



**A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second
Autologous Transplant Maintenance Therapy Versus Single
Autologous Stem Cell Transplant Followed by Matched Sibling Non-
myeloablative Allogeneic Stem Cell Transplant for Patients with
Multiple Myeloma**

**BMT CTN PROTOCOL 0102
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PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0102

A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by Matched Sibling Non-myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma

Co-Principal Investigators: David Maloney, M.D., Amrita Krishnan, M.D.

Study Design: The study is designed as a Phase III, multi-center trial of tandem autologous transplants versus the strategy of autologous followed by HLA-matched sibling non-myeloablative allogeneic transplant. Study subjects will be biologically assigned to the appropriate arm depending on the availability of an HLA-matched sibling. There is a nested randomized phase III trial of observation versus maintenance therapy following the second autologous transplant for patients on the tandem autologous transplant arm.

Primary Objective: Post-tandem autologous transplant randomized trial of maintenance versus observation: The primary objective is to compare progression-free survival at three years between the two arms.

Tandem autologous transplants versus autologous transplant followed by HLA-matched sibling non-myeloablative allogeneic transplant: The primary objective is to compare progression-free survival at three years between the two arms.

Secondary Objectives: Post-tandem autologous transplant randomized trial of maintenance versus observation: Secondary objectives are to compare ‘current’ myeloma-stable survival, three-year overall survival, and incidence of progression.

Tandem autologous transplants versus autologous transplant followed by HLA-matched sibling non-myeloablative allogeneic transplant: Secondary objectives are to compare ‘current’ myeloma-stable survival, three year overall survival, and incidence of progression.

Tertiary Objectives: Post-tandem autologous transplant randomized trial of maintenance versus observation: Tertiary objectives include complete remission (CR) rate and CR+partial remission (PR) rate at 2 and 12 months after the second transplant, time to CR and CR+PR, time to off-study therapy, rate of discontinuation of maintenance therapy and duration of maintenance therapy, incidence of toxicities Grade ≥ 3 according to the CTCAE Version 3.0, incidence of infections and quality of life.

Tandem autologous transplants versus autologous transplant followed by HLA-matched sibling non-myeloablative allogeneic transplant: Tertiary objectives include CR and CR+PR rates at 2 and 12 months after the allograft, time to CR and CR+PR, time to second transplant, time to off-study therapy, and quality of life.

Other tertiary outcomes to be evaluated only in the allogeneic transplant arm will include incidence of both primary and secondary graft failure and incidence and severity of graft-versus-host-disease.

- Eligibility Criteria:** Eligible patients are ≤ 70 years of age with Karnofsky scores ≥ 70 , who meet Durie and Salmon criteria for diagnosis of multiple myeloma, who have symptomatic MM requiring treatment, who have received at least three cycles of systemic therapy and who are within 2-10 months of initiation of the initial therapy (this time frame excludes the time for mobilization therapy). Patients must have available an autograft $\geq 4.0 \times 10^6$ CD34+ cells/kg patient weight unless it is known prior to enrollment that they will receive an allogeneic transplant after their initial autologous transplant. Patients with a consenting, eligible HLA-matched sibling must have an autograft $\geq 2.0 \times 10^6$ CD34+ cells/kg patient weight.
- Treatment Description:** Mobilization therapy will not be specified for the study. All patients will undergo a first autologous peripheral blood stem cell (PBSC) transplant with high-dose melphalan (200 mg/m^2 IV/day) given on Day -2. Melphalan will be given between 2 and 8 weeks after initiation of mobilization therapy.
- Patients with adequate recovery will receive either a second autologous PBSC transplant or a non-myeloablative PBSC allogeneic transplant from an HLA-matched sibling. This post-transplant therapy will be initiated at least 60 days (preferably 60-120 days) following the initial autologous transplant.
- Patients without an HLA-matched sibling donor will be randomized to either observation or one year of maintenance therapy with dexamethasone and thalidomide to begin following recovery from their second autologous PBSC transplant. This post-transplant therapy will be initiated at least 60 days (preferably 60-120 days) following the second autologous transplant.
- Quality of Life:** The FACT-BMT and MOS SF-36 instruments will be used to describe the health-related quality of life (HQL) of patients. A secondary analysis will compare the HQL between the two treatment arms. The self report questionnaires will be performed prior to both transplants and post second transplant at six months and yearly until three years for English and Spanish speaking patients only.
- Accrual Objective:** Study accrual and analysis is based on the number of standard risk multiple myeloma patients with an available HLA-matched sibling donor. A total of 150 standard risk multiple myeloma patients with an HLA-matched sibling donor will be accrued. During this time, it is expected that at least 350 standard risk multiple myeloma patients without a sibling donor will also be entered on the trial. In addition, high-risk patients with and without HLA-matched siblings will also be entered on the trial during the same period.
- Accrual Period:** The estimated accrual period is three years.
- Study Duration:** Patients will be followed for at least three years after their second transplant.

Outline of Treatment Plan

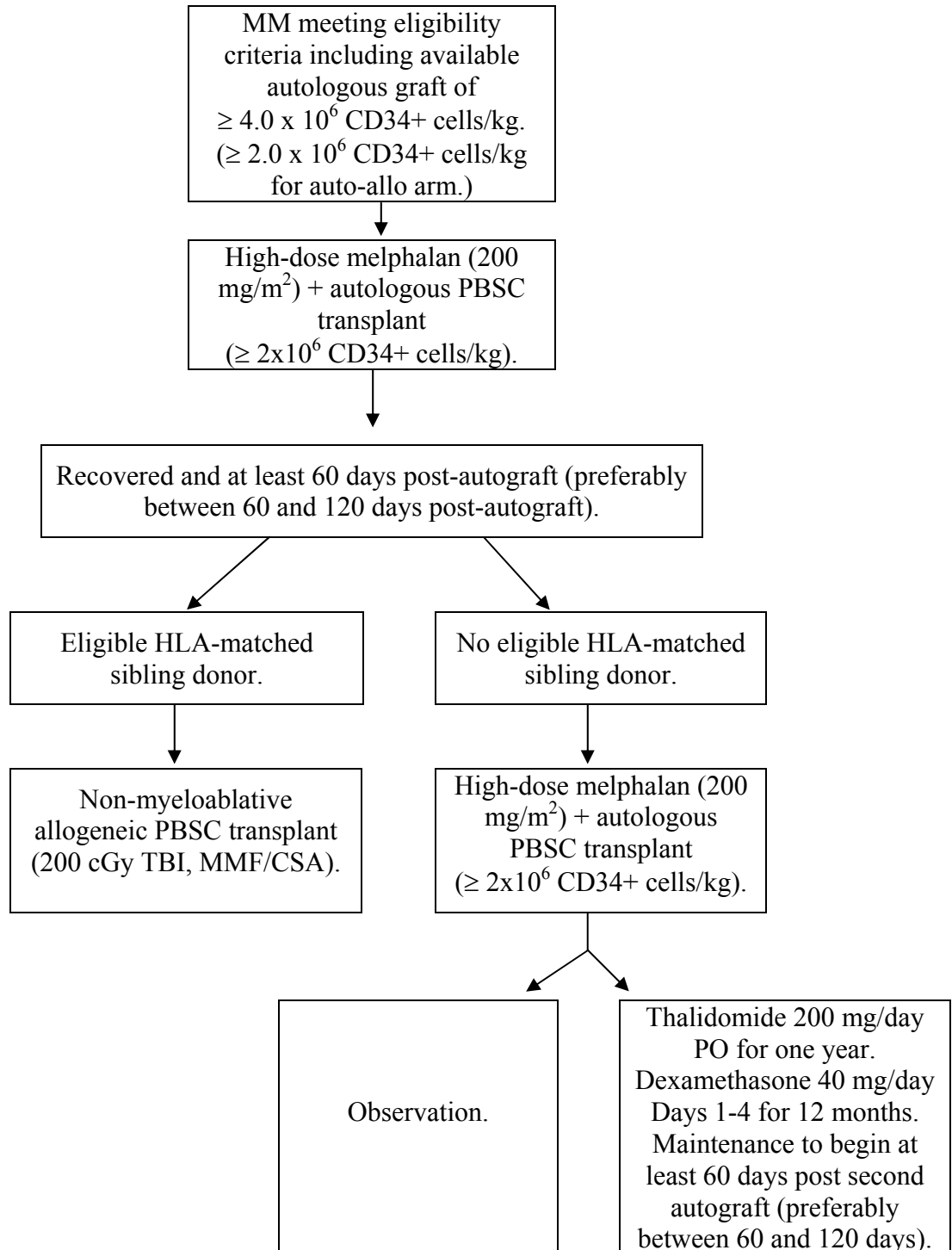


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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1 Background

Multiple myeloma (MM), characterized by malignant plasma cell proliferation, bone destruction and immunodeficiency, is a disease with a median age at diagnosis of approximately 65 years. It is responsible for about 1 percent of all cancer-related deaths in Western Countries¹. Conventional treatments with chemotherapy and radiation therapy are non-curative but improve quality of life and duration of survival. Attempts to cure myeloma through high-dose therapy followed by autografting or allografting have largely failed due to a combination of relapsed disease or transplant related mortality (TRM). High-dose therapy with autologous transplantation is safe and has low TRM (< 5%), but is associated with a continuing and nearly universal risk of disease progression and relapse. Even so, autologous transplantation is superior to continued conventional chemotherapy². Recent data discussed below indicate that tandem autologous transplants are superior to a single procedure³. Even with this approach, patients remain at risk of relapse and additional approaches are needed.

In contrast, results of allografting and donor lymphocyte infusions (DLI) for relapsed myeloma suggest that alloimmune reactions may provide long-term disease control. Unfortunately, conventional approaches to allografting are complicated by 40% TRM^{4,5}. In the experience at Fred Hutchinson Cancer Research Center (FHCRC), Day 100 TRM after conventional allografting exceeded 50% in patients \geq 50 years of age⁶. The inability of myeloma patients to tolerate allografting may relate to an inability of generally elderly and immune suppressed patients to tolerate the combined effects of high-dose therapy and allografting in a single procedure.

Recent data from a Phase II study using a two-step approach where high-dose melphalan and autologous stem cell transplantation was followed by a non-myeloablative allogeneic transplant show that donor engraftment can be established with a conditioning regimen of low dose total body irradiation (TBI) (200 cGy), cyclosporine (CSA) and mycophenolate mofetil (MMF) combined with peripheral blood stem cell (PBSC) allografting. This study demonstrated that allografting can be safely and effectively performed if the high-dose regimen is administered separate from the allografting procedure. In this study, approximately 60% of the patients achieved complete remission (CR) with an overall-survival of approximately 85% at one year⁷. One of the objectives of the study was to reduce TRM at three months to < 20%. This was achieved, as only 13% of patients experienced treatment-related mortality.

Another approach to improving autologous transplantation results is the use of post-transplant interventions, such as interferon and, more recently, antiangiogenesis agents such as thalidomide. Dexamethasone, an effective agent in myeloma, has been combined with thalidomide resulting in synergy and no unexpected toxicities⁸. Initial results suggest the combination of thalidomide and dexamethasone is well tolerated after autologous transplantation⁹.

Based on these early encouraging results, the following study is planned. All patients will undergo autologous stem cell transplantation after a conditioning regimen consisting of high-dose melphalan at a dose of 200 mg/m². Starting 60 days or more post-transplant, patients will receive either a second autologous transplant or a non-myeloablative allogeneic transplant, based on the availability of an HLA-matched sibling donor. Patients with an HLA-matched sibling donor will receive an allograft after conditioning with 200 cGy TBI and then receive post-transplant immunosuppression with CSA and MMF. Patients without an eligible HLA-matched sibling donor will receive a second autologous transplant after conditioning with melphalan 200 mg/m². Patients who receive tandem autografts will also be randomized to observation or to receive post-transplant treatment with thalidomide 200 mg/day for twelve months after their second transplant and dexamethasone 40 mg/day on Days 1-4 for 12 months after their second transplant. This approach will provide the proven benefit of high-dose therapy to all patients while exploring the long-term benefits/risks of allografting with non-myeloablative conditioning and the use of post autologous transplant treatment with dexamethasone and thalidomide.

1.2 Rationale for Study

1.2.1 High-dose Melphalan as a Treatment for MM

Until a decade ago, the treatment of MM had not significantly improved since the introduction of melphalan and prednisone, despite the introduction of several combination chemotherapy protocols. Melphalan-prednisone remained the standard chemotherapy regimen, with response rates between 40% to 60%, CR rates of less than 10%, and a median survival of about three years^{10, 11}. Furthermore, none of these therapeutic interventions resulted in cures for patients with MM. Pioneering studies by McElwain et al^{12, 13} demonstrated that treatment with high doses of melphalan could induce responses in refractory myeloma. The responses were brief and were complicated by a high toxic death rate, ranging from 17%-31% in the initial series^{13, 14}. Nonetheless, these results stimulated interest in further studies to address the role of high-dose therapy in myeloma. The demonstration by Barlogie et al^{14, 15} that the toxicity of high-dose melphalan could be decreased by autologous bone marrow transplantation and that the addition of TBI increased response rates led to wider application of high-dose therapy using autologous bone marrow support initially and, more recently, PBSC support.

From the multiple studies reporting the use of melphalan, it is clear that there is a steep dose-response relationship for this drug in MM. In a cohort of 47 patients with refractory MM, melphalan 100 mg/m² led to a 46% response rate with 6% CR but with a disease-free survival that was shorter than after melphalan 140 mg/m² or 200 mg/m²,¹⁹. Doses up to 280 mg/m² have been used in myeloma and other malignancies^{14, 15, 16}. In a recent Phase I trial involving MM patients¹⁷, melphalan at a dose of 200 mg/m² was estimated to be the maximum tolerated dose for two cycles administered within 90 days.

With bone marrow or PBSC support following high-dose melphalan, the toxic death rate is now less than 3% in most studies^{18, 19}. At a dose of 200 mg/m², high response rates in both untreated and previously treated patients are reported^{16, 20, 20, 21, 22, 23, 24}.

In addition, recent data indicate melphalan 200 mg/m² is less toxic but equally effective as melphalan with TBI^{25, 26}.

1.2.2 Tandem Autologous Transplantation

Recently, Barlogie et al showed the feasibility of tandem autologous PBSC transplants using melphalan 200 mg/m² for the first transplant and melphalan 200 mg/m² (79 patients) or melphalan 140 mg/m² plus TBI (1,125 cGy) (10 patients) for the second transplant. Of 123 patients, 87% completed one autologous transplantation and 76% completed a tandem second autologous transplantation by 7.5 and 13 months, respectively, with a median interval between autologous transplantations of 4.5 months. Patients were hospitalized a median of 14 days with the first autologous transplantation and only six days with the second. Cumulative TRM during the first 12 months was 4%²⁷. Barlogie reported 40% CR to tandem transplants and a median event-free survival of 49 months, based on an intent to treat analysis in this single center experience. Overall, these results suggest that doses of melphalan of 140 mg/m² or higher, supported by hematopoietic stem cell infusion, provide a high-dose anti-myeloma regimen with acceptable toxicity²⁸.

For responding patients, high-dose therapy followed by autologous PBSC rescue has been shown to be superior to continued treatment with conventional chemotherapy, leading to the widespread use of autologous transplantation for myeloma patients up to and beyond the age of 70^{29, 30}. Recently, several studies, including preliminary data from the IFM94 trial, suggest that tandem autologous transplants are superior to a single high-dose treatment^{3, 31}. In the IFM study, the progression free and overall survival curves separated after 3 years with improved disease free and overall survival at 6 years post-transplantation for the group that received tandem autologous transplants compared to those receiving single transplants. Overall the median event free survival was 31 versus 37 months, 6-year event free survival was 19% versus 28% and 6-year overall survival 26% versus 46% for single versus tandem transplants, respectively. The interim results of the “Bologna 96” trial presented at the 2002 ASH meeting further support the above findings regarding tandem transplants. In this randomized trial of single versus tandem autologous transplants as part of front line therapy for MM, both remission duration (44 months versus 27 months, p=0.005) and median event-free survival (44 months versus 27 months, p=0.05) were superior in the tandem autologous transplant arm³². While the conditioning regimens were used in these trials differ, as discussed above, subsequent randomized trials comparing melphalan/TBI to melphalan alone have demonstrated that single agent melphalan at 200 mg/m² has emerged as the preferred conditioning for autologous transplantation³³. While TRM rates observed in these studies are low, patients continued to remain at risk for disease relapse and progression, with only a minority of patients remaining disease free at six years.

The cause of relapse following autologous transplantation is either from residual myeloma cells left in the patient following conditioning or the re-infusion of myeloma cells with the autologous grafts. CD34+ selection of PBSC and other immune based selection methods have been used to decrease myeloma cell contamination of PBSC or bone marrow. On average, a 2-4 log depletion of neoplastic cells from PBSC grafts is reported by different groups^{34, 35}. Unfortunately, randomized studies have not shown that purging the graft improves transplant results or decreases the risk of relapse. Results of a recent randomized trial comparing the use of CD34+

selected versus unselected PBSC in autologous transplantation for patients with MM do not show a survival difference to date³⁶. In addition, more cells must be mobilized and collected because of inefficiencies in the cell selection procedure, making the collection procedure more difficult. Lastly, the non-specific removal of other immune cells, including T cells, monocytes, macrophages and natural killer cells results in increased immunodeficiency and may lead to infections, particularly early CMV reactivation. In a study at the FHCRC, patients receiving CD34+ selected PBSC autografts were found to have increased risk of infections³⁷. Of three MM patients, one died as a result of CMV and polymicrobial pneumonitis at Day 40 post-transplant. A second patient developed CMV pneumonitis and required gancyclovir therapy. Both of these patients were CMV sero-positive pre-transplant. A third patient, who was CMV sero-negative, developed CMV related infection at approximately three months post-transplant. For these reasons, the study described in this protocol will use unmodified PBSC for autografting.

1.2.3 Allografting in MM

Although high-dose therapy and autografting result in increased response rates and prolonged overall survival²⁹, it is also clear that this approach is seldom curative, since initial responses are almost uniformly followed by relapse^{18, 19}. The inability of autografting to achieve cure for patients with MM is emphasized by the update of the IFM 90 trial demonstrating six-year post-diagnosis event free survival after a single autologous transplant of only 24%³⁸. Data from the IFM94 trial comparing single versus tandem autologous transplants shows a 6-year event free survival of 19% in the single transplant arm compared with 28% in patients receiving tandem autologous transplants^{3, 31}. Additional strategies and new approaches are needed.

Despite the potential advantages of graft-versus-tumor immune responses and a tumor free source of stem cells, conventional high-dose conditioning with allogeneic bone marrow or PBSC transplantation is infrequently used for MM due to a high TRM risk. When used, it is generally limited to younger patients, in contrast to the advanced age profile of MM patients at diagnosis. In addition, the poor clinical condition of many patients and the relatively limited availability of HLA-compatible donors further limits this approach. A recent publication analyzing the outcomes of patients reported to the European Blood and Marrow Transplant Registry (EBMT) suggests that the TRM rate has decreased in recent years due to better control of infection and pulmonary toxicity³⁹. However, even in this group of young patients (median ages ~43-44), transplanted a median of 10 months from diagnosis, TRM following conventional allografting was 21% at 6 months and 30% overall at two years post-transplant. Although more toxic, allogeneic transplantation appears to be a more potent anti-MM therapy than autologous transplantation, with higher CR rates and a longer duration of disease free survival in assessable patients^{2, 40}. Based on reports of a few patients who are disease free 10 and 15 years following syngeneic bone marrow transplantation^{41, 42} and flattening of survival curves at 3-5 years post allogeneic transplant, it is likely that some patients are cured by this procedure.

