Autologous Hematopoietic System Cell Transplant for Patients with Systemic Sclerosis and Cardiac Dysfunction

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PROTOCOL TITLE:
Cardiac Safe Transplants "CAST" Protocol

TREATMENT:
Autologous hematopoietic stem cell transplant for patients with systemic sclerosis and cardiac dysfunction

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	N/A
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Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
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Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☒ Yes ☐ No
DSMB / DMC / IDMC	☒ Yes ☐ No

OBJECTIVES:

We propose a safer conditioning regimen for autologous hematopoietic stem cell transplant (HSCT) for patients with systemic sclerosis who also have disease-related cardiac dysfunction.

BACKGROUND:

Classification and Clinical Manifestations of Systemic Sclerosis:

Scleroderma is Greek for "hard skin." Scleroderma localized in isolated areas is called morphea or linear scleroderma and does not affect internal organs. Systemic sclerosis (SSc) is a type of scleroderma that not only affects skin, but also involves internal organs (e.g., esophagus, bowel, lungs, heart, kidneys). Limited cutaneous systemic sclerosis (lcSSc) has skin involvement limited to the fingers, hands, and face, but still has internal organ involvement. Diffuse cutaneous systemic sclerosis (dcSSc) has more extensive skin involvement and may involve hands, face, arms, chest, abdomen, thighs, and legs (1). Many patients with lcSSc have CREST syndrome, which stands for calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. The most common tool used to assess the severity of skin involvement in the modified Rodnan skin score (mRSS), with which an examiner assigns a score of zero to three to 17 areas of the skin, with a maximum score of 51. Zero indicates no involvement, and one, two, and three indicates mild, moderate, or severe thickening, respectively (2).

The most common general symptoms of SSc are fatigue, myalgias, arthralgias, stiff joints, loss of strength, pain, sleep difficulties, and skin discoloration. Skin involvement, characterized by skin thickening and hardening, is a universal feature of SSc, although a small percentage of patients have vascular and fibrotic features of systemic disease without skin involvement, referred to as SSc sine scleroderma (1). Skin involvement often begins with swelling and erythema in the hands, followed by progressive skin hardening and tightening, usually first noticeable in the hands, fingers, and face. Other skin manifestations include pruritis, skin hyper or hypopigmentation, appendicular hair loss, sclerodactyly (finger curling due to skin hardening), digital ulcers, pitting fingertips, telangiectasia, and calcinosis cutis (calcium deposits) (1).

One of the most common clinical manifestations in SSc as result of vascular dysfunction is Raynaud's phenomenon (1). While many otherwise healthy people may have Raynaud's phenomenon, it is one of the early signs in patients with SSc. Raynaud's is "reversible vasospasm due to dysfunctional changes in the digital arteries in the hands and feet", however may be more progressive with permanent changes in small blood vessels and blood flow in patients with SSc (1). Raynaud's is usually triggered by stress or temperature change, most often cold, and can cause white, blue, or red color changes in the digits. Other severe complications of vascular injury and tissue damage include ischemic digital ulcers that can become gangrenous or infected, gastric antral vascular ectasia (GAVE), pulmonary artery hypertension (PAH), scleroderma renal crisis, and myocardial fibrosis and/or infarction, which will be discussed separately (1).

Extracutaneous Organ Involvement in SSc

Organ involvement in SSc may include pulmonary, renal, gastrointestinal (GI) tract, cardiac and musculoskeletal. Pulmonary involvement with evidence of interstitial lung disease (e.g. nonspecific interstitial pneumonitis (NSIP), usual interstitial pneumonitis (UIP), or diffuse alveolar damage) is present in 55% of patients on high resolution chest CT at initial evaluation, however the prevalence is much higher (1, 3). Interstitial lung disease (ILD) is often an early complication of SSc with greater progression if the first four years, and is characterized by "ground glass" opacities on a high-resolution chest CT, bibasilar inspiratory crackles, and a restrictive ventilatory defect on a PFT (decreased FVC, TLC, and DLCO; FEV_1 may be preserved; FEV_1/FVC ratio may be normal or increased) (3). In addition, the presence of anti–topoisomerase I antibody is associated with an increased risk of SSc-ILD (sensitivity, 45%; specificity, 81%), whereas anti-centromere antibodies are usually not present in patients with SSc-ILD (3). Some patients are asymptomatic, but most will eventually develop dyspnea on exertion, fatigue, and/or a non-productive dry cough as the disease progresses. Some patients may eventually have dyspnea at rest and may require the use of oxygen. Another pulmonary condition that may develop is pulmonary vascular disease, which can lead to PAH. PAH, usually a late complication of SSc, is associated with both lcSSc and dcSSc and is characterized by dyspnea on exertion, exercise intolerance, and hypoxemia (1), PAH is usually progressive, and can lead to cor pulmonale, right-sided heart failure, and death (1).

Many patients with SSc will slowly develop kidney damage, evidenced by microalbuminuria, mild creatinine elevation, and hypertension; however, most remain asymptomatic and do not develop chronic renal failure (4). Scleroderma renal crisis is an acute, life-threatening, condition that occurs in 12-15% of patients with dcSSc, and usually occurs in the early stage of the disease (1, 5). Renal crisis is characterized by the acute onset of oliguric renal failure, microangiopathic hemolysis, thrombocytopenia, mild proteinuria on urinalysis, and moderate or marked malignant hypertension, although some patients are normotensive (1). Patients may also experience headaches, blurred vision, or pulmonary edema from the marked hypertension (1). Some patients with scleroderma renal crisis may require hemodialysis, which may be temporary or permanent. Treatment for scleroderma renal crisis is blood pressure control, with use of ace-inhibitors and calcium channel blockers. Other blood pressure agents may be required; however, beta-blockers should be avoided due to concurrent Raynaud's which can be worsened by beta blockers because of their effects on peripheral circulation (6).

GI involvement in common in both diffuse and limited cutaneous SSc, with more than 90% of patients being affected (1). Patulous esophagus and esophageal hypomotility or dysmotility is common and can result in gastroesophageal reflux, chronic esophagitis, stricture formation that may require dilation, Barrett's esophagus, and microaspiration. Dyphagia, hoarseness, cough after swallowing, heartburn, alternating constipation and diarrhea, fecal incontinence, pseudo-obstruction, and bacterial small bowel overgrowth with malabsorption are other GI complications that may develop (1).

Gastral antral vascular ectasia (GAVE), characterized by dilated capillaries in the lamina propria of the gastric antrum, is another complication of SSc that can result in acute or chronic intestinal bleeding and anemia (7). This condition is also sometimes call "watermelon stomach" because of the appearance of streaky, red spots arranged in stripes departing from the pylorus that resemble a watermelon rind (7). GAVE may cause intermittent oozing of blood or severe, acute, bleeding, and patients often report melena and/or hematochezia. Diagnosis is made by an upper endoscopy. First-line treatment is argon plasma coagulation (APC) (electro-cauterization), as it has been shown to be as effective as surgery and safer, however it may require several treatments (7, 8).

Cardiac involvement with SSc is associated with a poor prognosis, with a five-year mortality rate of 75% (1). Myocardial fibrosis, which is thought to result from recurrent vasospasm of small vessels in the heart (cardiac Raynaud's), can cause stiff ventricles and lead to systolic, and more commonly lead to diastolic ventricular dysfunction (1). Pericardial disease with pericarditis and pericardial effusions are seen with patients with SSc. Pericardial effusions have been associated with renal crisis, perhaps due to more severe disease, or possibly because a large pericardial effusion can reduce cardiac output, impair renal perfusion, and trigger events that may cause a renal crisis (1). Arrhythmias are also common in SSc because the conduction system and myocardium become impaired from fibrosis. Ventricular arrhythmias are a cause of sudden death in patients with SSc (1). There are reports of macrovascular involvement in SSc, increasing the risk of myocardial infarction (9).

Musculoskeletal complications of SSc include inflammatory arthritis with joint pain, contractures in the fingers, wrists, elbows, and ankles, immobility, and polymyositis

which may develop from fibrosis around the tendons. In some cases, tendon friction rubs, which may be a marker for more aggressive disease, can occur in the fingers, wrists, elbows, knees, and ankles (1). Although not well understood, patients with SSc are at increased risk of developing malignancy, particularly lung cancer (1). Patients with SSc are also at greater risk of developing venous thromboembolism, including dee p vein thrombosis and/or pulmonary embolism, especially in the first year after diagnosis (10). This may be due to the inflammatory nature of the disease with pro-inflammatory cytokines contributing to the activation of the coagulation cascade, or may be due to endothelial dysfunction (10). Erectile dysfunction is very common in men with SSc, developing in more than 80% of men in some reports, and usually appears early or may be one of the first symptoms of the disease (1). If neuromuscular involvement occurs, it may include peripheral and autonomic neuropathies, myopathy, or inflammatory myositis (1).

Pathogenesis of Systemic Sclerosis

The molecular pathogenesis of SSc has been elusive, although several processes are thought to be important, including vascular, fibrotic, inflammatory, and immunologic. The etiology is unknown, although it is likely that inflammatory and fibrotic responses are triggered by environmental exposures in those who have an underlying genetic predisposition (11). Proposed environmental exposures include vinyl chloride, silica dust, organic solvents, medications (bleomycin, cocaine, pentazocine), and viruses (cytomegalovirus, parvovirus B19), which may trigger the occurrence of the disease (11).

SSc is a connective tissue disease characterized by excessive synthesis of extracellular matrix resulting in collagen deposition on the skin and visceral organs (skin and lung fibrosis). SSc also causes diffuse vasculopathy or microangiopathy due to endothelial dysfunction (e.g. Raynauds, renal crisis, digital ulcers, GAVE, and PAH), and systemic immune activation (e.g. autoantibody production) (12). Mediators which may play a role in the vascular tone and endothelial changes include endothlin-1 (ET-1) (potent vasoconstrictor), nitrous oxide (balances the action of ET-1 in normal blood vessels), superoxide anions (inflammatory mediators), neural and hormonal mediators, hypoxia, and physical stress (12).

It is believed that autoimmunity, vasculopathy, and inflammatory cell infiltration precedes fibrosis (13). Infiltrated cells, such as endothelial cells and fibroblasts, may produce cytokines, chemokines, and growth factors that activate fibroblasts resulting in fibrosis (11, 13). The degree of cell infiltration correlates with the extent of skin thickening and progression (13).

Evidence of immune activation includes the presence of circulating antibodies and autoantibodies, which is present in more than 95% of patients (12). ANA antibodies are found in most patients with SSc. Autoantibody production is thought to be due to a disturbance in B-cell homeostasis (14), and autoantibodies such as anti-topoisomerase I, anti-centromere, and anti-RNA polymerase III are biomarkers that may be used for diagnosis, classification, and prediction of clinical features associated with SSc. See table below for serum autoantibodies associated with SSc (12).

Table 1: *Autoantibodies Associated with Systemic Sclerosis*

Antigen	Approximate Frequency (%)	Clinical Associations	Organ Involvement
SCl-70 (topoisomerase-1)	10 to 40	dcSSc	Lung fibrosis, isolated pulmonary HTN (less likely)
ANA	Most common Ab	dcSSc and lcSSc	
Centromere	15 t0 40	lcSSc	Associated with CREST
RNA polymerase III	4 to 25	dcSSc	Renal, skin, malignancy
U3 RNP (fibrillarin)	1 to 5	dcSSc, poor outcome black men	Pulmonary HTN, muscle
PM-Scl-100 PM-Scl-75	3 to 6	Overlap, mixed	Associated with myositis
U1 RNP	5 to 35	lcSSc, blacks, polymyositis overlap	Muscle
Th/To	1 to 7	lcSSc	Pulmonary HTN, lung fibrosis, small bowel
Anti-U11/U12	1 to 5	lcSSc and dcSSc	Lung fibrosis
Anti-Ku	1 to 3	Overlap SSc	Muscle and joint involvement, SLE overlap

Table 1: Adapted from UpToDate. Denton et. al. 2017 (12). (lcSCC: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; SLE: systemic lupus erythematosus; HTN: hypertension)

Diagnosis of Systemic Sclerosis

Three hallmark manifestations for diagnosis of SSc are fibrosis of the skin and/or internal organs, production of SSc-related autoantibodies, and evidence of vasculopathy. Typically, SSc should be suspected with the presence of swollen fingers and/or skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints without another condition to explain the findings, and other clinical symptoms are used to support the diagnosis (15). The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) met in 2013 to develop a classification criteria for SSc for inclusion in clinical studies (16). The table below describes the criteria. A score of nine or greater is supports the diagnosis of definite SSc (16).

Table 2: *ACR and EULAR 2013 Classification Criteria for Systemic Sclerosis in Clinical Studies*

Score of ≥9 supports diagnosis of definite SSc

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
	Sclerodacylyl 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 ulcers	3
Telangiectasia	–	2
Abnormal nail-fold capillaries	–	2

Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary artery 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 Anti-topoisomerase I Anti-RNA polymerase III	3

Table 2: van den Hoogen F, Khanna D, Fransen J, et al. 2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum 2013; 65:2737. (16).

Differential Diagnosis of Systemic Sclerosis

There are several conditions that can cause scleroderma-like skin changes, as well as differentials for Raynaud's and interstitial lung disease that should be considered when making the diagnosis of systemic sclerosis (15).

Table 3: *Differential Diagnosis of Systemic Sclerosis*

Differential Diagnosis	**Characteristics**
Scleredema	Symmetrical skin thickening on trunk, shoulders, and upper back. Key is back is involved. Face be affected but fingers are not. Raynuad's and autoantibodies are not present. Internal organ involvement is rare.
Scleromyxedema (popular mucinosis)	Waxy, yellow-red papules on head, neck, arms, upper trunk; may occur on thickened skin. Monoclonal protein IgG lambda detected by immunofixation supports diagnosis. May be associated with amyloid and multiple myeloma.
Overlap Syndrome: concurrent inflammatory autoimmune disorder including systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and Sjogrens syndrome	Diagnosis of SSc and another concurrent mixed connective tissue disease
Endocrine Disorders	Diabetes mellitus and myxedema from hypothyroidism may have skin induration. Type 1 diabetes can sometimes cause sclerodactyly.
Amyloidosis	Infiltration of skin can cause thickening and stiffness. Skin biopsy can confirm diagnosis.
Nephrogenic Systemic Fibrosis	Thickening and hardening of skin on trunk and extremities including hands and feet; can result from advanced renal failure or gadolinium from MRI.
Eosinophilic Fasciitis	Skin changes from thickened fascia that occurs proximal to wrists and ankles (feet and hands spared)

Table 3: adapted from UpToDate; Varga, Axford, & Curtis. Diagnosis and Differential Diagnosis of Systemic Sclerosis (Scleroderma) in Adults. 2017. (15).

