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A randomized, open-label trial to assess the optimal treatment strategy in early diffuse cutaneous systemic sclerosis: the UPSIDE Study protocol

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A randomized, open-label trial to assess the optimal treatment strategy in early diffuse cutaneous systemic sclerosis: the UPSIDE Study protocol

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Abstract

Introduction: Systemic sclerosis (SSc) is a chronic, autoimmune connective tissue disease associated with high morbidity and mortality, especially in diffuse cutaneous SSc (dcSSc). Currently there are several treatments available in early dcSSc that aim to change the disease course, including immunosuppressive agents and autologous hematopoietic stem cell transplantation (HSCT). HSCT has been adopted in international guidelines and is offered in current clinical care. However, optimal timing and patient selection for HSCT is still unclear. In particular, it is unclear whether HSCT should be positioned as upfront therapy or rescue treatment for patients refractory to immunosuppressive therapy. We hypothesise that upfront HSCT is superior and results in lower toxicity and lower long-term medical costs. Therefore, we propose this randomized trial aiming to determine the optimal treatment strategy for early dcSSc by comparing two strategies used in standard care: A. upfront autologous HSCT versus B. immunosuppressive therapy (intravenous cyclophosphamide pulse therapy followed by mycophenolate mofetil) with rescue HSCT in case of treatment failure.

Methods and analysis: The UPSIDE (Upfront autologous hematopoietic Stem cell transplantation versus Immunosuppressive medication in early DiffusE cutaneous systemic sclerosis) study is a multicentre, randomized, open label, controlled trial. In total, 120 patients with early dcSSc will be randomized. The primary outcome is event free survival at two years after randomisation. Secondary outcomes include serious adverse events, functional status, and health related quality of life. We will also evaluate changes in nailfold capillaroscopy pattern, pulmonary function, cardiac MR and High Resolution-CT of the chest. Follow-up visits will be scheduled 3-monthly for 2 years and annually in the following 3 years.

Ethics and dissemination The study was approved by the Dutch Central Committee on Research Concerning Human Subjects (NL72607.041.20). The results will be disseminated through patient associations and conventional scientific channels.

Trial registration number; NCT04464434, trial NL 8720

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Strengths and limitations of this study

- This study is a multicentre, randomized, controlled and open-label trial aiming to determine whether upfront autologous stem cell transplantation (HSCT) is superior to standard immunosuppressive treatment (with rescue HSCT for those who progress), in early diffuse cutaneous systemic sclerosis (dcSSc).
- Event free survival is the primary outcome measure and is defined as the time in days from randomisation until death due to any cause or the development of persistent major organ failure (heart, lung, or kidney).
- This clinical trial has the potential to change clinical practice in early dcSSc worldwide

Introduction

Systemic sclerosis (SSc) is a debilitating and incurable autoimmune connective tissue disease. Clinical features include vasculopathy, fibrosis and inflammation of skin and internal organs [1]. Presentation and disease course are very heterogenous. In the diffuse cutaneous subset of SSc (dcSSc) there is generalized skin thickening and often multiorgan involvement [2–4]. Due to its progressive character, the median 5 and 12-year mortality for dcSSc is ~25% and 70% respectively [5,6]. To prevent progression and death in SSc patients, it is key to identify individuals at risk at an early stage of the disease and initiate immunomodulating treatment. Methotrexate, mycophenolate mofetil and cyclophosphamide are commonly used in dcSSc, dependent on the organ system involved.

In three randomized controlled trials (RCT) in dcSSc, treatment with autologous hematopoietic stem cell transplantation (HSCT) improved survival, quality of life, skin fibrosis and prevented disease progression in dcSSc patients, when compared to cyclophosphamide pulse therapy [7–9]. Additionally, three systematic reviews were published on the efficacy and safety of HSCT in SSc.[10–12] In all reviews it was concluded that HSCT provided a survival benefit, improved skin involvement and stabilized pulmonary function compared to intravenous cyclophosphamide for 12 months. Heterogeneity between studies, however, prevented meta-analysis, yet a trend towards better outcome was observed in patients with a shorter disease duration prior to HSCT. HSCT has since been implemented in (inter)national treatment guidelines for SSc, made its way into regular clinical care and is reimbursed in several European countries [13,14]. However, recommendations regarding the optimal use and especially the preferred timing of HSCT and the efficacy of other therapies in the course of dcSSc are lacking. Particularly, it is unclear whether HSCT should be positioned as upfront or as rescue treatment for patients not responding to immunosuppressive therapy such as MMF or intravenous pulse CYC.

HSCT as upfront treatment might result in better outcomes, because the disease process is effectively targeted early in the disease at a time when there is less irreversible organ damage. On the other hand, HSCT is a treatment associated with a higher risk of adverse events compared to other treatments, as it is associated with a treatment related mortality of approximately 10% [8,15].

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However, there might be fewer transplant related adverse events due to the better health status of patients and limited immunosuppressive premedication if HSCT is commenced early, compared to the patients that need rescue HSCT after months or even years of other immunocompromising agents. So, in order to determine the optimal treatment strategy in early dcSSc, further investigation is needed.

This manuscript describes the protocol of the UPSIDE study (Upfront autologous hematopoietic Stem cell transplantation versus Immunosuppressive medication in early DiffusE cutaneous systemic sclerosis). The UPSIDE study is a multicentre randomized open-label controlled trial that aims to compare two treatment strategies used in standard care of adult patients with early dcSSc: upfront autologous HSCT versus intravenous cyclophosphamide pulse therapy followed by oral mycophenolate mofetil and rescue HSCT in case of treatment failure. Efficacy, safety, survival and cost-effectiveness will be evaluated.

Aims and objectives

The UPSIDE study aims to investigate the optimal timing of HSCT in early dcSSc by comparing two treatment strategies: the effect of HSCT as upfront therapy compared with that of immunosuppressive medication and HSCT in case of failure, with respect to (event-free) survival and prevention of major organ failure, safety and the impact on skin thickening, visceral involvement, functional status, and quality of life.

Secondary goals are to evaluate (in both treatment arms) whether disease activity correlates with immunological parameters, including immunopathology of skin, immune reconstitution, and autoantibodies. Cost-effectiveness of both therapeutic options and factors associated with response to treatment will also be examined.

Methods and analysis

Study design and setting

The UPSIDE study is a randomized controlled, multicentre, open-label trial.

SSc is a rare condition and stem cell mobilisation after intravenous cyclophosphamide administration and HSCT are treatments only performed in experienced tertiary treatment centres. Therefore, national, and international collaboration is of key importance to include the necessary number of patients. Participants will be recruited from fourteen participating centres from The Netherlands, Belgium, Germany, Italy, Sweden, Switzerland, and Croatia (table 1). Multidisciplinary expert teams in the field of SSc and HSCT are involved in each centre.

Study population and eligibility criteria

We will include 120 patients with early dcSSc who fulfil the inclusion criteria (table 2). These criteria are designed to select patients in an early stage of the disease, but at high risk of disease progression and subsequent death. We anticipate the accrual time will be 4 years. Baseline assessment prior to

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randomisation includes complete blood count, liver function, kidney function, urine portion analysis, viral serology tests, 12-lead ECG, cardiac ultrasound, cardiac MRI, right heart catheterization, lung HR-CT and pulmonary function tests.

Randomisation

Eligible patients who provided informed consent will be randomised 1:1 (variable block randomisation) using the validated algorithm within Castor, the Electronic Data Capture program used for the study. Blocks of 2, 4, or 6 patients will be randomly and blindly assigned, stratified by participating centre. The two treatment are: strategy arm A: upfront high dose non-myeloablative autologous HSCT or strategy arm B: intravenous pulse therapy with cyclophosphamide followed by at least 12 months oral mycophenolate mofetil daily and thereafter HSCT as rescue option. The treatment allocation will be coordinated by the principal investigator of the study site. The investigators and participants are not blinded to treatment allocation.

Interventions

A. Upfront autologous HSCT

Autologous, non-myeloablative HSCT comprises the following consecutive steps:

a. Mobilisation: PBSCs will be mobilised using a regimen consisting of infusion of cyclophosphamide 2g/m^2 for 1 day. Hyperhydration, alkalinisation of the urine and Mesna will be given in order to prevent haemorrhagic cystitis. The patients will receive filgrastim (G-CSF) 5 µg/kg/day subcutaneously once or twice a day for 5 days (or more when necessary), according to local practice.

b. Leukapheresis: Start of leukapheresis is required at a CD34+ cell count of ≥10-20/µL, according to local practice. This is expected to occur on day 5 or 6 of filgrastim treatment. Leukaphereses will be performed with the goal to obtain at least 6 x 10^6 CD34+ cells per kilogram body weight. The primary goal is to obtain a target dose of 6 x 10^6 CD34+ cells/kg, but a minimum of 2 x 10^6 CD34+ cells/kg after CD34+selection. The apheresis product will be 4-5^{log} T cell depleted. The CD34+ selected cells will be cryopreserved and stored in liquid nitrogen until reinfusion. In case of mobilisation failure, the patient will be treated with daily s.c. filgrastim 20 µg/kg,

c. Prior to conditioning: Echocardiography should be repeated prior to conditioning to evaluate possible subclinical cardiac toxicity caused by cyclophosphamide administered during mobilisation. Conditioning can be initiated if LVEF > 45% or has not decreased with >15% compared to pre-mobilisation, and there are no uncontrolled arrhythmias [16].

d. Conditioning: Conditioning is to be initiated preferably within 6 weeks after successful harvest. The conditioning regimen consists of cyclophosphamide 50 mg/kg/day intravenously for 4 consecutive days (total 200 mg/kg) and rabbit antithymocyte globulin (rbATG, Thymoglobulin®). The first dose of cyclophosphamide will be given on day -5 (day 0 = day of infusion of PBSC). Hyperhydration, alkalinisation of the urine and Mesna will be given in order to prevent haemorrhagic cystitis. A total dose of 7.5 mg/kg intravenous rbATG will be administered over three days. Intravenous methylprednisolone 2 mg/kg will be given on the days ATG will be administered, to improve tolerability of the ATG.

e. Peripheral stem cell infusion: The interval between the last dose of cyclophosphamide and infusion

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of the graft will be at least 48 hours. On day 0, CD34+-selected stem cells are thawed and infused according to local standard operating procedures. The number of CD34+ cells to be reinfused should be ≥ 2.0 x 10^6/kg, residual T cell content is targeted at ≤ 1.0 x 10^5 T cells/kg, calculated before freezing [17]. Exceptional release according to local practice is allowed and will be registered in the eCRF.

Arm B. Cyclophosphamide followed by mycophenolate mofetil and HSCT as rescue option

Immunosuppressive therapy in arm B consists of 12 monthly intravenous pulses of cyclophosphamide 750 mg/m2 (= 9 g/m^2 cumulative) followed by at least 12 months of oral mycophenolate mofetil daily (3 grams as maximum daily dosage) or mycophenolic acid (up to 2.160 grams daily), according to local practice. Hyperhydration, alkalinisation of urine and Mesna is recommended during the 12 monthly intravenous pulses cyclophosphamide, and will be given according to local protocols in order to prevent haemorrhagic cystitis.

