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Title: Maximizing Outcome of Multiple Sclerosis Transplantation: "MOST" Trial

IRB ID: STU00206133-CR0001

Northwestern | RESEARCH

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STUDY CLOSURE

DATE: October 9, 2019

TO: Dr. Richard Burt
FROM: Office of the IRB

The Northwestern University IRB has reviewed the submission described below:

Type of Submission:	Continuing Review
Title of Study:	Maximizing Outcome of Multiple Sclerosis Transplantation: "MOST" Trial
Principal Investigator:	Richard Burt
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The IRB closed the study effective **10/9/2019**. This action was taken because:

- The protocol is permanently closed to enrollment or was never open for enrollment;
- All subjects have completed all protocol-related interventions (if applicable);
- Collection of private identifiable information is completed (if applicable);
- Analysis of private identifiable information is completed (if applicable); and/or
- Remaining study activities are limited to data analysis.

PROTOCOL TITLE:
Maximizing Outcome of Multiple Sclerosis Transplantation: "MOST" Trial

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OBJECTIVES:

We propose a randomized study of autologous un-manipulated peripheral blood hematopoietic stem cell transplant (HSCT) comparing two different conditioning regimens: (1) cyclophosphamide and rabbit anti-thymoglobulin (rATG) versus (2) cyclophosphamide, rATG, and Intravenous Immunoglobulin (IVIg).

BACKGROUND:

Classification and Pathophysiology of Multiple Sclerosis

Multiple Sclerosis (MS) is the most common immune-mediated demyelinating disease of the central nervous system affecting more than 2.3 million people worldwide (1). The International Advisory Committee on Clinical Trials of MS re-defined MS disease phenotypes in 2012, with core phenotypes of MS categorized as relapsing and progressive disease, and clinical subtypes as follows: clinically isolated syndromes (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) (2). MS phenotypes are modified by disease activity, determined by clinical relapses and/or new or enlarged T2 lesions or gadolinium enhancing lesions on MRI, or by disease progression, which is characteristic of PPMS and SPMS (2). CIS is the first attack that shows characteristics of inflammatory demyelination (ie: optic neuritis), however does not yet fulfill the revised McDonald diagnostic criteria for MS (2). RRMS is inflammatory and accounts for approximately 85- 90% of cases at onset. It is characterized with distinct relapses with full recovery that may or may not leave residual neurological deficits and no progression of symptoms between flares (3). Over years or decades, most cases of RRMS transition into SPMS, which is non-inflammatory with gradual progression of neurologic deterioration that occurs independent of relapses (2). PPMS is a non- inflammatory form of MS that is progressive at onset, without a period of exacerbations prior to clinical progression (2).

Relapsing-remitting disease is often responsive to immune suppressive or disease-modifying therapies (DMTs), while immune based therapies are generally ineffective in patients with a progressive clinical course. This lack of response to immune suppression, as well as neuropathology and neuroimaging studies, suggest that disease progression is associated with axonal atrophy. Disability correlates better with measures of axonal atrophy than immune mediated demyelination. Therefore, immune based therapies, in order to be effective, need to be started early in the disease course while MS is predominately an immune-mediated and inflammatory disease.

Disease Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

To date, fifteen drugs have been FDA approved as disease modifying therapies (DMTs) to treat RRMS. Injectable drugs include: interferon betas (Avonex, Betaseron, Extavia, Rebif, and Plegridy), Copaxone Glatopa (glatiramer), and Zinbryta (daclizumab). Oral medications include Aubagio (teriflunomide), Gilenya (fingolimod), and Tecfidera (dimethyl fumarate). Intravenous infusions include Lemtrada (alemtuzumab), Novantrone (mitoxantrone), Ocrevus (ocrelizumab), and Tysabri (natalizumab) (4). There are also off label drugs that are being used such as Rituxan (rituximab) and IV immunoglobulin (IVIg). There have been several studies published on the efficacy and safety of DMTs. While many second and third line drugs such as natalizumab, alemtuzumab, fingolimod, and dimethyl fumarate show a decrease in relapse rates in RRMS compared to first line drugs such as interferon betas, they have not been shown to stop progression of disease and are associated with many side effects. Also, second and third line MS drugs have never been compared to each other in a randomized trial.

The Natalizumab Safety and Efficacy in RRMS (AFFIRM) study compared natalizumab to placebo in a randomized trial. Of 596 patients, 37% who received natalizumab and 7% who received placebo were without clinical relapse or with new MRI findings after 2 years (5). In another study, the Tysabri Observational Program (TOP), of 4,821 patients enrolled, there were no improvements in EDSS at the 5-year interim analysis (6). In addition, 18 patients developed Progressive Multifocal Leukoencephalopathy

(PML) and 24 developed malignancies. Of the 18 patients with PML, 14 had been treated with Tysabri for 2 or more years and 3 had previously been treated with mitoxantrone.
Mitoxantrone, which is no longer used in the United States for RRMS, can cause late congestive heart failure or myelodyplastic syndrome and leukemia and may also increase the risk of developing PML (7). Therefore, patients previously treated with mitoxantrone will be excluded from this study.

The CARE-MS II randomized study compared the efficacy of alemtuzumab and Rebif in patients with refractory RRMS who had previously been treated with interferon or glatiramer. On examination and MRI findings at two years, 32% who received alemtuzumab and 14% who received Rebif showed no evidence of progression (8). In patients who received alemtuzumab, EDSS scores reduced by -0.17 points, which while reported as a significant finding, is not a great enough change to significantly impact neurological functioning.

A Cochrane systematic review of 5,152 participants in six randomized controlled trials assessed the safety and benefit of oral Fingolimod compared to either placebo (n=923) or other DMTs (n=698) (9).
There was an increased probability of being relapse free in the Fingolimod group compared to placebo at 24 months and to interferon at 12 months, however, there was no difference in the groups in preventing progression and neurological decline. A major adverse reaction that has been associated with Fingolomod is cardiac arrhythmias and ECG abnormalities (10).

The table below shows the percentage of patients in several studies who achieved no evidence of disease activity (no clinical relapses, no progression, no new MRI activity) using DMTs (25). Many trials compared the use of second or third line DMTs to placebo or interferon beta. Most of the studies had a study duration of 1-2 years. No study achieved NEDA of greater than 47%, and most were much lower than that. In the CLIMB study, which looked at cohort data of MS patients over 7 years, only 6% with early MS showed NEDA.

NEDA in Clinical Studies

Clinical Study	Study Duration, y	Patients With NEDA Status, %
ADVANCE	1	Placebo, 15%; pegylated interferon beta-1a every 2 weeks, 34%
AFFIRM	1	Placebo, 15%; natalizumab, 47%
SELECT	1	Placebo, 11%; daclizumab, 39%
AFFIRM	2	Placebo, 7%; natalizumab, 37%
CARE-MS I	2	SC interferon beta-1a, 27%; alemtuzumab, 39%
CARE-MS II	2	SC interferon beta-1a, 13%; alemtuzumab, 32%
CLARITY	2	Placebo, 16%; cladribine, 46%
CLIMB	2	Early MS, 24%; established MS, 31%
FREEDOMS	2	Placebo, 13%; fingolimod, 33%
DEFINE	2	Placebo, 15%; dimethylfumarate, 28%
CombiRx	3	IM interferon beta-1a alone, 21%; glatiramer acetate alone, 19%; glatiramer acetate and IM interferon beta-1a, 33%
CLIMB	7	Early MS, 6%; established MS, 10%

Table 1 (Rotstein et. al., 2015)

In summary, while FDA approved therapy may slow disease activity and disability in some patients, no drug has been shown to prevent progressive disability, significantly reverse neurological disability on Expanded Disability Status Scale (EDSS), or significantly improve quality of life (5). Long term use of DMT's may lead to serious adverse reactions such as cardiac complications, PML and late malignancies. Most patients with RRMS will eventually enter SPMS in which disease modifying therapies have not been shown to be beneficial (6, 11). Some patients with aggressive forms of RRMS, do not respond to DMTs and rapidly develop permanent neurological disability (11).

