Official Title:	A Phase II Multi-Center Study of High-Dose Cyclophosphamide and Antithymocyte Globulin Followed by Autologous Hematopoietic Cell Transplantation with Post Transplant Maintenance for the Treatment of Systemic Sclerosis
NCT Number:	NCT01413100
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	6/7/2023

- absence of microangiopathy (red cell fragmentation on peripheral smear, elevation in LDH in absence of other explanation, thrombocytopenia without other explanation)
- absence of hypertensive encephalopathy or retinopathy

Severe hypertension will operationally be defined as an increase in SBP or DBP associated with hypertensive encephalopathy or retinopathy +/- significant microangiopathy with worsening renal function.

Pediatric hypertension will be assessed and monitored by pediatric nephrologist.

Treatment

Pediatric hypertension will be treated by pediatric nephrologist.

Adult patients:

- Mild hypertension treatment in the absence of active GI disease (e.g. infectious gastroenteritis, graft vs. host disease involving gut, scleroderma-related diarrhea or constipation):

  Increase the dose of oral lisinopril by 2.5 mg/day every 2 days until target blood pressure is reached. The maximum lisinopril dose is 80 mg/day.

- Moderate hypertension treatment, or mild hypertension in the presence of active GI disease:

  IV enalaprilat 0.625 to 1.25 mg (recommend 0.625 mg dose unless pt over 80 kg) over 5-10 minutes. Additional doses of 0.625 to 1.25 mg may be administered every 6 hours as needed to control blood pressure, with initial target of returning systolic blood pressure at least half way to baseline level.

- Severe (no BP improvement within one hour):
  Treat initially as outlined for moderate hypertension and consult Nephrology. Administer a second dose IV enalaprilat (0.625 to 1.25 mg.) if severe and no response to initial dose within one hour. Evaluate if patients require admission to intensive care bed. Inform Rheumatology of change in patient status.

Subsequent doses of enalaprilat should be given every 12-24 hours, starting with half the administered daily dose every 12 hours IV, with anticipated decreasing dose as levels of the drug increase over time. The usual half-life of enalaprilat is 11 hours, i.e. steady state anticipated after about 2-3 days and has a renal clearance. Onset of action is usually within 15 minutes with the peak effect of the first dose up to 4 hours after administration. The duration of action is 12-24 hours. Doses as high as 5 mg/dose every 6 hours have been tolerated for up to 36 hours. Serum creatinine and potassium require monitoring. Although serum creatinine may increase while taking ACE inhibitors, maintaining a normal blood pressure is a higher priority in the setting of scleroderma renal hypertensive crisis. A calcium channel blocker such as amlodipine may be used as an adjunct, but ACE-inhibitors are essential for effective management of hypertensive crisis in scleroderma patients. Nephrology and Rheumatology consultants may vary treatment for hypertension based on the clinical status of the patient.

6. ASSESSMENTS OF SAFETY AND EFFICACY

6.1. Evaluations at Scheduled Study Visits

The visit schedule and evaluation procedures for the screening and baseline, treatment, and follow-up periods are found in Appendix E and F.

6.1.1. Clinical Review

Initial eligibility determination will be completed by the rheumatologist. The study subject will be asked to sign a screening consent in order to assess for protocol eligibility. It is recommended that the rheumatologist perform the following tests and assessments (also found in Appendix E) in order to determine the patient's potential eligibility. These tests may be completed and reviewed prior to scheduling the Baseline Screen at the transplant center.

1. Medical / general health history and physical examination including vital signs.
2. Modified Rodnan Skin Score (Appendix B)
3. Fertility counseling (See below).
4. Pulmonary evaluations including pulmonary function tests (including FVC, FEV1 and hemoglobin adjusted DLCO) pre and post bronchodilator and resting O_2 saturation by pulse oximetry (finger and forehead). O_2 saturation must be ≥ 92% by forehead oximetry.
5. Chest x-ray. High-resolution chest CT (HRCT) scan, if clinically indicated.
6. Cardiac evaluation including echocardiogram and electrocardiogram (ECG).
7. CBC with differential, comprehensive metabolic panel and CPK.
8. Renal evaluations include complete urinalysis (UA) and spot urine collection for evaluation of protein, creatinine, and protein:creatinine ratio. Creatinine clearance will be calculated using serum creatinine and the Cockcroft Gault Formula[g].
9. Infectious Disease Screen: Hepatitis B and C, HIV.
10. Anti-ds-DNA to rule out lupus or overlap syndrome.
11. Serum or urine beta hCG pregnancy test for female subjects.

Fertility counseling. Cryopreservation of sperm should be offered to fertile male subjects. Testing and storage of sperm should be undertaken prior to any treatment on study. Fertile female subjects should be specifically counseled as to risks of infertility and possibility of in vitro fertilization and storage of fertilized embryos.

6.1.2. Baseline Screen

Assessments done at this visit will determine study eligibility as outlined in the protocol, Section 4. These tests must be done within 30 days prior to start of mobilization. Procedures and assessments already performed at the Clinical Review visit need not be repeated so long as they are within 30 days prior to start of mobilization.

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[g] Cockcroft-Gault Formula: CrCl= [(140-age) x weight in kg] / [72 x serum creatinine], in women (x 0.85)

As described in section 4.1, patients must have failed a prior ≥ 4-month course of either MMF or cyclophosphamide before being eligible for the study (determined at ≥ 1 week before start of mobilization). "Failure" is defined as evidence of disease progression or absence of improvement. The response to prior MMF or cyclophosphamide will be assessed by the participating site study rheumatologist.

The study subject will be asked to sign a research treatment informed consent once all the eligibility criteria have been met. Baseline Screen procedures as outlined below can also be found in Appendix E.

The following tests and evaluations in the baseline screen should be performed within the 30 days prior to the start of mobilization (see exceptions below).

1. Research Subject Registration Form (Appendix P).
2. Medical / general health history and physical examination including vital signs.
3. Rheumatologist detailed history (Appendix G) and physical examination with attention to skin (including Modified Rodnan skin score [Appendix B]), heart, lung, skeletal muscle and joints.
4. Dental evaluation (with referral to oral surgeon for abscess or infection if indicated).
5. Questionnaires to assess for functional abilities, quality of life, productivity, and health care utilization. This includes the Scleroderma Health Assessment Questionnaire (SHAQ), Children's Health Assessment Questionnaire (CHAQ), UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Instrument 2.0 (UCLA SCTC G.I.T), and Short Form 36 Health Survey (SF-36), PROMIS-29 v 1.0, UCSD Healthcare Utilization Survey, Anchors survey, and Work Productivity Survey (WPS). Refer to Appendices H, I, J, K, L, Q, R and S.
6. Pulmonary evaluations:
    a. Pulmonary function tests (including FVC, FEV1 and hemoglobin adjusted DLCO), pre and post bronchodilator.
    b. Resting O2 saturation by pulse oximetry (finger and forehead). O2 saturation must be ≥ 92% by forehead oximetry.
    c. High-resolution chest CT (HRCT) scan
    d. 6 minute walk test
    e. Dyspnea as measured by the St. George's Respiratory Questionnaire (SGRQ Appendix M).
    f. BAL (bronchalveolar lavage): For patients who are eligible for the study based on pulmonary disease with alveolitis, BAL is recommended if high resolution chest CT (HRCT) does not show ground glass, NSIP (non-specific interstitial pneumonia) or UIP (usual interstitial pneumonia) abnormalities. BAL slides will be evaluated locally to confirm alveolitis. Microbiology will also be done locally if clinically indicated.
7. Cardiac evaluations:
    a. Electrocardiogram (ECG)
    b. Echocardiogram (including tricuspid annular plane systolic excursion)
    c. 24 hour Holter monitor- if nonsustained Ventricular Tachycardia detected, consider Automated Implantable Cardioverter Defibrillator (AICD) use.

d. Right heart catheterization (with fluid challenge) only if the DETECT criteria for pulmonary hypertension are met (See Appendix X DETECT criteria).

e. Thallium stress test or stress echocardiogram, if clinically indicated.

f. Cardiac MRI with gadolinium (with T1 mapping for assessment of diffuse myocardial fibrosis)

g. Cardiology consult is recommended for all patients. Patients with a history/presence of arrhythmia on chemical anti-arrhythmic(s) must have cardiac consult to ensure the subject could safely proceed with protocol requirements.

8. Upper GI endoscopy to rule out GAVE or other exclusionary pathology, with biopsy indicated for any abnormality visualized (unless the procedure was performed in past 6 months with normal result which specifically ruled out GAVE, and there are no signs/symptoms of GI disease or anemia at the time of screening). Any subject on a proton pump inhibitor even without symptomatology at the time of screening will have the procedure repeated unless done in the past 6 months. Complete Appendix U.

9. Unilateral bone marrow aspiration with pathology, flow cytometry and cytogenetics for subjects who have received prior chemotherapy (regardless of dose and route), radiotherapy and/or for any subject presenting with abnormal peripheral blood counts in order to rule out myelodysplastic syndrome.

10. CBC with differential, comprehensive metabolic panel and CPK

11. PT, PTT, INR

12. Pre-albumin (transthyretin)

13. ESR

14. Autoantibodies: rheumatoid factor (RF), ANA (by immunofluorescence), Scl-70 (topoisomerase I), Anticentromere antibodies, RNA Polymerase III, SSA, SSB, RNP, Sm, ACA (anti-cardiolipin antibody), and Anti-dsDNA.

15. Renal evaluations include complete urinalysis (UA) and spot urine collection for evaluation of protein, creatinine, and protein:creatinine ratio. Creatinine clearance will be calculated using serum creatinine and the Cockcroft-Gault formula[h].

16. Infectious Disease Screen: Hepatitis B and C and HIVas well as CMV, EBV, VZV and HSV.

17. Thyroid Function Screen: T4 and TSH.

18. Serum or urine pregnancy test (beta-hCG).

19. Gonadotropin Levels will include estrogen, FSH and LH for females and testosterone, FSH and LH for males.

20. Serum IgG, IgM, IgA.

21. Clinical lab for quantitative T cell, B cell, NK cell panel to include CD3, CD4, CD8, CD20, and NK cells (CD56).

[h] Cockcroft-Gault Formula: CrCl= [(140-age) x weight in kg] / [72 x serum creatinine], in women (x 0.85)

23. Serum NT-proBNP (N-terminal pro-brain natriuretic peptide)
24. Serum urate (uric acid)
25. CIBMTR co-morbidity index (Appendix N).
26. DETECT algorithm for screening of PulmonaryArtery Hypertension (PAH) Appendix (X).
27. Skin biopsies (See MOP for further details).

Because there may be unexpected delays between the baseline screen and the start of mobilization, certain tests may not need to be repeated. If there has been no clinical change in patient health status and no change in the dose regimen of pre-transplant immunosuppression, the following items (from the baseline screen evaluation list above) do not necessarily need to be repeated if they are obtained within a 90 day window prior to start of mobilization:

Dental evaluation
High resolution chest CT scan
Bronchoalveolar lavage (BAL)
Cardiac evaluations including EKG, echocardiogram, 24 hour Holter, right heart catheterization, thallium/ echocardiogram stress test, cardiac MRI, cardiology consult.
Pre-albumin (transthyretin)
Autoantibodies
Thyroid function screen
Gonadotropin levels
Serum IgG, IgM, IgA
Clinical lab for quantitative T, B, NK cells.
Serum NT-pro-BNP
Serum urate (uric acid)

The bone marrow aspiration, skin biopsies and upper GI endoscopy will be performed within 6 months of the start of mobilization.

6.1.3. Pre-mobilization Visit

1. Research blood draws (if not obtained previously, see MOP for further details).

6.1.4. Pre-transplant Visit

The Pre-transplant visit occurs after the Baseline Screen when eligibility has been determined and the detailed research treatment informed consent form has been signed.

The testing done at the Baseline Screen will serve as the baseline study assessments. However, certain eligibility testing (i.e., PFTs, echocardiograms) may need to be repeated at the discretion of the investigators as clinically indicated to ensure patient safety. Pre-transplant procedures as outlined below can also be found in Appendix E.

1. Medical / general health history and physical examination including vital signs.
2. Safety Laboratory Tests: CBC with differential, comprehensive metabolic panel, and serum or urine beta hCG for female recipients.

3. Post-mobilization evaluation and prior to conditioning:

   a. CMV pp65 antigenemia or CMV DNA (by PCR or hybrid capture)

   b. Respiratory Virus Screen: Screening for respiratory viruses should be done with nasal wash and throat swab for DFA, culture, or PCR (the latter by Centers able to perform the assay, as it is the most sensitive indicator). If the screen is positive, transplant should be delayed for 3-4 weeks until repeat cultures/PCR are negative. Subjects with URI symptoms after transplants should be rescreened as above.

   c. EBV PCR if baseline serology is negative.

6.1.5. Study Procedures from Time of Transplantation

Study procedures as outlined below can be found in Appendix F (Posttransplant Evaluations).