Supportive Care

Supportive care measures, including prophylactic or therapeutic antibiotics, anti-viral or anti-fungal agents, transfusions, and anti-emetic agents will be taken according to local standard operating procedures for such patients. In case of HSCT, particular attention will be paid to the risk of EBV and CMV-reactivation. EBV and CMV-load will be monitored by PCR, weekly in the first three months following the transplantation, then monthly for the next 9 months. In case of reactivation, the patient will be treated according to standard of care guidelines.

Initiation of an ACE-inhibitor prior to HSCT is strongly recommended (i.e. enalapril 5mg once daily) to prevent scleroderma renal crisis based on the clinical experience from the ASTIS-trial [8].

Study outline

An overview of the study outline is shown in Figure 1 (study flow diagram). After randomisation, concurrent immunosuppressive therapy will be discontinued. Glucocorticoids may be continued at the lowest possible dose. Either treatment is to be initiated within six weeks after randomisation, i.e. mobilisation in patients randomised to Arm A, and the first pulse of cyclophosphamide in patients randomized to Arm B.

Rescue therapy may be considered in both arms in case of insufficient response or clinically relevant flare, but preferably not within the first 6 months after randomisation. For patients from Arm A methotrexate, mycophenolate mofetil or mycophenolic acid, or rituximab can be (re)instituted, according to local preference. Based on earlier studies, the clinical benefits of i.v. pulse cyclophosphamide may take between 6-12 months. Therefore it is recommended to then switch patients from arm B to HSCT only in case of rapidly progressive disease, which is arbitrarily defined as ≥30% increase in mRSS or ≥20% relative decline in FVC, TLC, or DLCO predicted.

Outcomes and follow-up

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The primary endpoint of the study will be event-free survival. Event-free survival is defined as the time in days from the day of randomisation until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney) defined as follows:

- Heart: left ventricular ejection fraction < 30% by cardiac MR (or cardiac echo)
- Lungs: respiratory failure = resting arterial oxygen tension (PaO2) < 8 kPa (< 60 mmHg) and/or resting arterial carbon dioxide tension (PaCO2) > 6.7 kPa (> 50 mmHg) without oxygen supply, or need of oxygen supply.
- Kidney: need for renal replacement therapy (i.e. dialysis)

Secondary outcome measures include:

1. Progression-free survival, defined as the time in days since the day of randomisation until any of the following relative changes from baseline has been documented: death, ≥ 10% drop in (F)VC predicted and/or ≥ 15% drop in DLCO predicted [18], ≥ 15% drop in LVEF by echo or cardiac MR, ≥ 15% drop in body weight, ≥ 30% drop in creatinine clearance, ≥ 25% and ≥ 5 points increase in skin score, ≥ 0.5 increase in SHAQ.
2. Treatment related mortality, defined as any death during the study period following randomisation that cannot be attributed to progression of the disease according to the consensus opinion of the Data and Safety Monitoring Board (DSMB).
3. Overall Survival
4. Treatment toxicity and adverse events, using WHO toxicity parameters (≥ grade 3 toxicity) during the study period
5. The area under the curve (AUC) of the combined response index for systemic sclerosis (CRISS) over time, measuring the 'predicted probability of being improved' over 2 years. This AUC is calculated based on 4 repeated measures (6, 12, 18 and 24 months) with back translation to the original scale between 0 and 1.
6. Change from baseline over time (i.e. during follow-up) of the following parameters: modified Rodnan Skin Score (mRSS), pulmonary involvement: diffusion capacity for carbon monoxide (DLCO and DLCO/VA), (forced)vital capacity ((F)VC), total lung capacity (TLC), residual volume (RV), mean pulmonary artery pressure by cardiac echo (or right heart catheterization), lung density measurement by thoracic CT and 18 FDG-PET scan lung, renal involvement: urine portion: creatinine/ protein ratio, myocardial involvement: left ventricular function as measured by cardiac MR, body weight (kg), changes in nailfold capillaroscopy, changes in Modified HAMIS (functional assessment of hand function), quality-of-life (EuroQol (EQ-5D-5L)), SHAQ including visual analogue scales (VAS) for scleroderma-specific symptoms, gastrointestinal symptom scale (UCL-SCTC GIT 2.0 questionnaire), sexual functioning (short IIEF-5 questionnaire (in men) and SFQ-28 (in women)), fatigue score (FACIT questionnaire), productivity losses due to health issues (customised iPCQ questionnaire), characteristics of the immune system: autoantibody concentration and avidity targeting host nuclear antigens, primarily focusing on anti-ATA, anti-RNAPIII and anti-CENP, isotype usage, isotype levels, Fc-glycosylation profiles of anti-topoisomerase and skewing of T cell receptor repertoire and determination of HLA profiles, composition of the microbiome in the gut and skin, inflammatory and

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fibrotic characteristics of the skin, levels of ATG in relation with changes in lymphocyte subsets and outcomes.

Follow-up appointments will be according to regular care: monthly the first half year, then three-monthly until two years after randomisation, followed by annual appointments for three years (table 3).

Statistical analyses

Sample size

The sample size is determined assuming a median event-free survival of 2 years in the control group and an (approximate) exponential survival curve based on the survival observed in the HSCT arm of the ASTIS trial [7]. We expect our proposed intervention to result in a considerable improvement (assumed hazard ratio of 0.5) and take a total study period of 5 years with 2 years follow up of the last patient enrolled (3 years for recruiting patients at a constant rate), 10% loss to follow up after 5 years in both groups and an alpha of 0.05 into account. Based on the above, we will need 60 patients per group to have at least 80% power to detect a difference as calculated using the SAS power procedure (two sample survival, log rank test). Based on the incidence of dcSSc and the collective treatment experience of the 15 trial sites, we anticipate we can enrol the required 120 patients (60 per group) within 3 years and complete the trial within 5 years [19,20].

Primary outcome

Data will be analysed on an intention-to-treat basis. Data regarding adverse events and SAEs will be provided using descriptive statistics and tables. Population characteristics will be provided using descriptive statistics. To compare event free survival (the primary endpoint) and other time-to-event outcomes between treatment groups, Kaplan Meyer (KM) curves will be constructed (based on first event) and tested using the log-rank test and Cox regression to take important prognostic covariates (sex, age, smoking status, cardiac function) and centre (stratification factor for randomisation), as determined a priori (before database lock) in SAP, into account. For all time-to-event outcome data is censored at the last visit. Based on a visual inspection of the KM curves also a treatment x time interaction will be modelled in the Cox regression analysis to allow for non-constant hazards over time. An intention to treat (ITT) analysis (primary) and per protocol (PP) analysis will be performed. In the primary analysis for patients leaving the study early (early dropout) this last visit will be treated as the censoring date, a multiple-imputation method for sensitivity analyses of time-to-event data accounting for possible informative censoring will also be performed.

Secondary outcomes

Secondary continuous outcomes (i.e. change from baseline in CRISS score)[21] measured over time will be analysed using mixed modelling approaches if needed based on graphical inspection including a treatment x time interaction, controlling for important prognostic covariates (sex, age, smoking habit) and centre (stratification factor for randomisation). For binary outcomes at a fixed timepoint, frequencies and proportions will be calculated and differences tested using Chi-square or Fisher exact tests. The effects of covariates will be evaluated using logistic regression. An intention to treat (ITT)

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analysis (primary) and per protocol (PP) analysis will be performed. A cost effectiveness analyses will be performed from a societal perspective including direct medical and non-medical and productivity costs. Cost-per-QALY gained as well as costs per life year and per event-free life year gained will be calculated. The economic evaluation will be done at 5 years in line with the duration of the trial and the evaluation will be performed in line with the Dutch guidelines for economic evaluations [22].

Interim analysis

There will be an interim analysis at 12 months after the first inclusion and/or after 60 patients have been included, whatever comes first, and at the DSMB request. Formal statistical methods for evaluating interim efficacy and toxicity results will be used as guidelines rather than absolute rules. An alpha spending function (O'Brien-Fleming) will be used. Reasons for DSMB decisions will be recorded.

Safety

The UPSIDE Trial will be overseen by an international DSMB. The DSMB consists of clinicians (including experts on SSc and on stem cell transplantation) and a biostatistician. Every 6 months, the DSMB will review the status and conduct of the clinical trial, evaluate all causes of death and adverse events and make recommendations to the clinical research group concerning the trial's continuation and modification.

Data collection in the study will be monitored by an independent monitor within Julius Centre, UMC Utrecht, the Netherlands. There will be five scheduled visits per centre, the first visit will be the initiation visit and thereafter once a year visits will be performed. The last visit is combined with the close-out visit.

Patient and public involvement

Our research question originates from clinical practice and a prior study that investigated patient's experiences, which showed that the lack of evidence to support the decision-making process in choosing the right treatment strategy is a burden for patients and caretakers [23]. A patient panel (international panel of representatives of patient organizations and patient partners) was involved in the design of this study, particularly in the selection of outcome measures and questionnaires and development of patient information and the consent form. Also, they assessed the burden of the interventions evaluated in this study. The panel will continue to be involved in the 6 monthly evaluation of the study progress and will support dissemination of information about the study among potential participants. After completion of the study, we intend to write a patient summary and publish and disseminate the results using media accessible by patients (including the magazine of patient organizations, social media and the study website). The Dutch patient organization for systemic sclerosis (NVLE) recognizes the importance of the research question and supports this study.

Ethics

The study will be performed according to the principles of the Declaration of Helsinki (Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended

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by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).

Patient information will be handled with care, taking into consideration the required confidentiality as stated by the Law for the Protection of Personal Information, the Law Common Treatment Agreement, the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (GDPR). All data will be stored in a pseudonymized database (CASTOR). A limited number of people have access to the data. These are the principal investigator, coordinating investigator and data manager. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor (Clinical Research Associate), auditors, employees from the Medical Research Ethics Committee (MREC) and the Health Care Inspectorate of the Ministry of Health, Welfare and Sport have access to the source data. All are subject to the pledge of confidentiality. The data are directly imputed in CASTOR and securely stored. Research data will be kept up to 15 years after ending the research.

Dissemination

The results will be presented on scientific conferences, and through publication of articles in peer-reviewed and patient journals. After publication of the main study results, study data will be made available upon request. The study protocol, statistical analysis plan and the informed consent form will be made available as well.