Several observations suggest the existence of graft-versus-myeloma immune activity following allogeneic transplantation. Bjorkstrand demonstrated indirect evidence in a case-matched analysis of 189 myeloma patients treated with either autologous transplant or allogeneic transplantation. He found a significantly higher rate of relapse from CR or disease progression

from PR in the autologous transplant group compared to patients who underwent allogeneic transplantation⁴⁰. In addition, the quality of remission appeared greater following allogeneic transplantation as molecular remissions were rarely (7%) achieved after autografting (n=15) compared to a 50% molecular remission rate seen after allografting (n=14)⁴³. These data suggest that the chemoresistance of myeloma cells might be overcome by immune antitumor effects of the allograft.

Alternatively, Bjorkstrand's data could be explained by the re-infusion of clonogenic tumor cells with the autologous graft and the availability of a tumor free graft in patients receiving allografts. Gahrton demonstrated some evidence in support of this in a case-matched study of syngeneic, autologous and allogeneic transplants for MM⁴⁴. While the CR rate in each group was similar, the relapse rate in the syngeneic group was similar to that in the allogeneic group, both of which were superior to the autologous group. The lower relapse rate was attributed to either graft contamination in the autologous transplant group contributing to relapse or to a graft-versus-MM effect in the syngeneic group. Despite this theoretical advantage of having a tumor-free graft, CD34+ selection of autologous grafts that resulted in a median 3.3 log depletion of tumor did not result in improvement on disease free or overall survival in MM patients³⁶. This failure may reflect inadequate purging but more likely represents the resistant nature of residual MM in the host.

The existence of a graft-versus-myeloma effect has been more directly confirmed by results of donor lymphocyte infusion (DLI) in patients who relapsed after failure of conventional allografts^{45, 46, 47}. Salama reported results on 25 patients who received DLI (median dose 1×10^8 mononuclear cells/kg) for MM relapsing after an allograft. Some patients received chemotherapy prior to the DLI and some received multiple escalating doses of DLI. Overall, 7 of 15 achieved a CR and 3, a partial response (PR). Lokhorst⁴⁷ reported on 27 patients receiving DLI following partially T cell depleted allotransplants. The DLI were given a median of 30 months post-transplant. Overall, 14 of 27 patients responded with 5 CRs. Responding patients received at least 1×10^8 mononuclear cells/kg.

However, despite these potential advantages, the high TRM associated with allografting limits its widespread use. The TRM associated with allogeneic bone marrow transplantation for MM exceeds that reported after allotransplantation for hematologic malignancies such as acute and chronic myeloid leukemias for unclear reasons. It possibly reflects the high incidence of comorbid disease, especially renal failure. The largest group of myeloma patients treated with allogeneic bone marrow transplantation, reported by Gahrton et al.^{4, 5}, included 162 patients treated in 35 different European centers from 1983 to 1993. Early toxicity was high with an approximately 40% mortality within the first six months. Bensinger et al.⁴⁸ reported on 80 patients treated between 1987-1994. Seventy-one percent of these patients were considered to have refractory disease at the time of transplant. TRM was high, with 42% deaths within the first 100 days and a few additional treatment-related deaths later. These results may be due in part to patient selection, since 71% of the patients in the Seattle study were considered refractory and had received more than one prior chemotherapy regimen. As discussed above,³⁹ a recent analysis of the EBMT data suggests some improvement in outcome with conventional allografting, likely due to better support and favorable patient selection.

1.2.4 Mixed Chimerism

1.2.4.1 Pre-clinical studies

The approach to be used in this protocol to establish mixed chimerism was based on pre-clinical studies performed at FHCRC in a dog model⁴⁹. These studies demonstrated that post-transplant immunosuppression with CSA/MMF could substitute for pre-transplant TBI as immunosuppression for establishing allografts for MHC-matched littermate donors. In these studies, the administration of CSA for 35 days post-transplant resulted in stable engraftment of marrow from seven of seven DLA-identical littermates after conditioning with 450 cGy of TBI⁵⁰, a dose that is myeloablative. In contrast, without post-grafting CSA, 60% of the dogs rejected grafts with this radiation dose. In subsequent studies⁴⁹ using bone marrow grafts from DLA-identical littermates given sub-lethal TBI (200 cGy), post-grafting CSA alone was ineffective for establishing donor grafts. Combination therapy consisting of MMF or methotrexate (MTX) and CSA was successful in allowing establishment of stable grafts. Three of six dogs receiving CSA/MTX had transient mixed chimerism between 3 and 11 weeks and three remained stable mixed chimeras for up to 130 weeks. Of 11 dogs receiving CSA/MMF, ten have become long-term stable mixed chimeras without graft-versus-host-disease (GVHD). At a lower dose of 100 cGy of TBI and using post-grafting MMF/CSA, all six dogs rejected bone marrow grafts, but two of five PBSC recipients have become stable mixed chimeras. Conclusions drawn from these studies were that CSA/MMF is a potent combination that can control both host-versus-graft and graft-versus-host reactions after low dose TBI, thus facilitating engraftment and stable long term survival. PBSC may offer advantages over bone marrow for this purpose.

1.2.4.2 Preliminary clinical studies

Early clinical data in patients treated at the FHCRC hospitals, Stanford University and the University of Leipzig have demonstrated the feasibility of translating this novel method of transplantation from young dogs to older human patients with a variety of hematopoietic malignancies⁵¹. In a series of 45 patients, the non-relapse mortality was 6.7%, and more than 50% of patients with sustained engraftment had complete remissions of their underlying disease. In these trials, patients without prior aggressive chemotherapy were at increased risk of non-fatal graft rejection (20% overall), which was subsequently eliminated by the addition of fludarabine to the conditioning regimen. Patients with a preceding autologous transplant had uniform engraftment with no graft rejections. Particularly attractive was the development of a tandem approach for patients with myeloma, utilizing a high-dose conditioning regimen with single agent melphalan followed by autologous PBSC rescue to cytoreduce the disease. Following resolution of conditioning toxicity (generally 30-90 days) patients received allografts from an HLA-identical related donor following non-myeloablative conditioning with 200 cGy TBI. Preliminary data from these patients led to the development of a tandem transplant protocol that was administered through the Seattle Consortium. Interim results of that study are summarized below.

Sixty-three patients were enrolled on a planned tandem two-step protocol using high-dose melphalan and autologous PBSC transplantation followed by non-myeloablative PBSC transplantation for treatment of MM at centers in the Seattle Consortium: FHCRC hospitals

(n=22), City of Hope (n=19), Stanford University (n=13), University of Toreno (n=3), University of Leipzig (n=2), and the University of Colorado (n=1). Preliminary data from patients with at least three months of follow-up following the allograft (as of December 2001) are presented below.

The median age was 52 (range 40-71) years. All 63 patients received the planned autograft and 60 patients received the non-myeloablative allotransplant. Three patients died prior to allografting, one due to CMV pneumonia (CD34+ selected graft) and two due to disease progression following treatment delay because of toxicity. Approximately 50% of patients (29/60) had responding disease at the time of autologous transplantation with seven patients in CR and 22 in PR. All patients receiving allografts had engraftment of donor cells. Grade II-IV acute GVHD occurred in 34/60 patients (40%), but was serious (Grade III/IV) in only four patients (6.6%). Chronic extensive GVHD requiring prolonged immunosuppression occurred in 26/60 patients (43%). As of December 21, 2001, seven patients have died of the following causes: progressive disease at Day 91 (n=1), GVHD with infection at Days 102, 136, 168 (n=3), respiratory failure at Day 104 (n=1), and complications of chronic GVHD at Days 212, 413 (n=2). Day 200 TRM was 4/60 (6.6%). Disease progression has occurred in four patients so far (6.6%). As of December 21, 2001, the CR rate was 50%, PR rate 30%, for an overall response rate of 80%. Responses occurred gradually following allografting with some patients requiring one year to achieve CR. At 12 months, the Kaplan-Meier estimate of survival and progression-free survival were 85% and 83%, respectively. Median follow-up is approximately one year, with survival up to three years post-allografting in some patients. Outcome data are available for 40 patients with >6 months follow-up.

Greater treatment details are available for the first 41 patients treated with this approach with a median follow-up of 14 months following the allograft. Sixty-six percent of the patients had Stage III disease. Forty three percent had relapsed or refractory disease, 40% were in PR and 15% were in CR at the time of autologous transplantation.

Four patients received CD34+ selected autologous PBSC transplants at FHCRC. Because a higher incidence of CMV infection was observed with CD34+ selected PBSC (including one patient dying on Day 31 post autologous CD34+ selected transplant from CMV pneumonia), subsequent patients underwent unselected autologous PBSC transplantation. Non-myeloablative allografting was performed at a median 69 days post autologous transplantation, in the outpatient setting. Median donor CD34+ cells were $8.49 \times 10^6/\text{kg}$ and donor CD-3 positive cells were $3.53 \times 10^8/\text{kg}$. Median days of hospitalization after allografting were 0 (0-37d). After allografting, the median duration of severe neutropenia (absolute neutrophils count [ANC] < 500) was 0 (0-19d) and median duration of severe thrombocytopenia (Plt < 20,000) was 0 (0-1d). ANC nadir after allograft was 714 (100-1879); platelet nadir was 94,000 (15,000-192,000) with a median RBC transfusion of 0 (0-11) and platelet transfusion of 0 (0-6) units, confirming the non-myeloablative nature of the 200 cGy TBI conditioning regimen. All patients engrafted with donor cells. There was no late graft rejection.

Acute GVHD Grade II-IV occurred in 19/40 patients (48%). Sixteen of forty patients had Grade II, one of forty had Grade III and two of forty had Grade IV GVHD. Chronic GVHD occurred in 25 (63%) of patients and 18 (45%) had extensive chronic GVHD.

Evaluating best disease response, with a median follow-up of 14 months, 24 patients (60%) achieved CR, and twelve patients (30%) achieved PR. Three surviving patients have relapsed/progressive disease and have received additional therapy.

One-year survival is 85%. Six patients have died. One died from progressive disease at Day 91, one from encephalopathy at Day 102, two from Grade IV acute GVHD at Days 136 and 168 and two patients from chronic GVHD and infection at Days 212 and 413. TRM following the allograft for this subgroup is 5/40 (13%). All of these deaths occurred after Day 100 and were related to either infection or complications of acute or chronic GVHD. However, these results demonstrate that combining autologous PBSC transplantation with non-myeloablative allogeneic transplantation is feasible and safe. The TRM of 13% for this group with at least one year of follow-up is significantly lower than the ~40% TRM generally associated with standard allogeneic transplantation or the 21% mortality reported more recently by Gahrton. Moreover, 60% of patients achieved CR, which is higher than the CR rate reported with standard autologous transplantation. Lastly, the immunosuppression induced by autologous PBSC transplantation is sufficient to allow donor engraftment after a non-myeloablative conditioning regimen with 200 cGy TBI alone.

1.3 Post Autologous Transplant Dexamethasone and Thalidomide

Convincing clinical data indicate that high-dose therapy and autologous transplantation produces better outcomes than conventional chemotherapy for MM. In the randomized study by Attal et al, the probability of 5-year event-free survival was 28% in patients treated with autologous transplant as compared to 10% in those treated with conventional chemotherapy. As discussed earlier, tandem autologous transplants appear to be superior to single autologous transplants in the IFM94 trial with 6-year event free survival of 19 versus 28%³. New treatments are needed to prevent relapse and disease progression.

Strategies to prevent relapse have included various post-transplant maintenance therapies. Of these, interferon is the most extensively studied. The evidence regarding the role of interferon post autologous transplant is conflicting. A single, relatively small, randomized trial showed a non-statistically significant trend to longer progression-free survival with interferon but no improvement in overall survival⁵². A moderately-sized retrospective EBMT study demonstrated a longer median progression-free survival (29 versus 20 months; $p=0.006$) and longer overall survival (78 versus 47 months; $p=0.007$) in patients receiving post-transplant interferon⁵³. Despite these results, interferon is not consistently used post-transplant, largely because of toxic side effects. Other agents used include corticosteroids; in the conventional chemotherapy setting, these have impacted survival, but have only recently been explored post-transplant⁵⁴.

Thalidomide was first introduced in 1953 as a sedative hypnotic, but a large increase in incidence of newborns with limb malformations led to its withdrawal in 1960. The immunosuppressive activity of thalidomide was first noted and used in the therapy of lepromatous leprosy⁵⁵. Its activity in chronic GVHD was reported in 1988⁵⁶. The exact mechanism of this activity is unknown but reports suggest diverse mechanisms including effects on the cell-mediated and humoral immunity as well as cytokine modulation^{57, 58}.

Folkman and colleagues demonstrated the importance of angiogenesis in tumor development⁵⁹. In a previous study, it was shown that bone marrow angiogenesis was present in patients with active MM, but not in patients with monoclonal gammopathy of undetermined significance (MGUS)⁶⁰. The extent of angiogenesis correlated with the labeling index (LI), an indicator of plasma cell proliferation.^{60, 61} Therefore, it was proposed that the level of angiogenesis can be used as a prognostic indicator for myeloma. Plasma cells and bone marrow stromal cells in myeloma are capable of expressing adhesion molecules and cytokines with angiogenic properties⁶¹. The etiology of angiogenesis in myeloma is unknown, and may be related to myeloma itself, viral infection, or cytokines such as VEGF.

Thalidomide inhibits angiogenesis in animal models and is active in myeloma with response rates of 30% even in patients with advanced and refractory disease⁶². Thalidomide also, in pre-clinical studies, inhibits the production of IL-6 by peripheral blood mononuclear cells^{63, 64}. Data suggest that IL-6 production by marrow stromal cells is important in the pathogenesis of MM⁶⁴. There are reports of possible benefits of thalidomide therapy in MM associated with reduction of tumor burden as well as a marked decrease in microvessel density in the bone marrow. Singhal and colleagues reported significant anti-tumor activity of thalidomide in patients with advanced and high-risk MM^{62, 65}. Barlogie and colleagues found combining thalidomide with combination chemotherapy produced encouraging results⁶⁵. Toxicities of thalidomide therapy include: neurologic (somnolence, dizziness, confusion, tremors, loss of co-ordination, tingling, numbness), gastrointestinal (constipation, nausea, vomiting, stomatitis), and constitutional (weakness, weight loss, fever). These toxicities are generally moderate with doses of thalidomide up to 400 mg/day.

Thalidomide has been used concomitantly with corticosteroids without the occurrence of unexpected toxicities and with possible synergistic effects⁸. The optimal dose of thalidomide is not established, although toxicities are dose-related. Responses are reported even at 50 mg/day. Current trials generally target the maximum tolerated dose up to a daily dose of 200 mg/day^{9, 66}.

High dose chemotherapy with autologous stem cell support is an effective method of inducing responses in patients with MM. Unfortunately, treatment is not curative and most, if not all, patients eventually relapse. Some patients achieve only partial or less than partial responses. Therefore, attempts to improve the quality of remission by treating minimal residual disease are logical. It is likely that disease residual after high-dose chemotherapy is resistant to conventional chemotherapeutic agents, and use of agents with other mechanisms of action is desirable. Thalidomide is such an agent. Moreover, because of the reported synergism and higher response rate (in the range of 40-70%) with combined thalidomide and dexamethasone with acceptable toxicity profile in newly diagnosed or relapsed patients with multiple myeloma, this combination seems a reasonable maintenance program to be tested in the post autologous transplantation setting. Recently, Alexanian et al reported a 57% response rate using the combination of thalidomide and dexamethasone in patients with MM who had PR following an autologous peripheral stem cell transplantation. Approximately 19% converted from PR to CR. Since achievement of CR is considered a prerequisite for prolonged disease free survival, this encouraging strategy warrants further study.

1.4 Study Approach and Treatment

The introduction of autologous transplantation for MM significantly improved survival for this population of patients, yet the potential for further improvement remains by adding additional therapy post-autografting. For those with an HLA-matched sibling, initial results of non-meloablative transplants hold promise while for those without, a second autologous transplant followed by combinations of effective, tolerable agents such as thalidomide plus dexamethasone are worthy of further testing.

Symptomatic patients with Stage II or III MM who have received at least three cycles of systemic therapy (with vincristine, adriamycin and dexamethasone [VAD], melphalan plus dexamethasone or other similar regimens), who are within 2-10 months of initiation of the initial therapy (exclusive of mobilization therapy) and who have an autologous graft of $\geq 4 \times 10^6$ CD34+ cells/kg patient weight are potentially eligible for the study. Patients known to have a consecutive eligible HLA-matched sibling may have an autograft 2×10^6 CD34+ cells/kg patient weight. Patients meeting the eligibility criteria will proceed to treatment with high-dose melphalan with autologous PBSC support (minimum 2×10^6 CD34+ cells/kg patient weight). Subsequent therapy will be based on biologic assignment to either an allogeneic non-meloablative transplant for those patients with an HLA-matched sibling or to a second autologous PBSC transplant for those lacking a donor. Additionally, patients without an HLA-matched sibling donor will be randomized to either observation or one year of maintenance therapy with thalidomide and dexamethasone, the latter to commence following the second autologous PBSC transplant.

The second phase of therapy will begin at least 60 days (preferably between 60 and 120 days) after the initial autograft, once the patient has recovered sufficiently from the acute toxicity of the high-dose melphalan regimen to proceed to the second phase of therapy. For patients with HLA-matched siblings, the conditioning regimen for the allograft will be TBI (200 cGy) combined with post-transplant CSA and MMF as an immunosuppressive regimen for achieving donor engraftment. Relatively high levels of CSA are targeted given the low intensity conditioning and the need to control host-versus-graft and graft-versus-host reactions.

