Exploring the optimal follow-up for systemic sclerosis patients: study protocol for a Dutch multicenter randomized controlled trial

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Trials

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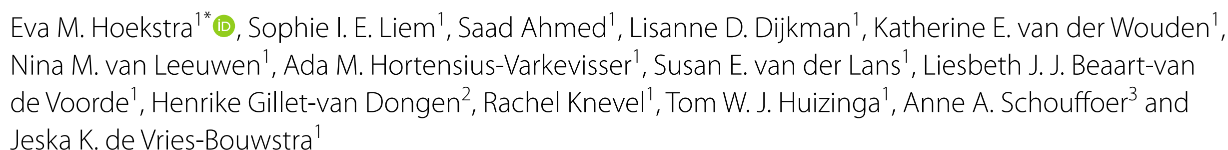

Eva M. Hoekstra[1*], Sophie I. E. Liem[1], Saad Ahmed[1], Lisanne D. Dijkman[1], Katherine E. van der Wouden[1], Nina M. van Leeuwen[1], Ada M. Hortensius-Varkevisser[1], Susan E. van der Lans[1], Liesbeth J. J. Beaart-van de Voorde[1], Henrike Gillet-van Dongen[2], Rachel Knevel[1], Tom W. J. Huizinga[1], Anne A. Schouffoer[3] and Jeska K. de Vries-Bouwstra[1]

Abstract

Background Currently, evidence-based guidelines for the frequency and intensity of follow-up of systemic sclerosis (SSc) patients are not available. Based on expert opinion, an annual extensive evaluation is recommended. A multidisciplinary Care Pathway that integrates this annual extensive evaluation at the Leiden University Medical Center has shown increased patient satisfaction, decreased healthcare utilization, and improved outcomes in SSc patients (1, 2). However, for a subgroup of SSc patients with relatively mild disease, this annual extensive evaluation might be redundant. Therefore, this study aims to evaluate whether assessment in a regular outpatient clinic setting is an acceptable alternative to extensive annual evaluation in the Care Pathway in SSc patients with a low risk of disease progression.

Methods This study is designed as a multicenter ($n = 3$) non-inferiority randomized controlled trial. SSc patients are categorized into three categories for risk of disease progression (low, intermediate, or high) based on a previously published risk prediction model (3). Patients with a predicted low or intermediate risk of disease progression are randomized between (1) follow-up in the outpatient clinic (intervention) and (2) follow-up via usual care according to the annual Care Pathway (control group). The year after the "study visit," all patients are evaluated in the Care Pathway. In this study, 250 patients will be recruited and randomized. The primary outcome is healthcare utilization, which will be assessed via questionnaires. Secondary outcome measures include disease progression, patients' perception of disease and care, and health-related quality of life. Healthcare utilization is defined as the number of contacts with a healthcare professional and will be analyzed using descriptive statistics and linear regression analysis.

Discussion There is an unmet need for tailor-made care for SSc patients in accordance with disease activity, and evidence-based guidelines regarding the follow-up of SSc patients are lacking. This is the first randomized controlled trial evaluating the optimal follow-up for SSc patients at low risk of disease progression. Results of this study will show whether routine assessment at the outpatient clinic is an acceptable alternative to assessment in a standardized care setting including an annual 6-min walk test, an ECG, lab, mRSS, and a pulmonary function test.

Trial registration ClinicalTrials.gov NCT05103553. Registered on October 11, 2021.

*Correspondence:
Eva M. Hoekstra
e.m.hoekstra.ana@lumc.nl
Full list of author information is available at the end of the article

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Keywords Systemic sclerosis, Healthcare utilization, Disease progression

Background

Systemic sclerosis (SSc) is a complex and rare disease in which vasculopathy and fibrosis affect multiple organ systems such as the skin, gastrointestinal tract, kidneys, heart, lungs, and the musculoskeletal system [1]. Involvement of these systems can have a severe impact on patients' mental, physical, and social functioning [1]. SSc has the highest case-specific mortality among rheumatic diseases; reported standardized mortality rates vary between 1.5 and 7.1 [2].