Authors' contributions: JS is the Coordinating Investigator, had overall responsibility for the trial design, drafted the trial protocol and manuscript. JL is the Principal Investigator, had overall responsibility for the trial design and trial protocol and contributed to the manuscript. AL, AR, AV, DD, DW, EDL, JH, JVB, KRG, MM, MS, MV, NDP, PL, RH, RS, RV, TK, UW, VS and WM contributed to trial design and contributed to the manuscript. PW is responsible for statistical and economic analysis. AM is the Trial Manager, JVB coordinates the substudies in this trial. Centre leads are AV (Amsterdam), DW (Lund), EDL (Leuven), JH (Tubingen), JVB (Leiden), KRG (Stockholm), MM (Zagreb), MS (Wurzburg), MV (Nijmegen), NDP (Milan), RS (Bochum), RV (Freiburg), UW (Basel) and VS (Ghent). All authors inputted to the trial protocol and commented on the manuscript.

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Competing interests statement: There are no competing conflicts of interest.

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Table 1. Participating centres

Country	**Centres and affiliated networks**
The Netherlands	Amsterdam UMC Leiden University Medical Centre Radboudumc Nijmegen University Medical Centre Utrecht (coordinating centre) National scleroderma network: Arthritis Research and Collaboration Hub (ARCH)
Belgium	University Hospital Ghent University Hospital Leuven National scleroderma network: Belgian Scleroderma Cohort.
Germany	Ruhr University Bochum University Hospital Freiburg Universitats Klinikum Tuebingen Universitats Klinikum Wurzburg
Sweden	Karolinska University Hospital Stockholm Skåne University Hospital Lund
Switzerland	University Hospital Basel
Italy	ASST Pini-CTO, Milano
Croatia	University Hospital Zagreb

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Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 18 and 65 years.	Pregnancy or unwillingness to use adequate contraception during study.
Fulfilling the 2013 ACR-EULAR classification criteria for dcSSc	Poor compliance of the patient as assessed by the referring physicians.
Disease duration ≤ 2 years (from onset of first non-Raynaud's symptoms) 1. mRSS ≥ 15 (diffuse skin pattern) **and/or** 2. clinically significant organ involvement as defined by either: a. respiratory involvement = i. DLCO and/or (F)VC ≤ 85% (of predicted) and evidence of interstitial lung disease on HR-CT scan with clinically relevant obstructive disease and emphysema excluded. ii. Patients with a DCLO and/or FVC > 85%, but with a progressive course of lung disease: defined as relative decline of ≥10% in FVC predicted and/or TLC predicted, or ≥15% in DLCO predicted within 12 months. Intercurrent infections excluded. b. renal involvement = any of the following criteria: hypertension (two successive BP readings of either systolic ≥ 160 mm Hg or diastolic > 110 mm Hg, at least 12 hours apart), persistent urinalysis abnormalities (proteinuria, haematuria, casts), microangiopathic haemolytic anaemia, new renal insufficiency (serum creatinine > upper limit of normal); non-scleroderma related causes (e.g. medication, infection etc.) must be reasonably excluded. c. cardiac involvement = any of the following criteria: reversible congestive heart failure, atrial or ventricular rhythm disturbances such as atrial fibrillation or flutter, atrial paroxysmal tachycardia or ventricular tachycardia, 2nd or 3rd degree AV block, pericardial effusion (not leading to hemodynamic problems), myocarditis; non-scleroderma related causes must have been reasonably excluded	Concomitant severe disease = a. respiratory: resting mean pulmonary artery pressure (mPAP) > 20 mmHg (by right heart catheterization), DLCO < 40% predicted, respiratory failure as defined by the primary endpoint b. renal: creatinine clearance < 40 ml/min (measured or estimated) c. cardiac: clinical evidence of refractory congestive heart failure; LVEF < 45% by cardiac echo or cardiac MR; chronic atrial fibrillation necessitating oral anticoagulation; uncontrolled ventricular arrhythmia; pericardial effusion with hemodynamic consequences [16] d. liver failure as defined by a sustained 3-fold increase in serum transaminase or bilirubin, or a Child-Pugh score C e. psychiatric disorders including active drug or alcohol abuse f. concurrent neoplasms or myelodysplasia g. bone marrow insufficiency defined as leukocytopenia < 4.0 x 10^9/L, thrombocytopenia < 50 x 10^9/L, anaemia < 8 gr/dL, CD4+ T lymphopenia < 200 x 10^6/L h. uncontrolled hypertension i. uncontrolled acute or chronic infection, including HIV, HTLV-1,2 positivity j. ZUBROD-ECOG-WHO Performance Status Scale > 2
Written Informed consent	Previous treatments with immunosuppressants > 6 months including mycophenolate mofetil, methotrexate, azathioprine, rituximab, tocilizumab, glucocorticoids.
	Previous treatments with TLI, TBI or alkylating agents including cyclophosphamide.
	Significant exposure to bleomycin, tainted rapeseed oil, vinyl chloride, trichlorethylene or silica
	Eosinophilic myalgia syndrome; eosinophilic fasciitis, morphea.

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Table 3. Data collection

	screening	baseline	3	6	9	12	15	18	21	24	annually
Survival status	Continuous registration										
Toxicity according to CTC criteria (=/>grade 3)	X	X	X	X	X	X	X	X	X	X	X
mRSS	X	X	X	X	X	X	X	X	X	X	X
Laboratory											
a. ESR, Hb, WBC with differential, platelet count, C3, C4, C1q	X			X		X				X	X
b. Electrolytes, renal, liver function tests, albumin	X			X		X				X	X
c. Autoantibody titers (ANA, Scl70, RNA pIII)		X									
d. Urine portion: creatinin/ protein ratio	X					X				X	X
e. Serology CMV, EBV, HBV, HCV, HIV, HSV, HTLV-1,2, VDRL, VZV	X			X		X				X	
f. Immunophenotyping by FACS of PBMCs: CD3+, CD4+, CD8+, CD4+ CD45RA, CD4+ CD45RO, CD3- CD56+ CD16+, CD19+, CD14+; IgG, IgA, IgM).	X	X				X				X	
g. Women: FSH, anti-Müllerian hormone Men: TSH, testosterone, prolactin		X		X							
h. Blood and urine samples for immunologic studies and ATG levels		X	X	X	X	X		X		X	X
Image studies											
a. HRCT		X				X					
b. Pulmonary function studies	X					X				X	X
c. 24 hour ECG Holter	X										
d. Cardiac echo	X					X				X	X
e. Cardiac MR	X					X					
f. Right heart catheterization	X										
g. 18F FDG-PET scan from the thorax		X				X					
h. Nailfold capillaroscopy		X		X		X		X		X	X
Sampling											
a. Two skin biopsies from affected skin		X				X					
b. Stool sample for microbiome studies		X				X					
Other scores											
a. Physician global assessment		X				X				X	X
b. Modified HAMIS		X		X		X				X	X
PROMS											
a. Patient global assessment		X		X		X		X		X	X
b. S-HAQ		X		X		X		X		X	X
c. VAS		X		X		X		X		X	X
d. EQ-5D-5L		X		X		X		X		X	X
e. UCL SCTC GIT 2.0		X		X		X		X		X	X
f. SFQ-28 (women) or IIEF-5 (men)		X		X		X		X		X	X
g. FACIT		X		X		X		X		X	X
h. Customized iPCQ		X		X		X		X		X	X

Abbreviations: ANA: antinuclear antibody, CMV: cytomegalovirus, CTC: common toxicity criteria, DLCO: diffusion capacity carbon monoxide, EBV: Ebstein Barr virus, ECG: electrocardiogram, EQ5D5L: EuroQol five dimensions, five levels, ESR: estimated sedimentation rate, FACIT: Functional Assessment of Chronic Illness Therapy, FDG-PET: fluorodeoxyglucose-positron emission tomography, FSH: follicle stimulating hormone, HAMIS: Hand Mobility in Scleroderma, HAQ-DI: Health Assessment Questionnaire Disability Index, Hb: hemoglobulin, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HRCT: high resolution computerized tomography, HSV: herpes simplex virus, HTLV-1,2: human T-cell lymphoma virus type, IIEF-5: International Index of Erectile Function, iPCQ: iProductivity Cost Questionnaire. MR: magnestic resonance, mRSS: modified Rodnan Skin Score, PBMCs: peripheral blood mononuclear cells, PROMs: patient reported outcome measure, RNA pIII: RNA polymerase, RV: residual volume, SFQ-28: Sexual Functioning Questionnaire, TLC: total lung capacity, TSH: thyroid stimulating hormone, UCL SCTC GIT: University College London Scleroderma

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Clinical Trials Consortium Gastrointestinal Tract, VAS: visual analogue scale, VC: vital capacity, VDRL: venereal disease research laboratory, VZV: varicella zoster virus, WBC: white blood count.

Legend
Figure 1: Study flow diagram

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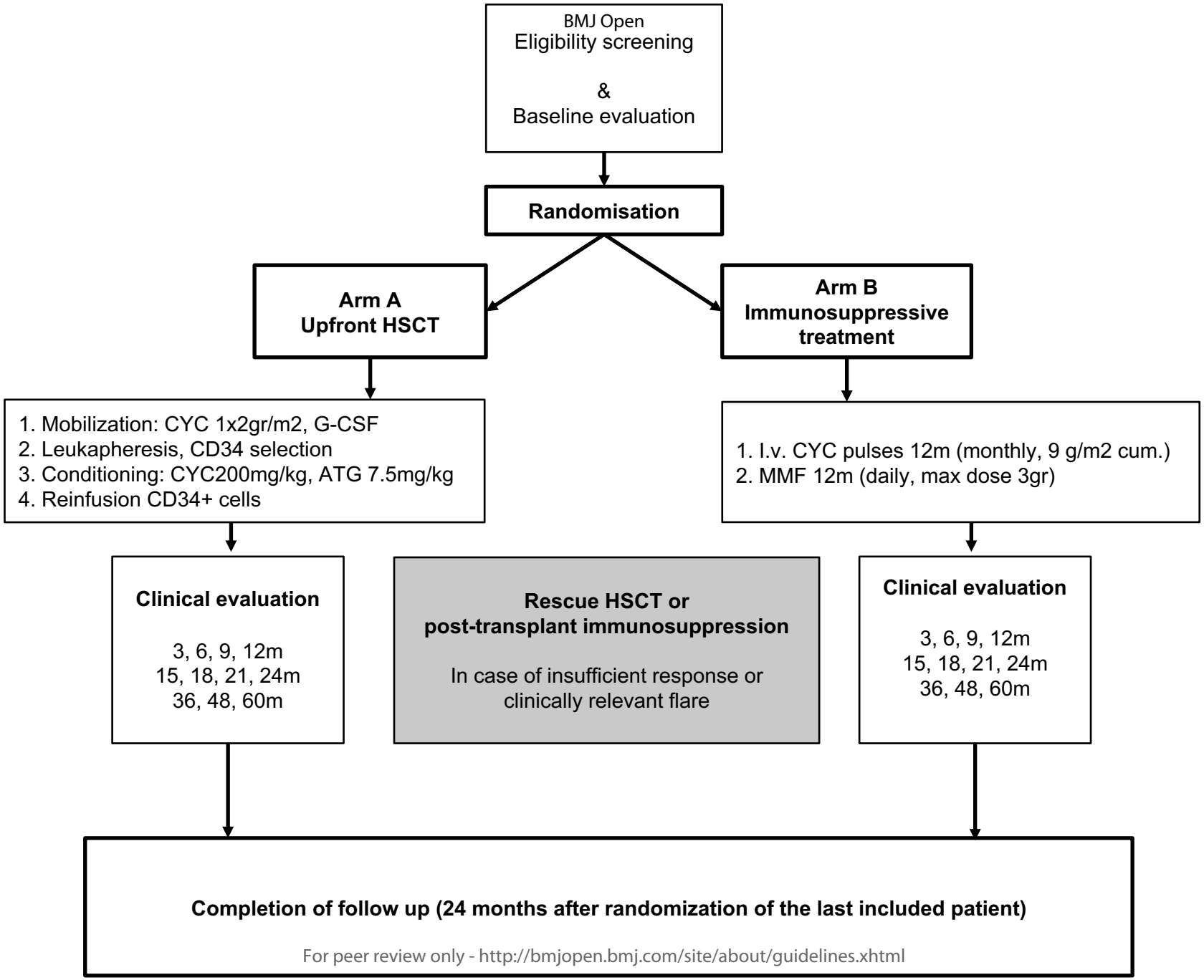