Treatment for Systemic Sclerosis

Treatment for SSc is tailored to each individual patient, and includes treatment of the disease itself with Immune-modulating and suppressive medications, as well as treatment of SSc specific organ involvement (17). Early diagnosis of disease, determination if SSc is diffuse or limited, assessment of disease severity and extent of

internal organ involvement, identification of patients at risk for developing organ involvement, and monitoring of disease progression can help guide treatment (17, 18). Immune-modulating and suppressive medications that are commonly used for the treatment of SSc include prednisone, methotrexate (MTX), azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), cyclosporine, and chloroquine. For diffuse skin involvement, MTX or MMF are generally preferred (17). Research with large randomized controlled trials is limited for all drugs used for the treatment of SSc, and none have demonstrated significant long-term efficacy.

Methotrexate (MTX)

MTX has been studied in two small randomized trials comparing treatment to placebo (19, 20). While both trials showed a decrease in mRSS scores in the MTX group, the results were not statistically significant in improving skin score or pulmonary function. Another large observational study that compared four treatments (MTX, MMF, cyclophosphamide, and no treatment) in 326 patients with an early diagnosis of dcSSc showed "modest" improvement in skin scores in all groups, however there was no significant different between the groups (21).

Mycophenolate Mofetil (MMF)

A systematic review of 21 studies and 487 patients with SSc assessed the safety and effectiveness of MMF (22). There were 90 non-lethal adverse events including: 43 gastrointestinal events such as nausea, diarrhea, and abdominal pain (47.7%), 34 infections (26%), six cytopenias (5%), and two malignancies (2%). There were 18 deaths, however MMF groups showed a significantly better survival compared to the other treatment groups. Skin scores significantly improved in five of eight studies; however, follow-up was only for 12 months in many of the studies, and the findings were no longer significant in two of the studies at 12 months (22). Of thirteen studies that reported on pulmonary function tests, two showed significant improvements in DLCO and one showed an improvement in FVC, but all other findings were not significant. Six studies showed evidence of improvement of degree of diseased lung of CT scans, however none of the findings were significant (22).

Cyclophosphamide

The immune suppressive drug most commonly used for SSc-related interstitial lung disease is cyclophosphamide, administered either orally or intravenously. Cyclophosphamide has been reported to provide efficacy in randomized trials comparing oral cyclophosphamide (23) and pulse intravenous cyclophosphamide (24) to placebo for SSc-ILD, however the results must be interpreted carefully. The largest study to date, conducted by the Scleroderma Lung Study I (23), evaluated oral daily cyclophosphamide for one year versus placebo in 158 patients. After one year, patients treated with daily cyclophosphamide had a mean worsening of DLCO by 4.2% that was not significantly worse than the 3.5% decline for patients receiving placebo (23). FVC scores were found to be significantly different between the two groups at one year, although it worsened in both the cyclophosphamide and placebo groups by 1% and 2.6%, respectively (23), and after 2 years, the difference in FVC decline between placebo and cyclophosphamide was not significantly different (25). Another cyclophosphamide study by Hoyles et al. (24), randomized 45 patients to receive low dose prednisolone and 6 monthly infusions of IV cyclophosphamide followed by

azathioprine versus placebo. While the authors report a trend toward an improved FVC in the treatment group at 1 year (80.1 to 82.5 percent predicted), the findings were not significant (p=0.08) (24).

Cyclophosphamide vs. MMF

The Scleroderma Lung Study Group completed a second study (SLS-II) (26) that compared oral cyclophosphamide for 12 months followed by placebo for 12 months (n=73) to 24 months of MMF (n=69). Both groups showed significant improvements in FVC, however there was no difference between the groups at two years, and 16 patients died from worsening ILD (11 cyclophosphamide, 5 MMF) (26). The SLS study group also compared the placebo group in the SLS-1 study (n=79) to the MMF group in the SLS II study (n=69) (27). Upon analysis, there were significant improvements in the MMF group in % predicted FVC, % predicted DLCO, mRSS, and dyspnea over two years (27). Authors concluded that MMF appears to be as effective as cyclophosphamide and safer for use (27).

IVIg, Rituximab, D-Penicillamine, Corticosteroids, and Cyclosporine

IVIg is a relatively newer treatment that has shown some improvements in skin and gastrointestinal complications in small trials, however larger randomized trials still need to be performed (28, 29). Several small studies with mixed results have assessed the efficacy of rituximab on lung and skin function as there may be a B-cell driven autoimmunity component in SSc (30). One small randomized controlled trial of 16 patients compared rituximab to placebo and did not find any significant difference in lung or skin (31). In a prospective study of 20 patients, there was improved FVC and TLC at 12 months in the rituximab group compared to standard treatment, however there is no long-term follow-up (32). D-penicillamine is a treatment that was used more often in the past, but is no longer commonly used, as it demonstrated no improvement in skin score in a randomized double-blinded trial (33). Corticosteroids and cyclosporine are still sometimes used, however are not as common because they have shown little efficacy and have been reported to precipitate renal crisis (3, 34, 35). Other drugs such as endothelin-1 antagonists, IL-6 blockade, tyrosine kinase inhibitors have been attempted for SSc-ILD, but have been found to be either ineffective, unsafe, or both (3).

Lung Transplantation

The literature is evolving for the use of lung transplantation for ILD with mixed results about the risk of mortality. Some studies have found an increase in mortality rate in lung transplantation for SSc-ILD compared to those without SSc (36), while other studies have not (37, 38). Severity of esophageal dysfunction is one factor that is thought to increase the risk of mortality due to aspiration, however two studies have found that the severity of esophageal dysfunction did not have an impact on mortality after lung transplantation (39, 40). Nonetheless, given that standard drugs do not improve lung function in SSc-ILD, lung transplant is being utilized more often.

Summary of Immune-Modulating Treatments

Although various immune suppressive treatments have been employed to treat SSc, none of them seem to have changed the natural history of scleroderma. Cyclophosphamide, the one immune suppressive medication thought most effective for SSc, lacks convincing data from randomized trials to unequivocally demonstrate its efficacy. Pulse IV cyclophosphamide was not found to be superior over placebo at one

year. The Scleroderma Lung Study Group reported "modest benefit" for oral cyclophosphamide compared to placebo, however lung function did not improve but rather that declined less compared to placebo over a 12-month interval, and by 2 years, the decline in lung function was no different between the groups (23, 25). Thus, oral cyclophosphamide treatment may slow progression of diseased lung at one year, but does not improve lung function at one or two years. MMF may be as effective as cyclophosphamide and safer for use, but no single drug has shown any significant improvement of lung disease or skin score past one year. Lung transplant is sometimes used as a last resort for SSc-ILD, but has been associated with high mortality.

Treatment for SSc-specific Organ Complications

In 2016, the European League against Rheumatism (EULAR) met to revise the 2009 pharmacologic treatments for SSc-specific organ complications (18). New recommendations were developed to address Raynaud's phenomenon (RP), digital ulcers (DUs), pulmonary artery hypertension (PAH), skin and lung disease, scleroderma renal crisis, and gastrointestinal involvement (18). The table below summarizes the recommendations and includes treatments for calcinosis, pruritis, and arthralgias. Of note, HSCT is a recommended treatment for severe skin and lung disease (18).

Table 4: *Systemic Sclerosis Organ-Specific Treatments (17, 18)*

SSc-Organ Complication	Pharmacological Recommendations
SSc-Raynaud's Phenomenon	1. Dihydropyridine-type calcium antagonists such as Nifedipine and PDE-5 inhibitors reduce the frequency and severity of SSc-RP attacks and should be considered first-line therapy (strength A). 2. IV iloprost reduces the frequency and severity of SSc-RP attacks and should be considered in severe cases after oral therapy (strength A). 3. Fluoxetine may improve SSc-RP attacks (strength C).
SSc-Digital Ulcers	4. IV iloprost is efficacious in healing DUs and should be considered for treatment (strength A). 5. PDE-5 inhibitors improve healing of DUs, may prevent new DUs, and should be considered for treatment (strength A). 6. Bosentan may reduce the number of new DUs, and should be considered for treatment for reduction of new ulcers, especially in patient with multiple ulcers despite the use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy (strength A).
SSc-Pulmonary Artery Hypertension	7. Endothelin receptor antagonists (ambrisentan, bosentan, mecitentain), PDE-5 inhibitors (sildenafil, tadalafil), and riociguat have been approved for connective tissue disease PAH, and should be considered to treat SSc- PAH (strength B). 8. Continuous IV epoprostenol improves exercise capacity, functional class, and hemodynamic measures and should be considered for severe SSC- PAH (strength A). 9. Prostacyclin analogues (iloprost, trepostinil) have been used and may be considered for treatment of SSc-PAH (strength B).
Skin and Lung Disease	10. Methotrexate improves skin score in early diffuse SSc (strength A). 11. Cyclophosphamide should be considered for SSc-ILD or progressive SSc- ILD (strength A). 12. HSCT should be considered for patients with rapidly progressive SSc at risk for organ failure. Careful selection of patients and experience of medical team is important when considering HSCT (strength A).

Scleroderma Renal Crisis	13. Cohort studies show benefit in survival with use of ACE-inhibitors and experts recommend immediate use for SRC (strength C). 14. Glucocorticoids are associated with higher risk of SRC. Blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids (strength C).
SSc-related gastrointestinal disease	15. PPI should be used for the treatment of SSc-related GERD and prevention of esophageal ulcers and strictures (strength B). 16. Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc.) (strength C). 17. Intermittent or rotating antibiotics should be used to treat symptomatic small intestine bacterial overgrowth (strength D).
Other Treatments	18. Calcinosis cutis with infection: oral minocycline 50 to 100 mg daily for 6-12 weeks (17). 19. Pruritis: antihistamines, capsaicin cream, low dose prednisone (less than 10 mg) (17). 20. Arthralgias/inflammatory arthritis: NSAIDS, low dose prednisone hydroxychloroquine 200 to 400 mg PO daily, physical therapy (17).

Table 4: adapted from Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis.* 2017;76(8):1327-1339.

Prognosis of Systemic Sclerosis

Systemic sclerosis has the highest mortality of all rheumatologic diseases, with a pooled standardized mortality ratio of 3.5 and an average loss of life expectancy of 16-34 years (41). More than half of the deaths are from the disease itself; however, many deaths are related to malignancy and atherosclerotic vascular disease that SSc patients are at higher risk for (41). The prognosis for lcSSc is significantly better than for dcSSc with a mortality of 1-4% versus 5-10% per year, respectively, and higher skin scores are associated with greater mortality (17, 42). Survival for patients with systemic sclerosis has improved over the last three decades, however mortality is still comparable to many types of cancer. Prevention and treatment for renal crises with angiotensin converting enzyme inhibitors and improvement in treatment for PAH with endothelin receptor antagonists has diminished renal and PAH related deaths, but there has been an ensuing increase in the proportion dying from interstitial lung disease (ILD), and PAH still remains one of the leading causes of death in SSc (3, 41). In a meta-analysis of 2,691 patients with SSc in a 40-month period, the standardized mortality ratio was approximately fourfold higher than age and sex matched controls in the general population (43). There were 732 deaths, in which 53% were thought to be related to SSc, 16% were unknown, and 30% were from other causes. Of the known deaths, heart involvement was the most frequent cause (29%), followed by lung involvement (23%), cancer (16%) and kidney involvement (11%).

Autologous HSCT for Systemic Sclerosis

Autologous hematopoietic stem cell transplantation works by giving an intense immune-suppressive therapy (conditioning regimen) that ablates the aberrant disease-causing immune cells, resulting in an immediate immune cease fire. The hematopoietic stem cells then regenerate in a non-inflammatory environment a new immune system that is self- tolerant. (48). Several retrospective and prospective phase I-II trials (table 5) have been published on auto-HSCT for SSc which have demonstrated significant improvements in mRSS score and pulmonary function, and also have formed the basis for randomized controlled trials in HSCT for SSc. Three randomized controlled trials comparing HSCT to standard therapy have been published (44, 45, 46), and all have

revealed the efficacy for HSCT with significant improvements in survival, skin scores on mRSS, FVC, and quality of life sustained for up to 4.5 years. In addition, Burt et al. (2011) showed evidence of decreased interstitial lung disease on high resolution chest CT (46). To date, this has been the first treatment to not only stop progression of the disease, but also to reverse the detrimental and life-threatening manifestations of the disease. Toxicity and treatment related mortality was generally high in the initial reports on HSCT for SSc, however this was decreased by reducing the regimen intensity, excluding patients with pulmonary artery hypertension or other evidence of right ventricular stress, and treating earlier in disease course (47, 48). Given the severity and poor prognosis of the disease, HSCT is the hope for survival in many patients.

Table 5 below summarizes the findings from all major studies on non-randomized studies that have been published on auto-HSCT to date. Following is detailed results from three randomized controlled trials (44, 45, 46) that have been published, and results from 90 patients that have been treated at Northwestern using ASSIST's conditioning regimen (51).