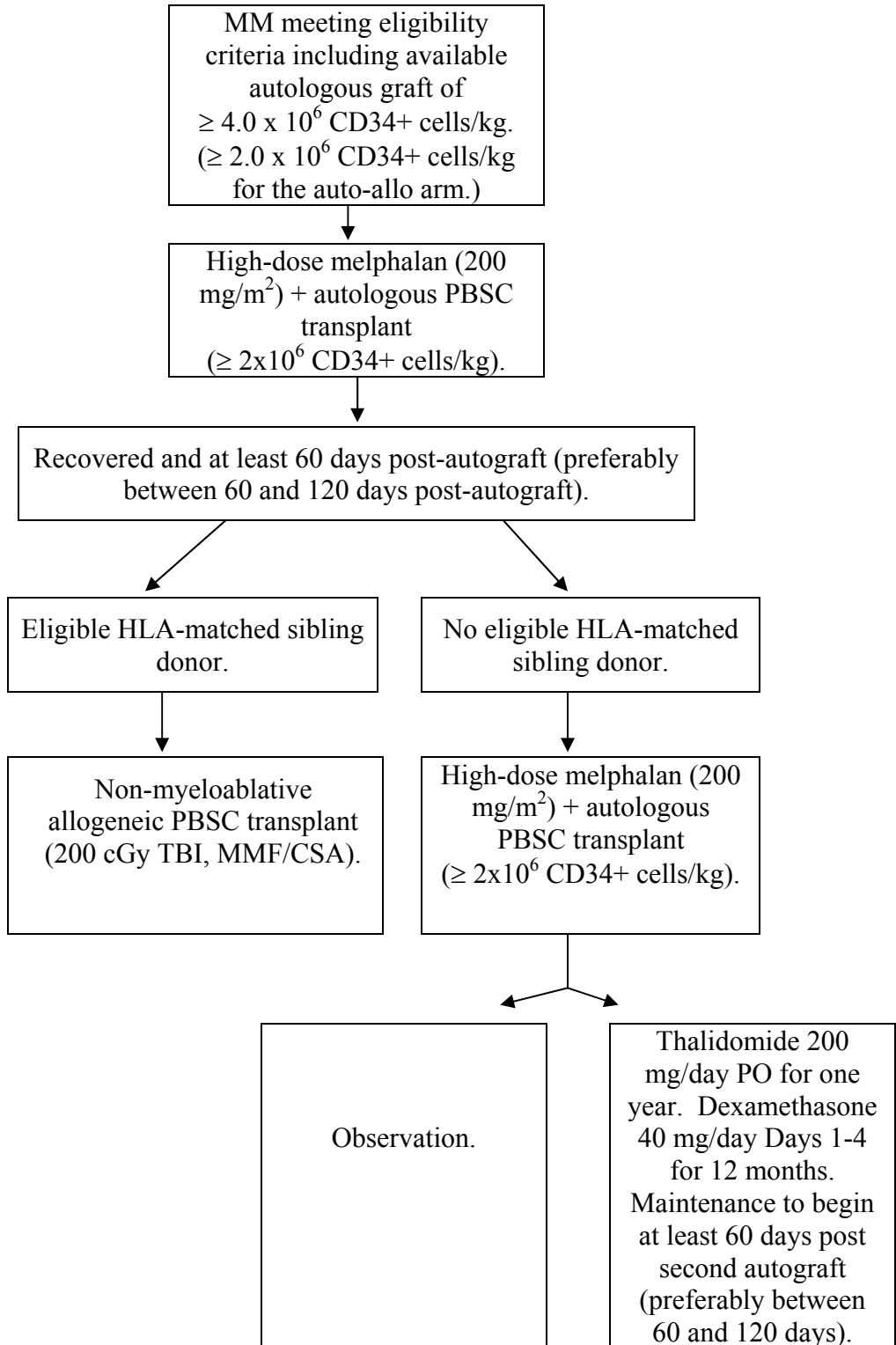
Patients without an available HLA-matched sibling donor will undergo a second course of high dose melphalan (200 mg/m^2) followed by autologous PBSC transplant. These patients will also be randomized to either observation or a one-year course of thalidomide 200 mg/day and dexamethasone 40 mg/day on Days 1-4 for 12 months following their second autologous PBSC transplant.

Two statistical comparisons will be made. To insure a 5% overall Type I Error, each of the comparisons is made at the 2.5% level. Comparisons are based on comparing three-year progression free survival (PFS) of standard risk myeloma patients in an intent to treat analysis. The first comparison is of the two tandem autologous transplant (auto-auto) arms, one with and one without post-transplant maintenance therapy. The goal here is to assess whether maintenance therapy increases the percent of patients alive and free of disease at three years after tandem autologous transplants. The expected number of available patients without an HLA-matched sibling allows for this randomized comparison within this group. The second

comparison is between the auto-auto patients and the auto-allo patients. Here, the patients to be included in the auto-auto arm depends on the results of the first test. If that test shows no indication of a difference between the two auto-auto arms, then these two arms will be pooled for this comparison. If the first test shows a significant advantage for one of the auto-auto arms, that arm will be used in the comparison against the auto-allo arm.

For this trial, myeloma patients will be grouped into a High Risk or a Standard Risk group. Standard Risk is defined as patients with a serum beta 2 microglobulin ≤ 4 mg/L and no chromosome 13 abnormalities on standard metaphase karyotype analysis. High Risk patients will include those MM patients with a serum beta 2 microglobulin level > 4 mg/L and/or chromosome 13 abnormalities on standard metaphase karyotype analysis. The standard risk patients are being analyzed as the primary group as there is a greater potential for imbalance in the assignment of high risk patients, in part because of the smaller numbers on study, and their outcome may be inferior to the standard risk patients. At the same time the high risk patients are included in the trial; it is important to gather information regarding the role of these therapies in this group of patients.

Table 1.4 -- Outline of Treatment Plan



CHAPTER 2

2. STUDY DESIGN

2.1 Study Overview

The overall study design is that of biologic assignment, based on the availability of an HLA-matched sibling, to one of two treatment strategies for MM patients. Patients without an HLA-matched sibling will undergo tandem autologous transplants. Patients with an HLA-matched sibling will undergo an autologous transplant followed by a non-myeloablative allogeneic transplant. In addition, the tandem autologous transplant recipients will be randomized to either observation or one year of maintenance therapy to begin following the second autologous transplant. The large number of MM patients without an HLA-matched sibling enables us to evaluate the role of maintenance therapy following tandem autologous transplants.

2.2 Hypothesis and Specific Objectives

2.2.1 Hypotheses

1. Therapy with dexamethasone and thalidomide following tandem autologous transplants will improve the response rate and progression free survival compared to observation.
2. By separating the high-dose therapy temporally from the allogeneic stem cell transplant procedure, we can achieve both the benefits of autografting (disease response and prolonged survival) and allografting (establishment of full donor chimerism and graft-versus-myeloma effects). This approach will lead to less toxicity, reduced TRM, and better opportunity to evaluate anti-tumor effects of allografting.

We hypothesize that for patients with an HLA-matched sibling, this strategy will prove superior to tandem autografts.

2.2.2 Study Objectives

There are two separate sets of objectives: those that relate to the question of post-tandem autologous transplant maintenance therapy for those without an HLA-matched sibling donor and those that relate to the comparison of tandem autologous transplants against an autologous transplant followed by a non-myeloablative HLA-matched sibling transplant.

2.2.2.1 Tandem autologous transplants versus tandem autologous transplants + maintenance therapy objectives

The primary objective of the randomized trial of maintenance therapy versus observation following tandem autologous transplants is to compare three-year PFS between the two arms.

Secondary objectives are to compare ‘current’ myeloma-stable survival, three-year overall survival and incidence of progression.

Tertiary objectives are CR and CR+PR rates at 2 and 12 months after the second transplant, time to CR and CR+PR, time to off-study therapy, rate of discontinuation of maintenance therapy, duration of maintenance therapy, incidence of toxicities Grade ≥ 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, incidence of infections and quality of life.

2.2.2.2 Tandem autologous transplants versus autologous transplant + non-myeloablative allogeneic transplant objectives

The primary objective of the trial of tandem autologous transplant versus autologous transplant followed by non-myeloablative HLA-matched sibling allogeneic transplant trial is to compare three-year PFS between the two arms.

Secondary objectives are to compare ‘current’ myeloma-stable survival, three-year overall survival, and incidence of progression.

Tertiary objectives are CR and CR+PR rates at 2 and 12 months after the second transplant, time to CR and CR+PR, time to second transplant, time to off-study therapy, and quality of life.

Tertiary objectives for patients who receive an allogeneic transplant are to describe the incidence of both primary and secondary graft failure and the incidence and severity of GVHD.

The relative safety of the two arms will be assessed through the collection and analysis of adverse events and routine laboratory monitoring.

2.3 Patient Eligibility

Patients must meet specified eligibility criteria to be registered on the study. Additional criteria must also be met to continue to successive stages of the protocol. All questions regarding eligibility criteria should be directed to the Protocol Coordinator at 301-251-1161.

2.3.1 Initial Patient Eligibility Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

1. Patients meeting the Durie and Salmon criteria for initial diagnosis of MM (Appendix A).
2. Patients with Stage II or III MM (Appendix A) at diagnosis or anytime thereafter.
3. Patients with symptomatic MM requiring treatment at diagnosis or anytime thereafter.
4. Patients who are 70 years of age, or younger, at time of first registration.
5. Patients who have received at least three cycles of initial systemic therapy and are within 2-10 months of initiation of the initial therapy (this time frame excludes the time for mobilization therapy).

6. Patients receiving chemotherapy-based mobilization regimens must be able to receive high-dose melphalan between 2 and 8 weeks after the initiation of mobilization therapy whether delivered at the transplant center or at a referring center.
7. Patients with adequate organ function as measured by:
 - a) Cardiac: Left ventricular ejection fraction at rest > 40%.
 - b) Hepatic: Bilirubin < 2x the upper limit of normal and ALT and AST < 3x the upper limit of normal.
 - c) Renal: Creatinine clearance > 40 ml/min (measured or calculated/estimated).
 - d) Pulmonary: DLCO, FEV1, FVC > 50% of predicted value (corrected for hemoglobin), or O₂ saturation > 92% of room air.
8. Patients with an adequate autologous graft defined as a cryopreserved PBSC graft containing $\geq 4.0 \times 10^6$ CD34+ cells/kg patient weight. If prior to enrollment, it is known that a patient will be on the auto-allo arm (i.e., a consenting, eligible HLA-matched sibling donor is available), the required autograft must contain at least 2.0×10^6 CD34+ cells/kg patient weight. The graft may not be CD34+ selected or otherwise manipulated to remove tumor or other cells. The graft can be collected at the transplanting institution or by a referring center. For patients without an HLA-matched sibling donor, the autograft must be stored so that there are two products each containing at least 2×10^6 CD34+ cells/kg patient weight.

2.3.2 Initial Patient Exclusion Criteria

Patients with the following will be ineligible for registration onto this study:

1. Patients that have never advanced beyond Stage I MM since diagnosis (Appendix A)
2. Patients with non-secretory MM [absence of a monoclonal protein (M protein) in serum as measured by electrophoresis and immunofixation and the absence of Bence Jones protein in the urine defined by use of conventional electrophoresis and immunofixation techniques].
3. Patients with plasma cell leukemia.
4. Karnofsky performance score less than 70%, unless approved by the Medical Monitor or one of the Protocol Chairs.
5. Patients with uncontrolled hypertension.
6. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and progression of clinical symptoms).
7. Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Medical Monitor or one of the Protocol Chairs. Cancer treated with curative intent > 5 years previously will be allowed.
8. Female patients who are pregnant (positive β -HCG) or breastfeeding.
9. Patients seropositive for the human immunodeficiency virus (HIV).

10. Fertile men or women unwilling to use contraceptive techniques during and for 12 months following treatment.
11. Prior allograft or prior autograft.
12. Patients who have received mid-intensity melphalan (>50 mg IV) as part of prior therapy.
13. Patients unable or unwilling to provide informed consent.
14. Prior organ transplant requiring immunosuppressive therapy.

2.3.3 Patient Eligibility Criteria for Second Transplant

In order to be eligible to continue on protocol and receive their second transplant (preferably between 60-120 days, but at least 60 days post first transplant), patients must have recovered sufficiently from their first transplant. Conditioning therapy for the second transplant must start at least 60 days post first transplant.

Recovery from high-dose melphalan and autografting will be defined by achievement of the following clinical criteria:

1. Mucositis and gastrointestinal symptoms resolved, off hyperalimentation and intravenous hydration.
2. Liver and renal function tests within the inclusion criteria for initial autograft.
3. Off antibiotics and Amphotericin B formulations or voriconazole for proven, probable or possible infections (defined in accordance with the EORTC/MSG criteria⁶⁷). Patients who have been treated for an infection but are continuing antibiotics, Amphotericin B or voriconazole for prophylaxis are eligible to continue on protocol with approval of the Medical Monitor or one of the Protocol Chairs.
4. Completed administration of any radiotherapy as per Section 2.4.1.5.
5. Patients who developed symptoms of cardiac insufficiency after initial enrollment will require repeat cardiac testing and must meet the same criteria as for initial study entry.
6. Pulmonary function tests must meet initial study entry criteria.

Fertile men and women must be willing to use contraceptive techniques during and for 12 months following treatment.

In addition, women of childbearing potential who are pregnant (β -HCG positive) or breastfeeding will be ineligible to receive their second transplant.

2.3.4 Patient Eligibility Criteria for Tandem Autologous Transplant Patients to Begin Maintenance Therapy

Patients without an HLA-matched sibling donor will be randomized to either observation or one year of maintenance therapy to begin after their second transplant. The randomization assignment will be revealed when the Post-tandem Autologous Transplant Checklist is completed, at least 60 days post second transplant. Patients without an HLA-matched sibling

donor must have recovered sufficiently from their second transplant (preferably between 60-120 days, but at least 60 days post second transplant) in order to initiate dexamethasone and thalidomide maintenance therapy.

Recovery from high-dose melphalan and autografting will be defined by achievement of the clinical criteria outlined in Section 2.3.3 above with the exception that patients do not require repeat cardiac or pulmonary testing.

In addition, a pregnancy test must be performed 24 hours prior to the initiation of maintenance therapy for all women of childbearing potential. Women are of childbearing potential unless they have had a hysterectomy or had no menses or have been post-menopausal for at least 24 months. If the patient is pregnant (positive β -HCG), they will be ineligible to receive maintenance therapy. Fertile men and women must continue use of contraceptive techniques until 4 weeks after completion of maintenance therapy.

2.3.5 Allograft Donor Eligibility Criteria

1. 6/6 HLA genotypically identical sibling (defined as a match at the serologic ‘split’ level).
2. Donor must consent to G-CSF administration and to leukapheresis for PBSC allograft.
3. Donor must have adequate veins for leukapheresis or agree to placement of central venous catheter (femoral, subclavian).
4. Age \leq 75 years at the time patient is initially registered on study.

2.3.6 Allograft Donor Exclusion Criteria

1. Identical twin.
2. Age less than 18 years.
3. Female patients who are pregnant (positive β -HCG) or breastfeeding.
4. Infection with HIV, viral hepatitis (B or C).
5. Known allergy to G-CSF.
6. Current serious systemic illness.
7. Uncontrolled bacterial, viral or fungal infection (currently taking medication and progression of clinical symptoms).
8. Donors receiving experimental therapy or investigational agents.
9. Donors with cancer other than treated basal cell or carcinoma in situ of cervix. Cancer treated with curative intent $>$ 5 years previous will be reviewed on a case-by-case basis by the Medical Monitor or one of the Protocol Chairs.

2.3.7 Timing of Biologic Assignment and Randomization

The timing of the biological assignment and randomization depends on the need to identify HLA-type and assess HLA-matched siblings for their ability to donate an allograft. For some

patients, this information will be known at the time of consenting for the trial. For some, the complete evaluation of potential sibling donors may be delayed until during or shortly after the initial autologous transplant. This protocol requires that potential sibling donors be HLA-typed at the earliest opportunity, and that blood for this purpose be drawn no later than three weeks after the initial autologous transplant.

The clinical center will re-register patients once the typing, donor eligibility results and consent are available (See Chapter 4.1 Enrollment Procedures). With this information, the Data Coordinating Center will then make the biological assignment. Patients with an HLA-matched sibling who is a consenting eligible donor will be assigned to the auto-allo arm, and those without will be assigned to the auto-auto arm. The auto-auto arm patients will, at the same time, be randomized to receive either maintenance therapy with thalidomide and dexamethasone, or observation to begin following the second autologous transplant. The randomization assignment will be revealed when the Post-tandem Autologous Transplant Checklist is completed, at least 60 days post second transplant.

To facilitate an intention-to-treat analysis, all patients will be assigned to one of the three treatment arms, even if they are no longer medically eligible for the second transplant or post-transplant maintenance therapy. Continued eligibility for the second transplant and for the initiation of maintenance therapy will be established at subsequent third and fourth registration time points, through the use of eligibility check-lists as outlined in Chapter 4.1 Enrollment Procedure.

2.4 Study Treatments

The immediate pre-transplant evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study. Similarly, special orders and procedures will be those defined by the BMT CTN Manual of Procedures (MOP). All patients enrolled on this protocol will be hospitalized in accordance with the procedures for recipients of autologous and non-myeloablative allogeneic transplants as defined by the treating institution. All questions regarding treatment should be directed to the Protocol Coordinator at 301-251-1161.

2.4.1 Cytoreductive Therapy and First Autologous Stem Cell Transplantation

High-dose melphalan must be given between 2 and 8 weeks after the initiation of mobilization therapy whether delivered at the transplant center or at a referring center. However, if G-CSF is employed as mobilization therapy, the transplant center's institutional guidelines should be followed for timing of melphalan dosing and graft collection.

Table 2.4.1 -- High-Dose Melphalan / Autologous SCT

Day	-2	-1	0	+5 to Engraftment
Melphalan (200 mg/m ² /IV)	X			
PBSC Infusion			X	
G-CSF (5 µg/kg/day*) SQ or IV until ANC > 500 x 2 days				X

* G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 5 µg/kg/day (e.g. < 70kg use 300 µg vial, 70 to 90 kg use 480 µg vial and > 90 kg use 2 x 300 µg vials).

2.4.1.1 Allopurinol

Patients may receive 300 mg/day of allopurinol, starting on Day -4 and ending on Day -1 according to local institutional practice.

2.4.1.2 Melphalan administration

1. Dosage:

Melphalan will be administered at a dose of 200 mg/m². Melphalan will be given in one dose infused on Day -2. Melaphalan dose is based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW).

Ideal Body Weight Formulas:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

For patients less than 5 feet, subtract 2.3 kg/inch

Adjusted Ideal Body Weight Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2. Administration:

High-dose melphalan is administered via a central venous catheter following reconstitution with the provided sterile diluent. High-dose melphalan should be administered undiluted as a bolus injection or diluted with sodium chloride and infused over 15-20 minutes.

3. Maintenance hydration:

Hydration to be administered according to local institutional guidelines.

2.4.1.3 Peripheral blood stem cell infusion

All patients will receive an autologous graft with a minimum cell dose of 2.0×10^6 CD34+ cells/kg patient weight. The graft may not be CD34+ selected or otherwise manipulated to remove tumor or other cells. The autologous graft may be infused on an outpatient basis. Patients must comply with all scheduled study visits whether receiving their transplant as an in-patient or an out-patient. Cryopreservation and thawing of product will be in keeping with FACT standards and local institutional practice. For autologous transplant, if excess cells were collected, all cells up to 5×10^6 CD34+ cells/kg, must be infused. Giving more than 5×10^6 CD34+ cells/kg is at the discretion of the center Principal Investigator.

2.4.1.4 G-CSF

Patients will receive $\sim 5 \mu\text{g/kg/day}$ of G-CSF subcutaneously from Day 5 post-transplant until $\text{ANC} > 500/\text{mm}^3$ for two days. G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximation of $5 \mu\text{g/kg/day}$ (e.g., $< 70 \text{ kg}$ use $300 \mu\text{g}$ vial, $70 \text{ to } 90 \text{ kg}$ use $480 \mu\text{g}$ vial and $> 90 \text{ kg}$ use $2 \times 300 \mu\text{g}$ vials). If the patient is unable to tolerate G-CSF subcutaneously, it may be administered intravenously as per package insert.