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A randomized, open-label trial to assess the optimal treatment strategy in early diffuse cutaneous systemic sclerosis: the UPSIDE Study protocol

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A randomized, open-label trial to assess the optimal treatment strategy in early diffuse cutaneous systemic sclerosis: the UPSIDE Study protocol

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Abstract

Introduction: Systemic sclerosis (SSc) is a chronic, autoimmune connective tissue disease associated with high morbidity and mortality, especially in diffuse cutaneous SSc (dcSSc). Currently there are several treatments available in early dcSSc that aim to change the disease course, including immunosuppressive agents and autologous hematopoietic stem cell transplantation (HSCT). HSCT has been adopted in international guidelines and is offered in current clinical care. However, optimal timing and patient selection for HSCT is still unclear. In particular, it is unclear whether HSCT should be positioned as upfront therapy or rescue treatment for patients refractory to immunosuppressive therapy. We hypothesise that upfront HSCT is superior and results in lower toxicity and lower long-term medical costs. Therefore, we propose this randomized trial aiming to determine the optimal treatment strategy for early dcSSc by comparing two strategies used in standard care: A. upfront autologous HSCT versus B. immunosuppressive therapy (intravenous cyclophosphamide pulse therapy followed by mycophenolate mofetil) with rescue HSCT in case of treatment failure.

Methods and analysis: The UPSIDE (Upfront autologous hematopoietic Stem cell transplantation versus Immunosuppressive medication in early DiffusE cutaneous systemic sclerosis) study is a multicentre, randomized, open label, controlled trial. In total, 120 patients with early dcSSc will be randomized. The primary outcome is event free survival at two years after randomisation. Secondary outcomes include serious adverse events, functional status, and health related quality of life. We will also evaluate changes in nailfold capillaroscopy pattern, pulmonary function, cardiac MR and High Resolution-CT of the chest. Follow-up visits will be scheduled 3-monthly for two years and annually in the following three years.

Ethics and dissemination The study was approved by the Dutch Central Committee on Research Concerning Human Subjects (NL72607.041.20). The results will be disseminated through patient associations and conventional scientific channels.

Trial registration number; NCT04464434, trial NL 8720

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Strengths and limitations of this study

- This study is a multicentre, randomized, controlled and open-label trial aiming to determine whether upfront autologous stem cell transplantation (HSCT) is superior to standard immunosuppressive treatment (with rescue HSCT for those who progress), in early diffuse cutaneous systemic sclerosis (dcSSc).
- Event free survival is the primary outcome measure and is defined as the time in days from randomisation until death due to any cause or the development of persistent major organ failure (heart, lung, or kidney).
- This clinical trial has the potential to change clinical practice in early dcSSc worldwide

Introduction

Systemic sclerosis (SSc) is a debilitating and incurable autoimmune connective tissue disease. Clinical features include vasculopathy, fibrosis and inflammation of skin and internal organs [1]. Presentation and disease course are very heterogenous. In the diffuse cutaneous subset of SSc (dcSSc) there is generalized skin thickening and often multiorgan involvement [2–4]. Due to its progressive character, the median 5 and 12-year mortality for dcSSc is ~25% and 70% respectively [5,6]. To prevent progression and death in SSc patients, it is key to identify individuals at risk at an early stage of the disease and initiate immunomodulating treatment. Methotrexate, mycophenolate mofetil and cyclophosphamide are commonly used in dcSSc, dependent on the organ system involved.

In three randomized controlled trials (RCT) in dcSSc, treatment with autologous hematopoietic stem cell transplantation (HSCT) improved survival, quality of life, skin fibrosis and prevented disease progression in dcSSc patients, when compared to cyclophosphamide pulse therapy [7–9]. Additionally, three systematic reviews were published on the efficacy and safety of HSCT in SSc.[10–12] In all reviews it was concluded that HSCT provided a survival benefit, improved skin involvement and stabilized pulmonary function compared to intravenous cyclophosphamide for 12 months. Heterogeneity between studies, however, prevented meta-analysis, yet a trend towards better outcome was observed in patients with a shorter disease duration prior to HSCT. HSCT has since been implemented in (inter)national treatment guidelines for SSc, made its way into regular clinical care and is reimbursed in several European countries [13,14]. However, recommendations regarding the optimal use and especially the preferred timing of HSCT and the efficacy of other therapies in the course of dcSSc are lacking. Particularly, it is unclear whether HSCT should be positioned as upfront or as rescue treatment for patients not responding to immunosuppressive therapy such as MMF or intravenous pulse CYC.

HSCT as upfront treatment might result in better outcomes, because the disease process is effectively targeted early in the disease at a time when there is less irreversible organ damage. On the other hand, HSCT is a treatment associated with a higher risk of adverse events compared to other treatments, as it is associated with a treatment related mortality of approximately 10% [8,15].

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However, there might be fewer transplant related adverse events due to the better health status of patients and limited immunosuppressive premedication if HSCT is commenced early, compared to the patients that need rescue HSCT after months or even years of other immunocompromising agents. So, in order to determine the optimal treatment strategy in early dcSSc, further investigation is needed.

This manuscript describes the protocol of the UPSIDE study (Upfront autologous hematopoietic Stem cell transplantation versus Immunosuppressive medication in early DiffusE cutaneous systemic sclerosis). The UPSIDE study is a multicentre randomized open-label controlled trial that aims to compare two treatment strategies used in standard care of adult patients with early dcSSc: upfront autologous HSCT versus intravenous cyclophosphamide pulse therapy followed by oral mycophenolate mofetil and rescue HSCT in case of treatment failure. Efficacy, safety, survival and cost-effectiveness will be evaluated.

Aims and objectives

The UPSIDE study aims to investigate the optimal timing of HSCT in early dcSSc by comparing two treatment strategies: the effect of HSCT as upfront therapy compared with that of immunosuppressive medication and HSCT in case of failure, with respect to (event-free) survival and prevention of major organ failure, safety and the impact on skin thickening, visceral involvement, functional status, and quality of life.

Secondary goals are to evaluate (in both treatment arms) whether disease activity correlates with immunological parameters, including immunopathology of skin, immune reconstitution, and autoantibodies. Cost-effectiveness of both therapeutic options and factors associated with response to treatment will also be examined.

Methods and analysis

This protocol has been developed in accordance to the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement (https://www.spirit-statement.org).

Study design and setting

The UPSIDE study is a randomized controlled, multicentre, open-label trial.

SSc is a rare condition and stem cell mobilisation after intravenous cyclophosphamide administration and HSCT are treatments only performed in experienced tertiary treatment centres. Therefore, national, and international collaboration is of key importance to include the necessary number of patients. Participants will be recruited from fourteen participating centres from The Netherlands, Belgium, Germany, Italy, Sweden, Switzerland, and Croatia (Table 1). Multidisciplinary expert teams in the field of SSc and HSCT are involved in each centre.

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Table 1. Participating centres

Country	Centres and affiliated networks
The Netherlands	Amsterdam UMC Leiden University Medical Centre Radboudumc Nijmegen University Medical Centre Utrecht (coordinating centre) National scleroderma network: Arthritis Research and Collaboration Hub (ARCH)
Belgium	University Hospital Ghent University Hospital Leuven National scleroderma network: Belgian Scleroderma Cohort.
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Sweden	Karolinska University Hospital Stockholm Skåne University Hospital Lund
Switzerland	University Hospital Basel
Italy	ASST Pini-CTO, Milano
Croatia	University Hospital Zagreb

Study population and eligibility criteria

We will include 120 patients with early dcSSc who fulfil the inclusion criteria (Table 2). These criteria are designed to select patients in an early stage of the disease, but at high risk of disease progression and subsequent death. Baseline assessment prior to randomisation includes complete blood count, liver function, kidney function, urine spot test (protein/creatinine ratio), viral serology tests, 12-lead ECG, cardiac ultrasound, cardiac MRI, right heart catheterization, lung HR-CT and pulmonary function tests. Patient recruitment started in September 2020. We anticipate the accrual time will be 3 years. Patients will be followed for five years.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 18 and 65 years.	Pregnancy or unwillingness to use adequate contraception during study.
Fulfilling the 2013 ACR-EULAR classification criteria for dcSSc	Poor compliance of the patient as assessed by the referring physicians.
Disease duration ≤ 2 years (from onset of first non-Raynaud's symptoms) 1. mRSS ≥ 15 (diffuse skin pattern) **and/or** 2. clinically significant organ involvement as defined by either: a. respiratory involvement = i. DLCO and/or (F)VC ≤ 85% (of predicted) and evidence of interstitial lung disease on HR-CT scan with clinically relevant obstructive disease and emphysema excluded. ii. Patients with a DCLO and/or FVC > 85%, but with a progressive course of lung disease: defined as relative decline of ≥10% in FVC predicted and/or TLC predicted, or	Concomitant severe disease = a. respiratory: resting mean pulmonary artery pressure (mPAP) > 20 mmHg (by right heart catheterization), DLCO < 40% predicted, respiratory failure as defined by the primary endpoint b. renal: creatinine clearance < 40 ml/min (measured or estimated) c. cardiac: clinical evidence of refractory congestive heart failure; LVEF < 45% by cardiac echo or cardiac MR; chronic atrial fibrillation necessitating oral anticoagulation; uncontrolled ventricular arrhythmia; pericardial effusion with hemodynamic consequences [16]