Because of its multisystemic nature and severe impact, care for patients with SSc is challenging and requires a multidisciplinary approach. Although the importance of comprehensive care involving pharmacological and non-pharmacological interventions in SSc is broadly recognized, unmet healthcare and information needs have been identified, and improvements in the organization and content of care have been suggested [3]. In 2007, SSc patients reported a mean of 6.9 visits to medical specialists other than a rheumatologist over a 12-month period, which is a considerable number [4]. Therefore, and in line with the principles of value-based health care, which advocates the development and institution of dedicated care pathways for patients with specific diagnoses [5], a multidisciplinary SSc Care Pathway was set up by the Department of Rheumatology of the Leiden University Medical Center (LUMC) in 2009 [6]. Here, patients are seen on a yearly basis by a multidisciplinary team, including a rheumatologist (or advanced nurse practitioner), pulmonologist, clinical nurse specialist, physical therapist, and, if needed, a dietician, occupational therapist, cardiologist, gastroenterologist, or dermatologist. Measurements of health status and outcomes (including patient-reported outcomes such as quality of life) are performed systematically alongside this Care Pathway. Furthermore, considerable emphasis is placed on patient education and supportive care, facilitated by the efforts of the paramedical team. The first evaluation of the Care Pathway showed that SSc patients did not have to visit the hospital as frequently as before, and that they were very satisfied with the mode of care delivery [6].

This approach to care delivery, however, presents a challenge to the healthcare system, due to the high demand on healthcare resources. While a substantial proportion of SSc patients experience an indolent form of the disease, only a small minority experience an aggressive disease with severe complications developing within a few years [7]. For patients with a more indolent type of disease, annual extensive follow-up might be redundant or may even lead to diagnostic overuse. As it remains difficult to accurately predict the disease course in an individual patient, and new onset of organ involvement is not confined to early disease [8], an expert consensus-based guideline advocates annual extensive assessment in all patients. This guideline describes points to address in annual assessment of patients with SSc [9]. Overall, 55 tools were identified, including clinical assessments, laboratory measurements, and imaging or functional investigations. Whether the proposed items are sufficient to identify disease progression timely in all patients and whether all these items need to be assessed annually in all patients need yet to be determined.

To conclude, the provision of comprehensive care in SSc is widely advocated, but there are a number of knowledge gaps regarding the intensity and frequency of follow-up. Specific care pathways for patients with SSc have been instituted, but their offering could possibly be better tailored to the health status. Moreover, personalized medicine holds significant potential to alleviate the increasing strain on healthcare resources and healthcare workers by promoting more efficient care. To develop tailor-made guidelines, risk stratification is of great importance. Our research group has developed a prediction model with the aim of identifying a subgroup of SSc patients in which the risk of disease progression is very low. We hypothesize that annual assessment of SSc patients (stratified as having a low risk of progression according to a previously published prediction model) in the regular outpatient clinic is as sufficient as assessment in an extensive Care Pathway without changes in healthcare utilization, disease burden, or safety.

Therefore, this study aims to evaluate whether assessment of SSc patients with a low risk of disease progression in the outpatient clinic, compared with assessment in the standardized Care Pathway, is an acceptable alternative to annual assessment in the standardized Care Pathway.

Study design

This study was designed as a three-center, non-inferiority, randomized (ratio 1:1) controlled clinical trial. Two hundred and fifty patients will be recruited in three Dutch hospitals (Leiden University Medical Center, Leiden; Haaglanden Medical Center, the Hague; the Haga Hospital, the Hague). This study consists of two parts. In the first part, we apply our prediction model to group the included SSc patients into three risk categories for disease progression: low, intermediate, or high risk. In the

	Study period						
	Enrolment	**Allocation**	**Post – allocation**				
TIMEPOINT	**-t_1**	**0**	**t_1** baseline	**t_2** 6 months	**t_3** 12 months	**t_4** 18 months	**t_5** 24 months
ENROLMENT							
Eligibility screening	X						
Informed consent	X						
Risk score calculation		X					
Allocation		X					
INTERVENTION							
Outpatient clinic					X		
Care Pathway					X		
ASSESSMENTS							
Clinical assessment in healthcare pathway			X				X
Questionnaires*			X	X	X	X	X