6.1.5.1. Clinical assessments at Month 1 (Day 28 ± 7 days)

The following evaluations will be performed at Month 1 (Day 28; +/- 7 days) after autologous stem cell transplant.

1. Detailed physical examination to include mRSS.
2. Quantitative Immunoglobulins (Serum IgG, IgM, and IgA).
3. CBC with differential and comprehensive metabolic panel.
4. CMV and EBV monitoring as described in section 5.3.5.
5. Clinical lab for quantitative T cell, B cell, NK cell panel to include CD3, CD4, CD8, CD20, and NK cells (CD56).
6. Research labs (see MOP for further details).

6.1.5.2. Clinical assessments at Week 8 to 12 (prior to start of MMF), Week 26 and then annually Year 1, 2, 3, 4 and 5 (+/- 4 weeks)

The following clinical assessments will be performed after transplant at the times above or as indicated:

1. Detailed physical examination to include mRSS.
2. PFTs with DLCO and FVC.
3. High-resolution CT of the chest (years 1, 2, 3, 4 and 5).
4. Dyspnea as measured by the St. George's Respiratory Questionnaire.
5. Pulse oximetry finger and forehead (years 1, 2, 3, 4 and 5).
6. 6-minute walk test (6 MWT).
7. Cardiac evaluations: ECG and echocardiogram (years 1, 2, 3, 4 and 5).
8. Questionnaires to include functional ability QOL, productivity, and healthcare utilization questionnaires (SF-36, SHAQ, UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Instrument 2.0, PROMIS-29 v 1.0, UCSD Healthcare Utilization Survey, Anchors survey, and Work Productivity Survey). Weeks 12, 26 and years 1, 2, 3, 4, and 5.
9. CBC with differential and comprehensive metabolic panel.

10. Renal evaluations include complete urinalysis (UA) and spot urine collection for evaluation of protein, creatinine, and protein:creatinine ratio. Creatinine clearance will be calculated using serum creatinine and the Cockcroft-Gault formula[i].
11. Quantitative Immunoglobulins (Serum IgG, IgM, and IgA). Clinical lab at weeks 12, 26 and years 1, 2, 3, 4, and 5.
12. Autoantibodies: rheumatoid factor (RF), ANA (by immunofluorescence), Scl-70 (topoisomerase I), Anticentromere antibodies, RNA Polymerase III, SSA, SSB, RNP, Sm, Anti-dsDNA, and ACA (anti-cardiolipin antibody); (years 1, 2, 3, 4 and 5).
13. Clinical lab for quantitative T cell, B cell, NK cell panel to include CD3, CD4, CD8, CD20, and NK cells (CD56) at weeks 12 and 26 and annually years 1, 2, and 3.
14. Research blood draws (week 12, 26 and years 1, 2, 3, 4, and 5; see MOP for further details).
15. Skin biopsies (years 1 and 2 only; see MOP for further details).
16. Mycophenolic acid (MPA) trough (pre-dose) blood level -- clinical lab at 26 weeks and 2 years.

6.1.5.3. Evaluation at the early withdrawal visit

The Endpoint Evaluation (year 5) is the study primary endpoint evaluation visit and will also be done as the Study Withdrawal Visit.

6.1.5.4. Early withdrawal visit

In case of early withdrawal from the study prior to year 5, subjects will be asked to return for a study withdrawal visit. All scheduled exams, procedures, and laboratory tests will be performed at this visit as if it were the endpoint evaluation visit (year 5).

7. SAFETY MONITORING AND REPORTING

7.1. Overview

Safety data will be reported to the coordinating site recorded on forms specifically designed for this purpose. All safety data will be reviewed monthly by the principal investigators and at least annually by the Data Safety and Monitoring Board (DSMB). The DSMB can recommend that any participant be withdrawn from the study and/or that the study be terminated because of safety findings.

7.2. Adverse Event Grading

Adverse Events will be graded according to the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4. The full text of the NCI CTCAE is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

7.3. FHCC IRB Policies and Forms for Reportable Events

As FHCC is the coordinating center, all reportable adverse events at FHCRC and participating sites will be collected and reported according to the FHCC reporting guidelines. Definitions, instructions and forms associated with reportable events can be found on the FHCC's Institutional Review Office (IRO) extranet website: http://extranet.fhcrc.org/EN/sections/iro/irb/ae.html.

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[i] Cockcroft-Gault Formula: CrCl= [(140-age) x weight in kg] / [72 x serum creatinine], in women (x 0.85)

Additional information about non-compliance and unanticipated problems can be found on the FHCC's IRB Policy and Procedures extranet website:
http://extranet.fhcrc.org/EN/sections/iro/irb/policy/index.html.

All investigators must report adverse events to their respective IRB as locally mandated by them.

7.4. Tracking of Events

Adverse events will be collected from the time the subject starts mobilization until day +365 after autologous HCT or until he/she prematurely withdraws from the study.

In the context of the underlying disease or the high-dose immunosuppressive regimen, grade 2 adverse events are not informative regarding the safety of this regimen. Therefore only grades 3, 4 and 5 adverse events will be tracked.

From the start of mobilization until day +100 after autologous HCT, grades 3, 4 and 5 adverse events will be captured. There are some exceptions that are outlined in Appendix O.

Grades 3 and 4 adverse events in organs involved with the SSc (e.g. lung, heart, kidney, gastrointestinal tract and skin) will be reported only if they represent a significant change from baseline (pre-transplant) status.

By day +100, it is expected that patients will have recovered from the regimen-related toxicities associated with high-dose chemotherapy. Therefore only Grades 4 and 5 will be reported from day +100 through day +365 after transplant.

After day +365, patients will be followed for disease response only since it is expected that events after this time point are disease-related and not treatment-related.

All deaths that occur throughout the course of the study, regardless of cause, will be reported to the IRB. Those occurring prior to day +100 will be reported in an expedited fashion and those occurring after day +100 will be reported with the annual renewal.

There are some categories of adverse events that will not be considered reportable events due to the lack of relevance to the evaluation of the protocol treatment (see Appendix O).

Certain adverse events are expected after high-dose immunosuppressive therapy and autologous HCT and are not informative and therefore will only be reported if they are $\geq$ Gr.4 from the start of mobilization until day +28. During this same period, there are some Gr. 3 and 4 adverse events that will not be reported at all (see Appendix O).

From day +29 until day +100, some grades 3 and 4 adverse events of the blood and lymphatic system will not be reported (see Appendix O).

7.5. Reporting to the Coordinating Center

As FHCC is the coordinating center, reportable events occurring at FHCC and participating sites will be collected by the FHCC PI and / or study coordinators and reported to the FHCC IRB. The trial coordinators at collaborating centers or the local PI's will verbally report all events requiring expedited reporting to the coordinating center (including but not limited to, all patient deaths regardless of cause occurring during the first 100 days post transplant) within 72 hours of learning of the event and an official report of the event must be faxed to the coordinating center within seven days utilizing the appropriate FHCC forms. Items that are considered questionable, inconsistent, or unexplained (including use of medications for what may be an unreported AE) will be referred to the site primary investigator for confirmation and response.

After the FHCC IRB has reviewed a reportable event, it will be disseminated to all the participating site investigators.

Reportable event follow-up information must be submitted to the coordinating center as soon as the relevant information is available.

7.6. DSMB Review

The DSMB will review any events as requested by the investigators of the coordinating center. They will review a listing of all AEs and SAEs reported to the coordinating center at least annually. Further, the DSMB will be informed of all SAEs that are determined by the Principal Investigators to be serious, unexpected and related to the investigational treatment. The DSMB will convene after every 5th patient has been enrolled or annually, whichever comes first. The DSMB may also convene at any time an AE occurs requiring DSMB notification.

7.7. Monitoring the Safety of Participants During the Progress of the Trial

This is a multi-center clinical trial that is monitored by the principal investigator (PI), the Protocol and Data Monitoring Committee (PDMC), the Data Safety and Monitoring Board and the Institutional Review Board (IRB) at the Fred Hutchinson Cancer Center (FHCC). Adverse events are reviewed with the PI on an ongoing basis in weekly meetings. The adverse event reporting in this clinical trial will follow the FHCC Guidelines for adverse event reporting http://extranet.fhcrc.org/EN/sections/iro/irb/ae.html.

For patients not being cared for at FHCC, the outside facilities will communicate with the coordinating center PI and study coordinator for these reporting purposes. The PI for this study is responsible for adverse event reporting and summarizing reports of the toxicities with the annual renewal. The stopping rules provide an additional safeguard for adverse event analysis and reporting in this protocol. All collaborating PI's will have fulfilled all NIH requirements for training in human subjects' protection.

All patients on study will be considered in the safety analysis. Although previous experience exists for high-dose therapy and autologous HCT for SSc, adverse events and transplant related mortality (TRM) will be closely monitored.

Rheumatologists that are co-investigators on this study will evaluate the disease responses. The potential safety and efficacy of the autograft approach will be evaluated by follow-up of patients over 5 years from the time of transplant.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1. Sample Size

This is a multi-center, single-arm Phase II study with the overall objective of demonstrating the potential for efficacy and safety of high-dose immunosuppressive therapy and transplantation of an unmanipulated autologous hematopoietic cell graft. The proposed sample size for this protocol is 30 transplanted subjects. Subjects who enroll in the study but fail to mobilize or withdraw from the study for other reasons prior to transplantation will be replaced in the study.

The sample size of 30 was not chosen based on traditional power analysis, rather it was chosen as a compromise between a number that we feel can be accrued in a reasonable time frame and a number that is large enough to provide a reasonably precise estimate of our primary endpoint (EFS at 5 years). Namely, if EFS at 5 years is 75%, we can be 80% confident that the estimated EFS is within 0.10 of the true EFS. Based on previous studies in this population, we will define the current approach as being

worthy of further study if the observed 5-year EFS is 80% or greater. If the true 5-year EFS is 70%, then the probability of observing an EFS of 80% or better among 30 patients (24 or more event-free survivors to 5 years) is .16. If the true 5-year EFS is .85, then the probability of 24 or more event-free survivors to 5 years is .85.

The number of subjects that can be included on this Phase II study is limited by:

1. SSc is an infrequently occurring disease.
2. The intensive resource utilization for treatment of study subjects and for monitoring of disease activity and immune reconstitution/mechanistic studies on study.

Although the primary objective is to estimate the 5-year durability of disease stabilization in SSc subjects after high-dose cyclophosphamide/ATGAM and autologous HCT, the evaluation of shorter-term secondary endpoints will also be considered when deciding whether to move to a Phase III trial.

8.2. Statistical Considerations

The analyses for this open-label, single-arm study will focus on characterizing outcomes in the single treatment arm.

8.2.1. Primary Analysis

The primary endpoint for this study is EFS at 5 years following HCT. An event is defined as (a) death from any cause in the 5 years after transplant or (b) disease activity during the 5-year period, as further defined in Section 3.1. For the primary analyses, EFS over the 5-year period following transplant will be treated as a binary outcome. The initial assessment for disease progression will take place at 6 months following transplantation and continue through the follow-up period.

8.2.2. Secondary Analysis

Secondary endpoints include overall survival, EFS, and non-progression mortality and disease progression. Other secondary endpoints are detailed in section 3.1.2. Each of these will be assessed using appropriate time-to-event methods. Historical controls from studies in which subjects underwent CD34-selection of the autologous hematopoietic cell grafts will be used as a comparison to estimate if there is an increased risk of disease relapse without CD34-slection.

8.2.3. Stopping Rules

If there is sufficient evidence to suggest that the true non-progression mortality by 3 months exceeds 10%, the protocol will be suspended for safety concerns. Sufficient evidence will be taken to be an observed proportion of nonrelapse mortality failures with an associated lower one-sided 80% confidence limit in excess of 0.10. Such limits will be examined after every 5th enrolled patient is evaluable. The following proportions would trigger such a rule: 2/5, 3/10, 3/15, 4/20, 5/25, 5/30. If the true probability of non-progression mortality is 5%, then the probability of study suspension after 20 or 30 patients is approximately .05 and .06, respectively. If the true probability is 25%, then the probability of study suspension after 20 or 30 patients is approximately .83 and .92, respectively (probabilities estimated from 5,000 simulations). In addition to this rule for non-progression mortality, the study will also be suspended for lack of efficacy once a 7th failure with respect to the EFS endpoint is observed, as such an occurrence would preclude the possibility of achieving the primary objective, namely an observed 5-year EFS of 80% or higher among the 30 patients. The study can also be suspended at any time based on concerns raised by the DSMB, which will meet regularly to evaluate the progress of the study.

8.2.4. Multi-Center Studies

This study will consist of 5-6 transplant/rheumatology centers. End points will be summarized overall and by transplant site.