Healthcare Costs of Multiple Sclerosis

Costs of DMTs have rapidly increased at rates higher than inflation with sales of nearly 9 billion dollars in 2012 (42). Average annual costs of both first and second generation DMTs are $60,000 US dollars per patient. First generation drugs have risen an average of 21%-36% per year while second generation drugs have risen 8%-17% per year since introduced, compared to general prescription drugs which have only increased 3%-5% per year during the same time period (12, 42). In addition to drug costs, there are other significant direct and indirect costs associated with MS, such as diagnostics and interventions, hospitalizations, complications from disease, disability, and loss of work productivity. Newly diagnosed MS patients are 3.5 times more likely to be hospitalized compared to healthy individuals (12). MS ranks second behind congestive heart failure in direct medical costs for chronic conditions (12). As disease burden progresses with disability as measured on the Expanded Disability Status Scale (EDSS), healthcare costs substantially increase. On average, annual costs for a patient with an EDSS of 3.0-3.5 is $30,000 compared to $50,000 for a patient with an EDSS of 3.5 to 6.5. For those who are wheelchair bound and dependent on caregivers to carry out activities of daily living, the average cost starts at $100,000 per year (12).

Autologous HSCT for Multiple Sclerosis

Autologous Hematopoietic Stem Cell Transplantation (HSCT) has been an investigational treatment for MS for more than two decades. Autologous HSCT "resets" the immune system by using a transplant conditioning regimen that ablates the aberrant disease causing immune cells while hematopoietic stem cells regenerate a new and antigen naïve immune system. The de novo development of the T and B cell repertoire from uncommitted progenitor cells in the presence of autoantigens is thought to default to self-tolerance in a non-inflammatory environment (13, 14).

Early clinical trials were restricted to patients with severe disability (mean EDSS 6.5-7.0) and used myeloablative conditioning regimens with drugs such as high dose busulfan and total body irradiation. These trials showed little efficacy in late progressive disease (EDSS > 6.0), but stabilized those earlier in its course (EDSS < 6.0), and in the few cases of RRMS and aggressive MS, manifesting as rapid and severe neurologic decline with MRI signs of inflammation, a significant neurologic improvement occurred after HSCT (15, 16). There was also high mortality in early phase 1 HSCT trials for MS, however it was during a time when there was no prior experience with HSCT for MS, and the studies selected patients with advanced progressive disease and utilized conditioning regimens that were high-intensity and reserved to treat malignancies (17, 18, 19). Since that time, while some investigators are still using unwarranted and excessive conditioning regimens, the field has matured and more recent publications since 2014 demonstrate the efficacy and safety of HSCT in MS.

Burman et al., (2014), Multi-Center Trial, Sweden

Burman et al. (2014) published the "Swedish experience" of autologous HSCT in forty-eight patients with MS (forty with RRMS, five with SPMS, two with PPMS, one with progressive-relapsing MS) in seven cities in Sweden from 2004 to 2013 (20). Two conditioning regimens were used: 41 patients received BEAM/ATG (BCNU 300 mg/m$_2$, etoposide 800 mg/m$_2$, cytosine-arabinoside 800 mg/m^2, melphalan 140 mg/m$_2$, ATG 7.5-10 mg/kg) and seven patients received cyclophosphamide (200 mg/kg) and rabbit anti- thymoglobulin (rATG) (10 mg/kg). 41 of 48 patients (RRMS=34, Progressive MS=7) had more than one year of follow up and were included in the analysis of results. Five patients had new MRI activity between six and 31 months post HSCT with a total of five new gadolinium enhancing lesions and eight new T2 lesions. Four of the five of these patients also had clinical relapses. The median EDSS improved from 6.0 to 4.0 with a median change of -0.75 from pre-HSCT to the latest follow up, however improved by -1.5 points upon analysis of patients with relapsing remitting disease. Eight patients had progression or worsening EDSS defined as change of 0.5 points sustained at follow

up visits. Five year relapse-free survival was 87%, MRI event free survival was 85%, EDSS score progression-free survival was 77%, and disease-free survival (no relapses, no new MRI lesions and no progression of EDSS) was 68%. In those with gadolinium enhancing lesions prior to HSCT, indicating inflammatory disease, there was 79% disease-free survival compared to 46% in those who did not have gadolinium enhancing lesions (p=0.028). There were no significant differences in outcomes when comparing the two different conditioning regimens and no treatment related deaths. During HSCT, one patient developed an invasive fungal infection treated with fluconazole. Seventeen patients had neutropenic fevers, 22 had positive blood cultures, and two developed *Clostridium difficile*. Post-HSCT, eight patients (17%) had reactivation of herpes zoster post-HSCT and four patients (8.3%) developed thyroid disease. There were no reports of malignancies post-HSCT.

Burt et al., (2015), Single-Center Trial, United States

Burt et al. (2015) published the results of 151 patients (123 with RRMS and 28 with SPMS, 55 on study protocol, 96 off study on compassionate basis) who underwent a HSCT using a non-myeloablative, low-intensity conditioning regimen at a single institution between 2003 and 2014 (21). Twenty-two patients received a conditioning regimen of alemtuzumab and cyclophosphamide (200 mg/kg over four days) while 129 patients received rATG (6 mg/kg) and cyclophosphamide (200 mg/kg over four days) followed by infusion of un-manipulated peripheral blood stem cells. The mean age of patients treated was 36 years and follow-up time points were analyzed at six months, one year, and then yearly for five years. Result analysis was completed on 145 patients with a median follow-up of two years (mean 2.5 years).

The primary end point was a change on the EDSS score of 1.0 or greater with a decrease in score indicating reversal of neurological disability and an increase indicating progression of disease. Results showed that EDSS scores improved significantly at all time points (p<.001) except five years (p=.009) with a pre-transplant median EDSS score of 4.0 and a post-SCT score of 3.0 at six months and one year, and 2.5 at three, four and five years.

Secondary end points included safety, relapse-free survival, progression-free survival, disease activity-free survival (no relapses, no progression, no new T2 lesions on MRI), change in the Neurological Rating Scale (NRS) of 10 or more, the Multiple Sclerosis Functional Composite Score (MSFC), quality of life using the Short Form 36 (SF36) questionnaire, new gadolinium enhanced lesions on brain MRI, and T2 weighted lesion volume on brain MRI.

There were no treatment-related deaths and the overall survival was 99.3% (one death occurred 30 months post-HSCT from hypertensive cardiovascular disease). Relapse-free survival was 89% at two years and 80% at four years while progression-free survival was 92% at two years and 87% at four years. Similar to Burman et al., (2014), disease activity-free survival was 80% at two years and 68% at four years. NRS scores improved significantly over time points (P<.001) and there were also significant improvements in MSFC scores. There were significant improvements in the quality of life scores from the SF-36 questionnaire (n=132) in the mental, physical and total scores. There was also a significant improvement in the number of gadolinium enhancing lesions post-HSCT at all time points with a mean number of lesions of 3.22 pre-transplant and 0.08 at five years post-HSCT. T2 lesion volume on MRI significantly decreased upon analysis of 128 patients with complete scans at 27 months with a median volume decrease of 33%. Post-hoc analysis showed significant improvements in EDSS scores among patients with RRMS (n=118), those with disease duration of 10 years or less (n=113), and those without sustained fever at three readings at least four hours apart in 24 hours during HSCT (n=106). EDSS scores did not improve in patients with SPMS (n=27), in those with disease duration of greater than 10 years (n=32) and in those with sustained fever of 38.5C (n=31).

There were no early or late infections of fungal, *pneumocystis jirovecii*, cytomegalovirus, Epstein-Barr virus or JC virus. Twelve patients had vancomycin resistant enterococcus and two had positive nasal cultures for methicillin-resistant Staphylococcus aureus at time of admission. Four patients developed *Clostridium difficile* and one patient had a positive blood culture of coagulase-negative Staphylococcus. Four patients developed late reactivation of herpes zoster treated with anti-viral medications. Of the 22 patients who received alemtuzumab in the conditioning regimen, three (14%) developed immune thrombocytopenia (ITP) compared to four of 129 (3.1%) patients who received rATG. ITP resolved in all patients after treatment with corticosteroids and intravenous immunoglobulin or rituximab. Seven patients developed a thyroid disorder after stem cell transplant. One patient who received alemtuzumab in the conditioning regimen developed breast carcinoma three years post-HSCT and another who received alemtuzumab and also been treated with mitoxantrone prior to HSCT developed lymphoma five years post-HSCT. In the patients who were treated with rATG and cyclophosphamide, there were no late cancers reported post-HSCT.

Nash et al., (2015), Multi-Center Trial, Europe

Nash et al. (2015) published three year interim results from a phase two, multi-center, single arm trial in Europe, the Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT- MS) (22). Patients aged 18-60 with RRMS who failed DMTs and had a baseline EDSS of 3.0-5.5 were included in the study. Results were analyzed for 24 patients who underwent HSCT between 2006 and 2009.