First Author, Year (ref)	Study Design	Center (number/ location)	# patients (HSCT vs control)	Study Enrollment Date Range	Regimen	Conditioning regimen	Study follow up	Skin Score mRSS	PFT or CT findings	Overall Mortality/ TRM	Survival/ progression free survival
Del Papa, 2017 (49)	Retrospective, compared to conventional therapies	Single Center (Italy)	18	2003 to 2011	Non-myeloablative	Cy 200 mg/kg +rATG 7.5 mg/k x3	5 years	Significant improvement in HSCT group compared to control	DLCO: no significant improvement	Not reported/ 5.6%	Significant Improvement in survival in HSCT group (>80%) compared to control group (39%), cyclophosphamide group (44%)
Henes, 2014 (50)	Retrospective	Single center (Germany)	6	December 2008 to May 2012	Non-myeloablative	Thiotepa 50 mg/kg x2, rATG 10 mg/kg x4	Median 1.6 years	mRSS significant improved at 6 and 12 month	Total lung volumes on CT significantly improved	Not reported/ 0%	83.3%/66%
Henes, 2012 (52)	Retrospective	Single Center (Germany)	26	November 1997 to October 2009	Non-myeloablative	Cy 200 mg/kg, rATG 10 mg/kg x4	3 years	Improved in 78.3% (18 of 23) at 6 months, 3 o improved after 6	FVC significantly improved at 6 (66%) and 12 months (76.1%); DLCO unchanged	27%/11% (3 of 26 died after mobilization)	74% at 3 years/ 53% at 3 years
Farge, 2010 (53)	Retrospective	Multi-Center (172 Europe)	175	1996 to December 2007	Mixed	TBI (7%), Cy 150-200 mg/kg (52%), busulfan (4%), BEAM (34%), ATG (55	5 years	Not reported	Not reported	Not reported	76%/55%
Vonk, 2008 (54)	Retrospective	Multi-Center (1 Dutch, 1 French)	26	March 1998 to May 2004	Non-myeloablative	Cy 200 mg/kg+ALG	7 years	Improved in 73% at 1 year and 94% at 5 years	No change	8% / 0%	96% at 5 years
Nash, 2007 (55)	Prospective	Multi-Center (5, USA)	34	July 1997 to March 2005	Myeloablative	TBI 800 cGy + lung shielding +120 mg/kg Cy + eATG 90 mg/k	8 years	Improved in 70%	Increased FVC / decreased DLCO	36% / 23%	64% at 5 years
Oyama, 2007 (56)	Prospective	Single Center (USA)	10	Not stated	Non-myeloablative	Cy 200 mg/kg + rATG 1.5 mg/kg x5	3 years	Improved in 100% but 20% relapse	No change	10% / 0%	90%
Tsukamoto, 2006 (57)	Prospective	Single (Japan)	8 (6 with	S Completed 2005	Non-myeloablative	Cy 200 mg/kg	Median 21 months	Improved in 100% at 12 months	Improved in PaO2 and HRCT	0%	100%
Farge, 2004 (58)	Retrospective	Multi-Center (22, Europe)	57	January 1996 2002	Non-myeloablative	Cy 150-200 mg/kg (61 %) or Cy 200 + ATG (21%)	Median 20 months	Improved 70% at 6 months, 66% at 12 month, 78% at 24 month, 60% at 36 month	No change	23% / 8.7%	72% at 5 years
Farge, 2002 (59)	Prospective	Multi-center	11	January 1998 January 2001	Mixed	Cy 200 mg/kg or melphalan 140 mg/m2	Median 18 months	Improved in 66%	No change	36% / 9.1%	Not reported
McSweeney, 2002 (60)	Prospective	Multi-center (4)	19	January 1997 1980	Myeloablative	TBI 800 cGy +/- lung shieldin +120 mg/kg Cy 90 mg/kg	Median 14.7 month	Improved in 100	Worse at 3 months then return to baseline	21% / 15%	79% at 2 years
Binks, 2001 (61)	Prospective	Multi-center (18)	41	January 1996 1999	Mixed	Mixed	At least 3 months	Improved in 69%	FVC and TLC no change	27% / 17%	73% at 1 year

Results of Randomized Trials for HSCT in Systemic Sclerosis

Three randomized trials, SCOT (44), ASTIS (45), and the American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) (46) have now demonstrated that autologous hematopoietic stem cell transplantation (HSCT) is superior to cyclophosphamide therapy for patients with systemic sclerosis (SSc) (Table 6). In these trials, autologous hematopoietic stem cells (HSC) have no direct therapeutic effect and are infused to shorten or prevent prolonged cytopenia in non-myeloablative and myeloablative regimens, respectively. Since toxicity and efficacy arises from patient selection and the conditioning regimen, physicians need to be aware of the different chemotherapy or radiotherapy regimens used in these trials to understand subtle differences in results.

Two trials (ASSIST, ASTIS) utilized a non-myeloablative regimen of cyclophosphamide and rabbit anti-thymocyte globulin (rATG). The main difference between the treatments in the two studies was that ASSIST mobilized stem cells with 2 g/m2 cyclophosphamide and infused unmanipulated peripheral blood stem cells (PBSC) while ASTIS mobilized stem cells with 4 g/m2 cyclophosphamide and infused PBSC that had been ex vivo purged of lymphocytes by CD34+ selection.

The primary endpoint of ASSIST was improvement in modified Rodman skin score (mRSS) or in pulmonary forced vital capacity (FVC). The ASSIST design allowed crossover for control failures plus an interim analysis. While ASSIST originally aimed to enroll 75 patients in each arm, the randomization was stopped after 19 patients due to failure to reach equipoise. The interim analysis demonstrated statistically significance improvement for HSCT, while the majority of patients worsened on the control arm and crossed-over to HSCT. Thereafter, the ASSIST treatment regimen was used with 90 patients undergoing HSCT (51) and resulted in significant improvement in mRSS, FVC, and all components of quality of life (QOL): physical component score (PCS), mental component score (MCS), and total score (TS) (46, 51). While diffusing capacity for carbon monoxide (DLCO) did not show improvement, DLCO did improve significantly in the subset of patients with normal pre-HSCT echocardiograms and electrocardiograms, emphasizing the underappreciated importance of cardiac function on DLCO.

The non-myeloablative ASTIS trial had a primary endpoint of event free survival (EFS) (death or persistent major organ failure) and allowed crossover after 2 years. At 2 years, HSCT demonstrated significant improvement in mRSS, FVC, total lung capacity (TLC) and the PCS of QOL. EFS and overall survival (OS) were significantly in favor of HSCT. Transplant related mortality (TRM) was 10%, and was attributed predominantly to SSc- related cardiac dysfunction (81). Recognizing that the safety of cyclophosphamide intense regimen could be improved with more extensive cardiac screening and exclusion of patients with SSc-related cardiac dysfunction, we and others (European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Group) subsequently recommended a pre-transplant right heart catheterization to exclude patients with a resting pulmonary artery systolic pressure (PASP) > 40 mmHg or mean pulmonary artery pressures (mPAP) pressure of > 25 mmHg and after a fluid challenge with a liter of intravenous normal saline, exclusion of a PASP > 45mmHg or mPAP > 30 mmHg (80). A pre-HSCT cardiac MRI was also recommended to exclude patients with septal flattening (D-sign) (80-82). By adopting more stringent

cardiac screening, the current European Society for Blood and Marrow Transplantation observational trial with 82 transplanted patients has a TRM of 6.1% at 2 years (83).

The main regimen difference between the SCOT versus ASTIS and ASSIST trials is a lower dose of cyclophosphamide (120 mg/kg instead of 200 mg/kg) and addition of total body irradiation (TBI) that makes the SCOT trial myeloablative. SCOT began in 2005 with a projected enrollment of 226 patients. In 2010, due to slow accrual, enrollment size was decreased to 114 patients. In 2011, SCOT was closed to further recruitment due to slow enrollment. Although in part attributed to failure of private insurance reimbursement, protocol design may have contributed, since for ethical reasons, both ASSIST and ASTIS allowed crossover to HSCT, while SCOT did not.

The SCOT trial was initially constructed in 2005 similar to ASTIS with similar control arms, enrollment criteria, and the same endpoint of EFS in order to allow comparison of the two different types of transplant regimens. In 2010, SCOT changed the primary endpoint to a non-clinical outcome of global rank composite score (GRCS) that had never been vetted in another SSc study. The GRCS is a hierarchical scoring system that compares each subject's relative order for the outcome variables of: death, EFS, FVC, health assessment questionnaire-disability index, and mRSS. EFS between the two arms was not significantly different at 54 months, while the new endpoint of GRCS was significantly in favor of HSCT. At 72 months, EFS was also significantly in favor of HSCT. When the GRCS was broken into its components (SCOT supplement), the FVC did not improve significantly, and post HSCT malignancies were 10% (two myelodysplastic syndromes (MDS), one medullary thyroid cancer).

Three randomized autologous HSCT trials have now demonstrated superiority of HSCT over monthly intravenous cyclophosphamide. TRM for SCOT was 6.0% (1 due to late MDS), for ASSIST 6.0%, for ASTIS 10%, and for the recent EBMT observational study 6.1%. The percent of patients with transplant-related grade 4 toxicities was higher in the SCOT trial (85%) (SCOT supplement) compared to ASTIS (37%). SCOT had three malignancies in the transplant arm that appear to be TBI-related and one in the control arm. The incidence of malignancies was the opposite for ASTIS with one malignancy in the transplant arm, and 5 malignancies in the control arm (ASTIS supplement). The TBI based SCOT regimen did not improve pulmonary function, while ASSIST and ASTIS significantly improved both FVC and TLC. In summary, a cyclophosphamide intense regimen is not well tolerated by compromised hearts, while a TBI based regimen does not improve lung function and increases risk of late cancer.

Trials of autologous HSCT for SSc are continuing with development of hopefully less toxic non-myeloablative regimens (Burt et al www.clinicaltrials.gov NCT01445821). As experience grows, HSCT regimens may be individualized according to a patient's cardiac function and risk for renal crises. To minimize a center effect, HSCT should be confined to centers of expertise in what is an aggressive but effective treatment for extremely ill patients with a lethal disease (84, 53).

Table 6 – Comparison of ASSIST (American Systemic Sclerosis Immune suppression versus Stem cell Trial), ASTIS (Autologous Stem Cell Transplantation International *Scleroderma)* and SCOT (Scleroderma Cyclophosphamide Or Transplantation)

Trial- first author	Journal year (ref)	# patients # HSCT # centers	Allows cross over	Years follow-up after HSCT	Stem cell collection Cy dose / PBSC selection	Regimen	Primary endpoint P value	mRSS P value	FVC / TLC P-value	SF-36 QOL P-value	HSCT related death	Cancer	Overall survival HSCT / control P- value
ASSIST Burt	Lancet 2011 (3)	19 10 HSCT 1 center	Yes after 1 year	2	Cy 2 g/m2 no selection	Non-myeloablative Cy 200 mg/kg rATG 6.5 mg/kg	Clinical improvement in mRSS or FVC P< 0.0001 (2 year)	P=0.0004	FVC P=0.006 TLC P= 0.005	PCS P=0.007 MCS P= 0.07 TS P=0.003	0%	none	100% both arms
ASSIST regimen Burt	Lancet 2013 (4)	90 HSCT 2 centers	All HSCT	5	Cy 2 g/m2 no selection	Non-myeloablative Cy 200 mg/kg rATG either 6.5 mg/kg or 4.5 mg/kg	OS = 78% RFS =70% (5 year)	P= 0.0003	FVC P= 0.004 (3 year) TLC NS @	PCS P < 0.001 MCS P <0.005 TS P<0.001	6.0% 5/90	NR	78% 5-year
ASTIS van Laar / Farge #	JAMA 2014 (2)	156 79 HSCT 29 centers	Yes-after 2 years	7	Cy 4 g/m2 CD34+ selected	Non-myeloablative Cy 200 mg/kg rATG 7.5 mg/kg	EFS P=0.04	P<0.001	FVC P=0.004 TLC P= 0.02	PCS P=0.01 MCS P=0.91 TS (NR)	10% 8/79	Control- 5 HSCT- 1	82% 5-year P= 0.03
SCOT Sullivan	NEJM 2018 (1)	75 36 HSCT 26 centers	No	4.5 some 6 year data	G-CSF only CD34+ selected	Myeloabaltive TBI 800cGy Cy 120 mg/kg eATG 90 mg/kg	EFS (2005 to 54 months ITT -P= 0.06 PP -P=0.02 GRCS (after 54 months ITT - P =0.01	ITT P= 0.05 PP P=0.01	FVC ITT:P=0.3 PP: P=0.5 TLC (NR)	PCS ITT:P=0.02 PP:P=0.003 MCS ITT:P=0.1 PP: P=0.1 TS (NR)	6% 2/36	Control- 1 HSCT - 3	86% 54 months P= 0.28 72 months P= 0.02

# equal contribution by both authors, @ DLCO improved significantly if pre-HSCT echocardiogram (p=0.005) or electrocardiogram (p=0.05) were normal.
Cy=cyclophosphamide, DLCO= diffusing capacity for carbon monoxide, EFS = event free survival, i.e. death due to any causes or major organ failure (heart lung kidney), eATG=equine anti-thymocyte globulin, FVC= forced vital capacity, G-CSF=granulocyte colony stimulating factor, GRCS =composite of death, EFS, FVC, HAQ-DI, and mRSS, HSCT=hematopoietic stem cell transplantation, ITT= intention to treat, MCS= mental health score, mRSS=modified Rodnan skin score, NR=not reported, NS=not significant, PCS= physical composite score, PBSC= peripheral blood stem cell, OS= overall survival, PP= per protocol QOL= quality of life , rATG=rabbit anti-thymocyte globulin, RFS=relapse free survival, TBI=total body irradiation, TS=total score

Cardiac Evaluation and Treatment-Related Mortality in HSCT: Burt et al., (2013) (51)

Burt et al. (2013) published a non-randomized study of 90 patients with systemic sclerosis (59 from Northwestern, Chicago IL and 31 from University of Sao Paulo Brazil) who underwent non-myeloablative autologous HSCT. In the study, five of 90 patients (6%) died of treatment-related causes, in which four of the deaths were cardiac related. Five-year survival was 78% (eight relapse-related deaths) and relapse-free survival was 70% at five years. Mean mRSS scores and FVC was significantly improved compared to baseline at one-year, two-year, and three-year time-points. Several important considerations for HSCT in SSc were highlighted in this study. First, it was noted that 14 patients had volume overload of more than 5 kg due to hyper-hydration of fluid during with cyclophosphamide. After the first 20 patients were treated, hydration was decreased to 50-100 ml/hr and continuous bladder irrigation was used for bladder protection during cyclophosphamide. After making this change, volume overload no longer occurred, indicating that patients with SSc cannot tolerate increased amounts of IV fluid. A second important point of the study was the evolution of additional cardiac screening prior to HSCT with echocardiogram, cardiac MRI, and right cardiac catheterization with fluid challenge in order to detect patients with cardiac involvement who may have increased risk of mortality. Specifically, diastolic flattening (D-sign) or septal bounce on MRI which is a sign of decreased ventricular compliance, myocardium scar detected by late gadolinium enhancement of myocardium as an indication of poor myocardial reserve, and left ventricular dysfunction detected on fluid challenge on cardiac catheterization were noted as ominous signs and should be taken into consideration prior to HSCT. Finally, the study revealed that any patient with evidence of cardiac involvement prior to HSCT, such as an abnormal echocardiogram or ECG, did not show improvement in DLCO, whereas patients with normal heart function, were more likely to show improvement in DLCO after HSCT.