8.2.5. Missing Data

Standard procedures will be used to ensure that data are as complete and accurate as possible. In the analyses, a full accounting will be made for all data items. In the primary analysis, a subject with missing follow-up data will be considered lost to follow-up at the time of last contact if no episode that might potentially meet the definition of an event for primary analysis has begun in that subject. Every effort will be made to obtain sufficient follow-up data to determine whether any ongoing episode that might have met the definition of a primary analysis event did in fact meet the definition. If the needed follow-up data cannot be obtained, any such ongoing episode of less than 3 months' duration will be considered a primary analysis event as of the time it would have reached a duration of 3 months. Should insufficient data on disease-progression components of event-free survival be obtained for any subject to establish whether that subject has met the primary endpoint of event-free survival with respect to the disease-progression components, the mortality data from that subject will be imputed as the EFS outcome for that subject. While this procedure will underestimate the probability of EFS, the number of subjects with a missing primary endpoint is expected to be minimal. Should any subjects have a primary missing endpoint, sensitivity analyses will be conducted that account for the range of outcomes that could have been exhibited by those subjects to evaluate whether the results of the analyses are robust to the imputation procedure. Details of the analytic approach and of the approaches used to address missing data for the secondary outcome variables will be provided in the Statistical Analysis Plan.

8.2.6. Changes to the Statistical Analysis Plan

The principal features of the design of this study and of the plan for statistical analysis of the data are outlined in this protocol. Any changes in these principal features will require a protocol amendment. Changes to the protocol may include the addition of a maintenance therapy after transplant if new data becomes available during the clinical trial regarding an excess risk of disease relapse after high-dose therapy and autologous HCT.

9. ACCESS TO SOURCE DATA AND DOCUMENTS

Each participating site will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, each site must permit authorized representatives of the sponsor(s), the coordinating center, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. Participating sites will normally be notified in advance of auditing visits.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented. Each investigator is required to ensure that all source documents are sent deidentified to the coordinating center for every subject entered in the trial. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies.

However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by the NIH.

The coordinating center is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

Data will be obtained from a variety of sources including laboratory notebooks, automated instrument output files, and clinical subject charts. Data from these source materials will be sent to the coordinating center. Data will be provided using the subject's screening or enrollment number or initials. Subjects will provide demographic information such as race, ethnicity, and birth date.
Data collected by the coordinating center will be held in the strictest confidence, and are protected from access that could reveal personally identifying information about any subject in the trial.

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APPENDICES

Appendix A
Infection Definition and Infectious Complications

A. DEFINITION OF INFECTIONS

1. Bacteremia
   Bacteremia will be defined as the occurrence of one or more positive blood cultures with any organism regardless of associated symptoms. A bacteremia event will be defined by the occurrence of a positive blood culture, even if it contains multiple organisms (polymicrobial). All positive cultures will be recorded. *Micrococcus* or *Corynebacterium* species or aerobic diphtheroids (other than JK) may be excluded as a laboratory contaminant after consultation with Infectious Disease.

2. Septicemia
   Septicemia will be defined as bacteremia in conjunction with:
   a. Hypotension [systolic blood pressure (BP) < 90, and/or a diastolic BP < 60 (definitions of hypotension in children include: 2-6 years old, < 90 and/or 60)] which occurs within 24 hours of the positive culture.
   b. Disseminated intravascular coagulation [decreased fibrinogen and increased fibrin degradation product] which is documented within 24 hours of the positive culture.

3. Fungemia
   Fungemia will be defined as the occurrence of one or more positive blood cultures with any fungus regardless of associated symptoms.

4. Fever
   Fever will be defined as one oral temperature > 38.5 C or two or more > 38 C in one 12-hour period. Fever associated with infection will be defined as fever in association with one or more of the categories: 1.0, 2.0, 3.0, or 5.0.

5. Local/Organ-specific Infection
   Cellulitis will be defined by:
   a. Localized erythema and/or swelling and a positive aspirate or biopsy culture of the area for an organism other than coagulase-negative Staphylococcus.
   b. Local erythema and swelling associated with a positive blood culture (or two or more positive blood cultures when the organism is coagulase-negative Staphylococcus) in the absence of a positive local culture.

6. Pneumonia
   Infectious pneumonia will be defined as a new or progressing pulmonary radiographic infiltrate (by retrospective review) and identification of an infectious pathogen by BAL, bronchial washing or lung tissue. This will include:
   a. Bacterial pneumonia will be diagnosed by identifying a culture yielding moderate to many colonies of a single or predominant organism or ≥ 10^3/ml for a pure culture or ≥ 10^5/ml for a mixed culture, or by the identification of *Legionella* or mycobacterial species on bronchoalveolar lavage (BAL), or any organism on biopsy tissue.
   b. Fungal pneumonia will be diagnosed by the identification of a culture yielding moderate to many colonies or ≥10^3/ml of *Candida* or septate hyphal elements (e.g., Aspergillus) with > one colony identified on culture in BAL, or any septate hyphal fungi histologically on biopsy tissue.

c. Pneumocystis pneumonia will be diagnosed by the presence of Pneumocystis on BAL or biopsy tissue.
d. Viral pneumonia will be diagnosed by the presence of a positive culture, FA or characteristic viral inclusions on BAL or biopsy tissue.

Infectious pneumonia can be further defined as focal (one lung zone), diffuse (> one lung zone), or interstitial by retrospective chest radiograph review. A zone is defined as the top or bottom 50% of each hemithorax, such that the right and left lung are each divided into 2 zones (upper and lower).

7. Idiopathic pneumonia syndrome (IPS) will be defined by a new or progressive diffuse infiltrate on chest radiograph (by retrospective review) and examination of lung tissue or BAL that has a negative evaluation for microbiologic causes.

8. Other organ site-specific infection
   a. Esophagus requires histologic evidence of invasive hyphal elements. Bacterial esophagitis will not be included.
   b. Liver, spleen, kidneys, brain will require aspiration or biopsy evidence for infection.
   c. Sterile closed space infection (e.g., CNS, peritoneal, pleural)
   d. A right atrial catheter infection is defined as local erythema at the exit site with purulent drainage positive for a single or predominant organism and/or inflammation (including redness and tenderness) at least 1 cm or more up the line from the exit site or at any other point along the tract with an associated positive blood culture in the absence of a positive local site culture.
   e. Urinary tract infection will be defined as a urine culture with ≥ 50,000 colonies of a single organism with or without symptoms.

   All definitions above involve the presence of a positive culture as essential for the definition of infection. Tissue histology may be used in instances where the culture is negative for the following:
   - Any positive FA for Legionella or herpes viruses (or other organism-specific monoclonal antibody)
   - Any separate or non-septate hyphal elements
   - Pneumocystis
   - Toxoplasma gondii
   - Fastidious bacteria such as Actinomycetes
   - Viral infections with diagnostic inclusion CMV, HSV, and adenovirus.

9. Recurrent Infection
   Recurrent infection will be defined as infection which is documented > 7 days after the discontinuation of appropriate antibiotics.

10. CMV Seropositivity
    Pretransplant CMV antibody testing is to be obtained at or before day -14 pretransplant. Test results are seropositive unless subjects are seronegative by EIA determination or have titers < 1:8 by complement fixation or latex agglutination assays.

11. Clinical Infection
    Clinical infection will be defined as an infection diagnosed with clinical features without identification of an organism.

B. EVALUATION OF FEVER AND DOCUMENTATION OF INFECTION

1. Fever in a posttransplant patient may be a serious development even in an absence of neutropenia. Fever should not be ascribed to drug reactions, graft-versus-host-disease or non-infections etiologies until infections have been carefully excluded.

2. Fever workups should include:
    a. Chest X-Ray (if indicated)
    b. Blood culture
    c. Urine and throat culture
    d. Careful physical examination.

3. Empiric intravenous antibiotic coverage may be indicated before culture results return if the clinical status warrants treatment.

4. Documentation of a clinical infection should include a diagnosis, clinical presentation, imaging studies (if available), therapy administered, and response to therapy.

Appendix B
Modified Rodnan Skin Score

Modified Rodnan Skin Score
Calculated by summing the scores from all evaluated anatomic areas.
A. Evaluation skin thickness rated by clinical palpation:
0 = normal skin thickness
1 = mild skin thickness
2 = moderate skin thickness
3 = severe skin thickness (inability to pinch skin into a fold)
B. Surface of anatomic areas evaluated *n* = 17

Patient: _____Date of exam:_____

Score			
Face		0-3	_____
Anterior Chest		0-3	_____
Abdomen		0-3	_____
Fingers	Rt.	0-3	_____
	Lt.	0-3	_____
Dorsum of Hands	Rt.	0-3	_____
	Lt.	0-3	_____
Forearms	Rt.	0-3	_____
	Lt.	0-3	_____
Upper Arms	Rt.	0-3	_____
	Lt.	0-3	_____
Thighs	Rt.	0-3	_____
	Lt.	0-3	_____
Lower Legs	Rt.	0-3	_____
	Lt.	0-3	_____
Dorsum of Feet	Rt.	0-3	_____
	Lt.	0-3	_____
TOTAL		**0-51**	_____

"Skin Thickness Score in Systemic Sclerosis: An Assessment of Interobserver Variability in 3 Independent Studies", Clements et al The Journal of Rheumatology 1993, 20:11,1892-1896.

Physician Signature: _____/Date_____

Appendix C
WHO/NYHA Functional Assessment of Pulmonary Hypertension

The following WHO Functional Assessment for Pulmonary Hypertension is modified after NYHA functional classification):

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

Class II: Patients with pulmonary hypertension resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

(Rich et al., WHO Symposium on PPH, Evian, France, 1998.)

Appendix D
New York Heart Association Classification of Heart Disease

Functional Capacity	Objective Assessment
Class I. Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix E
Screening and Pretransplant Evaluations
(Section 6.1)

Evaluations at the Screening and Pre-Treatment Visits	Clinical Review[a]	Basline screen[b]	Pre-mobilization[c]	Pre-transplant[c]
Visits	-4	-3	-2	-1
Consent	X	X		
Medical/General Health History[d]	X	X		X
Physical Exam and Vitals	X	X		X
Dental Evaluation		X		
Fertility Counseling	X			
Marrow Aspiration [e]		X		
mRSS[t]	X	X		
Pulmonary Evaluations				
Pulmonary Function Tests[f]	X	X		X[r]
O_2 saturation levels[f]	X	X		
Chest x-ray	X[r]			
High-resolution Chest CT-Scan	X[r]	X		
Bronchoalveolar Lavage[s]		X		
6 Minute Walk Test		X		
SGRQ (questionnaire)		X		
Cardiac Evaluations[g]				
ECG	X	X		X[r]
Echocardiogram	X	X		
24-hour Holter monitor		X		
DETECT criteria, R heart catheter[w]		X		
Cardiac MRI, + additional studies[x]		X		
Gastrointestinal Evaluation				
Upper GI endoscopy [u]		X		
Questionnaires				
CIBMTR Co-Morbidity Indices		X		
SHAQ/CHAQ		X		
UCLA SCTC GIT 2.0		X		
SF-36		X		
PROMISE-29 v 1.0		X		
UCSD Health Care Utilization		X		
Anchors survey		X		
WPS		X		
Laboratory Testing				
CBC w/diff, metabolic panel[h]	X	X		X
Renal Function Measures[j]	X	X		
CPK	X	X		
Pre-Albumin (transthyretin)		X		
Autoantibodies[j]		X		
Thyroid Function Screening [k]		X		
PT, PTT, INR		X		
Anti-ds-DNA[l]	X			
ESR		X		
Infectious Disease Screen[m]	X	X		
Serum IgG, IgM, IgA		X		
Serum or urine beta hCG	X	X		X
Gonadotropin Levels [n]		X		
CMV[q]				X
Quantitative T cell[o]		X		
Respiratory Virus Screen[p]				X
Research Blood Draws[v]			X	
Skin biopsies[v]			X	

[a] Clinical Review assessments will be conducted by the rheumatologist. This will establish potential initial eligibility prior to scheduling the Baseline Screen.

[b] Baseline Screen assessments will determine protocol eligibility as outlined in Section 4. These tests should be performed within 30 days of start of mobilization (exceptions to the 30 day limit are noted in Section 6.1.2)

[c] Pre-mobilization and pre-transplant assessments occur after protocol eligiblilty is determined.

[d] Medical History at the Baseline screen will include a description of the SSc medical history. A General Health history will be obtained at the Clinical Review visit and updated at the subsequent Baseline screen and Pre-Treatment Visits.

[e] Unilateral marrow aspiration for pathology, flow cytometry and cytogenetics to rule out myelodysplastic syndrome as indicated.

[f] Pulmonary function tests should include FVC, FEV1 and hemoglobin adjusted DLCO pre and post bronchodilator. Resting O_2 saturation by pulse oximetry: finger and forehead. O2 saturation must be ≥ 92% by forehead oximetry. PFT's should be completed in the same PFT lab throughout the study.

[g] Cardiac evaluations includes ECG and echocardiogram. A right heart catheterization may be required to confirm PAH. History/presence of arrhythmia (even controlled) on chemical anti-arrhythmic(s) must have cardiac consult to ensure the subject could safely proceed with protocol requirements. 24-hr Holter monitoring may be required.