2.4.1.5 Radiation therapy

No radiation therapy is permitted concurrent with administration of melphalan. When blood count recovery is adequate ($\text{ANC} > 1000/\text{mm}^3$, platelets $> 80,000/\text{mm}^3$) after autologous transplantation, radiation may be administered for the following indications after consultation with the Medical Monitor or one of the Protocol Chairs and a radiation oncologist:

1. Palliation of pain from bone lesions
2. Prevention of pathologic fractures
3. Relief of spinal cord compression or nerve root compression

The radiation oncologist will determine dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

In addition to blood count recovery, except for emergent indication (e.g. cord compression), patients must also be recovered from autologous transplantation with resolution of mucositis, resolution of fever, discontinuation of antibiotics and receiving adequate oral hydration and nutrition to receive radiation therapy.

2.4.2 Second Autologous Transplant for Patients without an HLA-matched Sibling

Conditioning for the second transplant will be initiated once the patient has recovered from the first transplant. Recovery from the first autograft will be defined as patients achieving the clinical criteria in Section 2.3.3. Upon recovery from the first autograft, but at least 60 days (preferably between 60-120 days) after the first autograft, patients without an HLA-matched sibling donor will receive a second autograft, also conditioned with melphalan 200 mg/m² as outlined in Section 2.4.1.1 through 2.4.1.5 and Table 2.4.1. If indicated, radiation to high-risk skeletal lesions may be given pre-transplant as per Section 2.4.1.5. For autologous transplant, if excess cells were collected, all cells up to 5 x 10⁶ CD34+ cells/kg, must be infused. Giving more than 5 x 10⁶ CD34+ cells/kg is at the discretion of the center Principal Investigator.

2.4.3 One Year of Dexamethasone and Thalidomide Maintenance Therapy or Observation for Patients without an HLA-matched Sibling

Recovery from high-dose melphalan and autografting will be defined as patients achieving the clinical criteria in Section 2.3.3 with the exception that repeat pulmonary function testing and assessment of LV ejection fraction are not required. As soon as evaluation of all potential donors is complete, all patients without an HLA-matched sibling will be randomized to receive the combination of thalidomide and dexamethasone maintenance therapy as outlined below or observation. Maintenance therapy will not begin until recovery from the **second autograft**. Recovery from the second autograft is defined as per Section 2.3.3 with the exception that repeat pulmonary function testing is not required.

Table 2.4.3 -- Dexamethasone and Thalidomide Treatment Schedule

	Months 1-12
Thalidomide 200 mg/day PO	Start 50 mg/day and increase 50 mg/day each week as tolerated to target dose of 200 mg/day
Dexamethasone 40 mg/day PO	Days 1-4 of each month

2.4.3.1 Thalidomide

Patients will be initiated on a starting dose of 50 mg/day. The dose will be increased weekly by 50 mg as tolerated to achieve a target dose of 200 mg/day. Patients will be treated for 12 months with thalidomide. See Table 2.4.3a for dose modifications for thalidomide based on subject toxicity.

Refer to Appendix D for the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.[™]) dosing and administration procedures for thalidomide.

Female patients taking thalidomide must either abstain from all reproductive sexual intercourse or use two methods of birth control or at least one highly active method (e.g., intrauterine device

[IUD], hormonal [birth control pills, injections or implants], tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), for at least four weeks before starting thalidomide therapy, during therapy, and for at least four weeks after discontinuing thalidomide therapy even when there has been a history of infertility, unless due to hysterectomy or because the patient has been post-menopausal or has had no menses (that is no menstrual period) for at least 24 consecutive months.

Female patients having any chance of becoming pregnant must have a pregnancy test performed. The test should be performed within 24 hours of beginning thalidomide, weekly for the first four weeks of treatment, and then every four weeks until 12 months post initiation of maintenance therapy if the patient's periods are regular or every two weeks if they are not.

Male patients must be counseled that thalidomide may be present in their semen. Men must use a latex condom every time they have sexual intercourse with a woman during therapy and for four weeks after discontinuing thalidomide, even if they have had a successful vasectomy. Male patients should request that female partners use a second method of birth control in addition to a male condom.

2.4.3.2 Dexamethasone

Patients will receive dexamethasone at a dose of 40 mg per day during Days 1-4 of each month for 12 months. The first dose of dexamethasone to be given the same day the patient starts thalidomide. See Table 2.4.3b for dose modifications for dexamethasone based on subject toxicity.

2.4.3.3 Dose Modifications for dexamethasone and thalidomide

Treatment modifications are based on toxicity. All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Table 2.4.3a THALIDOMIDE Dose Modification Based on Toxicity

CTCAE Category	Toxicity	Dosage Change ¹
BASED ON INTERVAL TOXICITY		
Dermatology	<p>Rash Grade 2-3</p> <p><u>Grade 2:</u> Macular or papular eruption or erythema with pruritus or other associated symptoms or localized desquamation or other lesions covering < 50% of body surface area.</p> <p><u>Grade 3:</u> Severe generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥ 50% of body surface area.</p>	<p>Dose should be held until toxicity resolves to baseline or ≤ Grade 1 and then restarted at a 50% dose reduction¹.</p> <p><u>Grade 1:</u> Macular or papular eruption or erythema without associated symptoms.</p>
	<p><u>Grade 4:</u> Stevens-Johnson syndrome and toxic epidermal necrolysis, generalized exfoliative, ulcerative or bullous dermatitis.</p>	<p>Discontinue thalidomide; no further treatment with thalidomide.</p>
Blood/bone Marrow	<p>Neutrophils</p> <p><u>Grade 3:</u> ANC ≥ 500 - < 1000/mm³.</p>	<p>Consider G-CSF.</p>
	<p><u>Grade 4:</u> ANC < 500/mm³.</p>	<p>Dose should be held until ANC ≥ 500 mm³, and then restarted at a 50% dose reduction¹.</p>
	<p>Platelets</p> <p><u>Grade 4:</u> Platelet count < 25,000 cells/mm³.</p>	<p>Dose should be held until toxicity resolves to baseline or ≤ Grade 2 and then restarted at a 50% dose reduction.</p> <p><u>Grade 1:</u> Platelets ≥ 75,000.</p> <p><u>Grade 2:</u> Platelets ≥ 50,000 - < 75,000.</p>

CTCAE Category	Toxicity	Dosage Change ¹
BASED ON INTERVAL TOXICITY		
Neurology	<p>Neuropathy motor</p> <p><u>Grade 2:</u> Symptomatic weakness interfering with function, but not interfering with activities of daily living.</p>	<p>Dose should be held until toxicity resolves to baseline or ≤ Grade 1 and then restarted at a 50% dose reduction^{1,2}.</p> <p><u>Grade 1:</u> Asymptomatic, weakness on exam/testing.</p>
	<p><u>Grade 3:</u> Weakness interfering with activities of daily living or bracing or assistance to walk indicated.</p> <p><u>Grade 4:</u> Life-threatening or disabling (paralysis).</p>	<p>Discontinue thalidomide permanently.</p>
	<p>Neuropathy sensory</p> <p><u>Grade 2:</u> Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living.</p>	<p>Dose should be held until toxicity resolves to baseline or ≤ Grade 1 and then restarted at a 50% dose reduction^{1,2}.</p> <p><u>Grade 1:</u> Asymptomatic; loss of deep tendon reflexes or paresthesia but not interfering with function.</p>
	<p><u>Grade 3:</u> Sensory alteration or paresthesia interfering with activities of daily living.</p> <p><u>Grade 4:</u> Disabling.</p>	<p>Discontinue thalidomide permanently.</p>

CTCAE Category	Toxicity	Dosage Change ¹
BASED ON INTERVAL TOXICITY		
Neurology <i>continued</i>	Somnolence/depressed level of consciousness <u>≥ Grade 3:</u> Obtundation or stupor or difficult to arouse or interfering with activities of daily living.	Dose should be held until toxicity resolves to baseline or ≤ Grade 1 and then restarted at a 50% dose reduction ¹ . <u>Grade 1:</u> no description <u>Grade 2:</u> Somnolence or sedation interfering with function, but not interfering with ADL.
	<u>Grade 4:</u> Coma.	Discontinue thalidomide permanently.
Gastrointestinal	Constipation <u>≥ Grade 3:</u> Symptoms interfering with ADL or obstipation with manual extraction indicated. <u>Grade 4:</u> Obstruction or toxic megacolon.	Hold until constipation ≤ Grade 1, then restart with additional prophylactic measures and/or lower dose ¹ . <u>Grade 1:</u> Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema. <u>Grade 2:</u> Persistent symptoms with regular use of laxatives or enemas indicated.

CTCAE Category	Toxicity	Dosage Change ¹
BASED ON INTERVAL TOXICITY		
Constitutional Symptoms	<p>Fatigue</p> <p>≥ <u>Grade 3</u>: Severe fatigue interfering with ADL.</p> <p><u>Grade 4</u>: Disabling.</p>	<p>Hold until toxicity resolves to baseline or ≤ Grade 1, then restart at 50% dose reduction¹.</p> <p><u>Grade 1</u>: Mild fatigue over baseline.</p> <p><u>Grade 2</u>: Moderate or causing difficulty performing some ADL.</p>
Other ≥ Grade 3 Toxicity		<p>Hold until toxicity resolves to baseline or ≤ Grade 1, then restart at 50% dose reduction¹.</p>

Notes:

¹If the patient is on 100 mg/day of thalidomide when the toxicity occurs, the dose should be lowered to 50 mg/day. The dose may subsequently be increased by 50 mg (1 capsule)/day increments as tolerated on a weekly basis up to 200 mg. Document all dose changes. Patients who cannot tolerate 50 mg/day should discontinue protocol therapy.

²Thalidomide treatment should be stopped if there is recurrence of dose-limiting peripheral neuropathy on the lower dose or failure to resolve to ≤ Grade 1.

Table 2.4.3b DEXAMETHASONE Dose Modification Based on Toxicity

CTCAE Category	Toxicity	Dosage Change
BASED ON INTERVAL TOXICITY		
Gastrointestinal	<u>Grade 1-2:</u> Requiring medical management. Dyspepsia, gastric or duodenal ulcer, gastritis.	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 50% permanently.
	\geq <u>Grade 3:</u> Requiring hospitalization or surgery.	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis.	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema \geq <u>Grade 3:</u> Limiting function and unresponsive to therapy or anasarca.	Diuretics as needed, and decrease dexamethasone dose by 25%; if edema persists despite above measures decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.

CTCAE Category	Toxicity	Dosage Change
BASED ON INTERVAL TOXICITY		
Neurology	Confusion or mood alteration ≥ <u>Grade 2</u> : Interfering with function but not interfering with activities of daily living.	Hold dexamethasone until symptoms resolve. Restart at 50% of current dose. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness ≥ <u>Grade 2</u> : Symptomatic and interfering with function but not interfering with activities of daily living.	Decrease dexamethasone dose by 25%; if weakness persists despite above measures decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Metabolic	Hyperglycemia ≥ <u>Grade 3 or higher</u> .	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 25% decrements until levels are satisfactory.

2.4.3.4 Minimal maintenance doses of thalidomide and dexamethasone

Whenever possible, for patients requiring dose reductions due to toxicity, an attempt should be made to maintain patients on minimal maintenance doses. Specifically, patients should be maintained, if possible, on a minimal dose of thalidomide of 50 mg/day and a minimal dose of dexamethasone of 20 mg/day on Days 1-4 of each month.

2.4.4 Allogeneic Non-myeloablative Transplantation for Patients with an HLA-matched Sibling

Upon recovery from their autograft, and at least Day 60 (preferably between 60-120 days) post-autograft, patients with an available 6/6 HLA matched sibling will receive an allograft after non-myeloablative conditioning. Recovery from high-dose melphalan and autograft will be defined by achievement of the clinical criteria established in Section 2.3.3. If indicated, radiation to high-risk skeletal lesions may be given pre-transplant as per Section 2.4.1.5.

Pre-transplant conditioning and PBSC infusion may be administered on an outpatient basis. Patients must comply with all scheduled study visits whether receiving their transplant as an inpatient or an outpatient.

Table 2.4.4 -- Non-myeloablative Transplant Schedule

	Day -3	Day 0	Day +1	Day +27	Day +84	Day +114	Day +180
TBI 200 cGy		X					
Cyclosporine 5 mg/kg bid PO *	Start				Initiate taper	Off if not in PR or CR and no GVHD on Day +84	Off if CR or PR and no GVHD on Day +84
Mycophenolate Mofetil (MMF) 15 mg/kg bid PO *		First dose 20:00hrs		Last dose			
PBSC Infusion **		X**	X***				

* See Section 2.4.4.2 for dose adjustments and for changes if disease progression / relapse.

** After TBI

*** If required

2.4.4.1 Conditioning regimen

On Day 0, patients will receive TBI 2.0 Gy from a linear accelerator at ≤20 cGy/min, followed by allogeneic PBSC infusion. It is recommended that TBI be administered between 11:00 a.m. and 2:00 p.m. to avoid proximity to CSA/MMF administration.

2.4.4.2 Peri non-myeloablative allogeneic transplant immunosuppression

Cyclosporine:

1. Commence CSA on Day –3 at 5 mg/kg bid PO for a daily dose of 10 mg/kg/day (round to the nearest 25 mg increment) through Day +84 based on actual body weight. Starting on Day 84, patients in PR or CR and in the absence of GVHD, will have CSA tapered such that the patient will be off CSA by Day 180 (approximately 6% decrease every seven days). Patients without at least a PR compared to registration evaluation but without disease progression [minimal response (MR), stable disease (SD)] and in the absence of GVHD, will have CSA tapered such that the patient will be off CSA by Day 114.
2. Dose Adjustments: CSA, whole blood "trough" levels (i.e., just prior to the next dose) will be evaluated on Day 0 (the day of transplant) and twice weekly during the first week of treatment and adjusted if necessary to maintain blood levels that target 500 ng/ml (upper end of therapeutic range) during the first month. Dose reductions should only be made if CSA toxicity is present or whole blood levels exceed 600 ng/ml in the absence of toxicity. Further CSA determinations should be performed weekly – until CSA is stopped unless high levels are detected (i.e., > 600 ng/ml), or toxicity is suspected, in which case more frequent monitoring will be performed as clinically indicated. Dose reductions for high levels without toxicity should be conservative e.g. 25%, to avoid inadequate immunosuppression. Patients with severe intolerance of cyclosporine, may be placed on FK506 (tacrolimus) after discussion with the Medical Monitor or one of the Protocol Chairs.

After Day 28, the CSA level is to be kept within 200-400 ng/mL, according to local institutional practice until the Day 84 taper is initiated.

3. If there is nausea and vomiting at anytime during CSA treatment, the drug should be given intravenously at the appropriate dose.
4. Drugs that may affect CSA levels are: dexamethasone, phenobarbital (may lower CSA levels), steroids, fluconazole, voriconazole, ketoconazole, cimetidine, itraconazole (may increase CSA levels). Patients requiring hemodialysis should have CSA levels maintained in the high therapeutic range (400 ng/ml).

Mycophenolate Mofetil:

1. Oral administration of MMF will be at a daily dose of 30 mg/kg/day (15 mg/kg twice daily 8:00 a.m. and 8:00 p.m.) from the evening of Day 0 (i.e. first dose to follow allograft infusion). Doses will be rounded to the nearest 250 mg (capsules are 250 mg). MMF dosing is based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW, based on actual body weight (ABW) for patients who weigh less than 100% of their IBW, and based on adjusted ideal body weight (AIBW) for patients who weigh more than 120% of their IBW. See Section 2.4.1.2 for body weight formulas.
2. MMF will be given until Day 27 post-transplant and then stopped without tapering. If there is nausea and/or vomiting at any time preventing the oral administration of MMF, MMF should be administered intravenously at 15 mg/kg bid.

3. Dose Adjustments: If, in the clinical judgment of the investigator, an observed toxicity is related to MMF administration, a dose adjustment will be made. Based on previous organ transplant studies, dose adjustments may occur because of hematopoietic or gastrointestinal adverse effects. Dose adjustments will not be made for hematopoietic toxicity unless severe neutropenia develops or persists after Day 21 post-transplant (ANC < 1000/mm³ for > 5 days). Any planned dose adjustments for hematologic toxicity must be discussed with one of the Protocol Chairs or Medical Monitor. In the event of gastrointestinal toxicity that requires medical intervention including medication for control of persistent vomiting or diarrhea and is *considered to be due to MMF*, a 20% dose reduction will be made. If there is no improvement within 72 hours, MMF will be reduced an additional 20%. For severe gastrointestinal toxicity related to MMF, MMF will be stopped. Patients should be evaluated by both a gastroenterology consultant and the site principal investigator to determine the need for dose adjustments.

2.4.4.3 Management of post-allotransplant immunosuppression in the setting of disease progression

If the patient progresses ≥ 28 days post-non-myeloablative transplant in the absence of GVHD, cyclosporine will be tapered off over two weeks to try to induce a graft-versus-myeloma reaction.

2.4.4.4 Management of post-allotransplant immunosuppression in the setting of low or decreasing donor peripheral blood t-cell chimerism

It is unlikely that donor chimerism will be low following the non-myeloablative allotransplant. Should low or decreasing donor peripheral blood T-cell chimerism be documented, no adjustments to MMF or CSA dosing are to be made without first discussing the situation with one of the Protocol Chairs or the Medical Monitor.

2.4.5 Collection and Infusion of Donor PBSC for Non-myeloablative Transplantation

2.4.5.1 G-CSF administration to donors

All donors will receive G-CSF 16 $\mu\text{g}/\text{kg}/\text{day}$ for five consecutive days from Day -4 to Day 0. G-CSF will be administered by daily subcutaneous injections. The dose of G-CSF may be rounded according to body weight and available G-CSF vial sizes to best approximate 16 $\mu\text{g}/\text{kg}$. If necessary, based on volume, the G-CSF dose can be given in multiple injection sites. If the patient is unable to tolerate G-CSF subcutaneously, it may be administered intravenously as per package insert. These doses will be administered before 10:00 a.m. each day. The schedule of G-CSF administration and PBSC collections can only be ascertained once Day 0 is identified.

2.4.5.2 PBSC collection and evaluation

Donors will preferably undergo vein to vein collections but may receive an appropriate central venous catheter inserted on or before the day of the apheresis. PBSCs will be collected in the afternoon of Day –1 and stored in the refrigerator at 2-8°C overnight. A second collection will be performed the following afternoon and both collections will be transfused. Each collection will be separately evaluated in the cryobiology laboratory for cellular composition in keeping with the BMT CTN MOP for graft characterization.

A minimum dose of 2.0×10^6 CD34+ cells/kg recipient weight will be collected from the donor (according to institutional practices) and given. If $\geq 10 \times 10^6$ CD34+ cells/kg are collected on Day –1, a second collection will not be necessary. If less than 2.0×10^6 CD34+ cells/kg recipient weight are collected with the first two aphereses, a third collection must be performed on Day +1. All cells collected should be infused. Cryopreservation of donor stem cells may be acceptable, but the Medical Monitor or one of the Protocol Chairs must be consulted.