Rationale for a New Conditioning Regimen: It's a Matter of the Heart

Some patients, independent of myeloablative or non-myeloablative intent, died of cardiac failure, leading to the need for careful pre-enrollment cardiac evaluation. SSc-related cardiac disease may increase the risk of transplant by several means: tamponade or occult constrictive pericarditis from pericardial disease, intramyocardial Raynaud's (microvascular coronary artery vasospasm), myocardial fibrosis, conduction defects, and arrhythmias precipitated by myocarditis, and right heart dysfunction and / or left ventricular diastolic dysfunction via interventricular septal flattening from pulmonary artery hypertension (62, 63, 64).

The future of stem cell transplant for SSc is developing conditioning regimens for HSCT that are safer, to avoid treatment related mortality. Cyclophosphamide, the drug that is used in many conditioning regimens for HSCT for SSc, is known to cause cardiac toxicity, which can be exacerbated and lead to death in a patient who already has cardiac involvement with SSc. However, due to the mortality of the disease, it becomes an ethical dilemma to decline HSCT in a patient when no other treatments have shown to be effective.

This led to the development of ASSIST 2b, which is currently open for enrollment at Northwestern University, and compares the conditioning regimen in the initial ASSIST

trial (control) to a conditioning regimen that is less cardiac toxic (treatment). In the new regimen in the treatment arm, the cyclophosphamide dose has been decreased to 120mg/kg (60mg/kg/day x 2) compared to 200mg/kg (50mg/kg/day x4) in the control arm. The regimen in the treatment arm also includes fludarabine (30 mg/m$_2$ IV for three days). Both arms are given rATG. While the trial is ongoing and the results are not yet published, initial data shows that the transplant is as effective as the standard regimen, and in theory, is less cardiotoxic compared to the standard regimen due to the lower dose of cyclophosphamide.

We now propose a non-randomized study for HSCT that uses a conditioning regimen that is even less cardio-toxic for patients who have severe SSc-related cardiac dysfunction and who are not eligible for the ASSIST 2b study due to cardiac exclusion criteria. The conditioning regimen would consist one just one dose of cyclophosphamide (60 mg/kg), with fludarabine, rATG, and rituximab. Given that cardiac dysfunction is the leading cause for mortality in SSc, the goal of the regimen is to offer these patients a chance of disease remission utilizing a safer HSCT conditioning regimen.

Conditioning Regimen Selection and Safety Considerations

The conditioning regimen should be chosen with careful consideration of the risks and benefits to maximize immune suppression and minimize toxicity. Non-myeloablative regimens should be utilized for HSCT in autoimmune diseases because they are designed to maximally suppress the immune system without destruction of the bone marrow stem cell compartment. Recovery from conditioning regimen cytopenia would occur without reinfusion of stem cells; however, the stem cells are given because they shorten the interval of neutropenia and duration of hospitalization. In addition to patient safety benefits from lower toxicity, non-myeloablative regimens are less expensive and less likely to be associated with late complications such as infertility or secondary solid tumors, MDS/leukemia (65-67). The risk of developing secondary cancers may be even higher in systemic sclerosis patients exposed to myeloablative regimens with total body irradiation because cells from SSc patients have a higher incidence of increased genetic instability with abnormal chromosome fragility and breakage compared to the general population (68-72).

The conditioning regimen for this trial will be non-myeloablative and will use the following drugs: cyclophosphamide, rATG, rituximab, fludarabine, and intravenous immunoglobulin (IVIg). Cyclophosphamide has been used as an active agent in patients with a wide variety of autoimmune diseases and has been used as a cytotoxic and immunosuppressive agent in several HSCT trials for autoimmune diseases without mortality. Cyclophosphamide is a potent immunosuppressive agent that has less chronic side effects and is not associated with late malignancies. Hemorrhagic cystitis can occur and is mediated by the acrolein metabolite. This can be prevented by co-administration of mesna, hydration, and / or bladder irrigation. Other notable side effects of cyclophosphamide include nausea, vomiting, alopecia, myelosuppression, and SIADH. One limiting dose-factor of cyclophosphamide is its cardiac toxicity. This cardiac safe transplant regimen will use just one dose of IV cyclophosphamide at a dose of 60 mg/kg, minimizing cardiac toxicity. Another advantage of only giving one dose of cyclophosphamide is that less hydration will be needed to prevent hemorrhagic cystitis, therefore decreasing the risk of pulmonary edema. Using only one dose of cyclophosphamide will also lessen the days of neutropenia, therefore decreasing the risk of transplant relate complications, such as infections.

In place of the cyclophosphamide, fludarabine will be used for immune suppression which is a chemotherapy drug that is often used to treat leukemia and lymphoma. Fludarabine is usually well tolerated, although may cause mild nausea and vomiting or fever. Fludarabine will lower blood counts and cause neutropenia, although typically patients become neutropenic later and recover sooner with fludarabine and a lower dose of cyclophosphamide compared to the higher dose of cyclophosphamide alone. Fludarabine is contraindicated for use in patients with renal dysfunction because it can lead to cerebellar dysfunction. All patients will received a 24 hour urine creatinine as part of pre-transplants testing. In addition, Fludarabine can be associated with cytopenias and /or viral infections. Patients will receive prophylaxis medications for six to 12 months after HSCT to prevent infections from occurring.

Rabbit-derived anti-human thymocyte globulin (rATG) is a gamma globulin preparation obtained from hyperimmune serum of rabbits immunized with human thymocytes. rATG is a predominantly lymphocyte-specific immunosuppressive agent. It contains antibodies specific to the antigens commonly found on the surface of T cells. After binding to these surface molecules, rATG promotes the depletion of T cells from the circulation through mechanisms which include opsonization and complement-assisted, antibody-dependent, cell-mediated cytotoxicity. The plasma half-life ranges from 1.5-12 days. We have used rATG in previous regimens safely without unexpected toxicity. It is administered intravenously at a dose of 0.5 mg/kg recipient body weight on day -5, and 1.5 mg/kg on day -4 through day -1. Starting at a low dose of 0.5 mg/kg minimizes "first infusion syndrome" caused by cytokine release that could initiate further lung injury and pulmonary edema (73-75). Unlike equine ATG, rabbit ATG does not require a pre-infusion skin test to check for hypersensitivity. Pre-medications of methylprednisolone (1 gram IV), acetaminophen, and diphenhydramine are given to prevent serum sickness and allergic reactions.

Rituximab is a chimeric monoclonal antibody used in the treatment of B cell non-Hodgkin's lymphoma, B cell leukemia, and numerous autoimmune disorders, including SSc. The recommended adult dosage for adult patients with autoimmune diseases is a flat dose of 500 mg intravenously. In autoimmune diseases, infusions may be given at weekly intervals for approximately four doses, once every two weeks and repeated doses two to three times, or monthly. For this conditioning regimen, one flat dose of rituximab (500 mg) will be given on day -6. Acetaminophen, diphenhydramine, Pepcid and methylprednisolone are given 30-60 minutes before the infusion to help reduce side effects. The majority of side effects occur during or after the first infusion and may include dizziness, feeling of swelling of tongue or throat, fever, chills, flushing of face, headache, itching, nausea, vomiting, rhinitis, shortness of breath, skin rash, and fatigue.

IVIg is pooled preparation of IgG from the plasma of thousands of donors. While the exact mechanism of IVIg is unknown for the treatment of autoimmune disorders, it has shown efficacy in several autoimmune diseases, including systemic sclerosis. In the regimen, IVIg will be given on day +2 and day +8 (or day of engraftment) at a dose of 400 mg/kg. Pre-medications of acetaminophen and diphenhydramine will be given prior to the infusion to prevent an allergic reaction.

Mobilization and Harvest of Stem Cells

Based on experience with pilot studies and autoimmune flares in patients utilizing growth colony stimulating factor (G-CSF) alone for mobilization, this protocol will mobilize stem cells with cyclophosphamide (2 g/m2) and granulocyte-colony stimulating factor (G-CSF) 5 to 10 mcg/kg daily that is initiated five days after the cyclophosphamide infusion until the harvest is complete. Mobilization with cyclophosphamide may cause one to two days of neutropenia approximately one week after infusion. Infection risk during this interval may be minimized with prophylactic antibiotics. Advantages for cyclophosphamide / G-CSF mobilization are higher stem cell yields, an in vivo purge effect by selectively killing lymphocytes in cell cycle, and a cyclophosphamide-mediated disease-ameliorating effect (79).

Apheresis to collect progenitor cells begins 10 days after the cyclophosphamide infusion (five days after G-CSF administration begins). A 15-liter peripheral blood apheresis performed in one day is usually adequate for collection of sufficient numbers of HSC. Occasionally, a consecutive second or third day of apheresis may be necessary.

CD34+ selection by removing lymphocytes is also a method of immune suppression and may increase the risk of post-HSCT infection. With our experience, CD34+ selection by removing lymphocytes is not necessary or superior to un-manipulated graft for transplanting SSc, and therefore, will not be used in this protocol. Effective in vivo purging of the graft is obtained by mobilization with 2.0 g/m2 cyclophosphamide and conditioning with rATG, an antibody with a long half-life directed against T and B lymphocytes. Following a non-myeloablative conditioning regimen, HSCs are infused only to shorten the duration of neutropenia since immune and hematopoietic reconstitution would occur even without HSC support.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

1. Age 18 - 65 years old at the time of pre-transplant evaluation
2. An established diagnosis of systemic sclerosis
3. Diffuse cutaneous systemic sclerosis with involvement proximal to the elbow or knee and a modified Rodnan Skin Score of ≥ 14 (see Appendix A)

AND

Any one of the following:

a. DLCO < 80% of predicted or decrease in lung function (DLCO, DLCO/VA or FVC) of 10% or more over 12 months.
b. Pulmonary fibrosis or alveolitis on CT scan or CXR (ground glass appearance of alveolitis).
c. Abnormal EKG (non-specific ST-T wave abnormalities, low QRS voltage, or ventricular hypertrophy), or pericardial effusion or pericardial enhancement without constriction on MRI
d. Gastrointestinal tract involvement confirmed on radiological study. Radiologic findings of scleroderma are small bowel radiographs showing thickened folds with dilated loops, segmentation, and flocculation +/- diverticula, or pseudo-diverticula. A hide-bound appearance may be present (e.g. dilated and crowded circular folds). GI involvement may also be confirmed by D-xylose malabsorption, patulous esophagus on HRCT, or esophageal manometry.

OR

Limited cutaneous SSc (modified Rodnan Skin Score <14) with lung involvement defined as active alveolitis on BAL, ground-glass opacity on CT scan, a DLCO < 80% predicted, or decrease in lung function (DLCO/VA, DLCO, FVC) of 10% or more in last 12 months.

Other Inclusion Criteria for "CAST" Conditioning Regimen (presence of any of the following):

a. Septal flattening or D-sign on MRI (without deep breathing)
b. PASP >40 mm Hg or >45 mm Hg with fluid challenge*
c. mPAP >25 mm Hg or >30 mm Hg with fluid challenge*
d. Non-ischemia diffuse ventricular hypokinesis or non-ischemia wall hypokinesis

*Fluid challenge is 1000 ml NS over 10 minutes. Fluid challenge will not be done if RA pressure is >13 mm Hg at rest or PCWP is >20 mm Hg a rest

Exclusion Criteria

a. Active ischemic heart disease or untreated coronary artery disease
b. Untreated life-threatening cardiac arrhythmia on EKG or 24-hour holter
c. Pericardial effusion > 1 cm on cardiac MRI unless successful pericardiocentesis has been performed
d. LVEF <35%
e. End-stage lung disease characterized by TLC<45% of predicted value, or DLCO hemoglobin corrected < 30 % predicted.
f. Creatinine clearance <40 mL/min by 24-hour urine
g. History of breast implants that have not been removed (unless they cannot be surgically removed due to risks of surgery)
h. Liver cirrhosis, transaminases >2x of normal limits, or bilirubin > 2.0 unless due to Gilbert's disease
i. Uncontrolled diabetes mellitus or any other illness that in the opinion of the investigators would jeopardize the ability of the patient to tolerate aggressive treatment
j. Prior history of malignancy
k. Positive pregnancy test, inability or unable to pursue effective means of birth control, or failure to willingly accept or comprehend irreversible sterility as a side effect of therapy
l. Psychiatric illness or mental deficiency making compliance with treatment or informed consent impossible
m. Major hematological abnormalities such as platelet count < 100,000/ul or ANC < 1000/ul
n. HIV positive
o. Hepatitis B or C positive
p. PASP >50 mmHg without fluid challenge
q. mPAP >34 mmHg without fluid challenge
r. Coronary artery disease not reversed by cardiology and interventional radiology

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Adults	50	50
Study-wide	Adults	50	50
Total:	Adults	50	50

STUDY-WIDE NUMBER OF PARTICIPANTS: One center study with 50 participants at Northwestern Medicine

STUDY-WIDE RECRUITMENT METHODS: There are no recruitment methods. All participants are referred to us by another physician, or contact us on their own or via www.clinicaltrials.gov.

MULTI-SITE RESEARCH: N/A

STUDY TIMELINES:

Duration of Participant's Participation in Study:

1. Eligibility screening and insurance approval: approximately three months
2. Pre-transplant testing, randomization, stem cell mobilization and stem cell transplant: two months
3. Patients will be followed for five years after completion of stem cell transplant at yearly follow-up appointments (contingent upon patient compliance with follow-up appointments).