Peripheral blood stem cells were mobilized with filgrastim (16 mcg/kg/day) for four days, were collected by leukapheresis and were CD34-selected. The patients were given prednisone for 10 days during mobilization to prevent flare of disease since cyclophosphamide was not given. Conditioning regimen was high dose BEAM with carmustine 300 mg/m$_2$ on day -6, etoposide 200 mg/m$_2$ and cytarabine 200 mg/m$_2$ day -5 to day -2 and melphalan 140 mg/m$_2$ on day -1. Rabbit ATG 2.5 mg/kg/day was given on day -2 and day -1. Prednisone was given day 7 to 21 to prevent fevers.

The median age of participants was 38, median disease duration was 4.9 years, and median EDSS was 4.5. The primary end point was time to treatment failure in five years defined by death or progression of disability with worsening EDSS of 0.5 points or more, clinical relapse, or two or more independent MRI findings with new T2 lesion or gadolinium enhancing lesions one or more years post-HSCT. Five of 24 patients reached the primary end point within three years post-HSCT and two additional patients met the study end point with MRI criteria after three years post-HSCT. Mortality occurred in two patients enrolled in the trial post-HSCT. One was due to MS progression 2.5 years post-HSCT and the other was due to worsening asthma three years post-HSCT. At three years, EDSS progression frees urvival was 90.9%, clinical relapse-free survival was 86.3%, MRI event-free survival was 100%, and overall event- free survival was 78.4%. EDSS scores improved with a median change from baseline to three years of -0.50 (p=.007). The MSFC scores also improved from baseline to three years by a median of 0.15 (p=.01).

Significant changes were seen in reduction of brain lesions from baseline to follow-up points. Adverse events were reported from time of consent to the follow-up period. Pneumonia was identified in two patients, *Clostridium difficile* in one patient, CMV reactivation in one patient, EBV reactivation in two patients, and pulmonary embolisms occurred in three patients.

Atkins et al. (2016), Multi-Center Trial, Canada

Atkins et al. (2016) published the results of a phase two single arm trial of 24 patients ages 18-50 who received an autologous HSCT at three hospitals in Canada between 2001 and 2009 (23). Eligibility criteria included high probability of disease progression, ongoing disease activity despite one year of treatment, and EDSS between 3.0 and 6.0. Conditioning regimen was busulfan every 6 hours for 16

doses, cyclophosphamide (50 mg/kg for four days), and rATG 1.25 mg/kg/day for four days, followed by CD34-selected infusion of previously harvested stem cells (4.5 g/m$_2$ of cyclophosphamide given for mobilization).

One patient who received 14.9 mg/kg of busulfan died from hepatic necrosis due to sinusoid obstruction syndrome (SOS) and sepsis 62 days after HSCT. A second patient given 12.7 mg/kg of busulfan also developed SOS and required ICU admission but fully recovered. Subsequently, the study was temporarily placed on hold and the dose and route of busulfan was changed. Other notable toxicities in this study are all patients had febrile neutropenia during HSCT, 14 had positive blood cultures, and 16 had fevers during stem cell mobilization. Late post-HSCT viral infections included shingles (six patients), plantar warts (two patients), and HSV pneumonia (one patient). Five patients developed thyroid disorders between four months and three years post HSCT. One patient developed ITP 4.5 years after HSCT and was treated with steroids.

The primary outcome was disease activity-free survival at three years (no new T2 or gadolinium enhancing lesions on MRI, no clinical relapse, no progression of EDSS). Similar to Burt et al. (2015) and Burman et al. (2014), activity-free survival at three years was 69.6% and no patient required disease modifying therapies post-HSCT. Pre-transplant, the patients had a combined total of 167 relapses and 94 gadolinium enhancing lesions on the most recent MRI scan prior to HSCT. Post-HSCT, the 23 surviving patients did not have any clinical relapses and there were no gadolinium enhancing lesions on 327 scans. There were four new T2 lesions on one scan completed one month after HSCT. Post-HSCT, 17 patients (70%) had no progression of EDSS score at median follow up of 6.7 years. The cumulative incidence of improvement of EDSS was 40%, with improvements ranging from 0.5 to 3.0 points. There were improvements in nystagmus, ataxia, strength, and functional capacity. Of 16 patients who had to quit school or work due to their disability, six were able to return.

Findings of the four studies are summarized in the table below:

Study	Clinical Relapse-Free Survival	MRI Event- Free Survival	EDSS Progression-Free Survival	Disease-Free Survival	Treatment Related Mortality
Burman et al. (2014)	87% at 5 years	85% at 5 years	77% at 5 years	68% (79% in inflammatory disease only) at 5 years	0%
Burt et al., (2015)	89% at 2 years 80% at 4 years	No analysis	92% at 2 years 87% at 4 years	80% at 2 years 68% at 4 years	0% (one death post SCT not treatment related)
Nash et al. (2015)	86.3% at 3 years	100% at 3 years	90.9% at 3 years	78.4% at 3 years	0% (two deaths post SCT not treatment related)
Atkins et al., (2016)	100% (median follow-up 6.7 years)	100% with no gadolinium enhancing lesions (median follow up 6.7 years)	70% (median follow-up 6.7 years)	69.6% at 3 years	4.2% (1/24)

Table 2: Summary table of clinical relapse-free survival, MRI event-free survival, EDSS progression-free survival, and treatment related mortality

Sormani et al., (2017), Meta-analysis

Sormani et al. (2017) published a meta-analysis of results of HSCT for Multiple Sclerosis between 1995 and 2016 (11). End points were transplant related mortality, rate of disease progression, and evidence of

disease activity. A total of 764 patients from 15 studies were included in the analysis. All of the studies were single arm observational studies except for one randomized trial that compared HSCT to mitoxantrone in RRMS and SPMS (ASTIMS Trial), however, only the experimental arm was included in the analysis. Studies were classified by conditioning regimen as either low, intermediate or high according to the European Society for Bone Marrow Transplantation. Studies using high dose busulfan or total body irradiation were classified as high (n=4), those using cyclophosphamide only were classified as low (n=2) and other regimens were intermediate or mixed. In the pool of patients, there were 16 transplant related deaths. Treatment related mortality (TRM) was 0.3% after 2005 (1/349 patients), whereas prior to 2005, TRM was 3.6% (15/415 patients). In the 119 patients who were treated on a low dose intensity regimen, there were no deaths. In studies with a higher proportion of patients with RRMS, TRM was significantly lower at 1% compared to studies with a lower proportion of patients with RRMS at 3.4%. A higher EDSS score also was significantly associated with a higher TRM. There was no significant correlation with age or conditioning regimen and TRM. Pooled rate of disability progression was 17.1% at two years and 23.3% at five years. Studies that enrolled a higher proportion of patients with RRMS (>44%) showed significantly less disability and progression at two years compared to studies that did not at 7.8% and 24.8% respectively. In studies that measured disease activity, there was noevidence of disease activity in 83.4% of patients at two years (5 studies, n=274) and in 67% of patients at five years (4 studies, n=233).

Long term follow-up of patients maintaining no evidence of disease activity: Standard therapy compared to HSCT

Sormani et al. (2016) published a study comparing no evidence of disease activity (NEDA), defined as no relapses, no disability progression, and no new or enlarging T2 lesions or gadolinium enhancing lesions on MRI in randomized trials using DMTs compared to placebo or first line injectable therapies compared to HSCT (24). He included the following studies in the analysis:

(1) 7-year longitudinal study of placebo arm on CLIMB study (25)
(2) Treatment arms of three clinical trials using DMTs
    a. ocrelizumab vs. Rebif in OPERA I and II studies (26)
    b. daclizumab vs. interferon beta in DECIDE trial (27)
    c. CLIMB data (25)
(3) CLIMB cohort mixed data: average patient received DMT 75% of time in 7 years (25)
(4) Long term NEDA assessment in DMTs (28)
(5) Auto-HSCT HALT Study (22)
(6) Auto-HSCT Swedish experience (20)

No study using DMT's achieved NEDA greater than 46% at two years (range 13-46%), compared to HSCT, which achieved NEDA at much higher percentage with longer follow-up.