Patients with $< 2.0 \times 10^6$ CD34+ cells/kg recipient weight available after 3 aphereses will not receive an allogeneic transplant on protocol. Subsequent management of these patients is at the discretion of their attending physician.

Table 2.4.5 -- Treatment Schedule for Donor

Days	-4	-3	-2	-1	0	1
G-CSF 16 µg/kg SQ or IV	X	X	X	X	X	X**
PBSC Collection				X	X*	X**
PBSC Administration					X	X**

* The second PBSC collection can be cancelled only if $\geq 10 \times 10^6$ CD34+ cells/kg recipient weight are collected with the first apheresis.

** A third collection is required if $< 2.0 \times 10^6$ CD34+ cells/kg recipient weight are collected with the 2 previous aphereses.

2.4.5.3 PBSC infusion

Patients will receive unmodified (other than volume reduction) G-CSF mobilized PBSC from an HLA-identical sibling on Day 0 of the treatment regimen. For patients with and HLA-identical sibling donor who requires three aphereses, Day 0 is defined as the day the patient receives the product of the first two aphereses. The PBSC is infused via a central venous catheter using standard blood infusion tubing. If more than 2×10^6 CD34+ cells/kg were collected from the donor, all available cells must be infused.

2.5 Supportive Care

2.5.1 Post Autologous Transplantation(s)

All supportive care will be given in keeping with BMT CTN MOP and local institutional practice.

2.5.1.1 Bisphosphonates

Monthly IV bisphosphonates (either Zometa or Pamidronate according to institutional preference) may be initiated (or re-initiated) after the first (or second) autograft according to local institutional practice.

2.5.1.2 Prophylaxis against infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peri-transplant period according to the BMT CTN MOP and local institutional practice. Additional specifications/requirements for this study are summarized below. Infectious prophylaxis will include prophylaxis for:

1. Anti-bacterial: In keeping with the BMT CTN MOP and local institutional standards.
2. Pneumocystis carinii: Prophylaxis will start at the time of engraftment or on Day 30 post autologous transplant according to institutional preference. Prophylaxis should be continued until at least six months post autologous transplantation.
3. Anti-fungal Therapy: Anti-fungal prophylaxis will be initiated peri-transplant according to local institutional practice and will continue until neutrophil recovery post autologous transplant.
4. HSV/VZV prophylaxis will be initiated according to local institutional practice peri-transplant and continue until six months post autologous transplantation.

2.5.1.3 Growth factors

Patients will receive ~5 µg/kg/day of G-CSF subcutaneously from Day 5 post autologous transplant until ANC > 500/mm³ for two days. G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 5 µg/kg/day (e.g., < 70 kg use 300 µg vial, 70 to 90 kg use 480 µg vial and > 90 kg use 2 x 300 µg vials). If the patient is unable to tolerate G-CSF subcutaneously, it may be administered intravenously as per package insert.

2.5.1.4 Blood products

Transfusion thresholds for blood product support will be in keeping with BMT CTN MOP and standard institutional guidelines. All blood products will be irradiated. Allogeneic transplant candidates who are CMV negative will receive CMV negative or filtered blood products from study entry.

2.5.1.5 Immunizations

Patients should initiate re-immunization programs at one year following the second autologous transplant according to local institutional practice and the BMT CTN MOP.

2.5.2 Post-initiation of Dexamethasone and Thalidomide

Continue with supportive care as outlined in Section 2.5.1. No routine extension of infection prophylaxis is planned for patients randomized to maintenance therapy.

Stevens-Johnson syndrome has been reported in a small number of MM patients receiving thalidomide, allopurinol and Bactrim. It is not clear which drugs in the combination were responsible for the development of this complication. Treating physicians should be aware of this potential risk and if desired use an alternative to Bactrim for PCP prophylaxis (e.g., dapsone) for patients on maintenance thalidomide and dexamethasone until it is discontinued at 12 months post initiation of maintenance therapy.

Female patients having any chance of becoming pregnant must have a pregnancy test performed. The test should be performed weekly for the first four weeks of treatment, and then every four weeks until 12 months post initiation of maintenance therapy if the patient's periods are regular or every two weeks if they are not.

Male patients must use a latex condom every time they have sexual intercourse with a woman during therapy and for four weeks after discontinuing thalidomide, even if they have had a successful vasectomy. Male patients should request that female partners use a second method of birth control in addition to a male condom.

2.5.2.1 Coumadin

Patients receiving dexamethasone and thalidomide as remission induction therapy for MM have an increased risk of developing deep vein thrombosis (DVT). This risk may be as high as 10%. It is unclear whether the risk is the same in patients receiving dexamethasone and thalidomide as maintenance therapy after autologous transplantation. Experience at MD Anderson Cancer Center (MDACC) and City of Hope, suggest it is likely lower (personal communication Sergio Giralt and Firoozeh Sahebi). Treating physicians should be aware of this risk and have heightened vigilance regarding this possible toxicity in patients randomized to the maintenance therapy arm.

Coumadin for DVT prophylaxis may be given according to institutional practice. Administration of coumadin and the incidence of DVT will be monitored by the BMT CTN Data Safety Monitoring Board.

2.5.3 Post Non-myeloablative Allogeneic Transplant

All supportive care will be given in keeping with BMT CTN MOP and local institutional practice.

2.5.3.1 Bisphosphonates

Monthly IV bisphosphonates (either Zometa or Pamidronate) may be initiated after the allograft according to local institutional preference.

2.5.3.2 Prophylaxis against infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peri-transplant period according to the BMT CTN MOP and local institutional practice. Additional specifications/requirements for this study are summarized below. Infectious prophylaxis will include prophylaxis for:

1. Anti-bacterial prophylaxis: In keeping with the BMT CTN MOP and local institutional standards for allogeneic transplants.
2. Pneumocystis carinii: Prophylaxis will start at the time of engraftment or on Day 30 post allogeneic transplant according to institutional preference. Prophylaxis should be continued until at least six months post allogeneic transplant.
3. Anti-fungal therapy: Anti-fungal prophylaxis will be initiated peri-transplant according to local institutional practice and will continue until at least Day 70 post allogeneic transplant.
4. HSV/VZV: Prophylaxis will be initiated peri-transplant according to local institutional practice and will continue until six months post allogeneic transplant.
5. CMV: Monitoring and preemptive treatment strategy will be in accordance with the BMT CTN Technical Committee (Infectious Disease) MOP and local institutional practice.

2.5.3.3 Post-transplant growth factors

Patients will not receive post-transplant growth factors while receiving MMF (Days 0-27 post allogeneic transplant). After Day 27 post allogeneic transplant, G-CSF should be given for severe neutropenia ($ANC < 500/mm^3$) as necessary to keep $ANC > 1000/mm^3$.

2.5.3.4 Blood products

See Section 2.5.1.4 for use of blood products.

2.5.3.5 Post-transplant immunization schedule

Once a patient is off all immunosuppressive therapy or has evidence of T cell function (approximately one-year post allogeneic transplant), immunizations may be given in keeping with the BMT CTN MOP and local institutional practice.

2.5.3.6 Post-transplant donor cellular infusions (DCI)

DCI may be given to patients for tumor progression but patients receiving DCI will be considered a failure for the primary study endpoint of progression free survival. Prior to initiating DCI, the indication must be reviewed with the Medical Monitor or one of the Protocol Chairs.

2.6 Participant Risks

Recipients of transplants incur risks from pre-transplant conditioning and post-transplant therapy, which must be weighed against the risk of the disease for which the transplant is prescribed. Major risks following transplantation include: 1) Infection, which can be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population; 2) GVHD, either acute or chronic in nature, may occur following allogeneic transplantation. The degree of GVHD varies from mild cutaneous reactions to extensive widespread and systemic involvement of skin, liver, and gastrointestinal tract. Probably due to a direct association, the incidence of fatal infection is greater in patients developing GVHD; 3) Graft Failure can occur and is associated with a high-risk of mortality; 4) End Organ Damage of all or any of the major organs may occur as a result of reactions to drugs (e.g., melphalan antibiotics, anti-fungal medications, MMF, CSA, etc.), and as a result of destructive processes (e.g., infection, GVHD, etc.), and may have a fatal outcome; 5) Relapse of MM may occur, especially in patients with advanced disease status at time of treatment; 6) Unknown Toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain. Brain damage can result in severe loss of cognitive or neurologic function; and, 7) Death.

2.7 Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 with BMT specific definitions when appropriate.

2.7.1 Total Body Irradiation (TBI)

TBI may cause nausea, vomiting, diarrhea, temporary hair loss, and painful swelling of the salivary glands for a few days. The dose of TBI in this protocol is approximately one-sixth of that used in standard transplant protocols. Therefore, these side effects most likely will be milder and severe acute side effects are not expected. It is also expected that the risk of infertility will be lower than standard transplant that uses higher doses of TBI. The risk of secondary malignancies after the low dose TBI is yet to be determined.

2.7.2 Mycophenolate Mofetil (MMF)

MMF is supplied in 250 mg hard gelatin capsules. Capsules can be stored at room temperature.

1. Mycophenolate mofetil has not been extensively studied in patients after marrow transplantation. Previous clinical studies in patients after renal allografting suggested that the principal adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, vomiting and a higher incidence of certain viral infections (CMV, VZV, Herpes Simplex). Patients will be monitored for the development of these complications.
2. Studies in solid organ transplant recipients suggest that MMF may be associated with vomiting and diarrhea, decline in hematocrit and white blood cell count, and infection. In the setting of marrow transplantation, several etiologic factors may contribute to alterations in GI and hematologic parameters. MMF has an increased incidence of digestive system adverse events, including GI tract ulceration and hemorrhage (3% of patients receiving MMF). Gastrointestinal tract perforations have rarely been observed. Most patients in these studies were also on other drugs known to be associated with these complications. Up to 2% of patients receiving MMF for prevention of rejection developed severe neutropenia (ANC <500/mm³). The development of neutropenia may be related to MMF itself, concomitant medications, viral infections or some combination of these causes.

MMF dose adjustments will be made if clinically indicated if, in the opinion of the attending physician, no other cause is thought to be responsible for the abnormality. These adjustments should be discussed with the Medical Monitor or one of the Protocol Chairs. Dose adjustments are described in Section 2.4.4.2.

2.7.3 Dexamethasone

Dexamethasone may cause nausea, vomiting, insomnia, agitation, weight gain, fluid retention, hypertension, metabolic disturbances (increased glucose, increased potassium, decreased bone density), increased risk of infection, gas and heartburn. Sometimes it may aggravate underlying peptic ulcer disease and may cause gastrointestinal bleeding. Dexamethasone may also cause secondary hypertension and hyperglycemia or may aggravate the underlying hypertension and diabetes. All toxicities will be scored according to the modified NCI toxicity criteria.

2.7.4 Thalidomide

1. Neurologic: Somnolence, dizziness, confusion, tremor, loss of co-ordination, paresthesia and numbness.
2. Gastrointestinal: Constipation, nausea, vomiting and stomatitis.
3. Constitutional: Weakness, weight loss, fever.
4. Reproductive: Severe birth defects.

Thalidomide will be withheld for any Grade 3 toxicity or higher attributable to thalidomide and not reversible or easily managed by standard supportive care such as antiemetics, antipyretics and intravenous fluids or for any serious medical complication of the transplant to which thalidomide is judged to be contributing. If such toxicity was not considered life-threatening, the thalidomide may be resumed at 50% of the original dose. Escalation of thalidomide dose should be considered after one week of therapy on the reduced dose. Recurrence of similar toxicities at Grade 3 or 4 despite dose reduction will be an indication for discontinuation of thalidomide and reinstitution will not be permitted. (See Section 2.4.3.3 for details of dose modification.)

2.7.5 G-CSF

1. Musculoskeletal: In clinical trials, medullary bone pain was the only consistently observed adverse event attributed to G-CSF and was reported in approximately 24% of patients across all indications. The bone pain was generally mild to moderate in severity and controllable in most patients with non-narcotic analgesia; infrequently, bone pain was severe enough to require narcotic analgesia.
2. Cardiovascular: Rarely fluid retention; transient hypotension; pericardial effusion.
3. Dermatologic: Local inflammation at the injection site; rarely cutaneous vasculitis.
4. Other: Transient, mild to moderate elevations of uric acid, LDH, alkaline phosphatase and leukocyte alkaline phosphatase when given with cytotoxic drugs.
5. Rarely, normal donors receiving G-CSF have experienced swelling of their spleen, and on occasion, internal bleeding from the spleen or rupture of the spleen. Bleeding from or rupture of the spleen can present as malaise, flank or abdominal pain, or loss of consciousness from low blood pressure. Rupture of the spleen can be very serious and is potentially life threatening. Management of this problem could require blood transfusions or surgery.

2.7.6 Cyclosporine

1. Hematologic: Leukopenia, anemia, thrombocytopenia.
2. Renal: Renal dysfunction. It is not unusual for serum creatinine and BUN levels to be elevated during CSA therapy. Overt nephrotoxicity early after transplantation is characterized by rapidly rising BUN and creatinine. This form is usually responsive to dosage reduction. Mild nephrotoxicity, generally noted 2-3 months after transplant is often responsive to dose reduction. A form of chronic progressive cyclosporine-associated nephrotoxicity characterized by serial deterioration in renal function and morphologic changes in the kidneys, will often fail to show a reduction in rising serum creatinine despite a decrease or discontinuation of cyclosporine.
3. Gastrointestinal: Gum hyperplasia, oral thrush, diarrhea, nausea, vomiting and abdominal discomfort.
4. Pulmonary: Sinusitis.
5. Skin: Hirsutism, acne.

6. General Nervous System: Tremor, convulsion, headache. Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy.
7. Cardiovascular: Hypertension (usually mild to moderate), cramps.
8. Other: Flushing, increased low-density lipoproteins. A few cases of anaphylactoid reactions have been reported in patients receiving Sandimmune injection, believed to be due to the Cremophor EL used as the vehicle for IV formulation. Close monitoring of patients receiving IV infusion is necessary.

2.7.7 High-dose Melphalan

High-dose melphalan is well tolerated by patients when they are supported with blood component transfusions, PBSC transplantation and broad-spectrum antibiotics. The duration of profound bone marrow suppression decreases with the use of PBSC transplantation and colony stimulating factors. Gastrointestinal toxicity, which includes potentially severe stomatitis, esophagitis and severe diarrhea, can become the dose-limiting toxicity in these patients. The majority of patients receiving high-dose melphalan will require parental narcotics for mucositis related pain, IV hydration and potentially IV alimentation and broad spectrum IV antibiotics. Despite moderate to severe symptoms in many patients, recovery is the norm, coincident with recovery of granulocytes. Other toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, and allergic reaction.

CHAPTER 3

3. STUDY ENDPOINTS AND DEFINITIONS

3.1 Definition of High Risk vs. Standard Risk Myeloma

Multiple myeloma patients on the study will be stratified for the purposes of statistical analysis into high risk and standard risk groups. The primary analysis will include only standard risk patients. It is expected that standard risk patients will account for 85% of the patients on the study. Secondary analyses will be conducted on the high risk group.

3.1.1 High Risk Myeloma Patients

High risk myeloma patients on this protocol are defined as having a serum Beta 2 microglobulin level > 4 mg/L and /or abnormalities of chromosome 13 on standard metaphase karyotype analysis at anytime prior to transplant.

3.1.2 Standard Risk Myeloma Patients

Standard Risk myeloma patients on this protocol have a serum beta 2 microglobulin \leq 4 mg/L and normal cytogenetics by standard metaphase karyotype analysis. Patients with no karyotype analysis or failed analysis are assumed to not have chromosome 13 abnormalities.

3.2 Definition of Disease Status

Patients at each data collection period are classified into one of the following states. Until progression, all disease classifications are relative to the patient's pre-transplantation disease status.

1. Complete Response (CR)

CR requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation maintained for a minimum of six weeks. The presence of new monoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.
- No increase in size or number of lytic bone lesions on radiological investigations, if performed (development of a compression fracture does not exclude response).
- Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial response (see below), providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

2. Continuing Complete Response (CCR)

CR continuing from CR prior to conditioning.

3. Partial Response (PR)

PR requires the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of six weeks.

OR

- Reduction in 24 hour urinary light chain excretion either by greater than or equal to 90% *or* to < 200 mg/24 hours, maintained for a minimum of six weeks, in light chain disease.
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in size or number of lytic bone lesions on radiological investigations, if performed (development of a compression fracture does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as minimal response (see below), providing the remaining criteria satisfy the requirements for minimal response.

4. Minimal Response (MR)

Minimal response requires **all** of the following:

- 25-49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of six weeks.

OR

- 50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hours, maintained for a minimum of six weeks.
- 25-49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in the size or number of lytic bone lesions on radiological investigations, if performed (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

5. Stable Disease (SD)

- Stable values (within 25% above or below value at time response is assessed) maintained for at least three months.

3.3 Relapse or Progressive Disease (PD)

3.3.1 Relapse

Relapse from CR requires **one or more** of the following:

- Reappearance of serum or urine paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further consecutive investigation within 2-4 weeks and excluding oligoclonal immune reconstitution.
- Greater than or equal to 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions. Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca > 11.5 mg/dL or > 2.8 mmol/L) not attributable to any other cause.

3.3.2 Progressive Disease (PD)

For patients not in CR, progressive disease requires **one or more** of the following:

- > 25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL and confirmed by at least one repeated investigation.
- > 25% increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hours and confirmed by at least one repeated investigation.
- > 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca > 11.5 mg/dL or > 2.8 mmol/L) not attributable to any other cause.

3.4 Primary Endpoint to be Compared Between Tandem Autologous Transplant Recipients Randomized to Maintenance Therapy vs. Observation Following Their Second Transplant

3.4.1 Three Year Progression Free Survival (PFS)

The primary endpoint to be compared between the two arms is 3-year PFS. Patients are considered a failure for this endpoint if they die or if they progress or relapse. The time to this event is the time from initiation of the first dose of high dose melphalan to relapse/progression, death, initiation of non-protocol anti-myeloma therapy, loss to follow-up or the end of the study, whichever comes first.

Patients initiating non-protocol anti-myeloma therapy are considered a failure of progression-free survival on this protocol.

3.5 Secondary Endpoints to be Compared Between Tandem Autologous Transplant Recipients Randomized to Maintenance Therapy vs. Observation Following Their Second Transplant

3.5.1 Current Myeloma-Stable Survival

This function is an estimate of the chance that a patient is alive with stable disease at a given point in time. Patients are said to have stable disease if they are in the state CR, PR, MR, or SD relative to their disease state at the most recent prior ascertainment of disease status. Unlike PFS where patients are counted as an event at the time of first progression/relapse, this outcome measure takes into account subsequent disease control/response that occurs following the second transplant. A similar approach has been used in analyzing the role of DLI following allogeneic transplants for chronic myelogenous leukemia where relapse is expected to be frequent but subsequent disease control is also expected after treatment of relapse with DLI⁶⁸. A multi-state model will estimate this with inputs being the patient's disease status at each potential examination time.