[h] Comprehensive metabolic panel includes sodium, potassium, chloride, total CO_2, glucose, blood urea-BUN, creatinine, total protein, albumin, total bilirubin, AST/SGOT, ALT/SGPT, alkaline phosphatase, calcium, LDH.

[l] Renal Function Measures include complete urinalysis (UA) and spot urine collection for evaluation of protein, creatinine, protein:creatinine ratio. Creatinine clearance is calculated using serum creatinine by Cockcroft Gault.

[j] Autoantibodies include Rheumatoid factor, ANA, Scl-70, anticentromere antibodies, poll III Ab (RNA polymerase III antibody), SSA, SSB, RNP, Sm, Anti-dsDNA, ACA.

[k] Thyroid Function Screening will include T4 and TSH.

[l] Anti-dsDNA is done at 1st Phase Screening to rule out lupus or overlap syndrome.

[m] Infectious Disease Screen includes Hep B and C and HIV at Clinical Review. Baseline Screen Phase includes: Hep ,B, and C, HIV, as well as CMV, EBV, VZV and HSV.

[n] Gonadotropin levels will include estrogen, FSH and LH for females and testosterone, FSH and LH for males.

[o] Clinical lab for quantitative T cell, B cell, NK cell panel to include CD3, CD4, CD8, CD20, and NK cells (CD56).

[p] ***Post mobilization:*** Respiratory Virus Screen: Screening for respiratory viruses (RSV, parainfluenza, and influenza) should be done with nasal wash and throat swab for DFA, culture, or PCR (the latter by Centers able to perform the assay, as it is the most sensitive indicator). If the screen is positive, transplant should be delayed for 3-4 weeks until repeat cultures/PCR are negative. Subjects with URI symptoms after transplant should be rescreened as above. CMV pp65 antigenemia or CMV DNA (by PCR or hybrid capture)

[q] ***Post mobilization:*** CMV pp65 antigenemia or CMV DNA (by PCR or hybrid capture)

[r] If clinically indicated.

[s] BAL: For patients who are eligible for the study based on pulmonary disease with alveolitis, BAL is required only if HRCT does not show ground glass abnormalities or NSIP or UIP. BAL slides will be evaluated locally to confirm alveolitis. Microbiology will also be done locally if clinically indicated.

[t] Modified Rodnan skin score should be performed by the same physician throughout the study.

[u] Upper GI endoscopy to rule out GAVE or other exclusionary pathology, with biopsy indicated for any abnormality visualized (unless the procedure was performed in past 6 months with normal result which specifically ruled out GAVE, and there are no signs/symptoms of GI disease or anemia at the time of screening. Refer to protocol section 6.1.2.12 for details.

[v] Research blood draw and skin biopsy may be obtained during baseline screen.

[w] DETECT criteria: see appendix X. Right heart catheterization with fluid challenge if DETECT criteria for pulmonary hypertension are met.

[x] Cardiac MRI with gadoliniuim (with T1 mapping for myocardial fibrosis), additional tests may include: stress thallium/echocardiogram stress test.

Cardiology consult recommended for all patients.

Appendix F
Post transplant Evaluations

Visits	Month 1[a]	Week 8-12	Week 26	Year 1	Year 2	Year 3	Year 4	Year 5
Clinical Evaluations[b]								
Physical Exam and Vitals	X	X	X	X	X	X	X	X
mRSS	X	X	X	X	X	X	X	X
Pulmonary Evaluations								
Pulmonary Function Tests		X	X	X	X	X	X	X
O_2 saturation		X	X	X	X	X	X	X
High-resolution Chest CT scan				X	X	X	X	X
6 Minute Walk Test		X	X	X	X	X	X	X
SGRQ		X	X	X	X	X	X	X
Cardiac Evaluations								
ECG				X	X	X	X	X
Echocardiogram[c]				X	X	X	X	X
Questionnaires								
SF-36		X	X	X	X	X	X	X
SHAQ/CHAQ		X	X	X	X	X	X	X
UCLA SCTC GIT		X	X	X	X	X	X	X
Promis-29		X	X	X	X	X	X	X
UCSD Healthcare utilization		X	X	X	X	X	X	X
Anchors survey		X	X	X	X	X	X	X
WPS		X	X	X	X	X	X	X
Laboratory Testing								
CBC w/diff, comprehensive metabolic panel[d]	X	X	X	X	X	X	X	X
Renal Function Measures[e]		X	X	X	X	X	X	X
CMV and EBV[f]	X	X	X					
Serum IgG, IgM, IgA[g]	X	X	X	X	X	X	X	X
Autoantibodies				X	X	X	X	X
Vaccinations/Vaccine Antibody Titers[i]			X	X	X			
Research Blood Draws	X	X	X	X	X	X	X	X
Quantitative T cell[h]	X	X	X	X	X	X		
Skin biopsies				X	X			
Mycophenolic acid (MPA) level			X		X			

[a]Day 0 of the Clinical Evaluation is the day of Autologous HCT.

[b]Visit window is +/- 4 weeks except for the day 28 visit which is +/- 7 days of the scheduled visit.

[c]Echocardiograms will be performed to assess ejection fraction and pulmonary artery hypertension.

[d]Comprehensive metabolic panel includes sodium, potassium, chloride, total CO_2, glucose, blood urea-BUN, creatinine, total protein, albumin, total bilirubin, AST/SGOT, ALT/SGPT, alkaline phosphatase, calcium, LDH.

[e]Renal Function Measures include complete urinalysis (UA) and spot urine collection for evaluation of protein, creatinine, and protein:creatinine ratio. Creatinine clearance will be calculated using serum creatinine and the Cockcroft Gault formula.

[f]CMV and EBV monitoring and treatment will be done according to section 5.3.5.

[g]Quantitative Immunoglobulins (Serum IgG, IgM, and IgA) levels will be measured at the regularly scheduled visits.

[h]Clinical lab for quantitative T cell, B cell, NK cell panel to include CD3, CD4, CD8, CD20, and NK cells (CD56) at weeks 4, 12 and 26 and annually years 1, 2, and 3.

[i]Vaccinations and vaccine antibody titers: Vaccinations will be performed according to institutional practice.

[j]Modified Rodnan skin score should be performed by the same physician throughout the study.

Appendix G
Guidelines for Detailed Systemic Sclerosis Medical History

1. History of collagen vascular disease manifestations:
   - Age at diagnosis and family history.
   - Age at onset of Raynaud's phenomenon and precipitating factors including exposure to vinyl chloride, presence or absence of digital ulcer, presence or absence of calcinosis, dates and results of nail capillaroscopy.
   - History of auto antibody states specifically the anticentromere antibody and Scl-70. Note, specifically when first tested, most recent tests and results. Record information on the presence or absence of other auto antibodies if available.
   - History of arthritis specifically joints involved and treatment

2. Treatment history and compliance:
   - Dates and amounts of therapy with steroids, ATG, CSP, D-penicillamine or other.
   - Frequency of physician visits and hospitalizations per year.
   - Compliance with prior medical treatment, clinic visits, and appointments.

3. Skin:
   - History of truncal and acral skin involvement with dates of onset, functional limitations secondary to loss in range of motion, rate of change in loss of function.
   - Presence or absence of sclerodactyly, calcinosis and telangiectasia. Note locations of calcinosis and telangiectasia.
   - Dates and results of skin biopsies.

4. Gastrointestinal tract:
   - History of dysphagia, heartburn, esophageal reflux, hiatus hernia and strictures.
   - Dates and results of esophageal manometry, transit time, barium studies or upper GI endoscopy.
   - History of weight loss, diarrhea, episodes of distention or pseudo-obstruction.
   - Dates of use of hyperalimentation.
   - Results of studies for abnormalities of the small bowel and for malabsorption and bacterial overgrowth in the GI tract, e.g., barium follow-through, ^{14}C xylose breath test, 3-day fecal fat and other.
   - History of constipation secondary to sigmoid/rectal hypomotility.

5. Cardiovascular system:
   - Dates of onset and treatment for symptoms related to cardiac dysfunction including dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, palpitations and atypical chest pain. If present, this would support the presence of myocardial fibrosis, pericarditis, conduction abnormalities or pulmonary hypertension. Note any prior cardiac studies including MUGA scan.
   - Dates of onset and treatment for hypertension if present.

6. Pulmonary:
   - Dates of onset of dyspnea, cough and abnormalities of chest x-ray.
   - Dates of and results of previous arterial blood gases, pulmonary function studies, bronchoalveolar lavage and high-resolution CT scan of the chest.
   - Dates and results of lung biopsy.
   - Dates and types of treatment for pulmonary disease.

7. Kidney:
   - Dates of onset of azotemia and proteinuria if present including any prior assessment of glomerular filtration rate.
   - History of dialysis or significant episodes of renal dysfunction.
   - Dates and results of prior renal biopsies.
   - Dates and types of treatment for renal disease.

8. Liver:
   - Dates of onset of hyperbilirubinemia and diagnosis if available.
   - Dates and results of prior liver biopsies.

9. Dermatomyositis:
   - Dates of onset of muscle weakness and if proximal or distal.
   - Dates and results of serum creatine phosphokinase and electromyography studies.
   - Dates and results of muscle biopsy if done

Appendix H
Modified Scleroderma Health Assessment Questionnaire (SHAQ)

Assessed by the patient (check one box only per question)

Ask the patient: **"At this moment are you able to:"**		Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dressing/ Grooming	1. Are you able to: • Dress yourself, including tying shoelaces and doing buttons? • Shampoo your hair?	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Arising	2. Are you able to: • Stand up from an armless straight chair? Get in and out of bed?	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Eating	3. Are you able to: • Cut your meat? • Lift a full cup or glass to your mouth? • Open a new carton of milk?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
Walking	4. Are you able to: • Walk outdoors on flat ground? • Climb up 5 steps?	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Hygiene	5. Are you able to: • Wash and dry your entire body? • Take a tub bath? • Get on and off the toilet?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
Reach	6. Are you able to: • Reach and get down a 5-pound object (such as a bag of sugar) from just above your head? • Bend down and pick up clothing from the floor?	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Grip	7. Are you able to: • Open car doors? • Open jars that have previously opened? • Turn regular taps on and off?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
Activities	8. Are you able to: • Run errands and shop? • Get in and out of a car? • Do chores such as vacuuming or yard work?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐

Please check any Aids or Devices that you usually use:

Cane	☐	Dressing Devices (button hook, long shoe horn, etc.)	☐
Walker	☐	Built up or Special Utensils	☐
Bathtub seat	☐	Long Handled Appliances for reach	☐
Bathtub Bar	☐	Long Handled Appliances for Bathroom	☐
Jar Opener	☐	Raised Toilet seat	☐
Crutches	☐	Special or Built-up Chair	☐
Wheelchair	☐	Other (Specify)	

Please check any categories for which you usually need help from another person:

Hygiene	☐	Gripping and Opening Things	☐
Reach	☐	Errands and Chores	☐
Arising	☐	Dressing and Grooming	☐
Eating	☐	Walking	☐

Place a mark on the line to indicate the severity of the pain.

*How much pain have you experienced because of your illness **in the past week**?*

No Pain **Very Severe Pain**

0 100

1. ***In the past week***, how much has your Raynaud's Phenomenon interfered with your activities?

Does not interfere **Very severe limitation**

2. ***In the past week***, how much has/have your finger ulcer(s) interfered with your activities?

Does not interfere **Very severe limitation**

3. ***In the past week***, how much have your intestinal problems interfered with your activities?

Does not interfere **Very severe limitation**

4. ***In the past week***, how much have your breathing problems interfered with your activities?

Does not interfere **Very severe limitation**

5. Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease ***today***?

No disease **Very severe**

Patient signature: _____ **Date:**_____

Appendix I
Childhood Health Assessment Questionnaire

In this questionnaire we are interested in learning how your child's illness affects his/ her ability to function in daily life. Please feel free to add any comments on the back of this page.

In the following questions please check the one response which best describes your child's usual activities (averaged over an entire day) OVER THE PAST WEEK. Only note those difficulties or limitations which are due to illness. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable." For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but NOT because he/she is RESTRICTED BY ILLNESS, please mark it as "Not Applicable."

