secondary to tightening around the joint

a. Small joints

DIP, PIPs (proximal interphalangeal joints), MCPs and/or wrists

- ☐ **Yes** ☐ **No** ☐ **Not available**

a. Large joints

Elbows, knees, hips, ankles

- ☐ **Yes** ☐ **No** ☐ **Not available**

24. Gastrointestinal tract

a. Esophageal

Dysphagia, heartburn and/or reflux, due to SSc (or requiring medications to alleviate these symptoms)

- ☐ **Yes** ☐ **No** ☐ **Not available**

b. Stomach

Early satiety and/or vomiting, due to SSc (or requiring medications to alleviate these symptoms)

- ☐ **Yes** ☐ **No** ☐ **Not available**

c. Intestinal

Diarrhea, bloating and/or constipation, due to SSc (or requiring medications to alleviate these symptoms)

- ☐ **Yes** ☐ **No** ☐ **Not available**

25. Interstitial lung disease

Bilateral fine reticular, reticulonodular or honeycombing markings which are most pronounced in basilar portions of the lungs as detected by chest radiography or HRCT; should not be attributable to another primary lung disease

- ☐ **Yes** ☐ **No** ☐ **Not available**

Kwakkenbos et al.
Scleroderma Patient-centered Intervention Network (SPIN)

26. Pulmonary arterial hypertension (PAH) by right heart catheterization (RHC)
MPAP (mean pulmonary artery pressure) \geq 25 mmHg and PCWP (pulmonary capillary wedge pressure)/LVEDP (left ventricular end diastolic pressure) \leq 15 mmHg

☐ **Yes** ☐ **No** ☐ **Not done**

27. History of scleroderma renal crisis

☐ **Yes** ☐ **No** ☐ **Not available**

28. Overlap syndrome

a. Systemic lupus erythematosus (*by ACR classification criteria*)

☐ **Yes** ☐ **No** ☐ **Not available**

b. Rheumatoid arthritis (*by ACR/EULAR 2010 classification criteria*)

☐ **Yes** ☐ **No** ☐ **Not available**

c. Sjogren’s syndrome
(positive for at least two of three objective diagnostic tests: 1) anti-SS-A/B blood test. There are two scenarios: a) Positive serum levels of either the SSA and/or SSB antibody and/or b) positive serum levels of the rheumatoid factor antibody (RA) and elevated antinuclear antibody (ANA) titers; 2) ocular surface staining (measures the dissipation rate of a specialized dye that is applied to the tear film that bathes the surface of the eye; a score of three or more is considered to be positive); 3) salivary gland biopsy (one or more sites of inflammation per four millimeters squared area is considered positive)

☐ **Yes** ☐ **No** ☐ **Not available**

d. Idiopathic inflammatory myositis
Either definite or probable polymyositis or dermatomyositis, according to the following criteria:

- 1. *symmetric proximal muscle weaknessmuscle biopsy evidence of myositis*
- 2. *elevation in serum skeletal muscle enzymes*
- 3. *characteristic EMG pattern of myositis*
- 4. *typical rash of dermatomyositis (heliotrope rash or Gottron’s papules).*

All of criteria 1-4 or any 3 of criteria 1-4 are required for definite or probable polymyositis, respectively. Criteria 5 plus any 3 of criteria 1-4 or criteria 5 plus any 2 of criteria 1-4 are required for definite or probable dermatomyositis, respectively. The absence of other forms of myopathy, including inclusion body, metabolic, inherited or infectious forms, is also

Kwakkenbos et al.

Scleroderma Patient-centered Intervention Network (SPIN)

required to diagnose PM/DM.

☐

Yes

☐

No

☐

Not available

e. Primary biliary cirrhosis (*diagnosed by the presence of: cholestatic indices, antimitochondrial antibodies, and liver histology diagnostic or compatible with PBC*)

☐

Yes

☐

No

☐

Not available

f. Autoimmune thyroid disease (*with a diagnosis supported by clinical presentation and the presence of either thyroid peroxidase (TPO) or thyroglobulin (Tg) antibodies*)

☐

Yes

☐

No

☐

Not available