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≥15% in DLCO predicted within 12 months. Intercurrent infections excluded. b. renal involvement = any of the following criteria: hypertension (two successive BP readings of either systolic ≥ 160 mm Hg or diastolic > 110 mm Hg, at least 12 hours apart), persistent urinalysis abnormalities (proteinuria, haematuria, casts), microangiopathic haemolytic anaemia, new renal insufficiency (serum creatinine > upper limit of normal); non-scleroderma related causes (e.g. medication, infection etc.) must be reasonably excluded. c. cardiac involvement = any of the following criteria: reversible congestive heart failure, atrial or ventricular rhythm disturbances such as atrial fibrillation or flutter, atrial paroxysmal tachycardia or ventricular tachycardia, 2nd or 3rd degree AV block, pericardial effusion (not leading to hemodynamic problems), myocarditis; non-scleroderma related causes must have been reasonably excluded	d. liver failure as defined by a sustained 3-fold increase in serum transaminase or bilirubin, or a Child-Pugh score C e. psychiatric disorders including active drug or alcohol abuse f. concurrent neoplasms or myelodysplasia g. bone marrow insufficiency defined as leukocytopenia < 4.0 x 10^9/L, thrombocytopenia < 50 x 10^9/L, anaemia < 8 gr/dL, CD4+ T lymphopenia < 200 x 10^6/L h. uncontrolled hypertension i. uncontrolled acute or chronic infection, including HIV, HTLV-1,2 positivity j. ZUBROD-ECOG-WHO Performance Status Scale > 2
Written Informed consent	Previous treatments with immunosuppressants > 6 months including mycophenolate mofetil, methotrexate, azathioprine, rituximab, tocilizumab, glucocorticoids.
	Previous treatments with TLI, TBI or alkylating agents including cyclophosphamide.
	Significant exposure to bleomycin, tainted rapeseed oil, vinyl chloride, trichlorethylene or silica
	Eosinophilic myalgia syndrome; eosinophilic fasciitis, morphea.

Randomisation

Eligible patients who provided informed consent will be randomised 1:1 (variable block randomisation) using the validated algorithm within Castor, the Electronic Data Capture program used for the study. Blocks of 2, 4, or 6 patients will be randomly and blindly assigned, stratified by participating centre. The two treatment are: strategy arm A: upfront high dose non-myeloablative autologous HSCT or strategy arm B: intravenous pulse therapy with cyclophosphamide followed by at least 12 months oral mycophenolate mofetil daily and thereafter HSCT as rescue option. The treatment allocation will be coordinated by the principal investigator of the study site. The investigators and participants are not blinded to treatment allocation.

Interventions

A. Upfront autologous HSCT

Autologous, non-myeloablative HSCT comprises the following consecutive steps:

a. Mobilisation: PBSCs will be mobilised using a regimen consisting of infusion of cyclophosphamide 2g/m^2 for 1 day. Hyperhydration, alkalinisation of the urine and Mesna will be given in order to prevent haemorrhagic cystitis. The patients will receive filgrastim (G-CSF) 5 µg/kg/day subcutaneously once or twice a day for 5 days (or more when necessary), according to local practice.

b. Leukapheresis: Start of leukapheresis is required at a CD34+ cell count of ≥10-20/µL, according to local practice. This is expected to occur on day 5 or 6 of filgrastim treatment. Leukaphereses will be

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performed with the goal to obtain at least 6 x 10^6 CD34+ cells per kilogram body weight. The primary goal is to obtain a target dose of 6 x 10^6 CD34+ cells/kg, but a minimum of 2 x 10^6 CD34+ cells/kg after CD34+selection. The apheresis product will be 4-5^{log} T cell depleted. The CD34+ selected cells will be cryopreserved and stored in liquid nitrogen until reinfusion. In case of mobilisation failure, the patient will be treated with daily s.c. filgrastim 20 µg/kg,

c. Prior to conditioning: Echocardiography should be repeated prior to conditioning to evaluate possible subclinical cardiac toxicity caused by cyclophosphamide administered during mobilisation. Conditioning can be initiated if LVEF > 45% or has not decreased with >15% compared to pre-mobilisation, and there are no uncontrolled arrhythmias [16].

d. Conditioning: Conditioning is to be initiated preferably within 6 weeks after successful harvest. The conditioning regimen consists of cyclophosphamide 50 mg/kg/day intravenously for 4 consecutive days (total 200 mg/kg) and rabbit antithymocyte globulin (rbATG, Thymoglobulin®). The first dose of cyclophosphamide will be given on day -5 (day 0 = day of infusion of PBSC). Hyperhydration, alkalinisation of the urine and Mesna will be given in order to prevent haemorrhagic cystitis. A total dose of 7.5 mg/kg intravenous rbATG will be administered over three days. Intravenous methylprednisolone 2 mg/kg will be given on the days ATG will be administered, to improve tolerability of the ATG.

e. Peripheral stem cell infusion: The interval between the last dose of cyclophosphamide and infusion of the graft will be at least 48 hours. On day 0, CD34+-selected stem cells are thawed and infused according to local standard operating procedures. The number of CD34+ cells to be reinfused should be ≥ 2.0 x 10^6/kg, residual T cell content is targeted at ≤ 1.0 x 10^5 T cells/kg, calculated before freezing [17]. Exceptional release according to local practice is allowed and will be registered in the eCRF.

Arm B. Cyclophosphamide followed by mycophenolate mofetil and HSCT as rescue option

Immunosuppressive therapy in arm B consists of 12 monthly intravenous pulses of cyclophosphamide 750 mg/m2 (= 9 g/m^2 cumulative) followed by at least 12 months of oral mycophenolate mofetil daily (3 grams as maximum daily dosage) or mycophenolic acid (up to 2.160 grams daily), according to local practice. Hyperhydration, alkalinisation of urine and Mesna is recommended during the 12 monthly intravenous pulses cyclophosphamide, and will be given according to local protocols in order to prevent haemorrhagic cystitis.

Supportive Care

Supportive care measures, including prophylactic or therapeutic antibiotics, anti-viral or anti-fungal agents, transfusions, and anti-emetic agents will be taken according to local standard operating procedures for such patients. In case of HSCT, particular attention will be paid to the risk of EBV and CMV-reactivation. EBV and CMV-load will be monitored by PCR, weekly in the first three months following the transplantation, then monthly for the next 9 months. In case of reactivation, the patient will be treated according to standard of care guidelines.

Initiation of an ACE-inhibitor prior to HSCT is strongly recommended (i.e. enalapril 5mg once daily) to prevent scleroderma renal crisis based on the clinical experience from the ASTIS-trial [8]. Monitoring

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of blood potassium levels after initiation of ACE-inhibitors is recommended, especially when combined with co-trimoxazole.

Study outline

An overview of the study outline is shown in Figure 1 (study flow diagram). After randomisation, concurrent immunosuppressive therapy will be discontinued. Glucocorticoids may be continued at the lowest possible dose. Either treatment is to be initiated within six weeks after randomisation, i.e. mobilisation in patients randomised to Arm A, and the first pulse of cyclophosphamide in patients randomized to Arm B.

Rescue therapy may be considered in both arms in case of insufficient response or clinically relevant flare, but preferably not within the first 6 months after randomisation. For patients from Arm A methotrexate, mycophenolate mofetil or mycophenolic acid, or rituximab can be (re)instituted, according to local preference. Based on earlier studies, the clinical benefits of i.v. pulse cyclophosphamide may take between 6-12 months. Therefore it is recommended to then switch patients from arm B to HSCT only in case of rapidly progressive disease, which is arbitrarily defined as ≥30% increase in mRSS or ≥20% relative decline in FVC, TLC, or DLCO predicted.

Outcomes and follow-up

The primary endpoint of the study will be event-free survival. Event-free survival is defined as the time in days from the day of randomisation until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney) defined as follows:

- Heart: left ventricular ejection fraction < 30% by cardiac MR (or cardiac echo)
- Lungs: respiratory failure = resting arterial oxygen tension (PaO2) < 8 kPa (< 60 mmHg) and/or resting arterial carbon dioxide tension (PaCO2) > 6.7 kPa (> 50 mmHg) without oxygen supply, or need of oxygen supply.
- Kidney: need for renal replacement therapy (i.e. dialysis)

Secondary outcome measures include:

1. Progression-free survival, defined as the time in days since the day of randomisation until any of the following relative changes from baseline has been documented: death, ≥ 10% drop in (F)VC predicted and/or ≥ 15% drop in DLCO predicted [18], ≥ 15% drop in LVEF by echo or cardiac MR, ≥ 15% drop in body weight, ≥ 30% drop in creatinine clearance, ≥ 25% and ≥ 5 points increase in skin score, ≥ 0.5 increase in SHAQ.
2. Treatment related mortality, defined as any death during the study period following randomisation that cannot be attributed to progression of the disease according to the consensus opinion of the Data and Safety Monitoring Board (DSMB).
3. Overall Survival
4. Treatment toxicity and adverse events, using WHO toxicity parameters (≥ grade 3 toxicity) during the study period

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5. The area under the curve (AUC) of the combined response index for systemic sclerosis (CRISS) over time, measuring the 'predicted probability of being improved' over two years. This AUC is calculated based on 4 repeated measures (6, 12, 18 and 24 months) with back translation to the original scale between 0 and 1.

6. Change from baseline over time (i.e. during follow-up) of the following parameters: modified Rodnan Skin Score (mRSS), pulmonary involvement: diffusion capacity for carbon monoxide (DLCO and DLCO/VA), (forced)vital capacity ((F)VC), total lung capacity (TLC), residual volume (RV), mean pulmonary artery pressure by cardiac echo (or right heart catheterization), lung density measurement by thoracic CT and 18 FDG-PET scan lung, renal involvement: urine spot test: creatinine/ protein ratio, myocardial involvement: left ventricular function as measured by cardiac MR, body weight (kg), changes in nailfold capillaroscopy, changes in Modified HAMIS (functional assessment of hand function), quality-of-life (EuroQol (EQ-5D-5L)), SHAQ including visual analogue scales (VAS) for scleroderma-specific symptoms, gastrointestinal symptom scale (UCL-SCTC GIT 2.0 questionnaire), sexual functioning (short IIEF-15 questionnaire (in men) and SFQ-28 (in women)), fatigue score (FACIT questionnaire), self-assessment of skin (PASTUL), productivity losses due to health issues (customised iPCQ questionnaire), characteristics of the immune system: autoantibody concentration and avidity targeting host nuclear antigens, primarily focusing on anti-ATA, anti-RNAPIII and anti-CENP, isotype usage, isotype levels, Fc-glycosylation profiles of anti-topoisomerase and skewing of T cell receptor repertoire and determination of HLA profiles, inflammatory and fibrotic characteristics of the skin, levels of ATG in relation with changes in lymphocyte subsets and outcomes.

Follow-up appointments will be according to regular care: monthly the first half year, then three-monthly until two years after randomisation, followed by annual appointments for three years (Table 3).