Fig. 1 Study design. *Questionnaires include the following: healthcare utilization survey, Brief Illness Perception Questionnaire (BIPQ), 36-Item Short Form Health Survey (SF-36), and the EuroQol-5D (EQ-5D)

second part, patients who are categorized into the low- or intermediate-risk category will be randomized to an outpatient clinic visit or a visit in the Care Pathway. One year after the study visit, every patient will be seen in the Care Pathway. Patients who are categorized as having a high risk of disease progression will be excluded from randomization and will be followed up in the annual Care Pathway evaluation. A figure containing the schedule of enrolment, intervention, and assessments is available in Fig. 1. The study's protocol and registration have been submitted and published in ClinicalTrials.gov on October 11, 2021 (NCT05103553). This study has been approved locally by the LUMC Medical Ethics Committee (P21.069). Written informed consent for participation will be obtained from all participants. The reporting of this study protocol is done according to the Standard

Protocol Items Recommendations for Interventional Trials (SPIRIT guideline) [10].

Patients

Accessibility of healthcare is generally high in the Netherlands [6]. Therefore, the Leiden Combined Care in Systemic Sclerosis (CCISS) cohort consists of both mild and severe patients, who all undergo annual assessment, as it has included patients fulfilling the very early diagnosis of SSc (VEDOSS) and the ACR/EULAR 2013 criteria since the start of the cohort in 2009. In a study conducted in the CCISS cohort, approximately 50% of SSc patients did not show any signs of progression over time (median follow-up duration: 5.2 years) [8].

Eligibility criteria

Patients from the CCISS cohort at the LUMC, the Haga Hospital, or the Haaglanden Medical Center (HMC) will be eligible for inclusion.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Participation in the prospective Haga Hospital, Haaglanden Medical Center, or LUMC cohorts
2. Clinical diagnosis of SSc
3. Age ≥ 18 years
4. Have had ≥ 2 evaluations in the Care Pathway
5. Written informed consent was obtained for this study.

   a. For participants at LUMC, additional written informed consent for the Leiden CCISS cohort is required.
   b. For participants in the Haga Hospital and the Haaglanden Medical Center, sufficient data should be available to be able to calculate the risk score.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Patients who are already participating in ongoing (randomized) trials
2. Patients who underwent autologous stem cell transplantation for SSc in the past 5 years

Included patients who are categorized as being at high risk of disease progression according to the prediction model are excluded from randomization.

Table 1 Interpretation of probability score

Probability score	Risk profile	Consequence
< 0.197	Low risk	Randomization
0.197–0.223	Intermediate risk	Randomization
> 0.223	High risk	Annual Care Pathway

Patient recruitment

Eligible patients will be identified by the treating healthcare professional. Patients who express interest in the trial will receive a patient information letter from the sub-investigator or coordinating investigator and a telephone call to answer any remaining questions. After this, patients will be given 7 days to decide if they want to participate. If the patient agrees to participate, informed consent will be signed by both the patient and the investigator.

Prediction model

With the use of a machine learning-assisted approach, a prediction model was developed by our research group that can identify patients with mild disease [11]. This model was able to stratify patients into different risk groups with low (29% of the patients, negative predictive value = 1), intermediate (27% of patients), or high risk (44% of patients) for disease progression. The prediction model estimates a probability score for future disease progression based on 10 variables (see Table 1). The 10 variables are collected during the Care Pathway visit at T0 (see Fig. 1) and include the following: Previous or current use of cyclophosphamide or corticosteroids, start with immunosuppressive drugs during the current visit, previous gastrointestinal progression, previous cardiovascular event, current cardiac progression, the presence of pulmonary arterial hypertension (PAH), current modified Rodnan Skin Score (mRSS), diffusing capacity for carbon monoxide (DLCO), and creatine kinase levels. Details on these variables are described in Supplementary file S2.