3.5.2 Three Year Overall Survival

The event is death from any cause. The time to this event is the time from initiation of the first dose of high dose melphalan to death, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation are considered censored.

3.5.3 Incidence of Progression

Patients are considered experiencing an event when they progress. Deaths without progression are considered as a competing risk. Patients alive with no history of progression are censored at time of last follow-up. Patients initiating non-protocol anti-myeloma therapy are considered to have progressed on this protocol.

3.6 Tertiary Endpoints to be Compared Between Tandem Autologous Transplant Recipients Randomized to Maintenance Therapy vs. Observation Following Their Second Transplant

3.6.1 CR and CR+PR Rates at Two and Twelve Months

The numerator for the estimate of the CR rate counts patients who are alive and in CR at two (or twelve) months post second autotransplant, and the denominator counts patients who have been followed for two (or twelve) months, regardless of survival or remission status. The numerator for the estimate of the CR+PR rate counts patients who are alive and in CR or PR at two (or twelve) months. The proportion of patients in CR and PR will be compared between treatment arms using standard techniques for categorical data.

3.6.2 Time to CR and CR+PR

Event is CR (CR or PR). The time to event is the time to CR (CR or PR). Patients who die in a state other than CR (CR or PR) are considered as failing from a competing risk. Patients alive and not in CR (CR or PR) at the time of last observation are considered as censored for this event.

3.6.3 Time to Off-study Therapy

This event is the initiation of anti-myeloma therapy other than those defined by the protocol treatment arms. Patients who die without initiation of an off-study therapy will be considered as experiencing a competing risk. Patients who do not receive an off-study therapy but are alive at the end of the study will be considered censored.

3.6.4 Quality of Life

The FACT-BMT⁶⁹ version 4.0 instrument is comprised of a general core questionnaire, the FACT-G, that evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the FACT-BMT data.

The MOS SF-36^{70, 71} instrument is a general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data.

HQL will be compared between the two groups utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. The questionnaires will be scored according to standard procedures and the quality of life will be compared at 3 years following the initiation of the first autologous transplant. The self report questionnaires will be performed prior to the first and second transplant, and at 6 months, 1, 2 and 3 years post second transplant. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial.

3.6.5 Incidence of Toxicities Grade \geq 3 According to the CTCAE Version 3.0

Grade \geq 3 toxicities will be tabulated for each patient at set intervals over the course of the study. The proportion of patients developing toxicity will be compared between treatment arms.

3.6.6 Incidence of Infections

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each patient. The proportion of patients in each treatment arm with these infections will be compared.

3.6.7 Drop Out Rate From Maintenance Therapy

Compliance with maintenance therapy will be assessed by collecting data from unused pills returned to the clinic. Data on the maximum dose tolerated by the patient will be collected at scheduled clinic visits.

3.6.8 Duration of Maintenance Therapy

The duration of maintenance therapy will be established from the date of initiation of therapy to the date of permanent discontinuation. If the medication is withdrawn through a series of dose reductions, the date of the last dose upon completion of the taper will be used.

3.7 Primary Endpoint to be Compared Between Tandem Autologous Transplant Recipients and Tandem Autologous + Non-myeloablative Matched Sibling Allogeneic Transplant Recipients

3.7.1 Three-Year Progression Free Survival (PFS)

The primary endpoint is three-year PFS. Patients are considered a failure for this endpoint if they die or if they progress or relapse. The time to this event is the time from initiation of the first dose of high dose melphalan to relapse/progression, death, initiation of non-protocol anti-myeloma therapy, loss to follow-up or the end of the study, whichever comes first.

Patients initiating non-protocol anti-myeloma therapy are considered a failure of progressive-free survival on this protocol.

3.8 Secondary Endpoints to be Compared Between Tandem Autologous Transplant Recipients and Tandem Autologous + Non-myeloablative Matched Sibling Allogeneic Transplant

3.8.1 Current Myeloma-Stable Survival

This function is an estimate of the chance that a patient is alive with stable disease at a given point in time. Patients are said to have stable disease if they are in the state CR, PR, MR, or SD relative to their disease state at the most recent prior ascertainment of disease status. Unlike PFS where patients are counted as an event at the time of first progression/relapse, this outcome measure takes into account subsequent disease control/response that occurs following the second transplant (see Section 3.4.1).

3.8.2 Three-Year Overall Survival

The event is death from any cause. Patients alive at the time of last observation are considered censored.

3.8.3 Incidence of Progression

Patients are considered experiencing an event when they progress. Deaths without progression are considered as a competing risk. Patients alive with no history of progression are censored at time of last follow-up.

Patients initiating non-protocol anti-myeloma therapy are considered to have progressed on this protocol.

3.9 Tertiary Endpoints to be Compared Between Tandem Autologous Transplant Recipients and Tandem Autologous + Non-myeloablative Matched Sibling Allogeneic Transplant

3.9.1 CR and CR+PR Rates at Two and Twelve Months

The numerator for the estimate of the CR rate counts patients who are alive and in CR at two (or twelve) months post second transplant, and the denominator counts patients who have been followed for two (or twelve) months, regardless of survival or remission status. The numerator for the estimate of the CR+PR rate counts patients who are alive and in CR or PR at two (or twelve) months. The proportion of patients in CR and PR will be compared between treatment arms using standard techniques for categorical data.

3.9.2 Time to CR and CR+PR

Event is CR (CR or PR). The time to event is the time to CR (CR or PR). Patients who die in a state other than CR (CR or PR) are considered as failing from a competing risk. Patients alive and not in CR (CR or PR) at the time of last observation are considered as censored for this event.

3.9.3 Time to Second Transplant

The event is the initiation of the conditioning regimen for the second transplant (non-myeloablative allotransplant for patients with donors, second high dose melphalan autologous transplant for other patients). Patients who die without initiation of their second transplant will be considered as experiencing a competing risk. Patients who do not receive an off-study transplant but are alive at the end of the study will be considered censored.

3.9.4 Time to Off-study Therapy

This event is the initiation of anti-myeloma therapy other than those defined by the protocol arms. Patients who die without initiation of an off-study therapy will be considered as experiencing a competing risk. Patients who do not receive a second therapy but are alive at the end of the study will be considered censored.

3.9.5 Quality of Life

The FACT-BMT⁶⁹ version 4.0 instrument is comprised of a general core questionnaire, the FACT-G, that evaluates the HQL of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the FACT-BMT data.

The MOS SF-36^{70, 71} instrument is a general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data.

HQL will be compared between the two groups utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. The questionnaires will be scored according to standard procedures and the quality of life will be compared at 3 years following the initiation of the first autologous transplant. The self report questionnaires will be performed prior to the first and second transplant, and at 6 months, 1, 2 and 3 years post second transplant. Only English and Spanish speaking patients are eligible to participate.

3.10 Tertiary Endpoints that Only Apply to Allograft Recipients

The following endpoints will be used to describe outcomes associated with only the recipients of the HLA-matched sibling allograft. They will not be compared between the two treatment arms.

3.10.1 Incidence of Primary and Secondary Graft Failure

Engraftment is defined as achieving > 5% donor chimerism by Day 56.

Primary graft failure is defined as a donor chimerism < 5% by Day 56 post-transplant. Methodology of chimerism is as described in the BMT CTN MOP.

Secondary graft failure is defined by documented engraftment followed by loss of graft as defined by donor chimerism < 5% as demonstrated by a chimerism assay.

3.10.2 Incidence and Severity of Graft-Versus-Host-Disease (GVHD)

See the BMT CTN MOP for definitions of acute and chronic GVHD.

3.11 Safety Monitoring Endpoints

3.11.1 Treatment-related Mortality

There are regimen-specific Treatment-related Mortality (TRM) monitoring plans for each of the three treatment arms. TRM is defined as death occurring in a patient from causes other than relapse or progression. Individuals who relapse or progress are censored for the event of TRM.

3.11.2 Regimen-related Toxicity

There are two regimen-related toxicity monitoring plans for each of the three treatment arms. The rates of deep vein thrombosis, sensory neuropathy, renal and hepatic toxicities will be monitored. The occurrence of one of these toxicities is considered an event, even if the condition reverses. Individuals who die are censored for the event of regimen-related toxicity.

1. Deep vein thrombosis, defined as grade III or higher toxicity from the CTCAE Version 3.0, under the adverse event type thrombosis/ thrombus/embolism.
2. Sensory neuropathy, defined as grade III or higher toxicity from the CTCAE Version 3.0, under the adverse event type neuropathy: sensory.
3. Renal toxicity is defined as use of dialysis.
4. Hepatic toxicity, defined as grade III or higher toxicity from the CTCAE Version 3.0, under the adverse event type bilirubin (hyperbilirubinemia).

Monitoring will be performed monthly as described in Chapter 5.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1 Enrollment Procedures

4.1.1 Screening and Eligibility Procedures

Patients will be registered using the Advantage Electronic Data Capture (AdvantageEDCSM) system. Southwest Oncology Group (SWOG) centers should follow instructions in Section 4.1.2 **prior** to following the instructions below. The following procedures should be followed:

1. An authorized user at the clinical center completes a screening form with demographic and primary eligibility screening questions. The eligibility screening includes a question confirming that the patient signed the informed consent form and that they have an adequate autologous graft available to them.
2. If the patient is eligible, a study number is generated.
3. A visit schedule based on transplant date is available for printing and is referred to as ‘Segment A Follow-up.’
4. The clinical center draws and HLA types blood samples from the patient and sibling(s) as soon as possible after initial evaluation to determine the availability of an HLA-matched sibling donor. If possible, this testing will be complete prior to the first autologous transplant but it is expected that full donor evaluations will not always be possible to complete by this time. Patient samples for HLA-testing **MUST** be drawn prior to the first autologous transplant and potential donor samples must be drawn no later than three weeks after the first autologous transplant.
5. Either at the time of first registration or as soon as evaluation of all potential donors is complete, whichever comes first, an authorized user at the clinical center completes a secondary eligibility form indicating whether or not the patient has an HLA-identical sibling donor. This form must be completed for every patient, even if the patient has become medically ineligible for a second transplant by the time the donor evaluation is complete. If an HLA-matched sibling is available, the donor and recipient HLA typing information is completed on the eligibility form. If an HLA-matched sibling is not available, the Sibling Information Form is required to obtain information pertaining to ineligibility of all siblings (non-donors, including those who were HLA typed and those who were not typed due to medical reasons). Patients with a donor are then assigned to the auto-allo arm. Patients without an HLA-matched sibling donor are then randomized to either tandem autologous followed by one year of observation or tandem autologous followed by one year of maintenance therapy.
6. After recovery from the 1st autologous transplantation (at least 60 days post first transplant), an authorized user at the clinical center completes the Post Autologous Transplant Checklist confirming that the patient has recovered and is eligible for either a non-myeloablative allogeneic transplant or second autologous transplant.

7. If the patient is eligible, the treatment plan is continued.
8. A visit schedule based on the second transplant date is displayed for printing and is referred to as ‘Segment B Follow-up.’
9. After recovery from the second autologous transplant (at least 60 days post second transplant), an authorized user at the clinical center completes the Post Tandem Autologous Checklist for ALL patients biologically assigned to the Tandem Autologous ± Maintenance Therapy arm. Completion of the Post-tandem Autologous Checklist will ensure comparable baseline data are collected for patients randomized to either one year of maintenance therapy with dexamethasone and thalidomide or one year of observation. The Post-tandem Autologous Checklist also confirms that the patient has recovered and is eligible to begin receiving one year of dexamethasone and thalidomide maintenance therapy. The randomization assignment (one year of observation or one year of dexamethasone and thalidomide maintenance therapy) will be revealed after the Post-tandem Autologous Transplant Checklist is completed.
10. If the patient is eligible, the visit schedule referred to as ‘Segment B Follow-up’ is continued.

4.1.2 SWOG Patient Registration Procedures

Patients from Southwest Oncology Group (SWOG) Member, CCOP and approved Affiliate institutions must be registered through the SWOG Data Operations Center in Seattle using the SWOG Web Registration System. Affiliate institutions not approved to register patients directly with the Data Operations Center must register through their Member institution. The Data Operation Center will request information from the SWOG Registration Form. The institution must have these documents completed entirely prior to registering the patient in the SWOG Web Registration System. In addition, the Data Operations Center will collect stratification information, will request the date informed consent and HIPAA authorization were obtained, and will obtain the date of IRB approval for each entry.

4.2 Study Monitoring

4.2.1 Follow-up Schedule

The Follow-up Schedule for scheduled study visits is outlined in Tables 4.2.1a, 4.2.1b and 4.2.1c. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook.

Follow-up Visits: Follow-up visits are based on segments. Segment A is defined as the period from high-dose melphalan administration until conditioning for the second transplant. Segment B is defined as the period after second transplantation including maintenance therapy (if applicable).

Table 4.2.1a -- Follow-up Schedule – Segment A

Study Visit	Target Day (± 7 Days Post-1st Transplant)
4 week	28 days
100 day ¹	100 days

¹ If patient has not received second transplant

**Table 4.2.1b -- Follow-up Schedule – Segment B
Allogeneic Transplant Patients**

Study Visit	Target Day (± 7 Days Prior to Day 100 Post Second Therapy) (± 28 Days after Day 100 Post Second Therapy)
1 week ^{1,2}	7 days
2 week ^{1,2}	14 days
3 week ^{1,2}	21 days
4 week ^{1,2}	28 days
5 week	35 days
6 week	42 days
7 week	49 days
8 week	56 days
9 week	63 days
10 week	70 days
11 week	77 days
12 week	84 days
13 week	91 days
14 week	98 days
120 day (4 months)	120 days
6 month	180 days
9 months	270 days
12 month	365 days
18 month	540 days
24 month	730 days
30 month	900 days
36 month	1,095 days

¹ Chemistry panel required twice per week.

² Refer to Section 4.2.4.4 for frequency of follow-up for CBC.

**Table 4.2.1c -- Follow-up Schedule -- Segment B
Tandem Autologous Transplant Patients**

Study Visit	Target Day (± 7 Days Prior to Day 100 Post Second Therapy) (± 28 Days after Day 100 Post Second Therapy)
1 week ^{1,2}	7 days
2 week ^{1,2}	14 days
3 week ^{1,2}	21 days
4 week ^{1,2}	28 days
8 week	56 days
Day 60	60 days
9 week ³	63 days
10 week ³	70 days
11 week ³	77 days
12 week	84 days
Day 100	100 days
16 week ³	112 days
20 week ³	140 days
24 week ³	168 days
6 month	180 days
28 week ³	196 days
32 week ³	224 days
36 week ³	252 days
9 months	270 days
40 week ³	280 days
44 week ³	308 days
48 week ³	336 days
52 week ³	364 days
12 month	365 days
56 week ³	392 days
18 month	540 days
24 month	730 days
30 month	900 days
36 month	1,095 days

¹ Chemistry panel required twice per week.² Refer to Section 4.2.4.4 for frequency of follow-up for CBC.³ For patients taking dexamethasone/thalidomide maintenance therapy.

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook. Forms that are not entered into the web-based data entry system within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the web based data entry system and integrated into the DCC's master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths: Recipient Death Information must be entered into the web-based data entry system within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in the web-based data entry system.

IBMTR Data Reporting: All transplant centers will be required to **pre-register** patients with the IBMTR for all transplants performed at their center whether or not they enroll in a BMT CTN Protocol. In addition, the transplant center must complete the IBMTR TED Day 100 Report Form (including the Core, Graft and Disease Inserts) and IBMTR TED Follow-up Form (including the Core and Disease Inserts) yearly for all patients enrolled in BMT CTN protocols. IBMTR forms will be submitted directly to the IBMTR at the times specified on the Forms Submission Schedule.

4.2.2 Weekly GVHD Monitoring Post Non-myeloablative Allogeneic Transplant

GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day 100 post-transplant for GVHD. After Day 100, patients will be assessed at each study visit for the presence of GVHD.

4.2.3 Adverse Event Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule.

4.2.4 Patient Assessments

Tables 4.2.5 and 4.2.5a summarize patient clinical assessments over the course of the study. All assessments prior to and after both transplants are considered standard of care.

4.2.4.1 Evaluations prior to the first autologous transplantation

The following observations must be determined ≤ 12 weeks prior to initiation of high-dose melphalan either before or after initiation of mobilization therapy depending on transplant center standard of practice. If these tests are done prior to mobilization therapy and there is clinical suspicion of cardiac or pulmonary toxicity following mobilization therapy, these tests must be repeated prior to the initiation of high-dose melphalan.

1. EKG.
2. LV ejection fraction by MUGA, echocardiogram or MRI according to local institutional practice.
3. DLCO, FEV1 and FVC (or O₂ saturation).

Infectious disease testing, including CMV titer, hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex titre, syphilis, HIV and HTLV1 antibody, should be determined in accordance with FACT guidelines (i.e., **30 days prior to the initiation of mobilization therapy**). If there is clinical suspicion of new infection, tests must be repeated prior to the initiation of high-dose melphalan.

The following observations are to be determined ≤ 8 weeks prior to the initiation of high-dose melphalan either before or after initiation of mobilization therapy depending on transplant center standard of practice.

1. History, physical examination, height and weight.
2. CBC with differential and platelet count, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT, sodium, magnesium, potassium, chloride and CO₂.
3. Baseline Disease Evaluation
 - a) Skeletal survey to include cranium, axial skeleton and proximal long bones.
 - b) Unilateral bone marrow biopsy and aspirates to pathology, aspirate to cytogenetics for standard metaphase karyotype analysis.
4. Laboratory Disease Evaluation
 - a) Quantitative serum immunoglobulin levels.
 - b) Serum protein electrophoresis (SPEP).
 - c) 24 hour urine collection to determine creatinine clearance and protein excretion, urine protein electrophoresis (UPEP). Creatinine clearance may be calculated.
 - d) Immunofixation of serum protein and urine protein regardless of SPEP and UPEP results.
 - e) Serum beta 2 microglobulin (B2M serum).
5. One vial (10cc) of nucleated cells and one vial (10cc) serum from patient's peripheral blood for future testing.
6. Flow cytometry analysis of autologous graft per the Graft Characterization section of the BMT CTN MOP.

The following observations should be determined ≤ 4 weeks prior to the initiation of high-dose melphalan before or after mobilization depending on transplant center standard of care.

1. Pregnancy test (for women of childbearing potential). Women are of childbearing potential unless they have had a hysterectomy or had no menses or have been post-menopausal for at least 24 months.
2. Health quality of life assessment (for English and Spanish speaking patients only).

The Karnofsky performance score should be determined ≤ 2 weeks prior to the initiation of high-dose melphalan.

Samples for HLA typing should be drawn from the patient and sibling(s) and typed as soon as possible after initial evaluation to determine the availability of an HLA-matched sibling donor. If possible, this testing should be complete prior to the first autologous transplant but it is expected that it will not always be possible to complete full donor evaluations by this time. Patient samples for HLA-testing MUST be drawn prior to the first autologous transplant and potential donor samples must be drawn no later than three weeks after the first autologous transplant. Testing MUST be complete prior to the second transplant. HLA Class I typing can be done by serologic or DNA methods. HLA Class II typing must be done using DNA methodology.