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
DRESSING & GROOMING				
Is your child able to:				
1. Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐
2. Shampoo his/her hair	☐	☐	☐	☐
3. Remove socks?	☐	☐	☐	☐
4. Cut fingernails?	☐	☐	☐	☐
ARISING				
Is your child able to:				
1. Stand up from a low chair or floor?	☐	☐	☐	☐
2. Get in and out of bed or stand up in a crib?	☐	☐	☐	☐
EATING				
Is your child able to:				
1. Cut his/her own meat?	☐	☐	☐	☐
2. Lift a cup or glass to mouth?	☐	☐	☐	☐
3. Open a new cereal box?	☐	☐	☐	☐
WALKING				
Is your child able to:				
1. Walk outdoors on a flat ground?	☐	☐	☐	☐
2. Climb up five steps?	☐	☐	☐	☐

Please check any Aids or Devices that your child usually uses for any of the previous activities:

Cane	☐	Dressing Devices (button hook, long shoe horn, etc.)	☐
Walker	☐	Built up or Special Utensils	☐
Bathtub seat	☐	Long Handled Appliances for reach	☐
Bathtub Bar	☐	Long Handled Appliances for Bathroom	☐
Jar Opener	☐	Raised Toilet seat	☐
Crutches	☐	Special or Built-up Chair	☐
Wheelchair	☐	Other (Specify)	☐

Please check any categories for which your child usually needs help from another person BECAUSE of ILLNESS:

Hygiene	☐	Gripping and Opening Things	☐
Reach	☐	Errands and Chores	☐

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
HYGIENE				
Is your child able to				
1. Wash and dry entire body?	☐	☐	☐	☐
2. Take a tub bath (get in & out of tub)?	☐	☐	☐	☐
3. Get on and off the toilet or potty chair?	☐	☐	☐	☐
4. Brush teeth?	☐	☐	☐	☐
5. Comb/brush hair?	☐	☐	☐	☐
REACH				
Is your child able to:				
1. Reach and get down a heavy object such as a large game or books from just above head?	☐	☐	☐	☐
2. Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐
3. Pull on a sweater over his/her head?	☐	☐	☐	☐
4. Turn neck to look over shoulder?	☐	☐	☐	☐
GRIP				
Is your child able to:				
1. Write or scribble with a pen or pencil?	☐	☐	☐	☐
2. Open car doors?	☐	☐	☐	☐
3. Open jars which have been previously opened?	☐	☐	☐	☐
4. Turn faucets on and off?	☐	☐	☐	☐
5. Push open a door when he/she has to turn knob?:	☐	☐	☐	☐

ERRANDS, CHORES AND PLAY

Is your child able to:

1. Run errands and shop?	☐	☐	☐	☐
2. Get in and out of car or toy car or school bus?	☐	☐	☐	☐
3. Ride bike or tricycle?	☐	☐	☐	☐
4. Do household chores (e.g. wash dishes, take out trash, vacuuming, yard work make bed)?	☐	☐	☐	☐
5. Run and play?	☐	☐	☐	☐

Please check any AIDS or DEVICES that your child usually used for any of the above activities:

_____Raised Toilet Seat
_____Bathtub Seat
_____Bathtub Bar
_____Jar Opener
_____Long Handled Appliances for Reach
_____Long Handled Appliances in Bathroom

Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:

_____Hygiene
_____Reach
_____Gripping and Opening things
_____Errands, Chores and Play

We are also interested in learning whether or not your child has been affected by pain because of his or her illness. How much pain do you think your child has had because of his/her illness IN THE PAST WEEK? Place a mark on the line below to indicate the severity of the pain.

_____
No Pain Very Bad Pain

Patient signature: _____Date:_____

Appendix J
UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Instrument 2.0
(UCLA SCTC GIT 2.0)

THE UCLA SCTC GIT 2.0 QUESTIONNAIRE

CORRESPONDENCE TO:

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The following questions ask about your gastrointestinal (gut, GI) symptoms and how they affected your life over the last 7 days. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

		In the past 1 week, how often did you …	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]	
REFLUX	1.	… have difficulty swallowing solid food?	☐	☐	☐	☐	1/8= 0.125 2/8= 0.25 3/8= 0.35 4/8= 0.5 5/8= 0.625 6/8= 0.75 7/8= 0.875 8/8= 1.0 9/8= 1.125 10/8= 1.25 11/8= 1.375 12/8= 1.5 13/8= 1.625 14/8= 1.75 15/8= 1.875 16/8= 2.0 17/8= 2.125 18/8= 2.25 19/8= 2.375 20/8= 2.5 21/8= 2.625 22/8= 2.75 23/8= 2.875 24/8= 3.0 SCORE R=
	2.	… have an unpleasant stinging or burning sensation in your chest (heartburn)?	☐	☐	☐	☐	
	3.	… have a sensation of bitter or sour fluid coming up from your stomach into your mouth (acid reflux)?	☐	☐	☐	☐	
	4.	… have heartburn on eating 'acidic' foods such as Tomatoes & Oranges?	☐	☐	☐	☐	
	5.	… regurgitate (throw up or bring up small amounts of previously eaten food)?	☐	☐	☐	☐	
	6.	… sleep in a 'raised' or an 'L shaped' position?	☐	☐	☐	☐	
	7.	… feel like vomiting or throwing up?	☐	☐	☐	☐	
	8.	… vomit or throw up?	☐	☐	☐	☐	
DISTENSION	9.	… feel bloated (a sensation of gas or air in the stomach)?	☐	☐	☐	☐	1/4= 0.25 2/4= 0.5 3/4= 0.75 4/4= 1.0 5/4= 1.25 6/4= 1.5 7/4= 1.75 8/4= 2.0 9/4= 2.25 10/4= 2.5 11/4= 2.75 12/4=3.0 SCORE D/B=
	10.	… notice an increase in your belly, sometimes requiring you to open your belt, pants or shirt?	☐	☐	☐	☐	
	11.	… feel full after eating a small meal?	☐	☐	☐	☐	
	12.	… pass excessive gas or flatulence?	☐	☐	☐	☐	
SOILAGE	13.	… accidentally soil (dirty) your underwear before being able to get to a bathroom?	☐	☐	☐	☐	1/1= 1.0 2/1= 2.0 3/1= 3.0 SCORE S=

DIARRHEA

	In the past 1 week, how often did you …	(CHECK ONE RESPONSE FOR EACH QUESTION)				
		No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]	
14.	… have loose stools (diarrhea)?	☐	☐	☐	☐	→

	In the past 1 week, have you noticed your stools becoming…	(CHECK ONE RESPONSE FOR EACH QUESTION)		
		Yes[1]	No[0]	
15.	… watery?	☐	☐	←

1/2= 0.5
2/2= 1.0
3/2= 1.5
4/2= 2.0

SCORE D=

SOCIAL FUNCTIONING

	In the past 1 week, how often did the following interfere with social activities (such as visiting friends or relatives)?	(CHECK ONE RESPONSE FOR EACH QUESTION)			
		No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
16.	… Nausea	☐	☐	☐	☐
17.	… Vomiting	☐	☐	☐	☐
18.	… Stomach ache or pain	☐	☐	☐	☐
19.	… Diarrhea	☐	☐	☐	☐
20.	… Worry you would accidentally soil your underwear	☐	☐	☐	☐
21.	… Bloated sensation	☐	☐	☐	☐

1/6= 0.16
2/6= 0.33
3/6= 0.5
4/6= 0.66
5/6= 0.83
6/6= 1.0
7/6= 1.16
8/6= 1.33
9/6= 1.5
10/6= 1.66
11/6= 1.83
12/6= 2.0
13/6= 2.16
14/6= 2.33
15/6= 2.5
16/6= 2.66
17/6= 2.83
18/6= 3.0

SCORE SF=

EMOTIONAL WELLBEING	In the past 1 week, how often did you …		(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
	22.	… feel worried or anxious about your bowel problems?	☐	☐	☐	☐
	23.	… feel embarrassed because of your bowel symptoms?	☐	☐	☐	☐
	24.	… have problems with sexual relations because of your bowel symptoms?	☐	☐	☐	☐
	25.	… fear not finding a bathroom?	☐	☐	☐	☐
	26.	… feel depressed or discouraged due to your bowel symptoms?	☐	☐	☐	☐
	27.	… avoid or delay traveling because of your bowel symptoms?	☐	☐	☐	☐
	28.	… feel angry or frustrated as a result of your bowel symptoms?	☐	☐	☐	☐
	29.	… have problems with your sleep as a result of your bowel symptoms?	☐	☐	☐	☐
	30.	… feel 'stress' or an upset mood worsens your bowel symptoms?	☐	☐	☐	☐

1/9= 0.11
2/9= 0.22
3/9= 0.33
4/9= 0.44
5/9= 0.55
6/9= 0.66
7/9= 0.77
8/9= 0.88
9/9= 1.0
10/9= 1.11
11/9= 1.22
12/9= 1.33
13/9= 1.44
14/9= 1.55
15/9= 1.66
16/9= 1.77
17/9= 1.88
18/9= 2.00
19/9= 2.11
20/9= 2.22
21/9= 2.33
22/9= 2.44
23/9= 2.55
24/9= 2.66
25/9= 2.77
26/9= 2.88
27/9= 3.0

SCORE
EWB=

CONSTIPATION

	In the past 1 week, have you noticed your stools becoming…	(CHECK ONE RESPONSE FOR EACH QUESTION) Yes[1]	No[0]
31.	… harder?	☐	☐

	In the past 1 week, how often …	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
32.	… were you constipated or unable to empty your bowels?	☐	☐	☐	☐
33.	… did you have hard stools?	☐	☐	☐	☐
34.	… did you have pain while passing your stools?	☐	☐	☐	☐

1/4= 0.25
2/4= 0.50
3/4= 0.75
4/4= 1.0
5/4= 1.25
6/4= 1.50
7/4= 1.75
8/4= 2.0
9/4= 2.25
10/4= 2.5

SCORE C=

Thank you for completing the questionnaire

To be completed by the physician

TOTAL SCORE= Reflux _____
+ Distention /Bloating _____
+ Fecal Soilage _____
+ Diarrhea _____
+ Social functioning _____
+ Emotional well-being _____
TOTAL SCORE= (_____) /6= _____

REMEMBER: CONSTIPATION SCORE IS NOT INCLUDED IN CALCULATION OF TOTAL SCORE

C=Constipation; D=Diarrhea; D/B=Distention/Bloating; EM=Emotional well-being; R=Reflux; SF=Social functioning; S=Fecal soilage

Patient signature: _____Date:_____

Appendix K
Short Form 36 Health Survey (SF-36)

INSTRUCTIONS: The survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent 1
Very Good 2
Good 3
Fair 4
Poor 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago 1
Somewhat better now than one week ago 2
About the same as one week ago 3
Somewhat worse now than one week ago 4
Much worse now than one week ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.			
b. Moderate activities, such as moving a table pushing a vacuum cleaner, bowling, or playing golf.			
c. Lifting or carrying groceries.			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs.			
f. Bending, kneeling, or stooping.			
g. Walking more than a mile.			
h. Walking several blocks.			
i. Walking one block.			
j. Bathing or dressing yourself.			

4. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities.		
b. Accomplished less than you would like.		
c. Were limited in the kind of work or other activities.		
d. Had difficulty performing the work or other activities (for example, it took extra effort).		

5. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities.		
b. Accomplished less than you would like.		
c. Don't do work or other activities as carefully as usual.		

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past week?

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very Severe 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past week --	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time
a. Did you feel full of pep?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and blue?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						

10. During the *past week,* how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

11. How TRUE or FALSE is *each* of the following statements for you?

Statement	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people.					
b. I am healthy as anybody I know.					
c. I expect my health to get worse.					
d. My health is excellent.					

Patient signature: _____Date:_____

Appendix L
PROMIS-29 Profile v1.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
1	Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
2	Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
3	Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
4	Are you able to run errands and shop?	☐	☐	☐	☐	☐
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
5	I felt fearful	☐	☐	☐	☐	☐
6	I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
7	My worries overwhelmed me	☐	☐	☐	☐	☐
8	I felt uneasy	☐	☐	☐	☐	☐
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
9	I felt worthless	☐	☐	☐	☐	☐
10	I felt helpless	☐	☐	☐	☐	☐
11	I felt depressed	☐	☐	☐	☐	☐
12	I felt hopeless	☐	☐	☐	☐	☐
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
13	I feel fatigued	☐	☐	☐	☐	☐
14	I have trouble starting things because I am tired	☐	☐	☐	☐	☐
	In the past 7 days…					
15	How run-down did you feel on average?	☐	☐	☐	☐	☐
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
16	How fatigued were you on average?	☐	☐	☐	☐	☐

PROMIS–29 Profile v1.0

	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
17	My sleep quality was.....	☐	☐	☐	☐	☐
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
18	My sleep was refreshing.....	☐	☐	☐	☐	☐
19	I had a problem with my sleep	☐	☐	☐	☐	☐
20	I had difficulty falling asleep	☐	☐	☐	☐	☐
	Satisfaction with Social Role **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
21	I am satisfied with how much work I can do (include work at home)	☐	☐	☐	☐	☐
22	I am satisfied with my ability to work (include work at home).....	☐	☐	☐	☐	☐
23	I am satisfied with my ability to do regular personal and household responsibilities	☐	☐	☐	☐	☐
24	I am satisfied with my ability to perform my daily routines.....	☐	☐	☐	☐	☐
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
25	How much did pain interfere with your day to day activities?.....	☐	☐	☐	☐	☐
26	How much did pain interfere with work around the home?.....	☐	☐	☐	☐	☐
27	How much did pain interfere with your ability to participate in social activities?	☐	☐	☐	☐	☐
28	How much did pain interfere with your household chores?.....	☐	☐	☐	☐	☐