The probability scores can be interpreted as follows: If a patient's probability score from the prediction model is < 0.197, the patient is categorized into the low-risk profile; if the patient's probability score from the prediction model is between 0.196 and 0.223, the patient is categorized into the intermediate-risk profile; and if the score is > 0.223, the patient is categorized into the high-risk profile.

Randomization

After following the Care Pathway evaluation at T0, patients with a low or intermediate risk of disease progression will be randomized 1:1 to the intervention

group (visit at a regular outpatient clinic) or to the control group (visit at the Care Pathway), using Castor (an eClinical Data Management Platform). Due to the nature of the intervention, the randomization process is not blinded.

Intervention: visit the outpatient clinic

For the annual assessment, patients in the intervention group are seen in the regular outpatient clinic by a rheumatologist. Laboratory tests will include a blood count, erythrocyte sedimentation rate, pro-brain natriuretic peptide, troponin T, estimated glomerular filtration rate, creatinine, and creatine kinase and can be elaborated as indicated by the treating physician. Cardiopulmonary complaints will be evaluated by the treating physician through history-taking and physical examination. On medical indication, additional investigations such as X-thorax, pulmonary function test, CT thorax, cardiac echocardiography, or a visit to a different medical specialist (pulmonologist, cardiologist) can be arranged.

Control group: visit to Care Pathway

In the control group, patients will be evaluated in the SSc Care Pathway, which consists of a visit to the rheumatologist (or an advanced nurse practitioner), a clinical nurse specialist, a pulmonologist, a cardiologist, a physical therapist, and, if needed, a dietician. Investigations include blood testing, X-thorax, 6-min walking test, mRSS, and, if indicated, cardiac echocardiography and/or CT thorax.

High-risk group

Patients who are categorized as having a high risk of disease progression will be excluded from randomization and followed up through an annual Care Pathway evaluation at T12 and T24 (Fig. 1).

Primary outcome measure: healthcare utilization

Healthcare utilization will be measured through a survey. The survey on healthcare utilization is comparable to the questionnaire employed in a previous study on healthcare usage in SSc patients [4] (see supplementary file S1). The survey includes the following categories of healthcare services (number of different healthcare professionals/services within a category): (1) Rheumatologist, (2) medical specialists other than rheumatologist, (3) general practitioner, (4) health professionals, (5) hospital admission, and (6) hospital-based day-care. The category medical specialists includes internist, nephrologist, pulmonologist, cardiologist, dermatologist, neurologist, psychiatrist, ear, nose, and throat specialist, and (plastic) surgeon. Health professionals include a physiotherapist, occupational therapist, clinical nurse specialist, and dietician. For each healthcare provider or service, patients will be asked the following: “Did you have contact with a… over the past 6 months?” (yes/no). If the answer is “yes” with respect to the past 6 months, patients are asked how many contacts or treatment days they have received in total and how many of these were face-to-face, phone consultations or video meetings. For each category, the number of contacts and visits within the last 6 months will be counted, including patients having one or more healthcare providers per category. Moreover, the number of additional investigations (ECG, pulmonary function test, echocardiography of the heart, high resolution computed tomography of the chest) that a patient received within the last 6 months will be collected. It will take approximately 10 min to complete the survey (depending on the number of healthcare contacts). Patients will be contacted by telephone to follow up on the completion of the questionnaires.

Secondary outcome measures

The secondary outcomes include patients’ perceptions of delivered care, health-related quality of life, and disease progression.

Illness perceptions will be assessed using the BIPQ [12]. The BIPQ is a widely used, validated instrument, which is designed to provide a simple and rapid assessment of illness perceptions. It consists of nine questions: eight questions that comprise (1) perceived consequences, (2) timeline (acute-chronic) personal control, (3) amount of perceived personal control, (4) treatment control, (5) identity (symptoms), (6) concern about the disease, (7) coherence of the illness, and (8) emotional representation. The last question assesses causal perception, in which the patient can give three factors that, in his or her opinion, have caused the disease.

Quality of life will be assessed using the Dutch version of the SF-36 and the EQ5D, which are collected annually in the SSc Care Pathway.