Table 3. Data collection

	screening	**baseline**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**annually**
Survival status	Continuous registration										
Toxicity according to CTC criteria (=/>grade 3)	X	X	X	X	X	X	X	X	X	X	X
mRSS	X	X	X	X	X	X	X	X	X	X	X
Laboratory											
a. ESR, Hb, WBC with differential, platelet count, C3, C4, C1q	X			X		X				X	X
b. Electrolytes, renal, liver function tests, albumin, troponin	X			X		X				X	X
c. Autoantibody titers (ANA, Scl70, RNA pIII)		X									
d. Urine spot test: creatinin/ protein ratio	X					X				X	X
e. Serology CMV, EBV, HBV, HCV, HIV, HSV, HTLV-1,2, VDRL, VZV	X			X		X				X	
f. Immunophenotyping by FACS of PBMCs: CD3+, CD4+, CD8+, CD4+ CD45RA, CD4+ CD45RO, CD3- CD56+ CD16+, CD19+, CD14+; IgG, IgA, IgM).	X	X				X				X	
g. Women: FSH, anti-Müllerian hormone Men: TSH, testosterone, prolactin		X		X							

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h. Blood and urine samples for immunologic studies and ATG levels		X	X	X	X	X		X		X	X
Image studies											
a. HRCT		X				X					
b. Pulmonary function studies	X					X				X	X
c. 24 hour ECG Holter	X										
d. Cardiac echo	X					X				X	X
e. Cardiac MR	X					X					
f. Right heart catheterization	X										
g. 18F FDG-PET scan from the thorax		X				X					
h. Nailfold capillaroscopy		X		X		X		X		X	X
Sampling											
Two skin biopsies from affected skin		X				X					
Other scores											
a. Physician global assessment		X				X				X	X
b. Modified HAMIS		X		X		X				X	X
PROMS											
a. Patient global assessment		X		X		X		X		X	X
b. S-HAQ		X		X		X		X		X	X
c. VAS		X		X		X		X		X	X
d. EQ-5D-5L		X		X		X		X		X	X
e. UCL SCTC GIT 2.0		X		X		X		X		X	X
f. SFQ-28 (women) or IIEF-15 (men)		X		X		X		X		X	X
g. FACIT		X		X		X		X		X	X
h. Customized iPCQ		X		X		X		X		X	X
i. PASTUL (self-assessment of skin)		X		X		X		X		X	X

Abbreviations: ANA: antinuclear antibody, CMV: cytomegalovirus, CTC: common toxicity criteria, DLCO: diffusion capacity carbon monoxide, EBV: Ebstein Barr virus, ECG: electrocardiogram, EQ5D5L: EuroQol five dimensions, five levels, ESR: estimated sedimentation rate, FACIT: Functional Assessment of Chronic Illness Therapy, FDG-PET: fluorodeoxyglucose-positron emission tomography, FSH: follicle stimulating hormone, HAMIS: Hand Mobility in Scleroderma, HAQ-DI: Health Assessment Questionnaire Disability Index, Hb: hemoglobulin, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HRCT: high resolution computerized tomography, HSV: herpes simplex virus, HTLV-1,2: human T-cell lymphoma virus type, IIEF-15: International Index of Erectile Function, iPCQ: iProductivity Cost Questionnaire. MR: magnetic resonance, mRSS: modified Rodnan Skin Score, PASTUL: Patient self-Assessment of Skin Thickness in Upper Limb, PBMCs: peripheral blood mononuclear cells, PROMs: patient reported outcome measure, RNA pIII: RNA polymerase, RV: residual volume, SFQ-28: Sexual Functioning Questionnaire, TLC: total lung capacity, TSH: thyroid stimulating hormone, UCL SCTC GIT: University College London Scleroderma Clinical Trials Consortium Gastrointestinal Tract, VAS: visual analogue scale, VC: vital capacity, VDRL: venereal disease research laboratory, VZV: varicella zoster virus, WBC: white blood count.

Statistical analyses

Sample size

The sample size is determined assuming a median event-free survival of two years in the control group and an (approximate) exponential survival curve based on the survival observed in the HSCT arm of the ASTIS trial [7]. We expect our proposed intervention to result in a considerable improvement (assumed hazard ratio of 0.5) and take a total study period of five years (three years for recruiting patients at a constant rate), 10% loss to follow up after five years in both groups and an alpha of 0.05 into account. Based on the above, we will need 60 patients per group to have at least 80% power to detect a difference as calculated using the SAS power procedure (two sample survival, log rank test). Based on the incidence of dcSSc and the collective treatment experience of the 15 trial sites, we anticipate we can enrol the required 120 patients (60 per group) within three years [19,20].

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Primary outcome

Data will be analysed on an intention-to-treat basis. Data regarding adverse events and SAEs will be provided using descriptive statistics and tables. Population characteristics will be provided using descriptive statistics. To compare event free survival (the primary endpoint) and other time-to-event outcomes between treatment groups, Kaplan Meyer (KM) curves will be constructed (based on first event) and tested using the log-rank test and Cox regression to take important prognostic covariates (sex, age, smoking status, cardiac function) and centre (stratification factor for randomisation), as determined a priori (before database lock) in SAP, into account. For all time-to-event outcome data is censored at the last visit. Based on a visual inspection of the KM curves also a treatment x time interaction will be modelled in the Cox regression analysis to allow for non-constant hazards over time. An intention to treat (ITT) analysis (primary) and per protocol (PP) analysis will be performed. In the primary analysis for patients leaving the study early (early dropout) this last visit will be treated as the censoring date, a multiple-imputation method for sensitivity analyses of time-to-event data accounting for possible informative censoring will also be performed.

Secondary outcomes

Secondary continuous outcomes (i.e. change from baseline in CRISS score)[21] measured over time will be analysed using mixed modelling approaches if needed based on graphical inspection including a treatment x time interaction, controlling for important prognostic covariates (sex, age, smoking habit) and centre (stratification factor for randomisation). For binary outcomes at a fixed timepoint, frequencies and proportions will be calculated and differences tested using Chi-square or Fisher exact tests. The effects of covariates will be evaluated using logistic regression. An intention to treat (ITT) analysis (primary) and per protocol (PP) analysis will be performed. A cost effectiveness analyses will be performed from a societal perspective including direct medical and non-medical and productivity costs. Cost-per-QALY gained as well as costs per life year and per event-free life year gained will be calculated. The economic evaluation will be done at five years in line with the duration of the trial and the evaluation will be performed in line with the Dutch guidelines for economic evaluations [22].

Interim analysis

There will be an interim analysis at 12 months after the first inclusion and/or after 60 patients have been included, whatever comes first, and at the DSMB request. Formal statistical methods for evaluating interim efficacy and toxicity results will be used as guidelines rather than absolute rules. An alpha spending function (O'Brien-Fleming) will be used. Reasons for DSMB decisions will be recorded.

Safety

The UPSIDE Trial will be overseen by an international DSMB. The DSMB consists of clinicians (including experts on SSc and on stem cell transplantation) and a biostatistician. Every 6 months, the DSMB will review the status and conduct of the clinical trial, evaluate all causes of death and adverse events and make recommendations to the clinical research group concerning the trial's continuation and modification.

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Data collection in the study will be monitored by an independent monitor within Julius Centre, UMC Utrecht, the Netherlands. There will be five scheduled visits per centre, the first visit will be the initiation visit and thereafter once a year visits will be performed. The last visit is combined with the close-out visit.

Patient and public involvement

Our research question originates from clinical practice and a prior study that investigated patient's experiences, which showed that the lack of evidence to support the decision-making process in choosing the right treatment strategy is a burden for patients and caretakers [23]. A patient panel (international panel of representatives of patient organizations and patient partners) was involved in the design of this study, particularly in the selection of outcome measures and questionnaires and development of patient information and the consent form. Also, they assessed the burden of the interventions evaluated in this study. The panel will continue to be involved in the 6 monthly evaluation of the study progress and will support dissemination of information about the study among potential participants. After completion of the study, we intend to write a patient summary and publish and disseminate the results using media accessible by patients (including the magazine of patient organizations, social media and the study website). The Dutch patient organization for systemic sclerosis (NVLE) recognizes the importance of the research question and supports this study.

Ethics

The study will be performed according to the principles of the Declaration of Helsinki (Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).

Patient information will be handled with care, taking into consideration the required confidentiality as stated by the Law for the Protection of Personal Information, the Law Common Treatment Agreement, the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (GDPR). All data will be stored in a pseudonymized database (CASTOR). A limited number of people have access to the data. These are the principal investigator, coordinating investigator and data manager. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor (Clinical Research Associate), auditors, employees from the Medical Research Ethics Committee (MREC) and the Health Care Inspectorate of the Ministry of Health, Welfare and Sport have access to the source data. All are subject to the pledge of confidentiality. The data are directly imputed in CASTOR and securely stored. Research data will be kept up to 15 years after ending the research.

Dissemination

The results will be presented on scientific conferences, and through publication of articles in peer-reviewed and patient journals. After publication of the main study results, study data will be made

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available upon request. The study protocol, statistical analysis plan and the informed consent form will be made available as well (see Supplementary material).

Authors' contributions: JS is the Coordinating Investigator, had overall responsibility for the trial design, drafted the trial protocol and manuscript. JL is the Principal Investigator, had overall responsibility for the trial design and trial protocol and contributed to the manuscript. AL, AR, AV, DD, DW, EDL, EM, JH, JVB, KRG, MM, MS, MV, NDP, PL, RH, RS, RV, TK, UW and VS contributed to trial design and contributed to the manuscript. PW is responsible for statistical and economic analysis. AM is the Trial Manager, JVB coordinates the substudies in this trial. Centre leads are AV (Amsterdam), DW (Lund), EDL (Leuven), JH (Tubingen), JVB (Leiden), KRG (Stockholm), MM (Zagreb), MS (Wurzburg), MV (Nijmegen), NDP (Milan), RS (Bochum), RV (Freiburg), UW (Basel) and VS (Ghent). All authors inputted to the trial protocol and commented on the manuscript.

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Competing interests statement: There are no competing conflicts of interest.