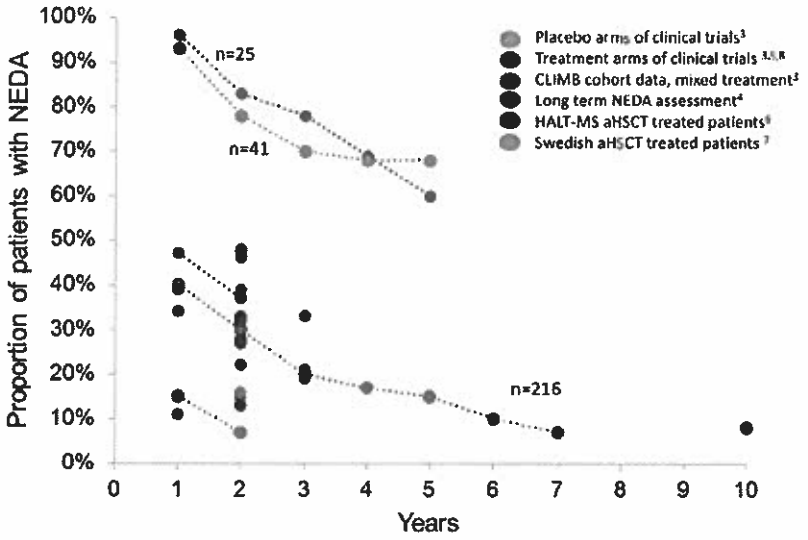
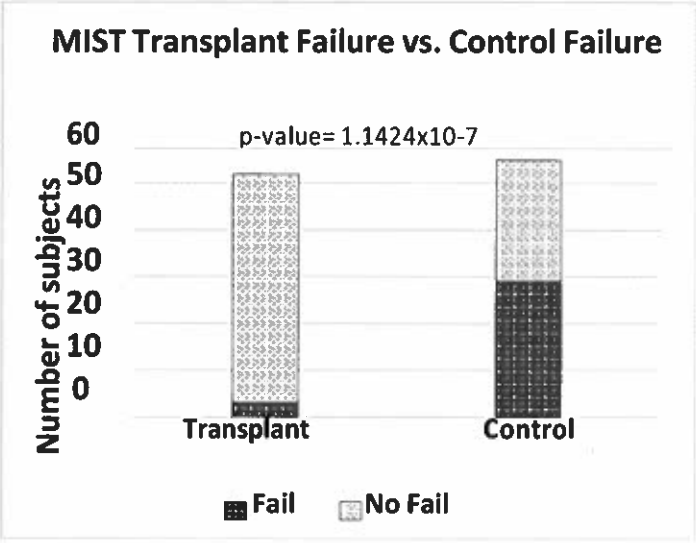


Figure 2: (Sormani et al., 2017): Proportion of patients maintaining the no evidence of disease activity (NEDA) status over time under different treatment strategies. Points connected by a line represent longitudinal observations in the same study

Autologous Hematopoietic Stem Cell Transplant Compared to Standard Therapy: MIST Trial
(Unpublished Data, Dr. Richard Burt)

In the only completed randomized trial, MIST trial, the primary endpoint is progression of disease measured by EDSS. The MIST trial is a randomization between HSCT versus continued standard of care for patients with highly active MS. The standard of care was provided by the local community physician and could include any FDA approved drug for MS except mitoxantrone or alemtuzumab. Failure is defined as sustained increase in EDSS of 1.0 points or more from the subject's baseline EDSS which was scored by a blinded neurologist. Subjects randomized to the transplant group received an autologous hematopoietic stem cell transplant. Subjects randomized to the control group remained on standard treatment (DMTs) for MS. The difference in failure of subjects between the transplant and control arms is found to be highly significant.



	Transplant	Control	Subjects
Fail	3	29	32
No Fail	49	26	75
Subjects	52	55	107

Figure 1: Number of subjects who had sustained increase in EDSS by 1.1 point or more in HSCT arm compared to control arm (DMTs). Difference is highly significant (p=1.1424x10-7)

Summary of Autologous Hematopoietic Stem Cell Transplant (HSCT) for Multiple Sclerosis Autologous HSCT appears to be an effective therapy to halt MRI lesion activity in the brain and spinal cord, stop clinical relapses, stop disease progression, reverse disability and improve quality of life. In fact, there is no other therapy that provides such a striking and long-term effects. Compared to HSCT, which is a one-time treatment that resets the immune system allowing for self-tolerance and the discontinuance of immune based treatments, DMTs are often used for decades to help control MS disease symptoms. However, they do not stop progression of disease or reverse disability and are continued indefinitely or until complications arise. They are inconvenient for patients, may have unpleasant and/or significant side effects, and contribute a substantial burden to healthcare costs (29).

In the meta-analysis by Sormani et al. (2017), aHSCT was shown to be superior to FDA-approved DMTs with a 68% of patients maintaining no evidence of disease activity at 5 years (11). No DMT has come close to showing this level of efficacy. Many of the studies published have included patients with SPMS, which have not been shown to respond as well to HSCT compared to patients with RRMS in post-hoc analysis (11, 21). Upon analysis of treatment related mortality, patients with greater disease progression and higher EDSS scores at baseline had significantly higher mortality compared to those with RRMS, implying that HSCT should be initiated earlier in selected patients with relapsing remitting disease before it enters a progressive course (11). Waiting until failure of a second line therapy such as Tysabri or Gilenya runs risk of losing the window of opportunity for optimal effective outcomes (13). In addition, drugs such as Tysabri, Gilenya, Tecfidera and Aubagio may increase the risk of PML. We therefore have allotted for sufficient time separating HSCT from these treatments as part of the inclusion criteria.

Other important considerations for safety in HSCT for MS is selection of a low intensity conditioning regimen using drugs that usually are used for autoimmune diseases and conducting the transplant at an institution that has extensive experience with transplanting patients with MS (13). Atkins et al., (2016) report that they chose a higher dose conditioning regimen to allow for greater immunoablation and better remission, however, the study was modified after observing treatment related mortality and severe adverse toxicities related to the high dose busulfan (23). The conditioning regimen matters, and should be chosen with careful consideration of the risks and benefits to maximize immune suppression and minimize toxicity.

Selection of the Conditioning Immunosuppressive Therapy
Non-myeloablative aHSCT stands on sound theoretical, scientific and empirical foundation as meaningful therapy for refractory and breakthrough MS with ominous prognosis. To justify any new therapy such as HSCT, the risk of dying from the disease must be higher than that expected from its treatment, or the morbidities associated with the disease must justify the treatment risks. As shown in previous studies, non-myeloablative aHSCT for RRMS can be performed with minimal toxicity and holds promise for patients with active inflammatory disease if performed before onset of significant irreversible axonal injury.

The goal of the conditioning regimen for HSCT in RRMS is "immune ablation," not myeloablation, and should comprise of only immune suppressive drugs and biologics that are normally used to treat autoimmune diseases, such cyclophosphamide and rATG which will induce an immediate immune ceasefire. Followed by infusion of harvested autologous hematopoietic stem cells, a new immune system regenerates that defaults to self-tolerance in a non-inflammatory post-conditioning environment. Now that recent trials having demonstrated that HSCT using a non-myeloablative regimen can safely be performed in RRMS with no treatment related mortality low toxicity (20, 21, 22), new randomized trials comparing conditioning regimens to further improve safety and efficacy need to be explored.

Randomized Trial Comparing Conditioning Regimens for Autologous HSCT

We propose a randomized trial comparing two arms of non-myelolablative conditioning regimens to determine their efficacy of treatment for RRMS. The first arm will be the control arm that will use the same conditioning regimen of cyclophosphamide and rATG that was used in the JAMA 2015 publication by Burt et al. and in the completed randomized MIST trial (pending publication). In the treatment arm, IVIg arm, participants will receive the same regimen of cyclophosphamide and rATG as used in the control arm, but will also receive IVIg (400 mg/kg) on day +1 and day +9 (or day of engraftment) to determine if there is a difference in study end-points and/or in the incidence of late ITP or hypo- or hyperthyroidism. It is hypothesized that in patients who receive IVIg, there may be fewer clinical relapses, and a lower incidence or complete prevention of ITP, and hypothyroidism and hyperthyroidism. The advantage of adding IVIg is that it does not increase the risk of infection or PML since it is not immune suppressive.