Disease progression is defined as the start of immunosuppressive treatment, death, or progression in one or more organ systems, including the following:

- Pulmonary progression: Defined as $\geq 10\%$ relative decline in forced vital capacity (FVC) with follow-up FVC $< 80\%$ predicted, or $\geq 5\%$ to $< 10\%$ relative decline in FVC, and either a $\geq 15\%$ relative decline in diffusing capacity for carbon monoxide (DLCO) with follow-up DLCO $< 80\%$ predicted or increase in lung involvement (interstitial lung disease (ILD)) as determined by HRCT
- Myocardial progression: Defined as either clinical cardiac involvement, decreased left ventricular ejec-

tion fraction < 54% (LVEF), and arrhythmias (> 2% ventricular extrasystoles or atrial fibrillation) or major cardiac events (including all acute coronary syndromes and pacemaker implantations)
- Pulmonary arterial hypertension development: Defined as an increase in mean pulmonary arterial pressure ≥ 20 mmHg at rest as assessed by right heart catheterization (RHC), a pulmonary capillary wedge pressure ≤ 15 mmHg, and a pulmonary vascular resistance > 3 Wood units on RHC in the absence of other causes of precapillary pulmonary hypertension, such as pulmonary hypertension due to lung diseases or other rare diseases
- Gastrointestinal progression: Is based on development of gastric antral vascular ectasia, decreased hemoglobin, AND weight loss (< 10% over 1 year)
- Skin progression: Defined as an increase in mRSS of ≥ 5 points and ≥ 25%
- Renal progression: Defined as a clinical diagnosis of scleroderma renal crisis (including hypertension, an increase in serum creatinine, oligo/anuric renal failure)
- Myositis development: Defined as a diagnosis of myositis based on biopsy confirmation or an increased serum creatine kinase (> 150 U/l) with muscle weakness
- Digital ulcer development: Requiring antibiotic therapy or intravenous vasodilatation

The use of immunomodulatory medications is collected at every visit and includes the following: cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, corticosteroids, hydroxychloroquine, and stem cell transplantation.

Data management

Data will be handled confidentially and pseudonymized in compliance with the EU General Data Protection Regulation (in Dutch: Uitvoeringswet AVG). Patient data are coded. For this purpose, patients will receive a unique new study code. The code is not based on any of the patient's characteristics. Only the investigators and data managers of this study have access to the identity of the patient linked to the code. All data will be entered twice to avoid mistakes. All coded source data will be saved and processed in the online protected database program Castor. The data can only be traced back to the participant with an encryption key that remains safely stored at the local research institute. Data also cannot be traced back to specific participants in reports and publications about the study. The data will be stored for 15 years at the research location (LUMC).

Participants are allowed to withdraw their consent to the use of personal data at any time during the study. Study data collected until the moment a participant withdraws their informed consent will still be used in the study.

A member of the coordinating study team (i.e., Leiden University Medical Center) will conduct an audit trial at the participating sites to evaluate study conduction according to the study operating procedure. The coordinating study team will be monitored once by internal monitors of the Leiden University Medical Center, before activation of participating study centers, according to a prespecified monitoring plan.

Safety monitoring

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedure. A serious adverse event (SAE) is any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalization or prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgement by the investigator. All (serious) adverse events reported spontaneously by the subject, or observed by the investigator or their staff during the trial period, will be recorded.

No interim analyses are planned because of the low-risk nature of this trial.

In case of trial conduct deviations from the protocol, these will be documented using a breach report form.

Sample size calculation

Sample size calculation is based on the expected difference in healthcare utilization. We calculated the sample size based on the raw data of a previous study performed in 2009 [4]. In this study, patients visited a medical specialist or a general practitioner six times in total during a period of 12 months for SSc-related problems, with a standard deviation of 4.6. With the start of the Care Pathway, SSc patients visited the hospital once a year on average for SSc-related problems. Power analyses were performed using a non-inferiority test to evaluate the difference of two means. With a group sample size of 113, we achieve 90% power to detect non-inferiority using a one-sided, two-sample *t*-test. The margin of non-inferiority is −2. We chose this margin because a difference of up to two is not relevant in daily practice and would therefore demonstrate non-inferiority. The true difference between the means is assumed to be zero as we

expect the intervention arm to perform equally or superiorly when compared to the control arm. The significance level (alpha) of the test is 0.025. The standard deviations for our primary outcome were assumed to be equal in both arms ($SD = 4.6$). If we account for a 10% dropout, the total number of patients will be 250.