Pain Intensity
In the past 7 days…

29	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

Patient signature: _____ **Date:** _____

Appendix M

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 3 months.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 3 months, I have coughed:	☒	☒	☒	☒	☒
2. Over the past 3 months, I have brought up phlegm (sputum):	☒	☒	☒	☒	☒
3. Over the past 3 months, I have had shortness of breath:	☒	☒	☒	☒	☒
4. Over the past 3 months, I have had wheezing attacks:	☒	☒	☒	☒	☒

5. How many times during the past 3 months have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☒
- 3 times ☒
- 2 times ☒
- 1 time ☒
- none of the time ☒

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☒
- 3 or more days ☒
- 1 or 2 days ☒
- less than a day ☒

7. Over the past 3 months, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☒
- 1 or 2 good days ☒
- 3 or 4 good days ☒
- nearly every day was good ☒
- every day was good ☒

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☒
- Yes ☒

USA / English version
«Past three months» version

continued…

St. George's Respiratory Questionnaire
PART 2

SECTION 1

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☒
- Causes me quite a lot of problems ☒
- Causes me a few problems ☒
- Causes no problems ☒

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☒
- My respiratory problems interfere with my job or made me change my job ☒
- My respiratory problems do not affect my job ☒

SECTION 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) ***the box*** that applies to you ***these days***:	True	False
Sitting or lying still	☒	☒
Washing or dressing yourself	☒	☒
Walking around the house	☒	☒
Walking outside on level ground	☒	☒
Walking up a flight of stairs	☒	☒
Walking up hills	☒	☒
Playing sports or other physical activities	☒	☒

USA / English version
«Past three months» version

continued…

St. George's Respiratory Questionnaire
PART 2

SECTION 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☒	☒
Coughing makes me tired	☒	☒
I am short of breath when I talk	☒	☒
I am short of breath when I bend over	☒	☒
My coughing or breathing disturbs my sleep	☒	☒
I get exhausted easily	☒	☒

SECTION 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☒	☒
My respiratory problems are a nuisance to my family, friends or neighbors	☒	☒
I get afraid or panic when I cannot catch my breath	☒	☒
I feel that I am not in control of my respiratory problems	☒	☒
I do not expect my respiratory problems to get any better	☒	☒
I have become frail or an invalid because of my respiratory problems	☒	☒
Exercise is not safe for me	☒	☒
Everything seems too much of an effort	☒	☒

SECTION 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☒	☒
I get embarrassed using my medication in public	☒	☒
I have unpleasant side effects from my medication	☒	☒
My treatment interferes with my life a lot	☒	☒

St. George's Respiratory Questionnaire
PART 2

SECTION 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I take a long time to get washed or dressed	☒	☒
I cannot take a bath or shower, or I take a long time to do it	☒	☒
I walk slower than other people my age, or I stop to rest	☒	☒
Jobs such as household chores take a long time, or I have to stop to rest	☒	☒
If I walk up one flight of stairs, I have to go slowly or stop	☒	☒
If I hurry or walk fast, I have to stop or slow down	☒	☒
My breathing makes it difficult to do things such as walk up hills, carry things, up stairs, light gardening such as weeding, dance, bowl or play golf	☒	☒
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☒	☒
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☒	☒

SECTION 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I cannot play sports or do other physical activities	☒	☒
I cannot go out for entertainment or recreation	☒	☒
I cannot go out of the house to do the shopping	☒	☒
I cannot do household chores	☒	☒
I cannot move far from my bed or chair	☒	☒

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog
Doing activities or chores at home or in the garden
Sexual intercourse
Going to a place of worship, or a place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .

. . . . . .

. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☒
It stops me from doing one or two things I would like to do ☒
It stops me from doing most of the things I would like to do ☒
It stops me from doing everything I would like to do ☒

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

Patient signature: _____ **Date:**_____

USA / US English version

Appendix N
Center for International Blood and Marrow Transplant Research (CIBMTR)
Co-Morbidity Index

Were there ***clinically significant*** co-existing disease or organ impairment at time of patient assessment prior to preparative regimen?

☐ Yes ☐ No ('Allo' continue with ***Box A*** below, 'auto' continue with ***Box B*** below)

Yes	No	NotDone	Comorbidity	Definitions
☐	☐	☐	Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias
☐	☐	☐	Cardiac	Coronary artery disease §, congestive heart failure, myocardial infarction, or EF ≤ 50%
☐	☐	☐	Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident
☐	☐	☐	Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone
☐	☐	☐	Heart valve disease	Except mitral valve prolapse
☐	☐	☐	Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN
☐	☐	☐	Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN
☐	☐	☐	Infection	Requiring continuation of antimicrobial treatment after day 0
☐	☐	☐	Inflammatory bowel disease	Crohn's disease or ulcerative colitis
☐	☐	☐	Obesity	Patients with a body mass index > 35 kg/m²
☐	☐	☐	Peptic ulcer	Requiring treatment
☐	☐	☐	Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment
☐	☐	☐	Pulmonary, moderate	DLco and/or FEV_1 66-80% or dyspnea on slight activity
☐	☐	☐	Pulmonary, severe	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen
☐	☐	☐	Renal, moderate/severe	Serum creatinine > 2 mg/dL or >177 μmol/L, on dialysis, or prior renal transplantation
☐	☐	☐	Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica
☐	☐	☐	Solid tumor, prior	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer
☐	☐	☐	Other	Specify:_____

§ One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.
EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.

Source: Blood, 2005 Oct 15;106(8):2912-2919

Patient study number: _____ Date of assessment:_____

Appendix O
Adverse Event Reporting

Adverse Events in certain categories that are not considered as reportable adverse events.

The following events under certain categories will not be considered reportable adverse events due to the lack of relevance to the evaluation of the protocol treatment. Furthermore, in many cases, the event if significant will be captured more appropriately under another adverse event category (e.g. it is most relevant to report the event causing pain rather than the pain event itself):

- Congenital, familial and genetic disorders
- Endocrine disorders: puberty and growth related events
- General disorders and administration site conditions: chills, edema, pain, fatigue, fever, flu-like symptoms, irritability and malaise.
- Investigations: elevations in liver enzymes without increase in bilirubin, gonadotropin, prolactin, decreased lymphocyte and CD4 T cell count since this is expected with transplant, increase in amylase or lipase without clinical evidence of pancreatitis and weight gain or loss.
- Metabolism and nutrition disorders: anorexia.
- Musculoskeletal and connective tissue disorders: exostosis, generalized muscle weakness, growth suppression, change in joint range of motion, kyphosis, lordosis, myalgia, myositis, scoliosis, trismus and unequal leg length.
- Pain
- Pregnancy, puerperium and perinatal conditions: all events listed
- Psychiatric disorders: agitation, anxiety, euphoria, insomnia, change in libido and restlessness
- Reproductive system and breast disorders: all events listed
- Skin and subcutaneous tissue disorders: dry skin, fat atrophy, hyperhidrosis, lipohypertrophy and pruritis
- Social circumstances: both events listed
- Vascular disorders: flushing, hot flashes
- Surgical and medical procedures

Grading of adverse events from the start of mobilization until day +28.

1) Grade 3 and 4 adverse events that will not be reported from start of mobilization until Day +28 :

Certain Grade 3 and 4 adverse events under particular categories in the CTC are expected as part of treatment or not uncommon in the HCT setting and do not represent a life-threatening event as detailed. These adverse events will not be reported at any time from the start of mobilization until day +28:

Anemia
Lymphocyte count decreased
Neutrophil count decreased
Platelet count decreased
White blood cell decreased

Fatigue
Fever
Anorexia
Insomnia
Chills
Weight gain
Weight loss
Vomiting
Hypokalemia
Hyponatremia
Hypomagnesemia
Hyperglycemia
Hypocalcemia
Hypophosphatemia

The primary hospitalization and re-hospitalizations to manage expected events will not be automatically reported.

2) Adverse events that will only be reported if ≥ Grade 4 from the start of mobilization until day +28:
Since the following events are to be expected in the setting of HSCT, they will only be reported if they are ≥ Grade 4 severity:

Blood and Lymphatic System Disorders
DIC
Thrombotic microangiopathy

Gastrointestinal Disorders
Colitis
Diarrhea associated with radiation or BMT studies
Dysphagia, esophagitis, odynophagia
Dysphagia-esophageal related to radiation
Dysphagia-pharyngeal related to radiation
Gastritis
GI bleeding
Ileus
Mucositis
Nausea
Pancreatitis
Stomatitis/pharyngitis/mucositis
Typhlitis
Vomiting

Hepatobiliary disorders
Hepatic hemorrhage
Infections
All infections

Investigations
Cholesterol high
Blood bilirubin increased

Creatinine increased

Metabolism and Nutrition Disorders
Dehydration
Acidosis
Alkalosis
Hypercalcemia
Hyperkalemia
Hypermagnesemia
Hypernatremia
Hypertriglyceridemia
Hyperuricemia
Hypoglycemia

Renal and urinary disorders
Acute kidney injury
Bladder spasms
Cystitis noninfective
Hematuria
Renal hemorrhage
Urinary electrolyte wasting
Urinary frequency/urgency
Urinary retention

Reproductive system and breast disorders
Menorrhagia

Respiratory, thoracic and mediastinal disorders
Cough
Hemoptysis
Bronchopulmonary hemorrhage
Hypoxia
Laryngeal hemorrhage
Pharyngeal hemorrhage
Pleural hemorrhage
Pleural effusion
Pneumonitis/pulmonary infiltrates
Voice alteration/stridor

Vascular Disorders
Hypertension
Hypotension

Grading of adverse events from day +29 to day +100.

1) Grade 3 and 4 events that will not be reported:

- Blood and lymphatic system disorders except for DIC, TTP and HUS.
- Decreases in blood counts including white blood cells, neutrophils, lymphocytes, hemoglobin (anemia) and platelets.

2) All other grade 3 and 4 events will be reported.

Appendix P
Research Subject Registration Form

Research Subject Initials:_____

Date of Birth: ___ ___/___ ___/ ___ ___ ___ ___
Month Day Year
Social Security Number (optional) _____

Ethnicity: *(Choose one)*
☐ **Hispanic or Latino** (A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. Term "Spanish Origin" can also be used in addition to "Hispanic" or "Latino"
☐ **Not Hispanic or Latino**
☐ **Refused to Report**

Race: *(check all that apply)*
☐ **American Indian/Alaska Native** (A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment)
☐ **Asian** (A person having origins in any of the original peoples of the Far East, Southeast, Asia, or the Indian subcontinent including, for example, Cambodia, China, India Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam)
☐ **Native Hawaiian/Pacific Islander** (A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands)
☐ **Black/African American** (A person having origins in any of the black racial groups of Africa.
☐ **White** (A person having origins in any of the original peoples of Europe, the Middle East or North Africa)

☐ **Unknown**
☐ **Refused to Report**

Gender:
☐ Male
☐ Female
☐ Unknown

HIPAA Authorization: (check one)

☐ Protocol covered under general HIPAA authorization
☐ Protocol specific HIPAA authorization required for
(Attach and submit with this form)

Name of person completing form (please print):

_____
Name Phone Number

_____
Date Submitted Time

ATTACH SIGNED CONSENT AND SEND TO RESEARECH COORDINATOR

FAX COVER LETTER

DATE:_____

TO: Research Coordinator

FAX: (206) 667-2284

RE: RESEARCH SUBJECT REGISTRATION FORM

FROM:_____

FAX:_____

PHONE:_____

THE INFORMATION CONTAINED IN THIS TRANSMISSION IS INTENDED ONLY FOR THE ADDRESSEE OR THE ADDRESSEE'S AUTHORIZED AGENT. THE FAX CONTAINS INFORMATION THAT MAY BE PRIVILEGED, CONFIDENTIAL AND EXEMPT FROM DISCLOSURE. IF THE READER OF THE MESSAGE IS NOT THE INTENDED RECIPIENT OR RECIPIENT'S AUTHORIZED AGENT THEN YOU ARE NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR COPYING OF THIS INFORMATION IS PROHIBITED.