The rationale behind the conditioning regimen is that the control regimen of cyclophosphamide and rATG has already been shown to be safe (Burt et al., 2015) and effective (MIST trial, publication pending) compared to continued DMD therapy. However, the control regimen has a low incidence of relapse (15%), late ITP (2%) and of autoimmune thyroid disorders (6%). Since IVIg is used to treat both MS and ITP and since IVIg increases Treg cells that are thought to maintain self-tolerance, it is hypothesized that IVIg may decrease relapse, as well as decrease the incidence of late ITP and/or autoimmune thyroid disorders without further increasing immune suppression.

Review of Cyclophosphamide and rATG

Previous studies have shown that HSCTs performed using non-myeloablative conditioning regimens with cyclophosphamide and rATG are just as effective as other conditioning regimens and are not associated with any transplant related mortality (20, 21, 30). Cyclophosphamide has been used as an active agent in patients with a wide variety of autoimmune diseases including RRMS 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 acute toxicity, less chronic side effects, and is not associated with late malignancies. It is an alkylating agent that requires hepatic metabolism to the active metabolites, phosphoramide mustard and acrolein. These active metabolites react with nucleophilic groups. The half-life of the parent compound is 5.3 hours in adults and the half-life of the major metabolite phosphoramide mustard is 8.5 hours. Liver or renal dysfunction will lead to prolonged serum half-life. For HSCT, cyclophosphamide is administered intravenously at a dosage of 50 mg/kg on each of four successive days (use adjusted ideal body weight if patient's actual body weight is greater than 100% ideal body weight). The major dose limiting side effect at high doses is cardiac necrosis. Hemorrhagic cystitis can occur and is mediated by the acrolein metabolite. This can be prevented by co-administration of Mesna or bladder irrigation. Other notable side effects include nausea, vomiting, alopecia, myelosuppression and SIADH.

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 , at 1.0 mg/kg recipient body weight on day -4, and at 1.5 mg/kg recipient body weight on days -3, -2, -1. Starting at a low dose of 1.5 mg/kg and dose escalating minimizes complications that may be associated with rATG. 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. Although rare, the major toxicity is anaphylaxis. Other possible side effects are chills, fevers, pruritus and serum sickness. Delayed fevers may occur and can be treated with steroids.

Intravenous Immunoglobulin (IVIg): Role in Immune Thrombocytopenia (ITP), RRMS, and HSCT
While HSCT has been proven to be safe with use of a non-myeloablative conditioning regimen and has significantly more favorable outcomes compared to any disease modifying therapy, one adverse effect that has been reported post-HSCT is ITP, which was seen in 4.6% of patients (7/151) in Burt et al. (2015) and was also reported in one patient 4.5 years post-HSCT in Atkins et al. (2016). While the presence of ITP decreased from 14% to 3.1% by switching alemtuzumab to rATG in the conditioning regimen in Burt et al. (2015), we hope to improve on the current conditioning regimen by decreasing or preventing the occurrence of ITP and also decreasing relapse and disease activity rates in RRMS post-HSCT.

Secondary ITP is an immune disorder that may be inherited or acquired and is characterized by thrombocytopenia (peripheral blood platelet count <100,000) due to T-cell mediated platelet destruction and anti-platelet IgG autoantibodies (31). While the exact mechanism of the development of a secondary autoimmunity disorder such as ITP or a thyroid disorder post-HSCT is poorly understood, it may be secondary to B-cell specific alterations (32). Alemtuzemab administered alone has been associated with ITP and thyroid disease in patients with RRMS (32).

Since the 1980s, ITP has been successfully treated with intravenous immunoglobulin (IVIg), which is pooled preparation of IgG from the plasma of thousands of donors (33, 34). In addition to being first line treatment for ITP, IVIg is also first line therapy for other inflammatory conditions such as Guillain-Barre syndrome and Chronic Inflammatory Demyelinating Polyneuropathy and is currently being explored as treatment for several other autoimmune diseases including RRMS (33, 35, 36).

While the exact mechanism is unknown, IVIg has been shown to benefit patients with autoimmune diseases through several possible mechanisms: (1) inhibition of activation of macrophages, dendritic cells and pathogenic T-cells, (2) modulation of B-cell responses and inhibition of autoantibody production, (3) modulation of inflammatory cytokines (IFN-γ), (4) stimulation of anti-inflammatory cytokines, and (5) inhibition of activation of endothelial cells and complement cascade pathway (31, 33). In addition, several papers report that IVIg has modulatory effect of T-cell subsets with a higher proportion and suppressive capacity of regulatory T-cells (31, 33, 37). Therefore, IVIg may have an advantageous role in HSCT in that it can increase Treg production after HSCT which is a necessary for immune equilibrium.

In a Cochrane systematic review, the use of IVIg for RRMS was beneficial and well tolerated (35). In six randomized double blinded trials (4 with RRMS and 2 with SPMS), patients with RRMS treated with IVIg had a reduction in relapse rate and an increased time to first relapse. Data was conflicting for reduction of T2 and enhancing lesions on MRI. Common mild side effects included headache, nausea, fever, chills, dizziness, rash, and fatigue. One study reported that 7/318 patients developed deep vein thrombosis with four having pulmonary embolism, however, all of these patients had SPMS and risk factors for thromboembolism (38).

Fevers and Steroids

Burt et al. (2015) showed that EDSS scores did not improve in patients who had sustained fever of 38.5 or higher on three readings at least four hours apart in 24 hours during HSCT (21). Therefore, it is important to select a regimen that avoids further damage to already injured axons and oligodendrocytes. Fever-related deterioration of neural function in MS, termed pseudo-exacerbations, due to conduction blocks in marginally functioning demyelinated axons should be avoided during HSCT by avoiding pyrogenic agents (39, 40). Similarly, the risk of infection-related fever should be minimized during HSCT by use of prophylactic antibiotics.

In Burt et al. (2015), there were neutropenic fevers post-SCT, however, blood cultures were negative in all patients except one that was thought to be a contaminant (21). Patients did not display any other evident signs or symptoms of infections. Fevers occurred most often on days +1 to day +4 post stem cell infusion, when patients were neutropenic. Because blood cultures are nearly always negative, the fevers are not thought to be from infection, but rather delayed fevers secondary to rATG. In order to prevent fevers and subsequent neurological deterioration that could be permanent, we have included a prednisone taper in the conditioning regimen that begins on day 0. For patients with breakthrough fevers, additional scheduled IV steroids are given along with acetaminophen. Patients are covered with broad spectrum antibiotics until blood cultures return negative. This regimen was successfully added to our previous protocol and has prevented patients from having sustained fevers that can result in irreversible neurological decline.

Mobilization and Harvest of Stem Cells in Patients with Multiple Sclerosis

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 (2.0 g/m_2) and granulocyte-colony stimulating factor (G-CSF) 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 (41).

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.

The majority of mononuclear cells collected by peripheral blood apheresis (or bone marrow harvest) are immune cells such as lymphocytes and monocytes, not hematopoietic stem cells (HSCs). While the true identity of HSCs remains elusive, purified $CD34_+$ or $AC133_+$ hematopoietic progenitor cells are sufficient for hematopoietic reconstitution. In general, a minimum number of 2 x 10_6 $CD34_+$ cells/kg recipient weight will ensure engraftment. HSCs may be positively selected or enriched by three to four logarithms using antibodies to CD34 or AC133 or purified by negative selection to remove lymphocytes.

$CD34_+$ 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 RRMS, and therefore, will not be used in this protocol. Effective in vivo purging of the graft is obtained by mobilization with 2.0 g/m_2

cyclophosphamide and conditioning with rATG, an antibody with a long half-life directed against T and B lymphocytes. Following NST, 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 between 18-58 years
2. Diagnosis of MS using revised McDonald criteria of clinically definite MS (Appendix A)
3. An EDSS score of 2.0 to 6.0 (Appendix B).
4. An EDSS >6.0 may be included if still relapsing-remitting disease and at least two enhancing lesions on MRI within the last three months
5. Inflammatory disease despite treatment with standard disease modifying therapy (DMT) including at least 6 months of interferon or Copaxone. Inflammatory disease is defined based on either MRI (gadolinium enhancing lesion, new T2 lesion) or *steroid- treated clinical relapses (prescribed by a neurologist)
6. Minimum disease activity required, any one of the following:
   a) Failed a first line DMT (Copaxone or Interferon), defined as two or more *steroid treated clinical relapses within the last 12 months. A clinical relapse may also be evidence of active inflammation on MRI (gadolinium enhancing lesion or new T2 lesion) in the last 12 months on two MRIs at least three months apart

   b) Failed a second or third line MS Drug: Zinbryta (daclizumab), Aubagio (teriflunomide), Gilenya (fingolimod), Tecifidera (dimethyl fumarate), Lemtrada (alemtuzumab), Ocrevus (ocrelizumab), Tysabri (natalizumab), Rituxan (rituximab) or IVIg, defined as one *steroid treated clinical relapse within the last 12 months or evidence of active inflammation on MRI (gadolinium enhancing lesion or new T2 lesion) in the last 12 months

   c) Cognitive dysfunction that prevents gainful employment, but competent to comply with treatment and informed consent

*A steroid-treated relapse will include a relapse that was severe enough to justify treatment but due to patient intolerance of steroids, they were offered but not used.