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Legend
Figure 1: Study flow diagram

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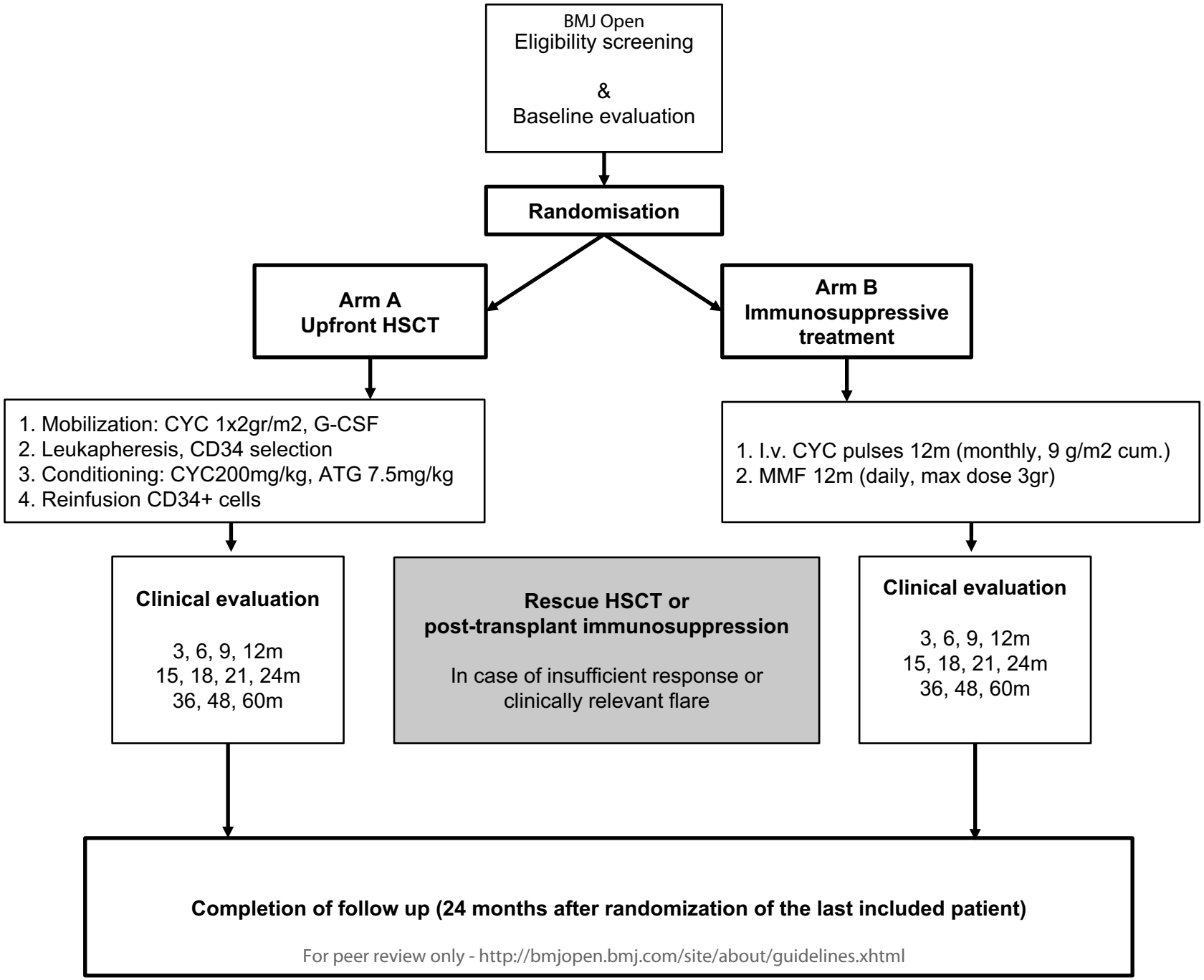

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Patient consent form UPSIDE study, version 2.0

Information for patients on participating in medical research

Autologous stem cell transplantation in diffuse cutaneous systemic sclerosis: early onset or only after failure of other treatments?

Official title: Upfront autologous hematopoietic stem cell transplantation versus immunosuppressive medication in early diffuse cutaneous systemic sclerosis (UPSIDE): an international multicenter, open-label, randomized, controlled trial

Dear Madam/Sir,

We are asking you to participate in a medical scientific study. Participation is voluntary, however your written permission is required in order to participate. You are receiving this letter because you have been diagnosed with diffuse cutaneous systemic sclerosis (dcSSc).
DcSSc is treated with immunosuppressive drugs, chemotherapy or autologous stem cell transplantation (ASCT). The choice for a specific treatment depends on the preference of patient and physician. With this study, we want to investigate which treatment strategy is best. Before you decide whether you want to participate in this study, you will receive information about what the study entails. Please read this information carefully and contact the researcher if you have any questions.

1. General information

This study has been initiated by the Utrecht University Medical Centre in the Netherlands, and is being carried out by rheumatologists in various expert centres for systemic sclerosis in Europe. The study will enrol 120 patients from different countries. In the Netherlands, 50 patients are expected to participate. The Utrecht Medical Ethics Committee has approved this study.

2. Aim of the study

The aim of this study is to determine the best treatment strategy for dcSSc. We will compare the efficacy and safety of ASCT with cyclophosphamide therapy followed by mycophenolate mofetil (MMF) and possibly ASCT if this treatment fails. Both treatment strategies are already used in current health care in dcSSc.

3. Background of the study

ASCT, cyclophosphamide and MMF are both treatments used to slow down disease progression. Two previous studies have shown that ASCT has a higher chance of survival compared to cyclophosphamide. However, ASCT also carries a higher risk of serious side effects is greater. The optimal treatment strategy in dcSSc is therefore not clear. Especially the question whether ASCT should be given directly or only for patients who do not respond to other treatments like methotrexate,

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MMF or cyclophosphamide. Given the risks associated with ASCT, it may be preferable to evaluate the response to other immune suppressive drugs before proceeding with ASCT. However, the use of ASCT in the event of failure of other drugs may lead to more disease damage and possibly a higher risk of complications during ASCT because the disease is more advanced.

4. What it means to participate

In this study all patients will be followed for five years. You will be randomly assigned to either 1. Direct ASCT or 2. Cyclophosphamide infusion therapy followed by MMF and possibly ASCT if this treatment fails. This random assignment means that your doctors cannot influence which treatment you receive.

Eligibility assessment

Before you can participate in this study, we will determine whether the treatments given in the study can be administered safely. This screening is done according to usual clinical care and consists of blood and urine tests, lung function tests, an ultrasound of the heart, a right heart catheterisation (to measure the pressure in the right heart side) and a 24-hour cardiac holter.

Treatments

We will not treat you with experimental treatments in this study, the therapies we investigate have been used in systemic sclerosis for some time. Half of the participants will be treated by treatment strategy A: ASCT, the other half by treatment strategy B: monthly infusion therapy with cyclophosphamide followed by MMF tablets, and possibly ASCT if this treatment fails.

Treatment strategy A: ASCT

Transplantation consists of the following steps:

Step 1. Pre-treatment and stem cell harvesting

This treatment will take place in the hospital's day care unit, or at the haematology department, depending on local practice of your hospital. Cyclophosphamide is administered via an infusion. Side effects are nausea and sometimes hair loss. To prevent cyclophosphamide from irritating the bladder, we give you plenty of fluids and medication. Sometimes the white blood cell count may drop in the weeks following the cyclophosphamide treatment, and if you develop a fever, antibiotic treatment may be necessary.

From the fifth day after the cyclophosphamide infusion, you will receive daily subcutaneous injections with G-CSF (filgrastim), which causes the bone marrow to make more cells. G-CSF can cause flu-like symptoms and muscle and joint pain. Cyclophosphamide and G-CSF make stem cells move from the bone marrow into the blood. Blood tests will be done to see if there are enough stem cells in the blood. If there are, they will be harvested through a leukapheresis machine. This involves one infusion in each arm. The leukapheresis machine is a bit like a kidney dialysis machine: the blood comes out of the infusion and into the machine, the machine removes the stem cells and the rest of the blood is returned. You will be hooked up to this machine for one to two consecutive days for about 4 hours (this can vary depending on the number of stem cells in your blood). The harvested cells are frozen until needed. Then you will go home to recover.

Cardiac monitoring

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Two to three weeks after the stem cell harvest, you will visit the haematologist and rheumatologist for a check-up. Blood test, an ultrasound of the heart will also be done.

Step 2. Stem cell transplantation

The next step takes place within 6 weeks after leukapheresis. For this, you will be admitted to the haematology department and stay in hospital for approximately 3-4 weeks. An infusion will be placed to take blood samples and to administer medication including chemotherapy.

You will receive a high dose of chemotherapy (cyclophosphamide), corticosteroids and ATG) with generous fluid infusion. You will be given medication to prevent nausea and to protect the bladder. You will also receive antibiotics to prevent infections. Cyclophosphamide often causes nausea, hair loss and mouth ulcers. There is a very small risk of heart damage caused by the chemotherapy. Due to the large amount of fluids, you may retain fluids, which will be closely monitored. Bone marrow cells (red and white blood cells and platelets) will drop sharply as a result of the treatment. Sometimes a transfusion is needed. The white blood cells will remain very low for about 10-14 days and during this period you are at risk of serious infections.

On the 3rd day that you receive cyclophosphamide, treatment with (r-ATG) a protein obtained from rabbit blood is also started. This drug will also be administered via infusion and can cause flu-like symptoms and fever. After these treatments, you will receive your own stem cells back; this procedure is similar to a blood transfusion.

There is a small risk of damage to the heart, kidneys and lungs with these treatments. The risk is greater in patients with existing heart or lung problems. Therefore, you will have extensive screening test before to assess whether we can give the treatments safely.

Treatment strategy B: Infusion therapy with cyclophosphamide followed by MMF tablets

Cyclophosphamide is given at the day care unit of the rheumatology department. You will receive an infusion once a month during 12 months. A common side-effects are nausea, which usually lasts a few days after the infusion and sometimes temporarily hair loss. Sometimes the white blood cell count may drop in the weeks following the cyclophosphamide treatment, if you develop a fever, antibiotic treatment may be necessary.

After 12 months the treatment is switched to mycophenolate mofetil (MMF). MMF tablets should be taken twice a day. This treatment can cause gastrointestinal complaints such as diarrhoea or nausea. Sometimes the white blood cell levels in the blood may drop, therefore blood tests are done every month.

If you do not respond well to the treatment you received, it is possible to switch from treatment strategy. This means that if you have received the treatment in arm A (ASCT), you will receive immunosuppressive treatment and ASCT may be started in arm B.

Monitoring after the treatment

All patients are closely monitored for 5 years, regardless the treatment assigned. We will ensure that appointments are combined with your usual care appointments. Hospital visits will take place 3, 6, 9, 12, 15, 18, 21 and 24 months and every year thereafter. The frequency of follow-up visits is the same as usual care. To evaluate the safety and effectiveness of both treatments, the following tests will be done. This is done according to usual clinical care.

During all visits:

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- blood count: liver tests, kidney function, sedimentation rate
- skin score (assessment of skin thickening)

Annually:
- Lung function test
- CT scan of the lungs
- Cardiogram (ECG)
- Echo of the heart
- MRI of the heart (only 1 year after treatment)
- Urine spot test

Other than for usual care

For research purposes, we will do nailfold microscopy and a hand mobility test during the follow-up. This will be done on the same day as your follow-up appointments in hospital.