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Appendix Q
UCSD Health Care Utilization Questionnaire

UCSD Health Care Utilization Questionnaire

Patient Signature: _____
Date: _____

During the past three months:	Write the answer below
1. How many visits did you make to a physician, osteopath, or nurse practitioner?	
2. How many telephone calls did you make to your doctor or your doctors staff:	
3. How may time did you use a triage or urgent care center or emergency room:	
4. How many visits did you have from a health care provider who came to your home (e.g. home health agency, nurse, physical or occupational therapist)?	
5. How many days were you in a hospital as an inpatient?	
5a. Of these days in the hospital, how many were spent in the intensive care unit (ICU)?	
5b. Please list any operations you had during these inpatient hospital days: 1. _____ 2. _____ 3. _____	
6. How many time did you have outpatient surgery or another procedure where you did not stay in the hospital overnight?	
7. Did you regularly use any medical supplies or equipment?	Yes ❑ No ❑
8. How many prescription medicines (including inhalers) do you take regularly? (Include the total number of medications, not the number of pills/doses per day)	
9. How many non- prescription medicines (including vitamins)do you take regularly? (Include the total number of medications, not the number of pills/doses per day)	
10. How many times did you use an ambulance?	
10a. How many of these ambulance trips resulted from you calling 911 for emergency?	
11. Did you have any other major medical expense during the past 3 months that has not been mentioned? If yes, please list: 1. _____ 2. _____ 3. _____	Yes ❑ No ❑

Appendix R
ANCHORS Questionnaire

Patient Signature:_____ **Date:**_____

Compared to the last visit, how would you rate the following:

1. Pain suffered due to scleroderma

1	2	3	4	5
Much better	Somewhat better	About the same	Somewhat worse	Much worse

2. Physical Limitation in regards to dressing, eating, walking, hygiene, reaching, gripping and general activities due to scleroderma

1	2	3	4	5
Much better	Somewhat better	About the same	Somewhat worse	Much worse

3. Overall scleroderma condition

1	2	3	4	5
Much better	Somewhat better	About the same	Somewhat worse	Much worse

4. Mental health such as depression, anxiety, and anger suffered due to scleroderma

1	2	3	4	5
Much better	Somewhat better	About the same	Somewhat worse	Much worse

5. Fatigue suffered due to scleroderma

1	2	3	4	5
Much better	Somewhat better	About the same	Somewhat worse	Much worse

The next 3 questions ask you about your Scleroderma in the LAST WEEK:
1. How much pain did you have due to your scleroderma over the LAST WEEK?

0	1	2	3	4
None	Mild	Moderate	Severe	Very severe

2. How much limitation in your day-to-day activity did you experience due to your scleroderma over the LAST WEEK?

0	1	2	3	4
None	Mild	Moderate	Severe	Very severe

3. Overall, considering pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your scleroderma?

	1	2	3	4
	Mild	Moderate	Severe	Very severe

Appendix S
Work Productivity Survey

Patient Signature: _____ Date: _____

1. Are you currently employed outside of home?
   - ❑ Yes -continue
   - ❑ No- go to question (b.)

   a. If yes:
      1. Indicate your occupation: _____
      2. Check the box that best describes your job function from the list below:
         - ❑ Non-manual (administrative, managerial, supervisory, office and other professional such as teacher)
         - ❑ Mixed, non-manual (sales and service occupations such as waitress, personal care attendant, patient care nurse, nurse's aide, driver)
         - ❑ Manual with no supervisory duties (carpenter, roofer, loader)

   b. If no, please check the box that best describes your status:
      - ❑ Home maker
      - ❑ Retired
      - ❑ Student
      - ❑ Unable to work due to Scleroderma
      - ❑ Unable to work due to non-Scleroderma health problems
      - ❑ Other (i.e. perform volunteer work) _____

2. How many days in the last month did you miss work or did not do household work because of Scleroderma? (If none, please write 0)

   _____days

3. How many days in the last month was your productivity at work or in household work reduced by half or more because of Scleroderma? Do not include days counted in question 2. (If none, please write 0)

   _____days

4. In the last month, how much has Scleroderma interfered with your work outside or inside of home on a scale of 1-10 wher 0+ "no interference and 10 = "complete interference"?

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
1	2	3	4	5	6	7	8	9	10

No interference **Complete Interference**

5. How many days in the last month did you miss family, social or leisure actibities because of Scleroderma? (If none, please write 0)

   _____days

6. How many days in the last month did you have to hire outside help (i.e. housekeeper) because of Scleroderma? (If none, please write 0)

   _____days

Appendix T
Abbreviations for the STAT Study

ABG	Arterial Blood Gas
ACA	Anti-cardiolipin Antibody
ACE	Angiotensin-Converting Enzyme
ACV	Acyclovir
AE	Adverse Event
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
AP	Anterior-Posterior
APGAR	Appearance, Pulse, Grimace, Activity and Respiration
AST	Aspartate Aminotransferase
ATG	Antithymocyte Globulin
ATGAM	Equine Antithymocyte Globulin
Auto-CD34+HPC	Hematopoietic Progenitor Cells, Apheresis-CD34 Enriched for Autologous Use
AZA	Azathioprine
BAL	Bronchoaveolar Lavage
BCNU	Bischloroethyl-nitrosourea
BID	Twice Daily (Every 12 Hours)
BMT	Bone Marrow Transplant
CBC	Complete Blood Count
CBI	Continuous Bladder Irrigation
CFR	Code of Federal Regulations
cGy	CentiGrays
CHAQ	Childhood Health Assessment Questionnaire
CHF	Congestive Heart Failure
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Controlled Substance Analogue
CT	Computed Tomography
CTC	Common Toxicity Criteria
CY	Cyclophosphamide
DAIT	Division of Allergy, Immunology and Transplantation
DBP	Diastolic Blood Pressure
dcSSc	Diffuse Cutaneous Systemic Sclerosis
DFA	Direct Fluorescent Antibody
DLCO	Diffusion in Liters of Carbon Monoxide
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
DTPA	Protein Free Ultrafiltered Plasma Method
EAE	Experimental Autoimmune Encephalomyelitis
EBMT	European Group for Blood and Marrow Transplantation

EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
EFS	Event-Free Survival
EMG	Electromyography
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FHCC	Fred Hutchinson Cancer Center
FVC	Forced Vital Capacity
GAVE	Gastric Antral Vascular Ectasia
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GCV	Ganciclovir
GI	Gastrointestinal
GRCS	Global rank composite score
GVHD	Graft-Versus-Host Disease
Hb	Hemoglobin
HCG	Human Chorionic Gonadotropin
HCT	Hematocrit
HDIT	High-Dose Immunosuppressive Therapy
HEPA	High Efficiency Particulate Air
Hib	Haemophilus Influenza Type b
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HPF	High-power Field
HSCT	Hematopoietic Stem Cell Transplantation
HSCTC	Hematopoietic Stem Cell Transplantation Consortium
HSV	Herpes Simplex Virus
HTN	Hypertension
HUS	Hemolytic Uremic Syndrome
HVL	Half-Value Layers
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IL	Interleukin
IL-2	Interleukin-2
IND	Investigational New Drug Application
IPS	Idiopathic Pneumonia Syndrome
IPV	Inactivated Polio Vaccine
IRB	Institutional Review Board
ITP	Idiopathic Thrombocytopenia Purpura
ITT	Intention-to-Treat
IV	Intravenous
IVP	Intravenous Pyelogram
LAF	Laminar Air Flow
LEF	Leflunomide
LVEF	Left Ventricular Ejection Fraction
MCS	SF-36 Mental Component Score
MDS	Myelodysplastic Syndrome
mHAQ-DI	Modified Health Assessment Questionnaire Disability Index

MITT	Modified Intention-to-Treat
MMF	Mycophenolate Mofetil
MMR	Measles-mumps-rubella
mRSS	Modified Rodnan Skin Score
MS	Multiple Sclerosis
MTX	Methotrexate
MUGA	Multiple Gated Acquisition
MV	Minute Volume
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NK	Natural Killer (cell)
NS	Normal Saline
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSIP	Non Specific Interstitial Pneumonia
NYHA	New York Heart Association
OPD	Outpatient Department
PA	Posteroanterior
PAH	Pulmonary Artery Hypertension
PAP	Pulmonary Arterial Pressure
PBMC	Peripheral Blood Mononuclear Cell
PBSC	Peripheral Blood Stem Cell
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
PCS	SF-36 Physical Component Score
PCV7	Heptavalent Pneumococcal Conuugate Vaccine
PFTs	Pulmonary Function Tests
PMN	Polymorphonuclear Neutrophil
pCO_2	Carbon Dioxide Partial Pressure
pO_2	Oxygen Partial Pressure
PPS	Per Protocol Set
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PTLD	PostTransplant Lymphoproliferative Disorder
QD	Daily
QID	Four Times Daily (Every 6 Hours)
RBC	Red Blood Cell
RC	Rheumatology Center
RNA	Ribonucleic Acid
RNP	Ribonucleoprotein
RSV	Respiratory Syncytial Virus
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCT	Stem Cell Transplantation
SF-36	Short Form 36
SGRQ	St. George's Respiratory Questionnaire
SHAQ	Modified Scleroderma Health Assessment Questionnaire
SIADH	Syndrome of Inappropriate Anti-diuretic Hormone Secretion
SLE	Systemic Lupus Erythematosus
Sm	Smith Antigen

SOPs	Standard Operating Procedures
SA	Safety Population
SPEP	Serum Protein Electrophoresis
SSA	Sjogren's Syndrome A Antigen
SSB	Sjogren's Syndrome B Antigen
SSc	Systemic Sclerosis
SSD	Source to Skin Distance
TAR	Percent Depth Dose
TBI	Total Body Irradiation
TC	Transplant Center
TCR	T Cell Receptor
TID	Three Times Daily (Every 8 Hours)
TLI	Total Lymphoid Irradiation
TMR	Tissue Maximum Ratio
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
TR	Tricuspid Regurgitation
TREC	T-Cell Rearrangement Excision Circles
TSH	Thyroid Stimulating Hormone
TTP	Thrombocytopenic Purpura
VZIG	Varicella Zoster Immunoglobulin
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WHO	World Health Organization
UA	Urinalysis
UCLA SCTC GIT 2.0	UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Instrument 2.0
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit of Normal
URI	Upper Respiratory Infection
US	United States
WPS	Work Productivity Survey

Appendix U
ENDOSCOPY FORM FOR STAT Trial

Patient: _____

Date of endoscopy procedure: _____

Esophagus:	Yes/present	No/absent
Normal	____	____
(if abnormal, check all that apply)		
Dilated	____	____
Stricture	____	____
Possible Barrett's	____	____
– biopsy taken	____	____
Reflux:	____	____
Hiatal Hernia:	____	____

Esophagitis (if esophagitis present)

Erythema only _____

Los Angeles classification esophagitis (CHECK ONE):

☐ **Grade A:** One or more mucosal breaks < 5 mm in maximal length

☐ **Grade B:** One or more mucosal breaks > 5mm, but without continuity across mucosal folds

☐ **Grade C:** Mucosal breaks continuous between > 2 mucosal folds, but involving less than 75% of the esophageal circumference

☐ **Grade D:** Mucosal breaks involving more than 75% of esophageal circumference

Stomach:	Yes/present	No/absent
Normal:	____	____

(If abnormal, check all that apply:)

- **Antrum:**
  - ☐ GAVE (typical appearance of watermelon stomach)
  - ☐ Erythema/Nonspecific gastropathy
  - ☐ Erosions
  - ☐ Ulcers
  - ☐ Polyps
  - ☐ Bleeding
- **Body of Stomach**:
  - ☐ Nonspecific erythema
  - ☐ Erosions
  - ☐ Ulcers
  - ☐ Polyps
  - ☐ Bleeding
- **Staining for H Pylori**: ☐ DONE ☐ NOT DONE
  If done: ☐ positive ☐ negative

Duodenum:	Yes/present	No/absent
Normal:	____	____

(If abnormal, check all that apply:)

- ☐ Erythema
- ☐ Ulcer
- ☐ Polyps
- ☐ Bleeding

Physician Signature_____ **Date** _____

Appendix V
Plerixafor Information.

The following information (adpted from FHCC Standard practice guidelines) is intended as a supplement/ additional guideline for the optional use of plerixafor in the mobilization of autologous peripheral blood stem cells. This information is not intended to replace accepted institutional standard practice guidelines.

Plerixafor Plus G-CSF For Mobilization Of Autologous Peripheral Blood Stem Cells
Introduction

Plerixafor (AMD3100) is a CXCR4 inhibitor. It is a selective, reversible inhibitor of the binding of stromal cell derived factor - 1α (SDF-1α), also known as chemokine (C-X-C motif) ligand 12(CXCL12) to its cognate receptor chemokine (C-X-C motif) receptor 4 (CXCR4) (1-3). Stem cells express CXCR4 and are known to migrate to the bone marrow through a chemo attractant effect of SDF-1α that is produced locally by bone marrow stromal cells. Once in the marrow, it is believed that stem cell CXCR4 can act to help "anchor" these cells to stromal cell surface SDF-1α. Thus, the SDF- 1α /CXCR4 complex plays a critical role in the retention of hematopoietic stem cells within the bone marrow (4, 5). Plerixafor-induced leukocytosis and elevations in circulating hematopoietic progenitor cell levels are thought to result from a disruption of these chemo attractant and cell adhesion effects, resulting in the appearance of both mature and pluripotent cells in the systemic circulation (6). Plerixafor has been shown to exert an additive synergistic effect on the number of circulating progenitor cells when administered with G-CSF. Plerixafor is US FDA approved in combination with G-CSF for the use of hematopoietic stem cell mobilization in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) and can minimize the number of apheresis days needed to collect autologous peripheral blood stem cells (PBSC) (7,8). In a randomized study comparing plerixafor/G-CSF vs. placebo/ G-CSF alone for mobilizing autologous PBSC in NHL patients, the primary endpoint was to achieve > 5 $x10^6$ CD34+ cells/kg in < 4 apheresis. Fifty-nine percent of the plerixafor/G-CSF treated patients met the goal vs. 20% in placebo/G-CSF group (p<.001; HR 3.64). Eighty-eight percent of the patients treated with plerixafor and G-CSF collected > 2 x 10^6 CD34+ cells/kg in 4 apheresis days vs. 47% in control group, p< 0001. Median time to engraftment post autologous PBSC transplant in both arms was the same. Nademanee et al (9) reported that for multiple myeloma patients with peripheral blood (PB) CD 34 cell count < 10 cell/microliter the median fold increase in PB CD34+ cells from day 4 to day 5 in the plerixafor/G-CSF vs. placebo/G-CSF arms were 9.6 vs. 2, respectively, p<0. 001. The proportion of patients who achieved > 6 $x10^6$ CD34 cells/kg in two apheresis days was significantly higher in plerixafor/G-CSF vs. placebo/G-CSF arm: 40.7% vs. 3.3% in patients with PB cell count <10 cells/microliter, p<0.001 and 55.4% vs. 15% in patients with PB cell count <20 cell/microliter, p<.0001. Plerixafor and G-CSF have also been used successfully to mobilize stem cells after initial failure to collect (10, 11). There is minimal published data on using Plerixafor in the setting of chemotherapy-based PBSC mobilization (12, 15).