Statistical analysis

The distribution of outcome variables will be analyzed using histograms and Q-Q plots. If needed, transformations (log or square root) are applied to reduce skewness of the distributions. Healthcare utilization in both the outpatient clinic and the Care Pathway will be analyzed using descriptive statistics and regressions. The main analysis is based on performing a linear regression and a one-sided CI at 2.5% for the regression coefficient of healthcare utilization in the intention-to-treat population. The lower and upper bounds of the CI are compared to the equivalence margin (zero + (OF−) margin). The CI is computed by first computing a two-sided CI for healthcare utilization at the 95% level and choosing only the upper or lower bound [13].

The secondary outcome measures are health-related quality of life, patients' perception of delivered care, and disease progression. Illness perceptions will be compared between the two groups, and mean scores on the BIPQ, SF-36, and EQ5D will be presented in both groups. Potential differences will be tested using a Mann–Whitney *U*-test, where appropriate. Univariable and multivariable linear regression can be used to assess possible associations with perceptions and QoL. Another secondary endpoint is the difference in disease progression between the intervention and control groups. The primary analysis will be performed on the whole dataset. Secondly, disease progression will be evaluated per organ system, to evaluate if a certain type of progression is less often noticed in the outpatient clinic. The progression rates will be described using descriptive statistics and frequencies. Difference in disease progression will be compared between the intervention and control group using chi-square tests, where appropriate.

In case of significant differences in patient characteristics between the intervention and control groups, for both main and secondary analyses, we will perform multivariable regression analyses to adjust for possible confounders with a known association with the outcome, such as age, sex, disease duration, autoantibody status, and smoking. This will be a multivariable logistic regression for the analysis of disease progression and a multivariable linear regression for all other outcomes.

Discussion

Systemic sclerosis is a complex, systemic, multi-organ disease that requires a multidisciplinary approach. Currently, evidence-based guidelines for the frequency and intensity of follow-up for SSc patients are not available. Based on expert consensus, an annual extensive evaluation is recommended [9]. However, data collected on disease progression in the Leiden CCISS cohort indicate that approximately 50% of SSc patients have relatively mild disease, highlighting a subset of patients for whom extensive annual screening might be redundant. To the best of our knowledge, this is the first randomized controlled trial evaluating the optimal follow-up for the subset of SSc patients with an estimated low risk of disease progression.

In the Netherlands, a multidisciplinary SSc Care Pathway was set up by the Department of Rheumatology at the Leiden University Medical Center. Since the installment of the Care Pathway, which integrates multidisciplinary and comprehensive care and places considerable emphasis on patient education and supportive care and facilitates extensive annual screening, it has been shown to reduce the number of healthcare visits [6], increase patient satisfaction [6], and, moreover, also improve morbidity and mortality [14]. This highlights the impact that healthcare system organization has on health outcomes. Moreover, this justifies our choice for healthcare utilization as a primary outcome measure and for including illness perception and health-related quality of life as secondary outcome measures. When considering disease progression as a secondary outcome, it is important to acknowledge that if disease progression is detected at T24, the exact timing of clinically apparent progression cannot be retrospectively determined, nor can it be determined whether it could have been prevented by a Care Pathway evaluation at T12.

During annual patient meetings with Care Pathway patients who have participated in the Care Pathway since its beginning, patients regularly question the usefulness of annual organ screening in stable patients yet at the same time confirm that the team care provided by experts, including education and physical therapy, is highly valued. This underlines the need for this trial and supports the chosen outcome measures. Furthermore, we can only hypothesize that evidence-based guidelines regarding follow-up and implementation of tailor-made care will further improve healthcare outcomes in SSc.