Exclusion Criteria

1. Any adult who is unable to consent (for adults who are cognitively impaired due to MS, consent may be obtained from the closest living relative or person who has power of attorney)
2. Individuals under the age of 18 or over the age of 58
3. Diagnosis of Primary Progressive MS, Secondary Progressive MS, or Clinically Isolated Syndrome (CIS)
4. Pregnant women (positive serum or urine HCG test)
5. Women who are breastfeeding
6. Prisoners
7. Any illness that in the opinion of the investigators would jeopardize the ability of the patient to tolerate aggressive chemotherapy
8. Prior history of malignancy except localized basal cell, squamous skin cancer or carcinoma

in situ of the cervix

9. Any prior chemotherapy or radiation therapy (except for cyclophosphamide used to treat MS disease)
10. History of sickle cell disease (SS), SC disease, coagulopathy, or if actively receiving anticoagulation therapy
11. History of insulin-dependent diabetes
12. Inability or unwillingness to pursue effective means of birth control from the time of evaluation for eligibility until 6 months post-transplant. Effective birth control is defined as (1) abstinence defined as refraining from all acts of vaginal intercourse, (2) consistent use of birth control pills, (3) injectable birth control methods (Depo-provera, Norplant), (4) tubal sterilization or male partner who has undergone vasectomy, (5) placement of an intrauterine device (IUD), or (6) with every act of intercourse, use of diaphragm with contraceptive jelly and/or use of condom with contraceptive foam
13. Failure to willingly accept or comprehend irreversible sterility as a side effect of therapy
14. $FEV_1/FVC < 60\%$ of predicted after bronchodilator therapy (if necessary)
15. DLCO < 60% of predicted
16. Resting LVEF < 50 %
17. Bilirubin > 2.0 mg/dl
18. Serum creatinine > 2.0 mg/dl
19. Known hypersensitivity to mouse, rabbit, or E. Coli derived proteins or to iron compounds/medications
20. Presence of metallic objects implanted in the body that would preclude the ability of the patient to safely have MRI exams
21. Platelet count < 100,000/ul
22. WBC < 1,500 cells/mm_3
23. Psychiatric illness, mental deficiency or cognitive dysfunction making compliance with treatment or informed consent impossible
24. Active infection except asymptomatic bacteriuria
25. Use of Tysabri (natalizumab) within the previous six months
26. Use of Gilenya (fingolimod) within the previous three months
27. Use of Tecfidera (dimethyl fumarate) within the previous three months
28. Use of Aubagio (teriflunomide) unless cleared from the body (plasma concentration <0.02mcg/ml) following elimination from the body with cholestyramine 8g three times a day for 11 days
29. Use of Lemtrada/Campath (alemtuzumab) within previous 12 months
30. Use of Rituxan (rituximab) or Ocrevus (ocrelizumab) within previous six months
31. Prior treatment with Novantrone (mitoxantrone)
32. Any hereditary neurological disease such as Charcot-Marie-Tooth disease (CMT), Spinocerebellar ataxia (SCA), or Parkinson's Disease
33. Severe or symptomatic cervical spinal stenosis unless surgically corrected
34. Myocardial infarction within last 12 months; if longer than 12 months, must pass dobutamine stress test and be cleared by cardiology

STUDY-WIDE NUMBER OF PARTICIPANTS: One center study: 200 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: Three years

Estimated date for investigators to complete study (primary analysis): January 1, 2023

STUDY ENDPOINTS:

Primary Endpoints:

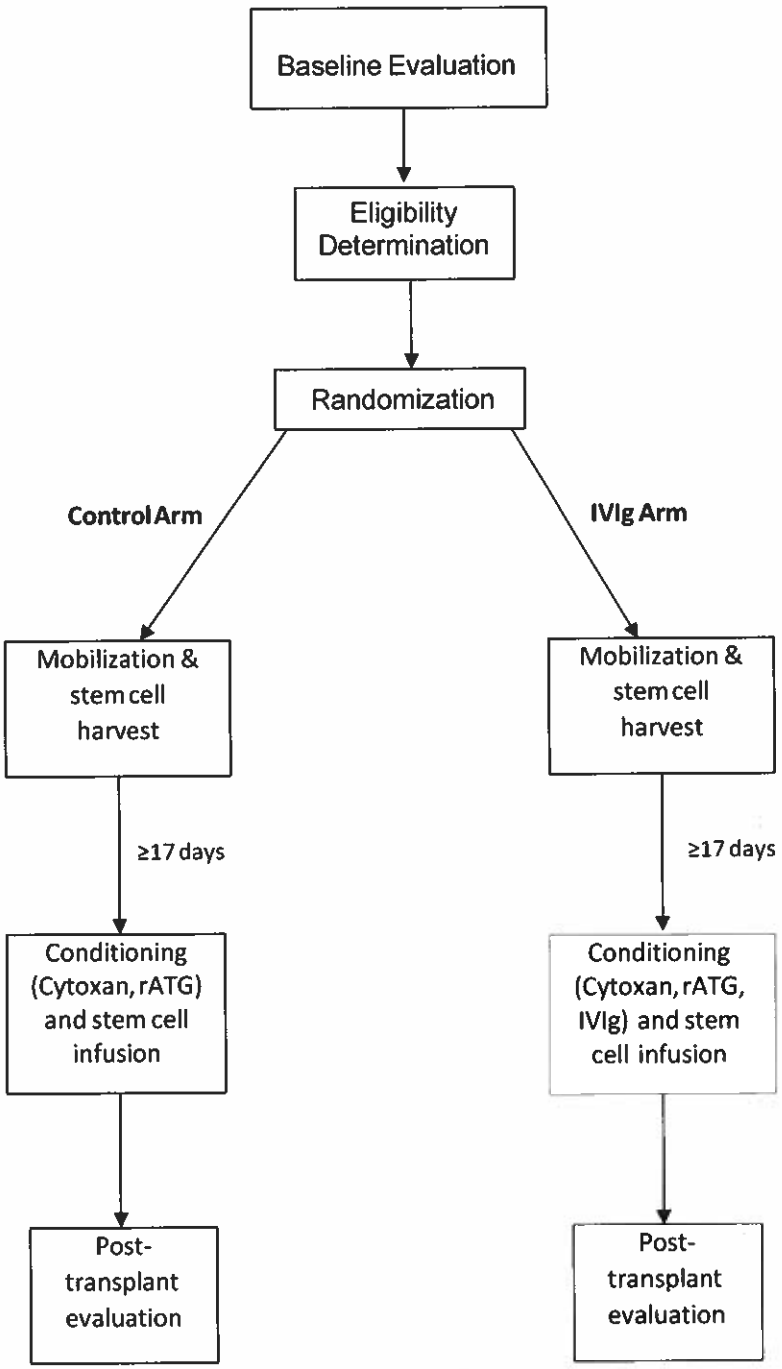
1. NEDA (no evidence of disease activity) defined as no relapse, no progression, no new or enhancing lesions on MRI

Secondary Endpoints:

1. Survival
2. Disease progression, defined as a 1.0-point increase in the Expanded Disability Status Scale (EDSS) on consecutive evaluations at least 6 months apart and not due to a non-MS disease process.
3. Improvement in EDSS defined by both a 0.5 or 1.0 points sustained for more than 6 months
4. Number of relapses, defined as acute neurologic deterioration occurring after engraftment and lasting more than 24 hours, accompanied by objective worsening on neurological examination that are documented by a neurologist and not explained by fever, infection, stress, heat, or related pseudoexacerbation. Supportive confirmation by enhancement on MRI is preferred but not mandatory.
5. MRI gadolinium enhancing lesions and T2 burden of disease on MRI (optional)
6. Scripps NRS (Appendix C)
7. Ambulation Index (Appendix D)
8. MSFC
    a. Twenty-five foot timed walk
    b. Nine hole PEG test (Appendix E)
    c. PASAT-3 second and PASAT-2 second (Appendix F)
9. SF-36 (Appendix G)