Duration anticipated to enroll all study patients: Five years

Estimated date for investigators to complete study (primary analysis): January 1, 2025

STUDY ENDPOINTS:

Primary Outcomes:

1. Improvement in skin score by mRSS (Appendix A)
2. Improvement in FVC on pulmonary function test

Disease Improvement Definition:

a. Skin Score: defined by at least a 25% improvement (decline) in skin score by mRSS if skin score is greater than 14 on enrollment. If skin score is less than 14 on enrollment, improvement is defined by at least a 5% improvement on mRSS.
b. FVC: 10% improvement (increase) in percent predicted FVC

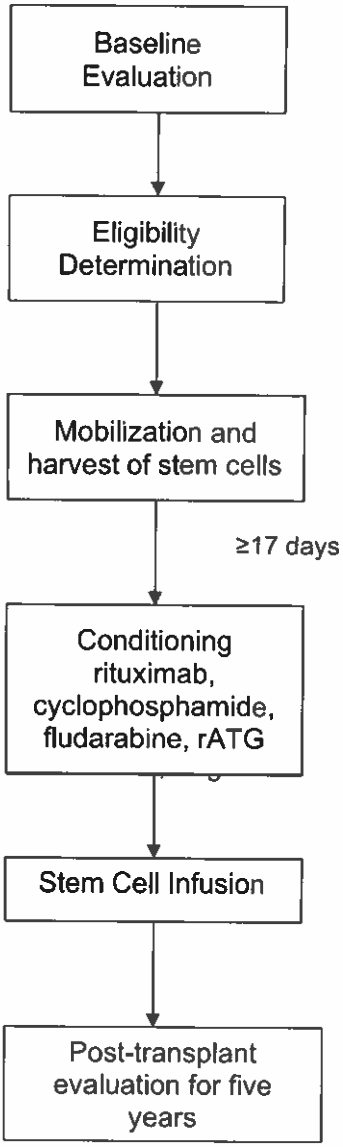
Secondary Outcomes:

1. Treatment related mortality
2. Overall Survival
3. Cardiac Function
    a. LVEF
    b. RVEF
    c. PASP
    d. mPAP
    e. ECV on MRI
4. Renal Outcome
    a. Cr Clearance
    b. Episodes of renal crisis
    c. Need and duration of dialysis

5. Pulmonary function test (TLC, DLCO)
6. Quality of Life by SF-36 (Appendix B)

PROCEDURES INVOLVED:

Study Design



Study Procedures and Testing Guidelines

	Pre-Testing[1]	During HSCT[2]	Post-HSCT[3]	Follow Up[4]
History & Physical Exam	X	X		X
Hx/Number of renal crises	X			X
Skin Score (mRSS)	X			X
Cr Clearance	X			
History of Anemia/GI Bleed/GAVE/telangiectasia	X			
Date of last colonoscopy/EGD (if applicable)	X			
History of oxygen use (if so, arrangements for oxygen complete)	X			
History of breast implants (remove if able to do so)	X			
IV access check for central line at mobilization	X			
Assess ability to administer G-CSF. If not, caregiver must accompany patient	X			
Skin ulcer assessment; If so, consider ID consult	X			
Baseline blood pressure and heart rate	X			
High resolution CT scan of chest without contrast	X			X
PFT w/ DLCO and FEV1/FVC	X			X
CXR PA and Lateral	X			
EKG	X			
Dobutamine stress echocardiogram with doppler and bubble study[5]	X			X[5]
Right cardiac cath at baseline and repeated with volume load of 500-100 mL NS over 10-20 minutes[6]	X			X[7]
MRI of heart with gadolinium (provided normal renal function)	X			X[7]
24-hour holter monitor (if history of palpitations)	X[8]			
CT enterography of abdomen (if weight loss or other clinical indication)	X[8]			
Upper endoscopy if anemic, iron deficient, with facial telangiectasia, history of GI bleed, or GAVE (colonoscopy may also be considered)	X[8]			
BNP	X	2x/week		X
CBC, platelet & differential	X	X (daily)	X	X
INR, PT, and PTT	X			
Basic Chemistry Panel[9]	X	X (daily)	X	X
Liver Function Test	X	2x/week	X	X
LDH, Uric acid, ESR, CRP	X			X
Autoimmune Disease Panel[10], anti-b2-GP1, LA[11], ACA[11]	X			X
CPK, aldolase	X			X If positive pre-HSCT
RNA polymerase III Cryoglobulin serum	X			X If positive pre-HSCT
CMV by PCR (quantitative)			X	
FDA Virologies[12]	X			
HSV, VZV, CMV	X			

Hepatitis A serology	X			
Urinalysis	X			
Quantiferon Gold	X			
TSH, T3, Free T4	X			X
Quantitative IgG/IgA/IgM	X			X
ABO/RHO	X			
Serum or Urine HCG	X	X		
Burt Panel (CD3, CD4, CD8, CD56, CD20	X (optional)			X (optional)
Dental consult	X (optional)			
Allergy Consult and Testing[13]	X[13]			
SF-36 Questionnaire	X			X

[1]Pre-Transplant: baseline data
[2]During HSCT: inpatient admission
[3]Post-HSCT: weekly for four weeks, every other week for eight weeks, monthly for 3 months
[4]Follow-up: 6 months (optional), then yearly for five years; although every attempt will be made for follow- up, some patients will not return for frequent visits in which event study tests and medical evaluation will be collected from a local physician. History may also be obtained by telephone or email by PI, co- investigator, APN, and/or clinical research nurse
[5] Echocardiography to include right ventricular assessment such as right ventricle dimensions and Tricuspid annular peak systolic excursion (TAPSE) and Tissue Doppler Imaging; Dobutamine may be omitted from echocardiogram if coronary angiograms are performed during cardiac cath; Dobutamine is not required for follow up testing after stem cell transplant unless clinically indicated
[6]Fluid bolus will not be given if RA pressure > 13 mm Hg or PCWP > 20 mm Hg at rest
[7]Right heart cardiac cath at 1-year and 2-year follow up (optional)
[8]If indicated in patient's medical history
[9]Basic chemistry panel to include: Na, K, Cl, bicarb, glucose, BUN, Creatinine, Mg, Phos
[10]Autoimmune Disease Panel to include: Scl-70 titer, Anti-DNA antibody, C3, C4, SSa, SSb, Jo-1, ANA = antinuclear antibody; ACLA = anti-cardiolipin antibodies
[11] LA = lupus anticoagulant, ACA=anti-centromere antibody
[12]FDA virologies to include: Anti-HBC, Anti-HCV, anti-HIV1/anti-HIV2, CMV, HBS ag, HTLV 1/2, procleix HBV, procleix HCV, procleix, procleix, HIV-1, RPR, T. cruzi AB, WNV TMA
[13]Allergy Testing indicated for history of penicillin or cephalosporin allergy

Screening

Participants will be emailed a screening form prior to scheduling an initial evaluation. The screening form helps determine eligibility. The screening form asks questions about diagnosis, duration of disease, organ involvement, and current and prior treatments (See Appendix C)

Initial Evaluation

Participants will be scheduled for evaluation in clinic by the PI and a cardiologist. The goals of initial evaluation are the following:

- To confirm the diagnosis of the disease being treated
- To confirm that the eligibility criteria for the treatment is met
- To determine if the treatment is thought to be beneficial
- To assess for any contraindications to treatment
- To assess for any conditions that could compromise safety
- To provide information about the treatment and address any questions

Pre-Transplant Testing
See study procedures and testing. All tests will be reviewed by PI and clinical research nurse prior to enrollment. Patients will undergo a thorough cardiac evaluation with an echocardiogram (may include dobutamine stress), right cardiac catheterization with fluid challenge, and cardiac MRI (See Appendix D for cardiac testing protocols).

Registration
Patients must be registered prior to starting treatment. When eligibility is confirmed and the enrollment form (Appendix E) is initialed and signed by the PI and clinical research nurse, the registrant is then added to the protocol registration list.

Treatment Plan for Cardiac Safe Transplant ("CAST") Protocol

Stem Cell Mobilization
Participants will be admitted to the hospital for approximately 24 hours to receive a cyclophosphamide infusion with IV hydration and mesna. Discharge instructions and emergency contact information will be given to participants verbally and in writing prior to discharge.

Mobilization and Peripheral Blood Stem Cell Harvest (Apheresis) Procedure Guideline:

Doses may be adjusted or discontinued if necessary for patient safety.

	Mobilization	Five days post-cyclophosphamide until apheresis	Ten days post-cyclophosphamide
Cyclophosphamide 2 g/m2	X		
Mesna 50 mg/kg IV	X		
Hydration	X		
G-CSF, subcutaneous 5-10 mcg/kg/day		X	
Prophylaxis Antifungal and Antibiotic (such as fluconazole and Augmentin)		X	
Harvest (apheresis)			X*

*Harvest will begin ten days post-cyclophosphamide and continue until greater than 2 x 10_6 $CD34_+$ cells/kg patient weight have been collected. A maximum of three apheresis collections may be performed. The G-CSF will continue until harvest is complete. Stem cell harvest will be performed peripherally with insertion of 2 large bore IV's, or through a central line (VasCath) that will be placed under fluoroscopy in interventional radiology and removed when harvest procedure is complete.

Interval between Mobilization and Conditioning
In order to avoid cumulative toxicity from cyclophosphamide, it is recommended that 17 to 24 days separate the administration of cyclophosphamide from mobilization and conditioning.

Conditioning Regimen Guideline (Systemic Sclerosis: Cardiac Safe Transplant) Patient is admitted to the hospital on day -6. Doses may be adjusted or discontinued if necessary for patient safety

DAY	-6	-5	-4	-3	-2	-1	0	+2	+4	+8
Rituximab 500 mg IV (flat dose)	X									
Fludarabine[A] 30 mg/m² IV	X	X	X	X						
Hydration					X					
Cyclophosphamide 60 mg/kg IV					X					
Mesna 50 mg/kg IV					X					
rATG mg/kg/day IV		0.5	1.5	1.5	1.5	1.5				
Methylprednisolone		1g	1g	1g	1g	1g				
Stem cell reinfusion							X			
IVIg 400 mg/kg IV								X		X
G-CSF, subcutaneous (until engraftment)									X	

[A]Fludarabine dosing will be adjusted according to CrCl as follows:

If CrCl is:	Fludarabine Dose Reduction
>80 mL/min	Full Dose
60-80 mL/min	20% reduction/dose
40-60 mL/min	40% reduction/dose
<40 mL/min	Not a Candidate

Concurrent Treatment and Supportive Care Guidelines and Procedures to Lessen Risks

Renal Protection Guideline (note: fludarabine is contraindicated in renal failure): For systemic sclerosis patients who are anti- polymerase antibody positive, bosentan (Tracleer), where available, will be started upon admission for stem cell transplant at 62.5 mg twice daily. If continued after discharge, the dose will be increased after 4 weeks to 125 mg twice daily (if tolerated). Patients may be started on an ACE-Inhibitor such as lisinopril or captopril during stem cell transplant if not already on one, as long as blood pressure tolerates. Dose will be adjusted by systolic blood pressure.

Rituximab Guideline: 500 mg IV infusion will be given on day -6. It will be infused per hospital protocol, usually over two to six hours. Vital signs will be

checked and the rate will be increased as the patient tolerates. The infusion will be stopped or slowed for signs of allergic reaction such as rash, itching, or shortness of breath and the patient will be treated with medications such as diphenhydramine and/or Pepcid IV.

- **Rituximab Pre-Medication Guideline:** Methylprednisolone 250 mg IV, acetaminophen 650 mg PO, diphenhydramine 25mg PO/IV, and famotidine 20 mg IVP 30 minutes before infusion.

Fludarabine Guideline: For patients with a CrCl >80 mL/min, 30 mg/m^2 IV infusion will be given on days -6, -5, -4 and -3 (4 doses). For patients with a CrCl between 60 and 80 mL/min, each dose will be reduced by 20%. For patients with a CrCl between 40 and 60 mL/min, each dose will be reduced by 40%. It will be infused in 100 mL of solution (NS or D5W) over 30 minutes. If actual weight is less than ideal weight, fludarabine will be given based on actual weight. If actual weight is greater than ideal weight, fludarabine will be given as adjusted weight. Adjusted weight = ideal weight + 25% of [actual weight - ideal weight].

Hydration Guideline: 0.9% normal saline at 100 mL/hour will start two hours before cyclophosphamide and then will decrease to 75ml/hr continued until 22 hours after the cyclophosphamide dose. The rate of hydration may be adjusted. Daily weights will be obtained. Amount of fluid can be modified based on patient's fluid status

Cyclophosphamide Guideline: 60 mg/kg will be given IV over 2 hours in 250-500 mL of D5W or NS on day -2. If actual weight is < ideal weight, cyclophosphamide will be given based on actual weight. If actual weight is > ideal weight, cyclophosphamide will be given as adjusted weight. Adjusted weight = ideal weight + 25% of actual weight minus ideal weight.

- **Cyclophosphamide Pre-Medication Guideline:** Ondansetron 16mg IVPB, dexamethasone 10mg IVP, lorazepam 0.5mg IVP or PO, aprepitant 125mg PO or 150 mg IV given 30 minutes prior to infusion

- **EKG Guideline:** EKG reviewed prior to each Cyclophosphamide

PRN Antiemetic Guideline: Prochloperazine 10mg IVP q 6 hours PRN, ondansetron 8mg IVP q 8 hours PRN (NTE 32mg in 24 hours), and lorazepam 0.5mg IVP q 6 hours PRN

Mesna Guideline: 50mg/kg will be given IV on day -2 starting two hours prior to cyclophosphamide and will be a continuous infusion for 24 hours.

Diuretic Guideline: IV diuretic such as furosemide will be given three times per day starting with cyclophosphamide and continued until 24 hours. Amount of diuretic and frequency can be modified based on patient's fluid status and weight.

rATG Guideline: 0.5 mg/kg IV will be given on day –5 and 1.5 mg/kg IV will be given on days -4, -3, -2 and -1. If actual weight is less than ideal weight, rATG will be given

based on actual weight. If actual weight is greater than ideal weight, rATG will be given as adjusted weight. Adjusted weight = ideal weight + 25% of [actual weight - ideal weight]. It will be given over 10 hours. An in-line 0.22 μm filter should be used for rATG administration.

- **rATG Pre-Medication Guideline:** Methylprednisolone 1g IV, acetaminophen 650 mg PO, and diphenhydramine 25mg PO/IV 30 minutes before infusion.

Methylprednisolone Guideline: 1g methylprednisolone IV will be given as a pre-medication 30 minutes prior to rATG on day -5 through -1 to prevent allergic reaction and rATG fever.