4.2.4.2 Post first autologous transplant

A toxicity assessment will be done at four weeks post first autologous transplant.

4.2.4.3 Evaluations prior to the second transplant (autologous or matched-sibling allogeneic)

The following observations will be done ≤ 4 weeks prior to initiation of conditioning for the second transplant (auto or allo). Observation 10 is required for the allogeneic arm only.

1. History, physical examination, height and weight.
2. Pregnancy test (for women of childbearing potential). Women are of childbearing potential unless they have had a hysterectomy or had no menses or have been post-menopausal for at least 24 months.
3. Karnofsky performance score.
4. CBC with differential, platelet count, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT, sodium, magnesium, potassium, chloride and CO₂.
5. Chest X-ray.
6. LV ejection fraction (if clinically significant cardiac symptoms/signs develop after the first autologous transplant).
7. DLCO, FEV1 and FVC (or O₂ saturation).

8. Laboratory Disease Evaluation
 - a) Quantitative serum immunoglobulin levels.
 - b) Serum protein electrophoresis (SPEP).
 - c) 24 hour urine collection to determine creatinine clearance and protein excretion, urine protein electrophoresis (UPEP).
 - d) Immunofixation of serum protein and urine protein regardless of SPEP and UPEP results.
 - e) Serum beta 2 microglobulin (B2M serum).
9. Unilateral bone marrow biopsy and aspirates to pathology only to confirm complete responses based on clinical and laboratory data. Bone marrow aspirate to cytogenetics only if previously documented abnormal cytogenetics.
10. Heparinized peripheral blood samples (10cc) from all patients on the allogeneic arm for chimerism assays.
11. Flow cytometry analysis of allogeneic graft per the Graft Characterization section of the BMT CTN MOP.
12. One vial (10cc) of nucleated cells and one vial (10cc) serum from patient's peripheral blood for future testing.
13. Health quality of life assessment (for English and Spanish speaking patients only).

4.2.4.4 Post second transplant evaluations

Post second autologous transplant for tandem autologous transplant group:

1. CBC twice per week until Day 28 (or four weeks), then at 8 weeks, 12 weeks, 6 months, one year, and then yearly until three years post-transplant.
2. Comprehensive chemistry panel defined as CBC with differential and platelet count, creatinine, bilirubin, alkaline phosphatase, ALT, magnesium, sodium, potassium, chloride, CO₂ twice a week until Day 28 (or four weeks) and then at 8 weeks, 12 weeks, 6 months, one year and then yearly until three years post-transplant.
3. Toxicity assessments at 4, 8, 12 weeks, 6 months, one year, and every 6 months until three years post-transplant.
4. One vial (10cc) of nucleated cells and one vial (10cc) serum from patient's peripheral blood for future testing at 8 weeks, 6 months, 9 months, one year and then every 6 months post-transplant.
5. Obtain the following laboratory data at 8 weeks*, 6 months, 9 months, one year and every 6 months until three years post-transplant.
 - a) Quantitative serum immunoglobulin levels.
 - b) Serum protein electrophoresis (SPEP).
 - c) 24-hour urine collection to determine protein excretion, urine protein electrophoresis (UPEP).

- d) Immunofixation of serum protein and urine protein regardless of SPEP and UPEP results.
- e) Serum beta 2 microglobulin (B2M serum).

*For tandem autologous patients, this evaluation may be replaced by the disease assessment required just prior to initiation of maintenance therapy. If the initiation of maintenance therapy is predicted to be delayed beyond three months post second transplant, a disease assessment at eight weeks must be carried out.

6. Skeletal survey will be repeated at 6 months and one year post second transplant and then yearly until three years post-transplant.
7. Bone marrow aspirate and biopsy to pathology to confirm complete responses based on clinical and laboratory data. At 8 weeks and 6 months, a bone marrow aspirate is sent to cytogenetics only if there has been previously documented abnormal cytogenetics. All patients are to have samples sent for cytogenetics at one year and then yearly until three years post-transplant for standard metaphase karyotype analysis. Bone marrow biopsy should be repeated at any time point to confirm relapsed MM.
8. Health quality of life assessment at 6 months, 1 year and then yearly until three years post-transplant (for English and Spanish speaking patients only).

Post non-myeloablative transplantation:

1. History and physical exam to assess GVHD weekly until Day 100 post-transplant, then at 4 months, 6 months, one year and then yearly until three years post-transplant. GVHD evaluation and grading to be in keeping with BMT CTN MOP.
2. CBC at least twice a week from Day 0 until ANC > 500 for 2 days after nadir reached. Thereafter CBC twice per week until Day 28 (or 4 weeks), then at 8 weeks, 12 weeks, 6 months, one year and then yearly until three years post-transplant.
3. Comprehensive chemistry panel defined as CBC with differential and platelet count, creatinine, bilirubin, alkaline phosphatase, ALT, magnesium, sodium, potassium, chloride, CO₂ twice a week until Day 28 (or four weeks) and then at 8 weeks, 12 weeks, 6 months, one year and then yearly until three years post-transplant.
4. Heparinized peripheral blood (10cc) for quantitation of chimerism on Weeks 4, 8, and 12, 6 months and one year post-transplant.
5. One vial (10cc) of nucleated cells and one vial (10cc) serum from patient's peripheral blood for future testing at 8 weeks, 6 months, 9 months, one year and then every 6 months until three years after post-transplant.
6. Toxicity assessments at 4, 8, 12 weeks, 6 months, one year and every 6 months until three years post-transplant.
7. Obtain the following laboratory data at 8 weeks, 6 months, 9 months, one year and every 6 months until three years post-transplant.
 - a) Quantitative serum immunoglobulin levels.
 - b) Serum protein electrophoresis (SPEP).

- c) 24-hour urine collection to determine protein excretion, urine protein electrophoresis (UPEP).
 - d) Immunofixation of serum protein and urine protein must be done regardless of SPEP and UPEP results.
 - e) Serum beta 2 microglobulin (B2M serum).
8. Skeletal survey will be repeated at 6 months and one year post-allograft and then yearly until three years post-transplant.
 9. Bone marrow aspirate and biopsy for pathology to confirm complete responses based on clinical and laboratory data. At 8 weeks and 6 months, a bone marrow aspirate is sent to cytogenetics only if previously documented abnormal cytogenetics. All patients must send a bone marrow aspirate to cytogenetics at one year, and then yearly until three years post-transplant for standard metaphase karyotype analysis. Bone marrow biopsy should be repeated at any time point to confirm relapsed / progressive MM.
 10. Health quality of life assessment at 6 months, one year and then yearly until three years post-transplant (for English and Spanish speaking patients only).

4.2.4.5 Prior to initiation of dexamethasone + thalidomide for tandem autologous transplant patients randomized to maintenance therapy post second autologous transplant

The following observations will be done ≤ 2 weeks prior to initiation of dexamethasone + thalidomide maintenance therapy. Observation 2 is required 24 hours prior to the initiation of thalidomide.

1. History, physical examination, height and weight.
2. Pregnancy test (for women of childbearing potential) within 24 hours prior to initiation of thalidomide. Women are of childbearing potential unless they have had a hysterectomy or had no menses or have been post-menopausal for at least 24 months.
3. Karnofsky performance score.
4. CBC with differential, platelet count, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT, sodium, magnesium, potassium, chloride and CO₂.
5. Bone marrow aspirate and biopsy for pathology to confirm complete responses based on clinical and laboratory data. Bone marrow aspirate for cytogenetics only if previously documented abnormal cytogenetics.
6. Laboratory Disease Evaluation
 - a) Quantitative serum immunoglobulin levels.
 - b) Serum protein electrophoresis (SPEP).
 - c) 24-hour urine collection to determine creatinine clearance and protein excretion, urine protein electrophoresis (UPEP).
 - d) Immunofixation of serum protein and urine protein regardless of SPEP and UPEP results.

e) Serum beta 2 microglobulin (B2M serum).

4.2.4.6 Post initiation of dexamethasone + thalidomide for tandem autologous transplant patients randomized to maintenance therapy post second autologous transplant

The post second transplant evaluation outlined in Section 4.2.4.4 for the tandem autologous transplant group should be continued. In addition, a pregnancy test (for women of childbearing potential) is required weekly for the first four weeks of maintenance therapy, and then every four weeks until 12 months post initiation of maintenance therapy if the patient's periods are regular or every two weeks if they are not. Women are of childbearing potential unless they have had a hysterectomy or had no menses or have been post-menopausal for at least 24 months.

Refer to Appendix D for the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.TM) dosing and administration procedure for thalidomide.

4.2.5 Required Observations for Donor

Routine pre-allografting work-up in keeping with FACT guidelines, BMT CTN MOP and institutional standard practice of care. Work-up to include the following:

1. HLA typing of heparinized peripheral blood sample to determine if eligible HLA-matched donor. If possible, testing should be complete prior to the first autologous transplant. All potential donor samples must be drawn no later than 3 weeks post first autologous transplant.
2. History, physical examination, height and weight.
3. Pregnancy test (for women of childbearing potential). Women are of childbearing potential unless they have had a hysterectomy or had no menses or have been post-menopausal for at least 24 months.
4. Lab tests: CBC with differential and platelet counts, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT, magnesium, sodium, potassium, chloride, CO₂, hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), CMV titer, herpes simplex, syphilis, HIV and HTLV I serologies and ABO Rh blood typing. If donor has antibodies against red cell antigens of the recipient, the titers will be determined. CBC will be checked prior to and after leukapheresis collection, and thereafter if clinically indicated.
5. Heparinized peripheral blood sample (20 cc) for chimerism assays.
6. Five cryovials, each containing 2-5 x 10⁶ nucleated cells from allograft blood stem cells to be obtained for the central repository per the Graft Characterization section of the BMT CTN MOP.
7. Evaluation of toxicities experienced post initiation of G-CSF.

Donors must be contacted by phone approximately 30 days post initiation of G-CSF for a toxicity evaluation.

Table 4.2.5 -- Pre-autologous Transplant, Pre-second Intervention and Donor Evaluations

Required Studies / Testing	Prior to 1 st Auto Transplant	4 Weeks Post-1st Autologous Transplant	Pre Second Transplant (Auto or Allo) ¹	Prior to Initiation of Maintenance Therapy	Donor
History, Physical Examination, Height and Weight	X		X	X	X
Pregnancy Test ²	X		X	X	X
Karnofsky Performance Score	X		X	X	
CBC with Differential, PLT, Creatinine Clearance ³ , Creatinine, Bilirubin, Alkaline Phosphatase, ALT, Sodium, Magnesium, Potassium, Chloride and CO ₂	X		X	X	X ^{4,5}
CMV Titer, Hepatitis Panel (A, B, C) Herpes Simplex, Syphilis	X				X
HIV/HTLV1 Antibody	X				X
Chest X-ray			X		
EKG	X				
LV Ejection Fraction	X		X ⁶		
DLCO/FEV1/FVC	X		X		
Toxicity Assessment		X			X ¹²
Skeletal Survey	X				
Bone Marrow Aspirate and Biopsy to Pathology; Bone Marrow Aspirate to Cytogenetics	X		X ^{7,8}	X ^{7,8}	
HLA Typing	X				X
Serum Immunoglobulin Levels	X		X	X	
SPEP and Immunofixation	X		X	X	
24 Hr Urine for UPEP and Immunofixation	X		X	X	
B2M Serum	X		X	X	
Chimerism Studies			X ⁹		X
Nucleated Cells ¹⁰					X
Nucleated Cells and Serum ¹¹	X		X		
Health Quality of Life	X		X		
Flow Cytometry Analyzing Graft	X		X ⁹		

¹ To be performed within 4 weeks of intervention.

² For women of childbearing potential.

³ Only required prior to the first autologous transplant and prior to the second autologous or allogeneic transplant.

⁴ Including ABO Rh blood typing. If donor has antibodies against red cell antigens of the recipient, the titers will be determined.

⁵ CBC will be checked prior to and after leukapheresis collection, and thereafter if clinically indicated.

⁶ If clinically significant cardiac symptoms/signs develop post-autograft.

⁷ Bone marrow aspirate to cytogenetics only if previously documented abnormal cytogenetics.

⁸ Unilateral bone marrow biopsy & aspirates to pathology only to confirm complete responses based on clinical & laboratory data.

⁹ For the allogeneic arm only.

¹⁰ Five vials, each containing 2-5 x 10⁶ nucleated cells from the allograft, cryopreserved for central repository.

¹¹ One vial (10cc) of nucleated cells and one vial (10cc) of serum from patient's peripheral blood for future testing.

¹² On Days 5 and 30 (via telephone) post-initiation of G-CSF.

Table 4.2.5.a – Post Second Transplant Evaluations

Study Assessments/ Testing	Weeks Post Second Therapy														Months Post Second Therapy							
	1	2	3	4	5	6	7	8 ⁸	9	10	11	12	13	14	4	6	9	12	18	24	30	36
GVHD Assessments ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X
Pregnancy Test ²	See Section 4.2.4.6																					
CBC ³	See Section 4.2.4.4							X				X				X		X		X		X
Chemistry Panel ⁴	2 x per week ⁷							X				X				X		X		X		X
Chimerism ¹				X			X					X				X		X				
Toxicity				X			X					X				X		X	X	X	X	X
Skeletal Survey																X		X		X		X
Nucleated Cells and Serum ⁹							X									X	X	X	X	X	X	X
BM Aspirate & Biopsy to Pathology, BM Aspirate to Cytogenetics ⁵							X									X		X		X		X
Serum Immunoglobulin Levels							X									X	X	X	X	X	X	X
SPEP and Immunofixation ⁶							X									X	X	X	X	X	X	X
24 Hour Urine for UPEP, Protein Excretion and Immunofixation ⁶							X									X	X	X	X	X	X	X
B2M Serum							X									X	X	X	X	X	X	X
Health Quality of Life																X		X		X		X

¹ For allogeneic transplant arm only.

² For women of childbearing potential.

³ Will be reported on case report form only on Day 28 to document engraftment for allogeneic arm only.

⁴ Chemistry panel: differential and platelet count, creatinine, bilirubin, alkaline phosphatase, ALT, magnesium, sodium, potassium, chloride, and CO₂

⁵ Bone marrow (BM) aspirate and biopsy to pathology to confirm complete responses based on clinical and laboratory data. Bone marrow aspirate to cytogenetics only if previously documented abnormal cytogenetics for week 8 and 6 month assessment. All patients must send a bone marrow aspirate to cytogenetics yearly post second transplant. Bone marrow biopsy should be repeated at anytime point to confirm relapse/progressive MM.

⁶ Regardless of results of SPEP and UPEP.

⁷ Will not be reported on case report form.

⁸ For tandem autologous patients only: This evaluation, except for the toxicity assessment, may be replaced by the disease assessment required just prior to initiation of maintenance therapy (see Table 4.2.5). If the initiation of maintenance therapy is predicted to be delayed beyond 3 months post second transplant, a disease assessment at 8 weeks must be carried out.

⁹ One vial (10cc) of nucleated cells and one vial (10cc) of serum from patient’s peripheral blood for future testing.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1 Study Overview

The overall study design is that of biologic assignment, based on the availability of an HLA-matched sibling, to one of two treatment strategies for MM patients. Patients without an HLA-matched sibling will undergo tandem autologous transplants (auto-auto). Patients with an HLA-matched sibling will undergo an autologous transplant followed by a non-myeloablative allogeneic transplant (auto-allo). In addition, the auto-auto patients will be randomized to either observation or one year of maintenance therapy to begin following their second autologous transplant. The large number of available patients without an HLA-matched sibling enables us to evaluate the role of maintenance therapy following tandem autologous transplants.

Two primary statistical comparisons will be made. To insure a 5% overall Type I Error each of the comparisons is made at the 2.5% level. Comparisons are based on comparing three-year PFS in an intent to treat analysis.

The first comparison is of the two auto-auto arms. The goal here is to assess whether maintenance therapy increases the percent of patients alive without disease progression three years after tandem autologous transplants.

The second comparison is between the auto-auto patients and the auto-allo patients. Here the auto-auto arm depends on the results of the first test. If that test shows no indication of a difference between the two auto-auto arms, then these two arms will be pooled for this comparison. If the first test shows a significant advantage for one of the auto-auto arms, that arm will be used in this comparison. The goal here is to assess whether a graft-versus-myeloma effect associated with the auto-allo strategy results in a better outcome for patients with MM.

5.1.1 Accrual

Accrual will remain open until, at a minimum, 150 standard risk patients are assigned to the auto-allo arm. It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Assuming that patients with HLA-matched sibling donors comprise between 20-30% of eligible patients, approximately 350-600 standard risk patients will likely be accrued to the auto-auto arm during the time it takes to accrue the target number of auto-allo patients.

Both Core and non-Core centers will participate. However, only centers that anticipate enrollment of at least 20 standard risk patients may participate in the trial. This requirement is necessary to ensure that all participating centers will enroll at least two patients on the auto-allo treatment arm.

A center that performs only autologous transplants may participate, provided that all patients who are eligible for the auto-allo arm are referred to the same transplant center for their non-

myeloablative allogeneic transplant. The allogeneic transplant center will serve as the center of record for the purposes of monitoring and analyzing accrual or other study data. This provision will permit fuller participation of the Southwest Oncology Group (SWOG), which is essential to reach the accrual goal.

5.1.2 Biologic Assignment and Randomization

To prevent bias in determining whether donors are eligible or not for donation, and resultant bias in the biological assignment, all available siblings will be HLA-typed and all HLA-matched siblings will be assessed for donation whenever feasible. If a patient is deemed unsuitable to be a donor, the reasoning will be reviewed with the Protocol Chair or the Protocol Officer. Patients with an HLA-matched sibling who is a suitable donor are biologically assigned to the auto-allo arm of the study. Those patients without a suitable HLA-matched sibling donor are assigned to the auto-auto arm. In order to facilitate an intent-to-treat analysis, the biological assignment will take place even if the patient becomes medically ineligible for the second transplant, or must be transplanted on a different treatment arm than their biological assignment would indicate.

The timing of the biological assignment and randomization depends on the need to identify, HLA-type, and assess HLA-matched siblings for their ability to donate an allograft. For most patients, this information will be known at the time of consenting for the trial. For some, the complete evaluation of potential sibling donors may be delayed until during or shortly after the initial autologous transplant. This protocol requires that potential sibling donors be HLA-typed at the earliest opportunity, and that blood for this purpose be drawn no later than three weeks after the initial autologous transplant.

The clinical center will re-register patients once the typing and donor eligibility results are available. At this time, the Coordinating Center will make a biological assignment. Patients with an HLA-matched sibling who is an eligible donor will be assigned to the auto-allo arm, and those without will be assigned to the auto-auto arm, and further randomized to receive either maintenance therapy with thalidomide and dexamethasone, or observation. To facilitate an intention-to-treat analysis, all patients will be assigned to one of the three treatment arms, even if they are no longer medically eligible for the second transplant or post-transplant maintenance therapy.