PROCEDURES INVOLVED:

Study Design



Study Procedures and Testing Guidelines

	Pre-HSCT Pre-transplant testing (Baseline data)	**During HSCT** Inpatient Admission	**Post-HSCT "First 100 days"** Weekly for 4 weeks then every 2 weeks for 8 weeks	**Follow Up[8]** 6 months, then yearly for 5 years
History, MS history, physical	X	X		X
MS Functional Composite (timed 25 foot walk, 9-hole peg test, PASAT)[1]	X			X
EDSS[2]	X			X
NRS[3]	X			X
Ambulation Index	X			X
MRI brain with gadolinium	X			X (optional)
MRI of cervical spine (and thoracic if suspect involved)	X			X (optional)
CBC, platelet & differential	X	X (daily)	X	X
INR, PT, and PTT	X			
Basic Chemistry Panel[4]	X	X (daily)	X	X
Liver Function Test	X	2x/week	X	X
CMV by PCR (quantitative)			X	
FDA Virologies[5]	X			
HSV, VZV, CMV	X			
Hepatitis A serology	X			
JC Virus Titer	X			X
NMO antibody, ANA, SSA, SSB	X (optional)			X
Urinalysis	X			
Quantiferon Gold	X			
TSH, T3, Free T4	X			X
Serum or Urine HCG	X	X		
PFT w/ DLCO and FEV1/FVC	X			
Echocardiography and EKG	X			
[6]Dobutamine Stress Test	X (if indicated)			
Chest x-ray	X			
[7]Allergy Consult and Testing	X (if indicated)			
Flow cytometry T cell studies: Naïve CD4: CD4+ RA+ (pos) Memory CD4: CD4+ RO+ (pos) Treg CD4: CD4+ CD25+ (intermediate/bright) CD27- (neg/low) Treg CD8: CD8+ CD24+ (intermediate/bright) CD27- (neg/low)	X			X
Flow cytometry B cell studies: Memory B Cell: CD19+ CD27+ Immature B Cell: CD19+ CD27- (neg) CD10+ CD38+ IgD+ Mature/Naïve B Cell: CD19+ CD27- (neg) CD10- (neg) IgD+ CD38+	X			X
Dental consult	X (optional)			
SF-36 questionnaire	X			X

[1]MS Functional Composite: includes timed 25-foot walk, 9-hole peg test and PASAT, will be performed by a trained clinical research nurse or PI and should take 30-45 minutes
[2]EDSS: will be performed by a neurologist, a trained clinical research nurse, or PI
[3]NRS: will be performed by a neurologist, a trained clinical research nurse, or PI
[4]Basic chemistry panel to include: Na, K, Cl, bicarb, glucose, BUN, Creatinine, Mg, Phos
[5]FDA virologies to include: Anti-HBC, Anti-HCV, anti-HIV1/anti-HIV2, CMV, HBS ag, HTLV 1/2, procleix HBV, procleix HCV, procleix HIV-1, RPR, T. cruzi AB, WNV TMA
[6]Dobutamine Stress Test: Indicated for history of stroke, hypertension, obesity, diabetes, treatment for hyperlipidemia or hypercholesterolemia, or significant family history of cardiovascular disease
[7]Allergy Testing: indicated for history of penicillin or cephalosporin allergy
[8]Although every attempt will be made for follow-up evaluation, 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, sub-investigator and clinical research nurse.

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, number of attacks in past 12 months, MRI history, degree of disability, current and prior treatment for MS, history of kidney problems, cancer or psychiatric illness, and neurologist name. (See Appendix I)

Initial Evaluation
Participants will be scheduled for evaluation in clinic by the PI and a study neurologist. 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.

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

Randomization
Treatment assignments will be provided to the clinical center by telephone or email by Dr. Borko Jovanovic or designate in the statistical department at Northwestern University. Each participant will be followed by an un-blinded PI and treating neurologist.

Mobilization
Participants will be admitted to the hospital for approximately 24 hours to receive a cyclophosphamide infusion with IV hydration and MESNA. For participants who have new clinical relapse symptoms or new enhancing lesions on most recent MRI, they may be given two days of IV methylprednisolone (1000 mg) during the hospital stay (day of admission and day of discharge). 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 mg/m2	X		
G-CSF 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 between 18 to 24 days separate the administration of cyclophosphamide from mobilization and conditioning.

Transplant Conditioning Regimens

Participants will be randomized to one of the two regimens below:

Multiple Sclerosis Conditioning Regimen Guideline: CONTROL ARM
Doses may be adjusted or discontinued if necessary for patient safety:

DAY	-5	-4	-3	-2	-1	0	+4
Hydration	X	X	X	X			
Cyclophosphamide 50 mg/kg/day IV	X	X	X	X			
MESNA 50 mg/kg/day IV	X	X	X	X			
rATG (Rabbit)	0.5	1.0	1.5	1.5	1.5		
Methylprednisolone	1g	1g	1g	1g	1g		
Stem cell reinfusion						X	
G-CSF (until engraftment)							X
Foley Catheter Guideline	X	X	X	X	X		

Multiple Sclerosis Conditioning Regimen Guideline: TREATMENT ARM (IVIg)
Doses may be adjusted or discontinued if necessary for patient safety:

DAY	-5	-4	-3	-2	-1	0	+2	+4	+9 or day of engraftmen
Hydration	X	X	X	X					
Cyclophosphamide 50 mg/kg/day IV	X	X	X	X					
MESNA 50 mg/kg/day IV	X	X	X	X					
rATG (Rabbit)	0.5	1.0	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 (until engraftment)								X	
Foley Catheter Guideline	X	X	X	X	X				

Prednisone Guideline: Treatment and Control Arm

DAY	0	+1	+2	+3	+4	+5	+6	+7	+8
Prednisone Guideline	60mg	60mg	60mg	40mg	40mg	20mg	20mg	10mg	10mg

Concurrent Treatment and Supportive Care Guidelines and Procedures to Lessen Risks

Hydration Guideline: 0.9% normal saline at 100 to 150 mL/hour should be given two hours before cyclophosphamide and continued until 24 hours after the last 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: 50 mg/kg/day will be given IV over 2 hours in 500mL D5W on day -5 through -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, aprepitant 125mg PO (Day -5), then 80mg PO (Day -4 and -3), 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), lorazepam 0.5mg IVP q 6 hours PRN

MESNA Guideline: 50mg/kg/day will be given IV starting two hours prior to starting cyclophosphamide until 24 hours after last dose of cyclophosphamide

IVIg Guideline (treatment arm only): 400mg/kg IVIg will be given on day +2 and day +9 (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

Diuretic Guideline: IV diuretic such as furosemide will be given three times per day starting with cyclophosphamide and continued until 24 hours after the last cyclophosphamide dose. 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, 1.0 mg/kg IV will be given on day -4, 1.5 mg/kg will be given IV on days -3,-2,-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.

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.

Foley Catheter Guideline: A foley catheter is placed on day -5 though day -1 (during cyclophosphamide) in patients with a history of urinary retention or delayed emptying. For patients who deny urinary retention, a post-void residual may be obtained using a bladder scanner. Foley catheters may not be needed for participants with a post-void residual less than 60 mL.

Prednisone Guideline: To prevent rATG fever, prednisone will be given day 0 through +8 as above.

Broad Spectrum Antibiotics Guideline: A broad spectrum antibiotic (ie: cefepime or piperacillin-tazobactam) will be initiated on day 0 or when patient's ANC or WBC begins to drop.
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 allergist for testing prior to stem cell transplant.

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. 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:** On day 0 (or 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. Once the WBC's 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:** Isavuconazonium (Cresemba) 372 mg by mouth daily will start on day +2 and continued until discharge from hospital. At discharge, prophylaxis will continue with fluconazole 400 mg PO daily for six months post-transplant. Other antifungals such as voriconazole, posaconazole, or amphotericin B 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 HSV and 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) 1500mg po daily, or Dapsone 100 mg PO daily. Medication may be held or discontinued for adverse side effects (ie: 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

until 24 hours after last dose

- IV Hydration: 0.9% normal saline at 100 to 150 mL/hour should 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 until 24 hours after the last cyclophosphamide dose. Amount of diuretic and frequency can be modified based on patient's fluid status and weight.
- Foley Catheter: A foley catheter will be placed in patients with a history of urinary retention or delayed emptying to ensure that they are fully emptying their bladder to minimize the retention of cyclophosphamide in the bladder. For patients who deny urinary retention, a post- void residual may be obtained using a bladder scanner. Foley catheters may not be necessary in patients with post-void residual less than 60mL.