In order to identify patients with mild disease, we used a prediction model that was previously developed by our research group. The model stratifies patients into three risk groups with low, intermediate, or high risk of disease progression based on a probability score. It is noteworthy that the cut-off value for the probability score was chosen

with the intention of not missing any disease progression. This is reflected in the negative predictive value of 1 for the occurrence of disease progression among patients in the low-risk profile. By minimizing the likelihood of missing progression among low-risk patients, our model — in this context — outperforms existing prediction models that are focused on identifying high-risk patients. However, due to this strict cutoff, only a relatively small proportion of included SSc patients in this trial are eligible for randomization. Recruitment started on March 14, 2023 (date of informed consent of first included patient); up until December 2024, approximately 49% of included patients have been excluded from randomization due to a high probability score for disease progression. Therefore, an extension of the study period has been approved by the medical ethics committee in the first amendment to the protocol (September 2024).

To conclude, this trial is the first to systematically study the optimal follow-up strategy for SSc patients. The provision of comprehensive care in SSc is widely advocated, but there are some knowledge gaps regarding the frequency and intensity of follow-up that have yet to be addressed. We hypothesize that for SSc patients with established mild disease, annual evaluation can be less extensive without changing the disease burden and the patients' perception of care. This trial will evaluate the optimal follow-up strategy for patients with mild SSc and ultimately contribute to better tailor-made care for SSc patients.

Trial status

Protocol version 4, June 20, 2024. Recruitment started in April 2022 and is expected to be complete by the end of June 2026.

Roles and responsibilities of committees

Overall trial management will be performed by the coordinating study team at the Leiden University Medical Center. The PI will be responsible for the data management oversight. Given the nature of the intervention, with low risk of (serious) adverse events related to the intervention, no Data Safety Monitoring Committee will be installed. Instead, a safety committee is installed, consisting of two independent rheumatologists from the Rheumatology Department of the Leiden University Medical Center. All reported SAEs and SUSARS will be reported to the safety committee within a month and will be discussed by the safety committee twice a year. Once 50 participants have completed the 2-year follow-up, we will evaluate whether there is any evidence of a higher incidence of (S)AEs in the intervention group and assess, together with the safety committee, the likelihood that these events are related to the intervention. In case of possible (S)AEs related to the intervention, the safety committee can advise on early termination of the study.

Protocol amendments

In case of protocol amendments, the PI will notify the other research centers. A copy of the revised protocol will be sent to the coordinating investigators of the Haaglanden Medical Center and the Haga Hospital, to be filed in the local Investigator Site File. The protocol will also be updated in the clinical trial registry.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09494-w.

Supplementary Material 1. Healthcare utilization survey.

Supplementary Material 2. Prediction model variables.

Supplementary Material 3. SPIRIT Checklist for Trials.

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Dissemination of findings
The results will be shared via a scientific publication.

Authors' contributions
EH helped to draft the manuscript, contributed to day-to-day trial management, and critically revised and reviewed the manuscript. SL, SA, LBV, HGD, AS, TH, and JVB contributed to the design of the study and critically reviewed and revised the manuscript. SL, NL, HGD, RK, TH, and JVB contributed to the development of the prediction model. EH, SA, LD, KW, AHV, and SvdL contributed to practical trial management (planning of study visits, performing study visits, and recruitment of trial participants). JVB is the principal investigator. HGD and AS are the coordinating investigators from the Haaglanden Medical Center and Haga Hospital, respectively. All authors read and approved the final manuscript.

Funding
None.

Data availability
Access to the trial database will be granted to all principal investigators at participating centers. The dataset with deidentified individual participant data could be made available upon reasonable request, as is the full protocol. Data sharing will have to follow the appropriate regulations under Dutch law.

Declarations

Ethics approval and consent to participate
All patients are requested to sign an informed consent form before participation in the study. This study has been approved locally by the LUMC Medical Ethics Committee (P21.069).

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Rheumatology, Leiden University Medical Center, Leiden, RC 2300, The Netherlands. [2]Department of Rheumatology, Haaglanden Medical Center, The Hague, The Netherlands. [3]Department of Rheumatology, Haga-Ziekenhuis, The Hague, The Netherlands.

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