In addition, you will receive an invitation by mail for online questionnaires at the start of the study, after 6, 12, 18 and 24 months and annually thereafter, to assess quality of life, daily functioning, fatigue, gastrointestinal complaints and sexual functioning. In addition, every three months you will be asked to score your skin thickness using an online questionnaire. We understand that questions on certain topics may be perceived as difficult or personal. You can therefore fill in the questionnaires when and where it suits you. Your answers will of course be treated with strict confidentiality.

Nailfold capillaroscopy

We will examine changes in the small blood vessels (capillaries) of the nail bed before and after treatment, and we will examine whether there are differences between treatments. The appointment for the nailfold capillaroscopy will be scheduled in combination with a routine hospital visit, so no additional hospital visits are necessary. Examination will be done at the start of the study and 6, 12, 24 months and annually up to 5 years after the treatment.

The examination will be done by a rheumatologist or nurse. You will sit at an examination table and position your hands flat on the table. The doctor will apply a drop of oil to your cuticles. Then he will gently place the capillaroscope, a cylindrical instrument, on your nail. The capillaroscope makes the small blood vessels in your nail bed visible on a computer screen. They are magnified 200 times. A photograph is then taken. The doctor examines all fingers, except for the thumbs. The examination takes about 30 minutes and is completely painless. The analysis of this data takes place at Ghent University Hospital, at the end of the study.

Hand mobility test

We will investigate which changes occur in hand mobility before and after treatment, and we will investigate if there are differences between treatments. This examination will be done at the start of the study and 6, 12, 24 months and annually up to 5 years after the start of the study. The examination will be done by a rheumatologist or nurse. You will sit at an examination table and a doctor or nurse will test your hand function in four ways. The examination takes about 15 minutes and is completely painless. The analysis of the results will take place at the University Hospital in Lund at the end of the study.

5. What is expected of you?

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When you are going to participate in this study, it is important to read the following agreements.

We expect you will:
1. take the medication according to the instructions.
2. do not take part in any other medical scientific research.
3. attend to hospital and study appointments

You will receive a research participant's card, we recommend to carry this with you. This card states that you are participating in this study. It will also tell you who to notify in case of an emergency. Show this card when you visit a doctor.

For the nailfold capillaroscopy, it is important that your fingers are at room temperature. We therefore ask you to be arrive at the clinics 15 minutes prior your appointment so that your hands can get used to this temperature. You should not wear nail polish or have a manicure just before the examination. You should also not smoke for at least 1 hour before the examination.

It is important that you contact the researcher:
- before taking any other medicine. Even if these are homeopathic medicines, natural medicines, vitamins and/or over-the-counter medicines.
- if you are hospitalised or treated in a hospital.
- if you suddenly experience health problems.
- If you no longer wish to participate in the study.
- if your contact details change.

Pregnancy and fertility
Women who are pregnant or breastfeeding cannot take part in this study. Women should also not become pregnant during the treatment. Only after at least 3 months after the last administration of medication pregnancy is regarded as safe. For men, their partner may not become pregnant during the entire study period. Please inform your partner about this. The treatments may have consequences for an unborn child. The researcher will talk to you about suitable contraceptives. Should you become pregnant during the study? Please inform the medical examiner immediately. If your partner becomes pregnant during the study, please ask her permission to tell the medical examiner. The pregnancy can then be monitored more closely.

Both men and women can become less fertile as a result of the treatment. We will discuss family planning with you and, if desired, the possibilities of freezing sperm and egg cells before the treatment starts.

6. Possible side effects

The treatments given in this study may cause side effects. Please contact the investigator if you experience any health problems. The main side effects for the study medication are listed below:

Side effects of cyclophosphamide
- nausea, mouth ulcers, hair loss

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- in- or subfertility, irritation of the bladder
- serious infections, severe bleeding
- increased long-term risk of leukaemia, lymphoma or bladder cancer

Side effects of G-CSF
- flu-like symptoms

Side effects of ATG (Anti-thymocyte Globulin):
- muscle and joint pain
- fever, flu-like symptoms
- rarely serum sickness (allergic reaction to foreign proteins, manifested by fever, rash and joint pain).

Side effects of MMF
- nausea, diarrhoea
- infections

At each visit, we will monitor for any side effects. If you experience any problems in between visits, you should inform the study doctor immediately. The regular study visits and blood tests are there for your safety.

7. Possible advantages and disadvantages

It is important that you balance the possible advantages and disadvantages before you decide to participate. ASCT, cyclophosphamide and MMF are all used in routine care in dcSSc. However, in this study we will use ASCT earlier in the disease course. The advantages of participating in this study may be that the disease progression is slowed down early and there will be fewer side effects. In addition, if there is a serious deterioration and the first treatment has insufficient effect, it may be possible to change treatment.
Disadvantages of participating in the study may be possible side effects of one of the above mentioned treatment strategies. Participation in the study also means that it takes extra time to fill in the questionnaires.

8. If you do not want to take part or want to stop the study

The decision to participate in the study is yours. Participation is voluntary. If you do not wish to take part, you will be treated for your condition as usual. You and your doctor will then decide on the treatment (immunosuppressive drugs, chemotherapy or ASCT). The researcher can tell you more about the treatment options available and their pros and cons.
If you do take part, you can always change your mind and stop, even during the study. You will then be treated according to usual care. You do not have to say why you want to stop. However, you must tell the researcher immediately. Discontinue your participation will not have any negative consequences for you, but stopping the treatment you have been assigned to may have negative consequences, such as worsening the disease. It is therefore important to discuss this with your doctor. The data collected up to this point will be used for the study.
If there is new information about the study that is important to you, the researcher will let you know. You will then be asked if you wish to continue to take part.

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9. End of the study

Your participation in the study will end when:
- all visits have been completed
- you decide to stop
- you become pregnant
- the end of the study has been reached
- the researcher feels it would be better for you to stop
- UMC Utrecht, the government or the reviewing medical ethics committee decide to stop the study.

The whole study ends when all participants have finished the follow-up period. After all data have been processed, the researcher will inform you of the main results of the study. The researcher will discuss how to continue your medical care.

10. Use and storage of your data

For this study, your personal data will be collected, used and stored. This includes data such as your name, age and data concerning your health. The collection, use and storage of your data is necessary to answer the questions posed in this study and to publish the results. We ask you for your permission to use your data.

Confidentiality of your data

In order to protect your privacy, your data will be coded. Your name and other data that can directly identify you are omitted. Only the key to the code can be used to trace the data back to you. The key to the code remains safely stored at the local research institute. The data sent to the principal investigator and other researchers will only contain the code, but not your name or any other data that could identify you. Also, reports and publications about the study do not contain any data that can be traced back to you.

Access to your data for control purposes

Some people at the research location may have access to your data. Also to the data without a code. This is necessary in order to check whether the research has been carried out properly and reliably. Persons who will have access to your data for control purposes are: the committee supervising the safety of the research, a monitor working for UMC Utrecht, national and international regulatory bodies, e.g. the Health Care Inspectorate. They will keep your data confidential. We ask your permission for this access.

Data retention period

By law, your data must be stored for 15 years at the research location and 15 years at the client's location. It will be stored to carry out new assessments in the course of this study, related to this study.

Retention and use of data for other research

Your data may still be of interest to other scientific research in the field of systemic sclerosis and stem cell transplantation after this research has ended. For this purpose your data will be stored for 15 years. You can indicate on the consent form whether you agree with this or not. If you do not agree, you can only participate in the current study.

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Information about unexpected findings
During the study, something unexpectedly may be found that is not important for the study but for you. If this is important for your health, you will be informed by your treating rheumatologist. You can then discuss with your specialist what needs to be done. We will ask your permission for this.

Withdrawing consent
You can always withdraw your permission for the use of your personal data. This applies to this study as well as to its storage and use in future studies. The research data that has been collected up until the moment you withdraw your permission will still be used in the research.

Transfer to countries outside the European Union (EU)
Your encrypted data will not be transferred to countries outside the EU.

More information on your rights regarding data processing
For general information about your rights regarding the processing of your personal data, please visit the website of the Dutch Data Protection Authority.
If you have any questions about your rights, please contact the person responsible for processing your personal data. If you have any questions or complaints about the processing of your personal data, we recommend that you first contact the research site. You can also contact the data protection officer of the institution or the Dutch Data Protection Authority.

Registration of the study
Information about this study can also be found on www.upsidetrial.com. This site does not contain any data that can be traced back to you. After the study, the website may show a summary of the study results.

11. Insurance for test subjects
Insurance has been taken out for everyone who participates in this study. The insurance covers any damage caused by the study.

12. Informing your GP
We will always send a letter to your GP and the specialist treating you to let them know you are taking part in the study. This is for your own safety.

13. Reimbursement for participation.
The treatment strategies investigated in the study will not cost you anything, as these are part of usual care and covered by your health insurance. You will not be paid for participating in this study. We will reimburse you for additional travel and parking costs.

14. Do you have any questions?
If you have any questions, please contact the researcher. For independent advice on participation in this study, you can contact our independent expert. He/she knows a lot about the study, but is not involved in it.
If you have any complaints about the study, you can discuss them with the researcher or your doctor, you can also contact the complaints officer.

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15. Signing the consent form

When you have had enough time to think, you will be asked to decide whether you wish to take part in this study. If you give your consent, we will ask you to confirm this in writing on the accompanying consent form. Your written consent indicates that you have understood the information and agree to participate in the study.

Both you and the researcher will receive a signed copy of this consent form.

Thank you for your interest and attention.

The UPSIDE study team

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Consent form

- I have read the information letter. I have also been able to ask questions. My questions have been answered sufficiently. I had enough time to make a decision.
- I know that participation is voluntary. I also know that I can decide at any time not to participate or to stop. I do not have to give a reason for this.
- I consent to inform my GP that I am participating in this study.
- I consent to the collection and use of my data for answering the research question as described in the information letter.
- I consent to forward my data/ in the context of this study as described in the information letter. The data will only be transferred in coded form, without my name and other personal details that can directly identify me.
- I consent to any random findings being discussed with me.
- I know that for the purpose of monitoring the study some people may have access to all my data. These people are mentioned in this information letter. I give permission for these people to have access to my data.
- I give permission for my GP and/or treating specialist to be informed of any unexpected findings that may be relevant to my health.
- I know that I am not allowed to become pregnant during the study until 3 months after the last administration of medication.
- The investigator has discussed the most suitable contraception for me.

□ I give
□ I give not

permission for my personal data to be stored for a longer period (up to 15 years) and used for future research in the field of systemic sclerosis.

□ I give
□ I give not

permission that they may contact me again for a follow-up study after this study.

I would like to participate in this study.

Name of participant: .....

Signature: ..... Date: .... /.... /.....

I declare that I have fully informed this patient about the research in question.

If, during the study, information becomes known that could influence the patient's consent, I will inform him/her in a timely manner.

Name researcher (or his representative): .....

Signature: ..... Date: .... /.... /.....

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,10
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9,10

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	1, 4,5, Table 1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,6

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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,7, Table 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4, 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5

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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-

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Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	suppl
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8, Table 3

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