Transaminase Elevation/ Veno-occlusive Disease Guideline:
Patients will be given ursodiol, 300 mg by mouth twice a day upon admission 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)

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:
To prevent delayed rATG related fever, prednisone will be given day 0 through +8 as outlined in the conditioning regimen. For breakthrough fever, patients will be given acetaminophen and IV methylprednisolone (125-250 mg IV daily) as needed to break fever. 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, other 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 will 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 (for stem cell transplant admission):

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 and then every other week for 8 weeks:
  - 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 H).

- **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.

Treatment of Relapses post-HSCT Guideline:

Relapse is defined as acute neurologic deterioration occurring after engraftment and lasting more than 24 hours with new objective signs on neurological examination documented by a neurologist. Supportive confirmation by enhancement on MRI is preferred but not mandatory. If MRI is not used to confirm a relapse, a pseudo-relapse must be excluded by confirmation of the absence of infection,

fever, illness or severe physiologic stress including transient worsening caused by the therapy. Relapse may be treated per PI preference but first relapse should be treated with IV methylprednisolone 1000 mg a day for three to five days with or without oral prednisone taper over seven to 10 days.

Treatment of Progressive Disease post-HSCT Guideline:
Progressive disease is defined as an increase in the EDSS by 1.0 or more points due to MS (any comorbid conditions affecting neurologic function excluded) obtained at a time point not associated with a clinical relapse and confirmed on two separate exams by a neurologist at least six months apart. Patients with progressive disease will continue to be followed for the five year duration. If necessary, patient may receive treatment from a local neurologist.

SOURCE RECORDS

- **MS Enrollment Form** (Appendix J): Form used to collect pre-transplant testing. Form gets reviewed and signed off on by clinical research nurse and PI prior to enrollment.

- **MS Inpatient Toxicity Form** (Appendix K): Form used to keep track of adverse events and toxicity grading using the Common Toxicity Criteria for Adverse Events (CTCAE) version 2.0 while patient is inpatient during stem cell transplant.

- **MS Adverse Events Case Report Form** (Appendix L): 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.

- **MS Outcomes Case Report Form** (Appendix M): 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 N): Form used to call patient and ask information in event that they are unable to return for follow up.

EVALUATION OF TOXICITY:
The Common Toxicity Criteria for Adverse Events (CTCAE) version 2.0 (See Appendix O) will be used to grade all non-hematologic toxicities. At the time of doing the discharge summary, an inpatient team member (i.e., 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-transplant testing reports, enrollment data, toxicity, 100 day labs post stem cell transplant, adverse events, 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), we will follow NMH policy which may change in the future, but currently states that cryopreserved 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 AND SPECIMEN MANAGEMENT:
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:
Treatment-related deaths will be reported to IRB within 10 working days of notification. Non-treatment related deaths and grade 4 toxicities will be reported in the annual continuing review (CR). If at the time of annual CR, any treatment appears significantly superior in terms of safety or outcome, 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 or stop the less effective arm of 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 death will be reported to IRB within 10 working days of knowledge of the event. Non-treatment related deaths will be reported to IRB on annual 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 O).
- 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 after randomization 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 lost 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.

- 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.

- 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. G-CSF has been reported to cause a flare (worsening of neurologic symptoms) in some subjects, but when combined with cyclophosphamide (as in this study) has not been reported to cause a flare of MS. In fact, some subjects may experience mild improvements in their symptoms following cyclophosphamide and G-CSF administration.

- 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.

- Immune Thrombocytopenia (ITP) may occur after transplantation. ITP is a disorder that can lead to easy or excessive bruising and bleeding from unusually low levels of platelets. Participants will be instructed to notify the Division of Immunotherapy and Autoimmune Diseases and to go to the emergency department immediately to get a CBC with platelet checked in the case that the following signs and symptoms of ITP occur:

  - Easy bruising (purpura) — your skin naturally bruises and bleeds more easily as you age, but this should not be confused with ITP
  - Superficial bleeding into your skin that appears as a rash of pinpoint-sized reddish-purple spots (petechiae), usually on your lower legs
  - Prolonged bleeding from cuts
  - Spontaneous bleeding from nose
  - Bleeding gums, especially after brushing teeth
  - Blood in urine or stool
  - Unusually heavy menstrual flow

  ITP can be cured with early attention from a blood specialist. Patients may be treated by local physician or will have the option to return to Northwestern Medicine for treatment if this occurs.

- Thyroid Disorders: Hypothyroidism or hyperthyroidism may occur after stem cell transplant.

- 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.

Risk of Procedures

- 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: 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 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 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.

  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 Neuropsychological Examination: There are no health risks related to the neuropsychological examination. However, patients may feel frustrated or uncomfortable with the cognitive testing. Every effort will be made by the evaluators to make the process as

comfortable as possible.

- 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:

- Multiple sclerosis will go into long-term remission
- Halt or slow progression of neurological disability
- Reverse neurological disability
- Ability to stop treatment drugs that can be associated with side effects and complications
- Improve quality of life

VULNERABLE POPULATIONS: N/A

COMMUNITY-BASEDPARTICIPATORYRESEARCH: N/A

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.

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 on multiple sclerosis patients for over 20 years. He recently completed the Hematopoietic Stem Cell Therapy for Patients with Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study (MIST). Through involvement with the MIST study, staff at this site has developed familiarity with the multiple sclerosis patient population, treatments for multiple sclerosis and the clinical manifestations of the disease. Multiple Sclerosis is the largest disease population treated and therefore, 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 multiple sclerosis such as EDSS testing, and how to assess for adverse reactions at follow up visits. Clinical research nurses have prior experience as nurses in inpatient hospital settings.

In fiscal year 2016, DIAD transplanted 90 patients with multiple sclerosis. The goal to enroll 200 participants in a three-year time frame is feasible given the number of transplants performed for multiple sclerosis patients in fiscal year 2016.

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 and every other week for eight weeks. 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 multiple 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.gov . 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 and a neurologist to verify MS 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: 200 participants at Northwestern Medicine. We plan to enroll approximately 100 participants in each arm.

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

We will be compliant 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 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 a 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
Participants come from all over the world in which English may not be their primary language. Certified medical interpreters or translation phones will be used for individuals who do not speak English.
Questions will be answered using an interpreter. If the participant requests, a written copy of the consent in his or her native language can be obtained.

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 due to Multiple Sclerosis, 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 multiple sclerosis. In that case, consent may be obtained by the closest living relative or by a person assigned as the power of attorney.

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.

DRUGS OR DEVICES:

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 names: N/A
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

IVIg

1. Other Names: Bivagam, Carimune NF, Flebogamma DIF, GamaSTAN S/D, Cuvitru, Gammagard, Gammagard S/D Less IgA, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Hizentra, Hyqvia, Octagam, Privigen
2. Description: Pooled immunoglobulin (IgG) from thousands of plasma donors that has immunomodulatory and anti-inflammatory effects.
3. Availability: IV and Subcutaneous; varies per brand, some possible solutions are: 1g/10 ml, 2.5 g/25ml, 5g/50 ml, 10g/100 ml, 20 g/200 ml, 40 g/400 ml
4. Dosing: 400 mg/kg/day IV over 2-6 hours (start slow at 0.8 to 1 mg/kg/minute for 30 minutes, monitor vitals, increase every 30 minutes up to max rate of 4 to 8 mg/kg/minute (actual rate of administration may vary based on brand)
5. Renal Dosing: Use with caution due to risk of immune globulin-induced renal dysfunction, monitor renal function during treatment
6. FDA Boxed Warning: Thrombosis may occur. Risk factors are advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central venous catheters, hyperviscosity, and cardiovascular risk factors. For patients at risk of thrombosis, administer at minimum dose and infusion rate that is practicable.
7. Side Effects: Most common are chills, fevers, flushing, skin rash/itching, or headache. 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, hemolytic anemia, Stevens-Johnson syndrome, renal dysfunction, acute renal failure, thrombosis, acute lung injury and viral transmission risk (hepatitis or HIV).

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