IVIg Guideline: 400mg/kg IVIg will be given on day +2 and day +8 (or day of engraftment) following the standard infusion guidelines. If a reaction occurs, infusion will be stopped, 25mg diphenhydramine IV and 100mg hydrocortisone IV will be given. Infusion may be restarted when reaction symptoms have resolved at a decreased rate from which the reaction occurred. Rate should not increase for the duration of infusion.

- **IVIg Pre-Medication Guideline:** Acetaminophen 650mg PO and Diphenhydramine 25mg IVP 30 minutes before infusion

G-CSF Guideline: 5- 10 mcg/kg/day will be started on day +4 and continued until the absolute neutrophil count reaches at least 500/μl. Dose may be rounded up or down based on patient's weight.

Transfusion Support Guideline:
All blood products are to be irradiated (25 Gy or institutional protocol), leukocyte reduced, and CMV safe. Prior to administration of blood products, patients may be medicated with diphenhydramine 25-50 mg IV or PO and acetaminophen 650 mg PO to prevent febrile or transfusion related reactions.

- **Red Blood Cells:** (irradiated, leukocyte reduced, CMV safe) for Hgb < 8.0 g/dl (Hct >27) transfuse 1-2 units, ABO/Rh matched units.

- **Platelets:** (irradiated, leukocyte reduced, CMV safe) for platelet count less than 20 x 10^9/L, transfuse 1 unit. Additional platelet transfusions may be required to reach goal. For procedures associated with a high risk of hemorrhage, including major surgical procedures, deep tissue biopsies, lumbar puncture, placement of central vascular catheter, and/or endoscopy of the gastrointestinal tract, maintain platelet counts greater than 50 x 10^9/L. For patients with GAVE, goal platelet count is 40x10^9/L. Platelets should be transfused just before an invasive procedure. In addition to the platelet count, INR, PT/PTT, fibrinogen and other measures of coagulation may be helpful in some patients for defining the extent of any clotting dysfunction.

Infection Prophylaxis Guideline:
All prophylactic antibiotics may be changed or discontinued according to clinical

circumstances (e.g., patient allergy) as determined by the PI or nurse practitioners.

- **Antibacterial Prophylaxis Guideline:** When WBC/ANC drops, a broad spectrum intravenous antibiotic such as piperacillin/tazobactam or cefepime (pseudomonal coverage is needed) will be initiated regardless of temperature until the ANC returns to > 500/ul. If fever occurs or patient has a history of surgical hardware or other risk for infection, antibiotic coverage will be expanded to include vancomycin (unless allergy). Patients with a history of allergy to penicillin or cephalosporin must be evaluated by an allergist for testing prior to stem cell transplant. Once the WBC engraft and patient is without sign of infection and/or fever, intravenous antibiotics will be stopped. Administration of antibiotics will be done according to the institutional standard of practice of the participating center.

- **Antifungal Prophylaxis Guideline:** Cresemba 372 mg by mouth daily will start on day +2 and continued until discharge from hospital. At discharge, antifungal will be switched to fluconazole 400 mg PO daily for six months post-transplant. Other antifungals such as voriconazole or posaconazole may be used. Antifungal medications may be held, discontinued, or switched for adverse side effects, for elevated transaminases, or to change coverage of fungal organism depending on clinical situation.

- **Antiviral Prophylaxis Guideline:** Valacyclovir 500mg PO twice daily or acyclovir 400 mg PO twice daily will be administered for herpes simplex virus (HSV) and varicella zoster virus (VZV) prevention from day of transplant admission until 12 months post-transplant. Antiviral medications may be held or discontinued for adverse side effects.

- **Pneumocystis carinii pneumonia (PCP) Prophylaxis Guideline:** Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim) DS tablet PO every Monday, Wednesday and Friday starting after engraftment and continued for 3 months. If the patient experiences a side effect to Bactrim (e.g., rash), a different agent may be substituted such as aerosolized pentamidine 300 mg inhaled monthly, atovaquone (Mepron) 1500 mg PO daily, or Dapsone 100 mg PO daily. Medication may be held or discontinued for adverse side effects (i.e., thrombocytopenia, leukopenia)

CMV Prophylaxis Guideline: Patient's CMV PCR (quantitative) will be checked weekly from time of discharge for four weeks and then every two weeks until three months post-HSCT. If detected and PCR value increases for more than two weeks, valganciclovir (Valcyte) 900mg PO twice daily will be given for two weeks or until PCR is negative. For high PCR, treatment may be initiated immediately. Patient may require inpatient admission for IV treatment if unable to obtain Valcyte. Other anti-viral prophylaxis will be held during CMV treatment.

Hemorrhagic Cystitis Prophylaxis Guideline:
The following procedures will be done to minimize the risk of hemorrhagic cystitis, a possible side effect of cyclophosphamide:

- Mesna: 50mg/kg/day will be given IV starting two hours prior to

starting cyclophosphamide and will be a continuous infusion for 24 hours

- IV Hydration: 0.9% normal saline at 75-100 mL/hour will be given two hours before cyclophosphamide and continued until 24 hours after the last cyclophosphamide dose. The rate of hydration may be adjusted. Amount of fluid can be modified based on patient's fluid status.
- Diuretics: IV diuretic (furosemide) will be given three times per day starting with cyclophosphamide and continued for 24 hours. Amount of diuretic and frequency can be modified based on patient's fluid status and weight.
- Continuous Bladder Irrigation Guideline (if applicable, generally not needed for one day of cyclophosphamide): 0.9 NS at 125 mL per hour starting with Cytoxan and continuing for 24 hours. If necessary, urology will be consulted to place irrigation foley catheter.

Transaminase Elevation/ Veno-occlusive Disease Guideline:
Patients will be given ursodiol, 300 mg by mouth twice a day upon admission (day -6) until day +5. The dose or frequency may be adjusted or it may be held or discontinued in the case of adverse side effects (most common: diarrhea, nausea)

Atelectasis Prevention Guideline
Incentive spirometry will be performed several times/day to prevent atelectasis. Patients are encouraged to walk the transplant unit.

Raynaud's Treatment Guideline
A calcium channel blocker or bosentan as tolerated will be taken orally and continued indefinitely to protect from Raynaud's.

Aspiration Precautions Guideline
Patient will be instructed to sleep at night with head of bed elevated to prevent reflux and aspiration if there is GI involvement/patulous esophagus.

GI Involvement Guidelines
Reglan will be given if needed for GI hypomotility.

For patients with severe GI involved and significant weight loss, TPN may be started per clinical judgment.

For patients with GERD, they will be treated with a proton pump inhibitor

Pulmonary Artery Hypertension Treatment Guideline
Bosentan or sildenafil (Viagra) may be given as indicated per PAH.

GI Stress Ulcer Guideline:
A proton pump inhibitor will be initiated upon admission to prevent GI stress ulcers from high-dose steroids. Carafate may be added for patients with dyspepsia.

DVT/ VTE Guideline:
For patients who have a history of or are at high risk of developing DVT or VTE,

prophylactic treatment such as low molecular weight heparin may be initiated. Platelet count will be monitored daily and treatment may be discontinued once platelet counts are <50 x 10^9/L to avoid bleeding. PI may modify treatment and goals as needed.

Fever Guideline:
Blood cultures will be obtained and broad coverage IV antibiotics may be given until blood cultures result. If negative, some antibiotics may be discontinued. If indicated, blood cultures or tests may be checked such as urine culture, C. difficile, respiratory viral panel, and chest x-ray.

Electrolytes Guideline:
The stem cell transplant electrolyte replacement protocol will be initiated upon admission for stem cell transplant. Electrolytes will be checked daily and as needed. In addition, while patient is receiving diuretics and hydration with cyclophosphamide, potassium will be checked twice daily and the following oral electrolytes may be ordered:

- Potassium: KCl 20 meq PO twice a day
- Calcium: Tums 500 mg PO twice a day
- Phosphorus: Na-K-Phos powder PO twice a day

Electrolyte replacements may be adjusted or discontinued depending on lab values.

Fall Prevention Guideline:
To prevent falls, which could be life threatening in the setting of thrombocytopenia, the following practices are in place:

- Orthostatic vital signs are obtained twice a day. Nursing is instructed to call MD or APN for patients who have positive orthostatic vital signs or who are symptomatic. Patient will be given additional IV fluids or bolus per MD/APN discretion.
- Patients are given the following instructions: *Sit for 30 seconds before standing. Once you stand, remain in place for at least 30 seconds before walking. If you feel dizzy, lightheaded or weak, sit back down and call for help. Do not attempt to walk.*
- For patients who are high risk, they are instructed to always have someone assist them during ambulation, getting out of bed, or going to bathroom.

Hospital Discharge Guideline (post HSCT):

1. Afebrile
2. No parenteral feeding required
3. Platelet count stable or increasing without transfusions
4. Neutrophil count greater than 500/ul
5. Patient or family member is able to provide care
6. Arrangements for follow-up with primary physician (if indicated)

Post-Stem Cell Transplant (First 100 days) Guideline:

- **Discharge Summary Guideline:** Inpatient team member (Nurse practitioner, Physician Assistant, Fellow or PI) will complete a discharge summary after stem cell transplant and will provide patient with a copy. Discharge summaries may be sent to local doctors.

- **Lab Guideline:** Participants will be given orders and instructed to have the following labs drawn every week for 4 weeks, every other week for 8 weeks and then monthly for 3 months:
    - CBC with platelet and differential
    - Comprehensive Metabolic Panel (including liver function tests)
    - Magnesium
    - Phosphorus
    - CMV PCR (quantitative)

  Additional lab draws may be required. A nurse practitioner or inpatient team member will monitor and record lab results in the 100-day lab and communication form and will notify patient of results by phone or email (see appendix F).

- **Post-HSCT Medications:** See medication prophylaxis guidelines above.

- **Communication Guideline:** Inpatient team member will communicate with participant upon discharge and regularly (approximately every 1-2 weeks or as needed) for the first three months post stem-cell transplant to monitor the following: patient progress, adverse events, medications, and lab results.

- **Physical Therapy/Occupational Therapy Guideline:** Participants in need will be encouraged to participate in PT/OT post stem cell transplant. An order will be provided prior to discharge.

SOURCE RECORD GUIDELINES:

- **Systemic Sclerosis Enrollment Form** (Appendix E): Form used to collect pre- transplant testing. Form gets reviewed and signed off on by clinical research nurse and PI prior to enrollment.
- **Systemic Sclerosis Adverse Events Case Report Form** (Appendix G): Form used at follow-up visits at 6 months, 1 year, 2 years, 3 years, 4 years and 5 years post stem cell transplant to assess for late adverse events post stem cell transplant such as infections, hospitalizations, cancers, or secondary autoimmune diseases.
- **Systemic Sclerosis Outcomes Case Report Form** (Appendix H): Form used pre-transplant (baseline) and at follow-up visits at 6 months, 1 year, 2 years, 3 years, 4 years and 5 years to keep track of study-specific outcome measures.
- **Telephone Follow-up Form** (Appendix I): Form used to call patient and ask information in event that they are unable to return for follow up.

EVALUATION OF TOXICITY GUIDELINES:
The Common Toxicity Criteria for Adverse Events (CTCAE) version 2.0 (See Appendix

J) will be used to grade all non-hematologic toxicities. At the time of doing the discharge summary, an inpatient team member (ie: nurse practitioner, PI) will document all grade 3 and grade 4 transplant toxicities in the source book. Adverse events, hospitalizations and/or infections will also be recorded in the source book at 100 days post stem cell transplant and at all follow-up visits.

DATA AND SPECIMEN BANKING

Records to be Kept: Pre-testing reports, enrollment data, toxicity, 100 day labs post stem cell transplant, adverse events, notes from treating neurologist for control arm patients, and follow-up study visit reports will be kept in the Office of Division of Immunotherapy and Autoimmune Diseases at Northwestern in patient charts. Inpatient hospitalization records such as history and physicals and daily progress notes, clinic visits, harvest notes, discharge instructions and summaries will be stored in the electronic medical record of Northwestern Medicine.

Additional Harvested Stem Cells: In the event that a participant undergoes stem cell harvest but the stem cells are not infused back (i.e., withdrawal from study or additional bags of stem cells collected that are not used for stem cell transplant), the cells will be retained per our standard practice for at least five years. The cells may be used at a later date for only the patient if indicated.

DATA MANAGEMENT AND CONFIDENTIALITY:

Collection of data, management, checking and verification will be performed by the PI and his team at Northwestern University. All staff members will undergo IRB and human subjects training and will re-certify when indicated. All staff members will receive orientation and training prior to enrolling and managing care for patients. Training manuals and materials are kept in the office of the Division of Immunotherapy and Autoimmune Disease. Correspondence about patients enrolled in the study will be done in person in the office, via telephone, or on password protected and encrypted computers.

General Clinical Research Center statistician, Dr. Jovanovic or designate, will be available to assist with data management and analysis. Analysis will be performed by student T test or other instruments as determined by the statistician. The study will be considered significant for $p<0.05$.

Data will be entered in a spreadsheet by a clinical research nurse and will be stored on a password protected computer. The clinical research nurse and regulatory coordinator will audit the spreadsheet with each continuing review.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

Non-treatment related deaths and grade 4 toxicities will be reported in the annual continuing review (CR). If at the time of annual CR, if any treatment appears to be affecting the safety or outcome of the study, a statistical analysis will be performed and if significant, the IRB and data safety monitor (DSM) will be notified. At that time, a decision will be made as to continue the study.

ADVERSE EVENT REPORTING

Death of an Enrolled Participant

- All deaths, treatment related or non-treatment related will be reported immediately to Dr. Richard Burt (PI) by phone or email.
- Treatment-related deaths will be reported to IRB via phone call or email within 24 hours of knowledge of the cause of death. If the death occurs on a weekend or holiday, the IRB will be notified within 24 hours of the next business day.

Other

- Any unexpected harm, risk, or breach of confidentiality will be reported to the IRB within five business days.
- Non-treatment-related deaths and grade 4 toxicities will be reported in the annual continuing review (CR).

Adverse Events/Toxicities

- The toxicity grading for grade 3 and 4 adverse events is according to NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 2.0 at website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf (see Appendix J).
- Grade 4 transplant related toxicities will be reported to IRB on annual CR.