The use of plerixafor should be considered in any of the following situations:

- Patients who have failed a previous attempt at mobilization
- Patients who are not successfully mobilizing on chemo-mobilization therapy and G-CSF
- Patients who have received prior radiation to pelvic area
- Patients who have been heavily pretreated with chemotherapy

Mobilization with growth factor alone

If attempting to collect stem cells off of filgrastim alone, the first dose of plerixafor should be administered on the evening of the fourth day of filgrastim if the blood CD34+ cell count in the morning

of the fourth day is between 5-10 cells/microliter. Plerixafor should be discontinued after four doses of plerixafor have been administered, or sooner if apheresis is completed before all four doses are given.

Mobilization including chemotherapy

If attempting to collect stem cells after combined cyclophosphamide chemotherapy and growth factor it is recommended to first increase the dose of filgrastim to 16 mcg/kg administered subcutaneously twice daily, before adding plerixafor. This dosing schedule should be continued for a number of days up to 4-7 days before adding plerixafor. Follow daily blood CD34 cell counts prior to initiation of plerixafor and consider adding plerixafor if the peripheral blood CD34 cell count reaches at least between 5- 10 cells/microliter. If the decision is made to administer plerixafor, filgrastim should only be administered once daily in the morning beginning the morning after the first evening dose of plerixafor.

Dosing and administration recommendations

The standard dose of plerixafor is 240mcg/kg (not to exceed 40mg/day) given subcutaneously in the evening. Plerixafor should be administered between 9:00-10:00p.m., with plans to begin apheresis at 8:00a.m. the following morning. If clinically able, a large volume collection should be performed to maximize the number of stem cells collected. Peripheral blood CD34 cell counts are not required once plerixafor is administered. Plerixafor and G-CSF should not be administered when the white blood cell count is > 100,000. Alternative dosing of plerixafor should be considered in the following situations:

Renal dysfunction: Plerixafor is excreted renally and should be dose-reduced in the presence of renal dysfunction. Plerixafor is not given to patient requiring dialysis.

For protocol 2533, patients are not allowed to enroll with the following impaired renal function

i. Estimated CrCl < 40 mL/min (using Cockcroft-Gault formula based on actual body weight) **and** serum creatinine > 2.0 mg/dL; OR
ii. Active, untreated SSc renal crisis at the time of enrollment.

Table 1. Dosing of plerixafor based on renal function

Creatine clearance (CrCl)	**Recommended dose of plerixafor**	**Dose not to exceed**
> 50 mL/min	240 mcg/kg	40 mg
≤ 50mL/min (not on dialysis)	160 mcg/kg	27 mg
Dialysis dependent	Not Recommended	

Obesity: Plerixafor dose calculation will be based on the patient's actual weight at screening, except if patient weighs >30% over their ideal body weight (IBW), then use adjusted weight.

Table 2. Ideal body weight calculation for plerixafor

Sex	Ideal body weight calculation	
Males	IBW (kg)	= 50 + [(2.3) x (Height in inches – 60)] = 50 + [(2.3) x {(Height cm) x (0.394) – 60}]
Females	IBW (kg)	= 45.5 + [(2.3) x (Height in inches – 60)] = 45.5 + [(2.3) x {(Height cm) x (0.394) – 60}]

The adjusted body weight (ABW) is calculated as: ABW(kg) = IBW + 0.4(actual weight – IBW)

Plerixafor should only be ordered as a single dose. If more than one dose is necessary, a new order must be written each time. The attending physician's signature must be present on an order for plerixafor.
Side effects from plerixafor are generally mild and include:

Gastrointestinal

Gastrointestinal side effects including diarrhea (37%), nausea (34%), vomiting (10%), flatulence(7%), abdominal pain, abdominal distention, dry mouth, stomach discomfort, oral hypoesthesia, constipation, and dyspepsia have been reported.

Local

Local side effects including injection site reactions (34%) have been reported. Mild to moderate injection site reactions at the site of subcutaneous administration of plerixafor have included erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, swelling, and urticaria.

General

General side effects including fatigue (27%) and malaise have been reported.

Nervous system

Nervous system side effects including headache (22%), dizziness (11%), and vasovagal reactions have been reported.

Musculoskeletal

Musculoskeletal side effects including arthralgia (13%) and musculoskeletal pain have been reported.

Psychiatric

Psychiatric side effects including insomnia (7%) have been reported.

Note: Advise female patients with reproductive potential to use effective contraceptive methods during plerixafor use because of risk to unborn.

References for Appendix V

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Appendix W
Criteria for the classification of systemic sclerosis

From: van den Hoogen F, Khanna D, Fransen J, et al., Ann Rheum Dis 2013; 72:1747-1755.

Table 1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis*

Item	Sub-item(s)	Weight/ score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

*These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (eg, nephrogenic sclerosing fibrosis, generalised morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
†The total score is determined by adding the maximum weight (score) in each category. Patients witha total score of ≥9 are classified as having definite systemic sclerosis.
SSc, systemic sclerosis.

Table 2 Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis

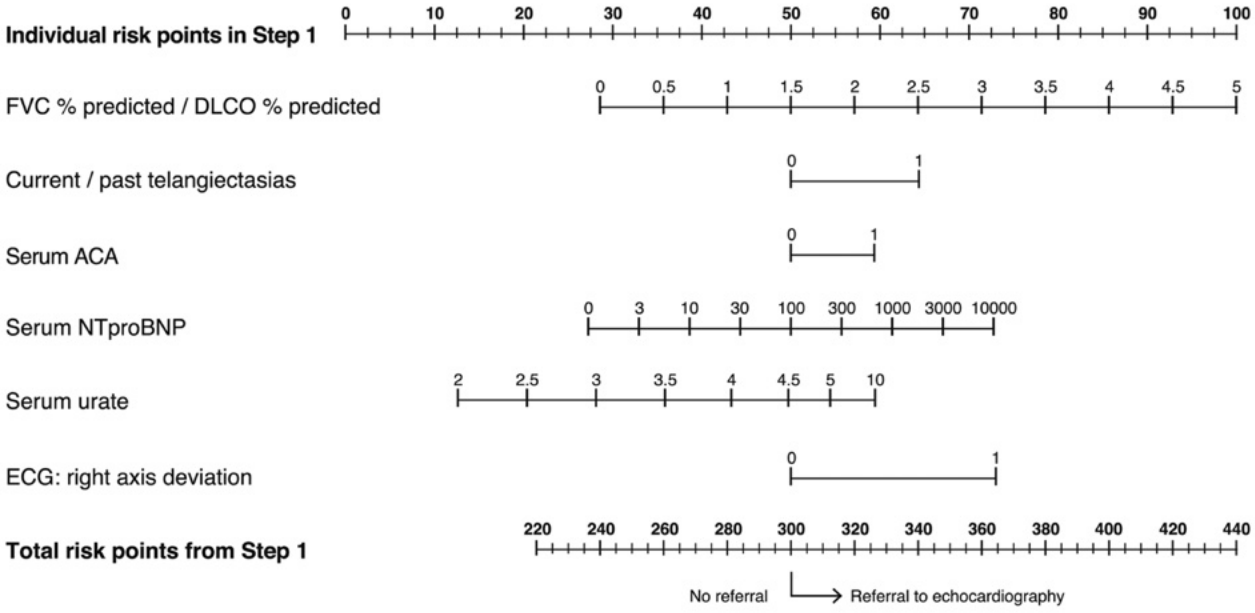
Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits–a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of 'Velcro' crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase colour change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related auto antibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti– RNA polymerase III antibody. Positive according to local laboratory standards.

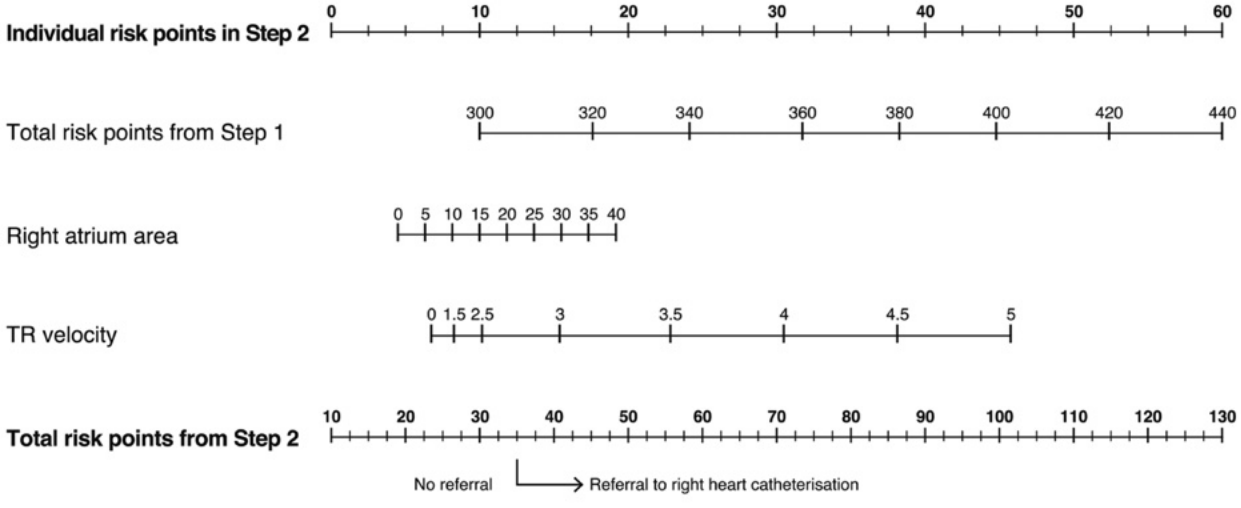
SSc, systemic sclerosis.

Appendix X
DETECT Criteria

The DETECT criteria were developed in a prospective, validated study to identify clinical risk factors for pulmonary hypertension in patients with systemic sclerosis. The DETECT criteria will provide guidelines for evaluation of patients prior to transplant who may require cardiac catheterization to evaluate pulmonary artery pressures.

Appendix X: Nomogram for application of DETECT algorithm
Clinical and epidemiological research (published by group.bmjcom)





Nomograms for practical application of the DETECT algorithm: determination of the likelihood of pulmonary arterial hypertension and cut-off points for decision to refer a patient to echocardiography (Step 1) and subsequent right heart catheterisation (Step 2).

At Step 1 (top panel), risk points for each of the six non-echocardiographic variables are calculated by reading from 'Individual risk points in Step 1' and adding them up to obtain a total. If the 'Total risk points from Step 1' is >300 (corresponding to a sensitivity of 97% as selected by the Study Scientific Committee) the patient is referred to echocardiography. Similarly, at Step 2 (bottom panel), risk points for the carried forward 'Total risk points from Step 1' and the two echocardiographic variables are calculated by reading from the 'Individual risk points in Step 2'. If the 'Total risk points from Step 2' is >35 (corresponding to a specificity of 35% as selected by the Study Scientific Committee) the patient is referred to right heart catheterisation. Alternatively, being less conservative (65% predefined specificity at Step 2), the patient would be referred to right heart catheterisation if 'Total risk points from Step 2' is >40 (compare table 3 for the performance of these two options). Note that all variables will always contribute risk points irrespective of the measured value; for example, a negative serum ACA will contribute 50 risk points. Exclusion of any single variable from the DETECT algorithm has only a small impact on model performance (see online supplementary appendix 9). If a single Step 1 variable is missing it should be assigned 50 risk points, with the exception of current/past telangiectasias which should be assigned 65 points. If a single Step 2 variable is missing it should be assigned 10 points. The nomograms cannot be reliably used if more than one variable out of the eight total variables is missing. ACA, anticentromere antibody; DLCO, pulmonary diffusing capacity for carbon monoxide; FVC, forced vital capacity; NTproBNP, N-terminal probrain natriuretic peptide; TR, tricuspid regurgitant jet.