WITHDRAWAL OF PARTICIPANTS:

The following are circumstances in which participants will be withdrawn from the research without their consent:

- Pregnancy after randomization but prior to starting therapy (pregnancy test will be checked at mobilization and stem cell transplant admissions prior to receiving chemotherapy)
- Disease progression that is discovered making travel and follow-up studies of such inconvenience that they impose a significant risk or burden to the patient.
- Discovery of any co-morbidity or exclusion criteria prior to beginning the conditioning regimen. Patient withdrawal may occur after randomization, mobilization and harvest of stem cells.
- Patient loss to follow-up

Procedure for Termination

Participants will be notified in person or by phone if they are being removed from the study. They will be offered a referral to a physician for any health condition that requires medical attention if they do not already have a physician managing their care. Participant information on how to revoke authorization for use of disclosure of health information or data already collected is in the consent form.

Procedures when participants withdraw from research, including partial withdrawal from procedures with continued data collection

Participants may revoke consent to participation in this research at any time and in any format. In order to revoke authorization for use or disclosure of health information or

data that is already collected, participants will be requested to do so in writing to:

Richard Burt, MD
Northwestern Medicine
Division of Immunotherapy and Autoimmune Diseases
446 E. Ontario, Suite 10-1000
Chicago, IL 60611

RISKS TO PARTICIPANTS:

Risk of Treatment Drugs

- Cyclophosphamide: The more common side effects of cyclophosphamide include nausea, vomiting, loss of appetite, diarrhea, mouth sores, hair loss, sterility, and decreased blood counts causing anemia and placing you at risk for bleeding and infections. Less frequent side effects include headache, skin rash, flushing or redness of the face. Cyclophosphamide can cause inflammation of the bladder causing painful, bloody urination. Other side effects include heart failure, inflammation of the lining around the heart, disturbances in the normal rhythm of the heart, inflammation of the lungs, and abnormal function of the liver causing yellowing of the skin and eyes. Other unwanted effects may not occur until months or years after cyclophosphamide is used. These may include developing certain types of cancer, such as leukemia, lymphoma, or bladder cancer.

- Fludarabine: The most common side effects of fludarabine are fever; chills; fatigue; pain rash; mild nausea, vomiting, diarrhea, mouth sores and bleeding of the gastrointestinal tract; edema; urinary infection; decrease in blood counts causing anemia and placing you at risk for bleeding and infections; numbing or tingling in the fingers and toes; muscle aches; infection or inflammation of the lungs causing shortness of breath, fever, and cough. Less common side effects include headache, loss of hair, loss of appetite, altered mental status, drowsiness, liver problems, twitching, hearing loss, high blood sugar levels, and heart failure.

- Rabbit anti-thymocyte globulin (rATG): The most common effects of rATG are fever and chills. Other side effects include pain, swelling, or redness at the infusion site and "serum sickness" (a hypersensitivity reaction consisting of fever, chills, joint pain, muscle aches, kidney disease, blurry vision, and other flu-like symptoms). Finally, a severe allergic reaction may occur, although this is rare. Symptoms of an allergic reaction include: shortness of breath, rash, lower back pain, chest pain, and low blood pressure. A sudden, severe allergic reaction could result in death.

- Rituximab: The majority of side effects occur after or during the first infusion of the drug. Some common side effects include dizziness, feeling of swelling of tongue or throat, fever and chills, flushing of face, headache, itching, nausea and vomiting, runny nose, shortness of breath, skin rash, and unusual fatigue.

- Intravenous Immunoglobulin (IVIg): The most common adverse reactions include chills, fevers, flushing, skin rash/itching, or headache. These symptoms are usually mild and temporary and can be treated by stopping or slowing the infusion or with Tylenol, Benadryl and/or steroids. Other possible side effects are cough, upper respiratory infection, nausea/vomiting, back pain, rigors, fatigue, chest tightness, muscle cramps, back pain, blood pressure changes and elevated BUN/Cr (kidney function tests). More serious and rare reactions include anaphylaxis, aseptic meningitis, pseudohyponatremia (false low sodium), hemolytic anemia, Stevens-Johnson syndrome, renal dysfunction, acute renal failure, thrombosis (blood clot), acute lung injury and viral transmission risk (hepatitis or HIV).

- Methylprednisolone: Methylprednisolone is a steroid that may cause high blood pressure, high blood glucose, muscle wasting, muscle pain or weakness, weakening and destruction of bone, increased risk of infection, fluid retention, low potassium, cataracts, glaucoma, nausea, vomiting, loss of appetite, stomach distress, inflammation of the esophagus and stomach, headache, inability to sleep, restlessness, mood swings, depression, and anxiety.

    - Corticosteroid-Induced Psychosis: Steroids such as methylprednisolone or prednisone may temporarily cause more severe psychiatric symptoms such as hypomania, mania, delirium, extreme depression and anxiety, and mood changes. In rare cases, corticosteroid-induced psychosis can cause suicidal ideation. This can be treated with anti-psychotic medications such as Zyprexa and/or Haldol. Psychiatry services will be consulted if needed for severe symptoms.

- G-CSF (granulocyte colony stimulating factor): The more common side-effects of G-CSF include headache, pain in the arms or legs, pain in joints or muscles, pain in lower back or pelvis, and skin rash or itching. Rare side effects include fever, rapid or irregular heartbeat, sores on skin, and wheezing.

- Mesna: Because mesna is always administered with chemotherapy, it is difficult to determine side effects caused solely by mesna. However, possible side effects include headache, nausea, vomiting, diarrhea, and bad taste in the mouth.

General Risks of Stem Cell Transplantation

- Risk of unknown: Life-threatening side effects and/or death may occur

- Infections may occur at any time after transplantation. Bacterial infections are most common when the white blood cells are low. Fungal infections may occur during this period of low white blood cells. Viral infections can occur early, but are most frequent between two and six months after transplant. Any infection is possibly serious, but most can be treated successfully with antibiotics. A particularly lethal or severe viral infection that may occur in patients with MS is progressive multifocal leukoencephalopathy (PML).

- Bleeding may occur from low platelets. The most dangerous bleeding occurs inside the head, in the bowel, or in the lungs. Patients will be given platelet transfusions as needed to decrease the risk of bleeding.

- Inflammation of the bladder with bleeding (Hemorrhagic Cystitis): If this complication occurs, the urine becomes bloody and urination is painful. It is caused either by cyclophosphamide or by a virus. If inflammation of the bladder occurs, pain medication, fluids, and bladder irrigation may be required.

- Veno-occlusive Disease: In subjects who receive high-dose chemotherapy, clots may form in the small blood vessels of the liver, which make it difficult for the blood to flow through the liver. Symptoms are weight gain, pain in the liver area, free fluid in the abdomen (ascites), and jaundice (yellow skin). Since the dose of drugs used in this study is lower than in most transplants, this side effect is not expected to be very common or severe.

- Atelectasis: Tiny sacs in their lungs collapse due to poor lung expansion. Patients will be given an incentive spirometer during stem cell transplant hospitalization to minimize this risk.

- Transient Neutropenia (from viral infections): Transient neutropenia after the stem cell transplant secondary to a viral infection. If this occurs, it may be necessary to take growth colony stimulating factor (G-CSF) to help the counts recover. It may also be necessary to receive IVIg and/or steroid infusions if this occurs.

- Infertility: The drug cyclophosphamide, which is used in this study, may cause a decrease in the production of human sperm and eggs resulting in sterility and inability to have children. In order to preserve the ability to have children, patients will need to undergo sperm or oocyte preservation by a fertility specialist.

- Mania or psychosis may be induced by corticosteroids. The symptoms are transient and will be treated with Haldol or Zyprexa.

- Breach of confidentiality: the study involves the use of identifiable, personal information and there is a chance that a loss of confidentiality could occur. Procedures are in place to lessen the possibility of this happening.

Risk of Procedures (if applicable)

- Radiation Exposure: Procedures such as CT scans, x-rays and/or radioactive drugs may be used during the treatment. The cumulative radiation exposure from these tests is considered small, however can add up over a lifetime, and it is possible that having several of these tests may add to risk of injury.

- Risk of Echocardiogram (with dobutamine): On rare occasions, stopping of the

heart may occur during the test. Participants will be closely supervised during the test. The test team will watch for and be able to treat emergencies if they happen. There may be side effects from the drugs used in dobutamine stress tests such as lowering of blood pressure, nausea, irregular heart rhythms, temporary dry mouth, or temporary blurred vision

- Risk of Right Heart Catheterization
  Possible risks of a right heart catheterization are bruising of the skin at the site where the catheter is inserted, excessive bleeding because of puncture of the vein during catheter insertion, pneumothorax (partial collapse of the lung) if the neck or chest veins are used to insert the catheter. Other, rare complications may include: abnormal heart rhythms, such as ventricular tachycardia (fast heart rate in the lower heart chambers), cardiac tamponade (fluid buildup around the heart that affects the heart's ability to pump blood effectively), low blood pressure, infection, air embolism (air leaking into the heart or chest area), blood clots at the tip of the catheter that can block blood flow, pulmonary artery rupture (damage to the main artery in the lung, which can result in serious bleeding, making it difficult to breathe).

- Risk of MRI (Magnetic Resonance Imaging): The use of gadolinium-based contrast agents in patients who already have serious kidney problems or who have had a liver transplant may lead to a possibly fatal disease, nephrogenic systemic fibrosis (NSF) involving the skin, muscle and internal organs. Patients will be screened for kidney problems and liver transplant prior to receiving an MRI. Kidney function blood tests will be checked. The contrast agent to be used which contains gadolinium is Gadavist and the dose to be given is 0.1 mmol/kg which is within FDA approved guidelines. This is the standard dose and agent used by Northwestern Medicine.

  Patients will also be asked about surgeries of blood vessels of brain or heart valves which may be a contraindication to MRI. They will also be asked about metal from surgeries, implanted electronic devices such as (but not limited to) a cardiac pacemaker, cardiac defibrillator, cochlear implant, or nerve stimulator that could be damaged from an MRI. Other possible side effects are fatigue or claustrophobia in the MRI scanner.

- Risk of Upper Endoscopy/Colonoscopy: Rare complications include bleeding, infection, or tearing of the GI tract. For colonoscopy, there is a low risk for tear or perforation of the rectum or colon wall. Sedation is typically used for these procedures and there could be an adverse reaction to a sedative used during the exam.

- Risk of Apheresis: The most common complication of apheresis is hypocalcemia from citrate used during the procedure. Symptoms of low calcium are usually mild (numbness in the lips and fingers), but may be moderate (cramping in the arms and legs) or, rarely, severe (nausea, vomiting, or seizure). Risk will be minimized by calcium replacement during the procedure, slowing the flow rate if needed, and/or taking calcium supplements by mouth.

Other complications are infrequent, but may include low blood pressure, fainting, or infection.

- Risk of Blood Withdrawal: The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

- Risk of Blood Product Transfusions: All blood products are carefully screened, but they may contain infectious diseases such as HIV, hepatitis, CMV, malaria, and bacterial infections, although the risk is very low. The specific risk of getting the more common infections are: HIV (1 in 1,900,000 units), Hepatitis A virus (1 in 1,000,000 units), Hepatitis B virus (1 in 63,000 units), Hepatitis C virus (1 in 1,600,000 units), Human T-cell leukemia virus (1 in 641,000 units), and bacterial infections (rare with red blood cell transfusions; 1 in 15,000 units with platelet transfusions).

- Risk of Stem Cell Reinfusion: There is a low risk that blood stem cells may be contaminated with an infectious bacteria during the collection procedure. The contaminated blood product could cause a serious, life-threatening infection or other unwanted reactions. All stem cells will be checked for culture. Care will be taken to prevent any problems that could cause contamination.

- Failure of Engraftment: It is possible, but very unlikely, that the stem cells will fail to grow (engraft). If this happens, patients own stem cells in their body will grow. If the infused stem cells fail to grow, it will take approximately five days longer for neutropenia to recover.

- Risk of Central Line Placement: Placement of a central line such as a VasCath (central line for the collection of stem cells) or a PICC (central line for stem cell transplant) is a routine procedure that may be done under local or general anesthesia. Potential complications include clotting in or around the line, bleeding, air or blood around the lung, or changes in heart beats that could lower your blood pressure. The catheter or line may become infected and require treatment with antibiotics and/or removal.

POTENTIAL BENEFITS TO PARTICIPANTS:
We cannot promise any benefits to participants in this research study. Possible participant benefits include:

- Systemic Sclerosis will go into long-term remission
- Ability to stop treatment drugs that can be associated with side effects and complications
- Improvement in quality of life

SHARING OF RESULTS WITH PARTICIPANTS:
Patients will have access to all of their laboratory tests via MyChart, which is a secure electronic portal for patients to access their own medical records. Patients may contact medical records at any time and request all hospital records including laboratory tests, procedures (reports and CDs), hospital notes, clinic notes, and discharge summaries.

Northwestern Medicine procedures for release of medical information will be followed.

Patients will be notified of any incidental findings during transplant testing and will be offered a physician referral if indicated for further monitoring and/or treatment.

Patients will be notified of general study results as data is analyzed upon request.

Hospital discharge summaries and any other pertinent medical records will be sent to patients' primary care physicians via fax or email with patient permission.

SETTING (FLOORS OR ROOMS MAY CHANGE PER NMH PROTOCOL):
The site of this research is located at Northwestern Medicine Hospital in Chicago, IL. Specifically, clinic visits will take place on the 14th floor of the Galter Pavilion, stem cell harvests will take place at Rube Walker Blood Center located in the Galter Pavilion, and inpatient admissions for stem cell mobilization and stem cell transplant will be in Prentice Women's Hospital on the designated stem cell transplant floor. Actual locations may be subject to change, however no research will be conducted outside of the Northwestern Medicine Institution. No community advisory board is involved in the research. Participants are not recruited but elect to come to Northwestern for a second opinion regarding the treatment of their multiple sclerosis. Participants learn about this treatment option through word of mouth or physician referrals.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE:
The Division of Immunotherapy and Autoimmune Diseases (DIAD) is a center dedicated specifically to stem cell transplants for autoimmune diseases. The principal investigator (PI) of this study pioneered stem cell transplants for autoimmune diseases and has performed stem cell transplants in patients for over 20 years. Through involvement with other systemic sclerosis studies, staff at this site has developed familiarity with the systemic sclerosis patient population, treatments for systemic sclerosis, and the clinical manifestations and risks of the disease. DIAD staff is knowledgeable of the disease and the unique medical needs of these patients. Inpatient providers (Nurse Practitioners, Physician Assistants and Fellows) are trained directly under the PI.

New staff members receive an orientation manual and are required to demonstrate competency in order to complete training. Clinical research nurses and inpatient providers are trained specifically for transplant of autoimmune diseases.

Clinical research nurses are trained in the study protocol and work directly with the PI to determine participant eligibility and coordinate pre-transplant procedures. They are trained on how to obtain consent for participation in the study. They also are trained on how to perform specialized tests specific to systemic sclerosis, such as the Modified Rodnan Skin Score (mRSS) and how to assess for adverse events at follow up visits. Clinical research nurses have prior experience as nurses in inpatient hospital settings.

The goal to enroll 50 participants in a five-year time frame is feasible given the number of transplants performed for Systemic Sclerosis in recent years. The participants will be admitted to Prentice Women's Hospital on a specialized floor dedicated to stem cell transplant patients. There is a high-efficiency particulate air (HEPA) filtration system on

the stem cell transplant floors that constantly filters the air inside of the hospital and decreases the risk of infection for participants. Nursing staff are specially trained for care of stem cell transplant recipients, including training in chemotherapy and stem cell infusions. DIAD staff has provided additional training and education regarding stem cell transplants for autoimmune diseases to the registered nurses on the floor via in-services and emailed resources. An inpatient nurse training manual, *Autoimmune Inpatient Manual (AIM)*, has been developed and will be used for training.

Stem cell harvests will take place in Rube Walker Blood Center using an apheresis machine. Registered nurses at Rube Walker Blood Center receive specialized training to use apheresis machines. A hematologist is available in case of any complications that may occur during the procedure. DIAD nurse practitioners will examine participants during their stem cell harvest at Rube Walker Blood Center and answer any questions or concerns they have. Nurse practitioners are also available by pager for questions or concerns from Rube Walker nursing staff.

Flow cytometry lab uses ISH AGE protocol for CD34 counts which is the recommended protocol for testing CD34 counts. Stem cells are cryopreserved and stored in Cell Therapy, a stem cell processing lab. A remote alarm company monitors freezers and alarms if temperature drops below a specific threshold. Trained medical technologists staff the stem cell therapy lab. Stem cell infusions take place in the hospital room at Prentice Women's Hospital. The specialized medical technologists are responsible for bringing stem cells to bedside and thawing cells prior to administration. Northwestern procedures to ensure that the correct stem cells are provided to the correct patient are followed prior to infusion.

Participants' medical records are stored on encrypted password protected computers through Northwestern Medicine's electronic medical record. Paper medical charts are stored in a locked facility at the office of the Division of Immunotherapy and Autoimmune Diseases.

Medical and psychological resources will be available to all participants. Psychologists will be consulted on an as needed basis prior to transplant for patients with history of psychiatric disorders. During hospitalization, if participants verbalize needing further psychological assistance, Northwestern Psychiatry department will be available for consult.

Participants will have contact information to medical staff familiar with this procedure at all times through the paging system (emergencies), by phone or email. During hospitalizations, the DIAD team will assess participants daily. After work hours, a hospitalist service will be available for medical needs overnight and DIAD staff can be paged for any specific questions or emergencies. When discharged from hospital, patients are encouraged to reconnect with local physicians since many are from other cities, however, DIAD staff will continue to monitor participants and are available for any questions regarding recovery from stem cell transplant or emergencies.

After transplant, participants will be instructed to have labs drawn weekly for four weeks, every other week for eight weeks, and monthly for three months. DIAD staff will monitor lab results and remain in contact with participants to inform them of lab results.

Participants will be asked to return to clinic for follow-up visits with the PI at 6 months (optional), 1 year and then every year for five years post-transplant. Follow-up visits will occur in the immunotherapy clinic on the 14th floor of Galter Pavilion.

A copy of the research protocol will be kept in the DIAD office and available for all staff. DIAD has monthly staff meetings where protocol and responsibilities will be reviewed. Multiple research studies have been completed by DIAD making staff experienced in research procedures and familiar with their duties and functions in a research study. The PI will oversee all staff to ensure adherence to protocols and fulfillment of individual duties and functions.

PRIOR APPROVALS:
There will be no prior approvals prior to commencing the research, including external sites, funding, or agencies.

RECRUITMENT METHODS:
Participants are not recruited but elect to come to Northwestern for a second opinion of their systemic sclerosis and to be evaluated for consideration for stem cell transplant. Participants learn about this treatment option through word of mouth or physician referrals or division website or www.clinicaltrials.com . When a potential candidate contacts the Division of Immunotherapy and Autoimmune Diseases for an evaluation, he or she will be directed to a study nurse who will send them information about the procedure. If interested in coming to Northwestern Medicine for an evaluation, they will be asked to fill out a screening form and to send pertinent medical records to the study nurse for review prior to scheduling an appointment. If the person appears to be a candidate, an initial evaluation will be scheduled in which the patient will meet with the principle investigator to verify a systemic sclerosis diagnosis and eligibility. If found to be eligible for transplant, the candidate will be asked to participate in the research study. Study candidates will not be offered any payment for their participation in the study.

NUMBER OF LOCAL PARTICIPANTS:
One center study with 50 participants at Northwestern Medicine.

CONFIDENTIALITY IN MULTICENTER STUDY: N/A

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
Efforts will be made to limit the use and disclosure of participants' personal information, including research study and medical records, to people who have a need to review for this information.

Participant names and other identifying information will be kept confidential in publications, teaching, and presentations at scientific meetings.

Health information that we may collect and use for this research includes:
- All information in a medical record
- Results of physical examinations
- Medical history

- Lab tests, or certain health information indicating or relating to a particular condition as well as diaries and questionnaires
- Records about study medication or drugs
- HIV testing results

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
We will be complaint with Northwestern Medicine's HIPAA Policy to ensure participants privacy interests. Team members will undergo annual training per hospital policy.

The confidentiality policy will be explained to participants in the consent form.

The following groups of people may access patient information via the electronic medical record, the source book, or by contacting a previous health care provider or office on a need to review basis:

- All current and previous health care providers, including but not limited to the Shirley Ryan AbilityLab, Northwestern Medical Group (NMG), Northwestern Medicine HealthCare (NHC), Northwestern University
- Treatment monitors and auditors who make sure that the treatment is being done properly
- Northwestern University IRB
- Northwestern Office of Research Integrity (ORI)
- The treatment doctor must report positive HIV tests to the Illinois Department of Public Health (IDPH). The IDPH keeps track of all persons in the state with positive HIV tests.

COMPENSATION FOR RESEARCH-RELATED INJURY:
N/A

ECONOMIC BURDEN TO PARTICIPANTS:
Taking part in this research study may lead to added costs for participants. Participants or their insurance company will be responsible for payment of all physician fees, hospital charges, laboratory tests, drugs, and procedures in connection with the stem cell transplant. In addition, transportation and housing costs will be the participants' responsibility.

CONSENT PROCESS:
There will be a discussion of possible risks of the procedures between the principal investigator (PI) and the process for randomization to the participant prior to enrollment. Time devoted to consent discussion between the PI and the participant will be during an office visit, which may last 30-60 minutes, however, any questions or concerns regarding the consent may be addressed to the PI or team member at any time.

Consent will be obtained by the clinical research nurse in person, either during a clinic office visit or in the hospital. The participant will then be given time (hours to days) to read the consent. During this time, a team member will be available for questions. Once the participant has read the consent, he or she will sign it in front of the clinical

research nurse. The nurse will then sign on the witness line. Both signatures will be dated. A copy of the signed consent will be made and given to the participant. The original signed consent will be stored in the patient's chart.

To ensure ongoing consent, the risks of the procedure are reviewed by the inpatient providers with the participant during mobilization and transplant admissions. The participant and family members are given the opportunity to ask questions. Participants may withdraw from the study at any time without penalty. Participants are not being offered compensation for the study. The consent states that participants can choose not to take part in the study, or they can agree now and later change their mind and leave the study. It also states that their decision will not be held against them.

Participants will be given the opportunity to ask questions prior to signing the consent and each time the risks are reviewed. Participants will be asked if they understand the risks and wish to proceed. Verbal agreement will ensure understanding.

For Non-English Speaking Participants
While we do not anticipate enrolling participants who do not speak English, participants come from all over the world who may not speak English. In this case, a written summary of the consent and the short-form consent will be used to obtain consent. This information will be sent to the IRB for review. Certified medical interpreters or translation phones will be used to orally present this information to participant or a legally authorized representative. Questions will be answered using an interpreter. The written summary of the consent will be signed by the participant and the person obtaining consent. The short-form consent will be signed by the participant and a witness (who may be the interpreter or a person who is fluent in both languages, but will not be the person obtaining consent). If the participant requests, a written copy of the consent in his or her native language can be obtained.

PROCESS TO DOCUMENT CONSENT IN WRITING:
Consent: See Attached Document

Consent of the participant is documented by placing the signed consent in the patient's chart (source book). The enrollment list of participants is kept in the protocol binder. The date of signed consent and the team member obtaining consent will be documented next to each participant.

Waiver or Alteration of Consent Process:
N/A

Participants who are not yet adults (infants, children, teenagers)
N/A

Cognitively Impaired Adults
An individual will be determined capable of consent based on the PI's assessment of the individual's cognitive function. If the individual is deemed incapable of consent due to cognitive impairment, consent may be obtained by the closest living relative or by a person assigned as the power of attorney.

Adults Unable to Consent
Adults who cannot consent will be excluded from the study, unless an adult is deemed cognitively impaired from their disease. In that case, consent may be obtained by the following in order of priority:

1. The court appointed guardian of the person if that guardian has the right to make healthcare decisions.
2. The agent under a Durable Power of Attorney for healthcare.
3. A surrogate under the Healthcare Surrogate Act, which includes: the patient's court appointed guardian of the person if that person has the right to make healthcare decisions; the patient's spouse; any adult child of the patient; a parent of the patient; any adult sibling of the patient; any adult grandchild of the patient.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
Drugs used in the study are standard immune suppressive drugs. No experimental drugs are used. The stem cells themselves have no therapeutic effect and are simply a supportive blood transfusion product. Drugs are stored and prepared by pharmacists and pharmacy technicians at Northwestern Medicine. There is a bar code on the drug label and on the patient wrist band that gets scanned to verify that the correct drug is being administered to the correct patient. Drug, dose, time of administration, and name of the nurse administering the medication is recorded into the electronic medical record.

Cyclophosphamide
1. Other names: Cytoxan®, Neosar®
2. Chemical: 2-bis (2-chloroethyl) amino tetrahydro-2H-1, 3, 2- oxazaphosphorine-2-oxide monohydrate.
3. Classification: Alkylating agent.
4. Action: Causes prevention of cell division by forming adducts with DNA.
5. Metabolism: Metabolized to active compounds by microsomal enzymes in the liver. Excreted by the kidney in both the original form and as metabolites.
6. Availability: 25 mg and 50 mg tablets (tablets cannot be split); 100 mg, 200 mg, 500 mg, 2000 mg vials Mead Johnson and Adria.
7. Storage: Stable at room temperature indefinitely before reconstitution. After reconstitution, stable for 6 days upon refrigeration or for 24 hours at room temperature.
8. Administration: Dissolved in 250-500 ml 0.9 NS and administered over 120 minutes IV (may slow rate and give over 2-4 hours). Hyper-hydration with isotonic IV fluid is given before, during and for 24 hours after infusion. If the rate of required hydration is not tolerated, bladder irrigation may need to be substituted.
9. Side effects: Myelosuppression, leukopenia (nadir 8-14 days), hemorrhagic cystitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), bladder carcinoma, cellular dysplasias, mucositis, rash, alopecia, anorexia, nausea, vomiting, sterile phlebitis, rare pulmonary toxicity, teratogenicity, hemorrhage,

myocarditis, infertility, secondary leukemia; With rapid IV push: oropharyngeal tingling, metallic taste, headache, urticaria, facial swelling. Metabolic abnormalities following cyclophosphamide-induced cell lysis can require dialysis in patients with underlying renal insufficiency.

Mesna

1. Other name: Mesnex®
2. Description: hemorrhagic cystitis prophylaxis, binds to urotoxic metabolytes
3. Availability: PO and IV
4. Drug Administration: will be given IV at same dose as Cyclophosphamide dose. Dissolved in 250-500 ml 0.9 NS and administered over 24 hours.
5. Side Effects: Anaphylaxis or hypersensitivity reaction, headache, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, cough, rigors, back pain, rash, conjunctivitis, arthralgia, rhinitis, constipation

G-CSF

1. Other names: Neupogen®, Filgrastim, Granix®, Zarxio®
2. Description: Hematopoietic growth factor.
3. Drug administration: Subcutaneous administration 5-15 mcg/kg/day.
4. Storage and Stability: 300 mcg and 480 mcg vials stored in refrigerator.
5. Side Effects: Myalgias, headache, flu-like symptoms, fever, bone pain in approximately 20% of patients, possible elevation of uric acid, transaminases, and LDH.

ATG Rabbit

1. Other names: Thymoglobulin®
2. Description: A rabbit polyclonal antibody to lymphocytes.
3. Drug administration: 0.5-1.5 mg/kg in D5W or NS infused over 10 hours. An in-line 0.22 µm filter should be used for rATG administration.
4. Storage and Stability: 50mg/ml (5 mL ampule) vial stored in refrigerator.
5. Side Effects: anaphylaxis, serum sickness, chills, arthralgia, myalgia, headache, nausea, vomiting, diarrhea, constipation, chest-pain, back pain, hypotension or hypertension, tachycardia, peripheral edema, dyspnea, lung disorder, abdominal pain. Other side effects include hyperlipidemia, thrombocytopenia, anemia, and hypokalemia or hyperkalemia

Fludarabine

1. Other names: Fludara
2. Chemical: 9H-purin-6-amine, 2-fluoro-9-(5-0-phosphonon-beta-D-arabinofuranansyl)
3. Classification: purine analog
4. Action: inhibits DNA synthesis or repair.
5. Metabolism: Unknown.