At a third registration time point, after recovery from the first autologous transplant, the clinical center will complete a third eligibility questionnaire confirming that the patient has recovered and is eligible for either the non-myeloablative allogeneic transplant, or the second autologous transplant, depending on the biological assignment received at the second registration. At a fourth registration time point, the clinical center will complete a final eligibility questionnaire for auto-auto patients, confirming that the patient meets criteria for receipt of thalidomide and dexamethasone.

5.1.3 Intention-to-Treat Principle

In the primary analysis of three-year progression-free survival, patients will be classified according to their original assignment to one of the three treatment arms, even if they are later

found to be medically ineligible to receive a second transplant or thalidomide/dexamethasone maintenance therapy, in accordance with the intent-to-treat principle. Some tertiary analyses such as the assessment of Health Quality of Life, GVHD or the assessment of compliance and duration of maintenance therapy, may be conducted on an as-treated rather than intention-to-treat basis.

5.1.4 Primary Endpoint

The primary endpoint for the study is three-year progression-free survival.

5.2 Statistical Issues Related to Non-randomized Assignment

It is not feasible to randomly assign patients to tandem autologous transplants versus an autologous followed by an allogeneic transplant. A randomized study would entail enrolling only patients potentially eligible for the allogeneic transplant. Based on the experience of transplant physicians and population studies, patients with HLA-matched sibling donors comprise only 20-30% of the patient population. Restricting enrollment to such patients would make it impossible to meet the accrual goals for the study in a timely fashion.

There are many possible sources of heterogeneity in a multi-center clinical trial. In a large randomized trial, chance ensures balance of both known and unknown risk factors across treatment arms. A non-randomized study is vulnerable to differential assignment of higher risk patients to one or the other treatment arm. Potential sources of heterogeneity include: (1) selection of patients to screen for the study; (2) degree of compliance with biological allocation; (3) differences in clinical care practices at participating institutions; (4) baseline disease risk status; (5) baseline factors such as donor/recipient age, donor/recipient gender, and recipient performance status; and (6) time to recovery from auto transplant. The data analytic plan for each of these is discussed briefly.

5.2.1 Selection of Patients to Screen for the Study

Each clinical center is required to register consecutive transplant recipients with the International Bone Marrow Transplant Registry (IBMTR). Data are collected on all transplanted patients, irrespective of whether they are enrolled in a BMT CTN trial. These data will be used to determine if the proportion of allograft recipients, demographic composition, performance status, and disease risk of patients screened and entered in the study are representative of the population of transplant patients treated at that center who were potentially eligible for entry in the study based on disease, disease stage and duration, age and performance score reported on IBMTR registration forms. Comparison of registered and enrolled patients will be performed every four months.

5.2.2 Compliance with Biological Assignment

The procedures for the biological assignment of patients are described in detail in Section 5.1 above. The DCC will query the transplant center for additional data as needed to validate the biological assignment, and to ensure that the patient is correctly classified in the final intent-to-

treat analysis. For example, if the patient did not receive an allograft, the DCC will follow-up on all siblings who were not typed to determine if any were eligible donors. If an HLA-matched sibling is deemed unsuitable to be a donor, the reasoning will be reviewed with the Protocol Chair or the Protocol Officer.

The DCC will monitor each clinical Center's compliance with the biological assignment procedures. It is anticipated that the rates of donor refusal for the allograft transplant will be roughly comparable across institutions, and that the treating physician will refuse to perform the allograft transplant in fewer than 5% of cases based on toxicity of the initial autograft. Refusal rates will be monitored closely over the course of the study.

5.2.3 Effects of Clinical Center

In a multi-center trial, center effects are particularly important given the large number of treatment decisions that are left to the centers. It is important to avoid a study design that confounds center and treatment effects. In a large randomized trial, chance ensures that the ratio of patients assigned to each treatment arm does not vary greatly across clinical centers, and these ratios can be fixed by design using center-specific or stratified randomization. In this biological assignment study, center effects are accounted for by using stratification in the analysis of the primary endpoint.

Since the primary analysis is stratified by clinical center, it is crucial to ensure that each clinical center enrolls patients in both treatment arms. At least two individuals are required to estimate variability within a stratum, so, at a minimum, each center must enroll two patients in each treatment arm. A clinical center that fails to meet this goal will comprise an empty stratum that does not contribute to the final test statistic.

A two-step process will be used to ensure that this does not occur. First, only centers that expect to enroll at least 20 standard risk patients will participate. If a center enrolls at least 20 standard risk patients, chance should result in the assignment of at least two standard risk patients to the allograft treatment arm. The second provision employs a statistical stopping guideline for accrual. These procedures are further described in Section 5.4.

At the close of enrollment, it is still possible that despite these precautions, one or more centers will have fewer than two standard risk patients on the allograft arm. All of the sites will be ranked in terms of the number of standard risk allograft subjects enrolled, and the smallest sites will be pooled together until this criterion is met. The rationale behind the pooling procedure is that the size of a center, i.e., the number of transplants it performs is more predictive of outcome than other factors, such as geographic region.

5.2.4 Effects of Disease Risk Status

It is anticipated that approximately 15% of all presenting patients will be high-risk, as predicted by bone marrow cytogenetic results showing abnormalities of chromosome 13 by standard metaphase analysis, or a β_2 microglobulin level > 4.0 mg/L. Differential assignment of high-risk patients to one or other of the treatment arms could bias subsequent treatment comparisons.

Because so few patients are categorized as high-risk, and the anticipated differences in outcome associated with risk are great, it is anticipated that post-hoc modeling will not suffice to adjust for this risk

Separate analyses of data from standard risk and high-risk patients will be performed to avoid biased treatment comparisons if the allocation of high-risk patients is not balanced across treatment arms. The analysis in standard risk patients will be considered primary, and there is adequate statistical power for this primary comparison. The analysis in high-risk patients will be exploratory, and will aid in designing future studies. Center effects will be accounted for in the primary analysis by stratifying on clinical center.

5.2.5 Effects of Baseline Factors

A post-hoc analysis will be performed assessing the comparability of patients allocated to each treatment arm with respect to baseline Karnofsky performance status, age and $\beta 2$ microglobulin levels. It is anticipated that these factors will be highly prognostic, and that their effects may not be completely captured in a single low/high-risk status indicator. Specifically, although high-risk patients are defined as those having a $\beta 2$ microglobulin level above 4 mg/L, there may be additional prognostic value for different $\beta 2$ microglobulin levels below 4 mg/L.

Other baseline demographic factors such as donor age and gender were considered, and rejected, as candidates for post-hoc adjustment. Donor age is highly correlated with recipient age when HLA-identical siblings are serving as donors. The range of ages in the study population is not anticipated to be wide enough to lead to imbalances between the treatment arms. Recipient-donor gender mismatch is not anticipated to be a strong predictor of outcome in the allograft transplant setting, and thus does not warrant adjustment.

Performance status will be compared using a chi-squared test, while age and $\beta 2$ microglobulin levels will be compared using a Wilcoxon test. If statistically significant ($p < 10$) differences in the treatment arms are found with respect to either of these baseline prognostic factors, a secondary analysis of the primary endpoint will be performed adjusting for these covariates in a Cox proportional hazards model.

5.2.6 Effects of Time to Recovery from the Auto transplant

Based on data from the Seattle Consortium, it is anticipated that fewer than 5% of patients allocated to the auto-allo arm will be unable to receive an allograft because of toxicity from the auto transplant. As described previously, these patients will be analyzed as if they received the allograft, according to the intent-to-treat principle.

The course of the initial auto transplant is a risk factor for the outcome of the subsequent allogeneic transplant. The time to recovery from the initial auto transplant contributes to the time to initiation of the second intervention, which will be compared between treatment arms using a log-rank test. Details of the analysis, including definitions of the event of interest, the

competing risks and censoring events are described in Section 5.5.2, Analysis of Secondary Endpoints.

5.3 Sample Size and Power Calculations

The study sample size is specified in terms of the target number of standard risk patients with an HLA matched sibling donor. Accrual will remain open until, at a minimum, 150 standard risk patients are assigned to the auto-allo arm. During the accrual period, enrollment will be open to all eligible patients, including high-risk patients and those without HLA-matched sibling donors. The exact composition of the study population will depend on the series of eligible patients presenting at each clinic. During the accrual period we anticipate enrollment of 150 standard risk patients on the auto-allo arm and between 350-600 patients on the auto-auto arms.

Power depends on the number of standard risk patients with an eligible HLA-matched sibling donor, and the proportion of the total population of eligible patients who have such a donor. There is debate on the value of this proportion, and power calculations were based on a range of values from .20 to .30. The value of .2 is in line with estimates based on census data on family sizes in the 1960s. The value of .3 is reported in the literature but may be high given that this is an older population and some siblings may be medically ineligible to act as donors.

Table 5.3 provides estimates of the probability of making various decisions under different likelihoods that a patient has a donor and on different combinations of 3-year PFS. The table is based on 10,000 simulated samples. The baseline estimate of a 45% 3-year PFS in the worst case is based on data from the French IFM-94 randomized trial of single versus tandem autologous stem cell transplants for MM. This estimate is supported by data from the ABMTR database. The 3-year PFS following APBSCT for MM in patients > 18 years of age is 42% ± 5%. The 3-year PFS was not different in patients <60 years (44 ± 6%) and those > 60 years (35% ± 10%). From the table we see that the proposed design has approximately 80% power of detecting a difference of 15% in PFS between the auto and allo arms or between the two auto arms. It has approximately the correct type I error rate as well.

Table 5.3 -- Simulated Probabilities of Making Primary Decision

Prob Of HLA-Sib	PFS Auto Arm 1	PFS Auto Arm 1	PFS Allo Arm 1	Prob Accept Both H₀	Prob. Reject Auto Accept Auto-Allo	Prob. Accept Auto Reject Auto-Allo	Prob Reject Both H₀	Power of Auto-Auto Test	Power of Auto-Allo Test
0.20	0.45	0.45	0.45	95.28	2.18	2.35	0.19	2.37	2.54
0.20	0.45	0.45	0.60	14.39	1.57	83.06	0.98	2.55	84.04
0.20	0.45	0.45	0.65	1.26	0.57	96.24	1.93	2.50	98.17
0.20	0.45	0.55	0.65	5.91	39.89	35.97	18.23	58.12	54.20
0.20	0.45	0.55	0.70	0.61	15.51	41.36	42.52	58.03	83.88
0.20	0.45	0.60	0.60	5.68	89.94	2.37	2.01	91.95	4.38
0.20	0.45	0.50	0.60	25.66	12.75	58.54	3.05	15.80	61.59
0.20	0.45	0.50	0.65	4.41	6.59	79.81	9.19	15.78	89.00
0.25	0.45	0.45	0.45	94.71	2.43	2.56	0.30	2.73	2.86
0.25	0.45	0.45	0.60	16.30	1.81	81.26	0.63	2.44	81.89
0.25	0.45	0.45	0.65	1.86	0.70	95.66	1.78	2.48	97.44
0.25	0.45	0.55	0.65	8.88	35.77	45.71	9.64	45.41	55.35
0.25	0.45	0.55	0.70	1.03	16.41	54.41	28.15	44.56	82.56
0.25	0.45	0.60	0.60	12.84	80.90	4.35	1.91	82.81	6.26
0.25	0.45	0.50	0.60	29.62	10.84	58.26	1.28	12.12	59.54
0.25	0.45	0.50	0.65	5.75	6.43	82.51	5.31	11.74	87.82
0.30	0.45	0.50	0.65	7.64	6.62	82.27	3.47	10.09	85.74
0.30	0.45	0.45	0.45	94.89	2.34	2.52	0.25	2.59	2.77
0.30	0.45	0.45	0.60	19.00	1.81	78.68	0.51	2.32	79.19
0.30	0.45	0.45	0.65	2.80	1.36	94.36	1.48	2.84	95.84
0.30	0.45	0.55	0.65	12.35	30.73	51.59	5.33	36.06	56.92
0.30	0.45	0.55	0.7	1.48	17.05	62.71	18.76	35.81	81.47
0.30	0.45	0.60	0.6	21.55	69.76	6.96	1.73	71.49	8.69
0.30	0.45	0.50	0.6	33.77	9.26	56.21	0.76	10.02	56.97

5.4 Statistical Stopping Guidelines

There are several statistical stopping guidelines employed in this study. These guidelines are designed to assist an independent Data and Safety Monitoring Board (DSMB) in overseeing the study. The DSMB may also request additional interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of patients in the study.

Monitoring of key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures.

The first center-specific stopping guideline monitors accrual of standard risk patients at each clinical center and is designed to guard against a clinical site enrolling fewer than two patients on the auto-allo arm. Enrollment is temporarily suspended at centers where the stopping guideline is invoked while the DCC evaluates screening and referral practices.

A second set of stopping guidelines monitor the incidence of TRM. After the first auto transplant, which all subject receive, three-month TRM will be monitored in a single study-wide cohort. After the second transplant, six-month TRM will be monitored separately by intent-to-treat assignment to the auto-allo or two auto-auto arms. A fifth TRM stopping rule will consider nine-month TRM (pooled over all treatment arms and both transplants) in the cohort of patients ≥ 65 years of age.

Monitoring for TRM associated with the first transplant will commence with the initiation of conditioning for the first transplant and will continue until the initiation of conditioning for the second transplant, or if a second transplant is not performed, until six months post first transplant. Monitoring for TRM associated with the second transplant will commence with initiation of conditioning for the second transplant and extend for six months post second transplant. Monitoring for TRM in the cohort of patients ≥ 65 years of age will commence with initiation of conditioning for the first transplant, and extend for six months post second transplant, or if a second transplant is not performed, until six months post first transplant.

A third set of stopping guidelines monitor the incidence of regimen-related toxicities. DVT and sensory neuropathy have been reported with the dexamethasone/thalidomide regimen, but will be monitored in both auto-auto arms to provide a randomized internal control group. Cyclosporine associated renal and hepatic toxicity will be monitored in the auto-allo arm.

Monitoring for the specific toxicities will commence with the initiation of conditioning for the second transplant. Monitoring for DVT and sensory neuropathy will extend for 12 months following the second autologous transplant. Monitoring for renal and hepatic toxicity will extend for 12 months following the allogeneic non-myeloablative transplant.

The null hypotheses for sequential monitoring are that the true rate of six-month TRM is less than 5% after auto transplant and less than 20% after allo transplant, that the true rate of nine-month TRM is less than 20% in subjects 65 years of age or older, and that the 12-month incidence of each post second transplant regimen-related toxicity is less than 10%. If any of the

observed incidence rates are substantially in excess of these targets, the null hypothesis will be rejected, and the NHLBI will be notified. These guidelines are provided as an “early warning” system. Suspension of enrollment is not automatic, but at the discretion of the NHLBI upon recommendation of the DSMB, which will have the opportunity to request and review additional analyses.

There are no planned interim analyses for efficacy in this study, because the anticipated accrual period is three years, and the primary endpoint is three-year disease-free survival. However, if accrual is much slower than anticipated, the Data and Safety Monitoring Board will be consulted, and consideration will be given to interim analyses for efficacy in the fourth or fifth year of the study, using either group sequential methods or stochastic curtailment to conserve type I error.

5.4.1 Statistical Stopping Guideline for Monitoring Accrual of Patients on the Auto-Allo Arm

To guard against a clinical site enrolling fewer than two patients on the auto-allo arm, accrual of standard risk patients at each clinical center will be monitored. Monitoring begins with the 11th patient, and is then conducted continuously as each subsequent patient is enrolled. Table 5.4.1 shows the criteria that would trigger a Data Coordinating Center (DCC) review of screening and referral practices for an individual center. Note that only standard risk patients are tallied.

Table 5.4.1 -- DCC Screening and Referral Practices Review

<u>Total Enrolled</u>	<u>Assigned to Allograft</u>
0 – 11	No review
12 – 17	Review if 0 patients assigned to the allograft arm
18 – 23	Review if 1 or fewer patients assigned to the allograft arm
24 – 29	Review if 2 or fewer patients assigned to the allograft arm
30 – 35	Review if 3 or fewer patients assigned to the allograft arm
36 – 41	Review if 4 or fewer patients assigned to the allograft arm
42 – 47	Review if 5 or fewer patients assigned to the allograft arm
48 – 53	Review if 6 or fewer patients assigned to the allograft arm

If any of the criteria in Table 5.4.1 are met, enrollment at the site is suspended while the DCC conducts a review. However, this monitoring scheme is designed to provide minimal impediments to accrual. If the true proportion of patients with HLA-matched sibling donors is 0.25, the probability that the DCC would review screening and referral practices at any given clinical center is only .055 if the center enrolls 20 patients, and 0.10 if the center enrolls 50 patients.

The monitoring scheme is based on the lower boundary of a truncated level 0.10 sequential probability ratio test (SPRT). This SPRT requires 50 patients to achieve 90% power to reject the null hypothesis of an allograft proportion of 0.25 versus the alternative of 0.10. After 20 patients are enrolled, power is only 48%. However, the goal of monitoring is merely to prevent sparse strata, not to definitively test this hypothesis.

5.4.2 Guidelines for Safety Monitoring

Transplant Related Mortality (TRM)

The rate of TRM will be monitored monthly until enrollment to the applicable cohort is closed. Each month, the null hypothesis that six month post second transplant TRM is less than or equal to 20% after allo transplantation or 5% after auto transplantation will be tested against the alternative that it is greater. For the purpose of the stopping rule, TRM is defined as death without relapse or progression, and subjects who relapse or progress are censored. An extension of the SPRT will be used. A description of this sequential testing procedure is provided below.

The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of observed deaths. The continuation region of the SPRT is defined by two parallel lines. Only the lower boundary will be used for monitoring each treatment arm to protect against poor six month post second transplant non-relapse survival. If the graph falls below the lower boundary, the SPRT rejects the null hypothesis, and concludes that there are more deaths than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment to the treatment arm reaches the target goal.

This procedure assumes an exponential distribution for the time until failure during the first six months following the second transplant, but censors follow-up time after six months. Only deaths without relapse or progression that occur on or before the patient has been followed for six months post-initiation of the second transplant are counted. Total time for monitoring the TRM is from initiation of the second transplant to death, relapse or progression, or to six months, whichever comes first, summed for all individuals on study.

There are five stopping guidelines for TRM: one for TRM associated with the first transplant in the entire study population, three treatment-specific guidelines for TRM associated with the second transplant, and a guideline for TRM associated with either transplant in the age group ≥ 65 years. These stopping guidelines were all developed from an SPRT contrasting 20% versus 30% six-month TRM for TRM after allotransplant, and 5% versus 10% for six-month TRM after autotransplant. The parameters of the SPRT were adjusted so that the probability of stopping would be approximately 1%, 10%, and 90% if six-month TRM were 15%, 20%, and 30%, respectively after allotransplant, or 2.5%, 5% and 10.0% after autotransplant.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The actual operating characteristics of the truncated test, shown in Table 5.4.2a, were determined in a simulation study. The simulation assumed exponential time to failure after the first transplant, and uniform accrual of 600 patients over a three-year time period, of whom 42 patients (7% of 600) were over age 65. Assuming 5% of patients never receive a second transplant, 142 patients were assigned to the allograft arm, and 214 patients were assigned to each of the two autograft arms.

Table 5.4.2a
Operating Characteristics of Sequential Testing Procedure for
Transplant-related Mortality from a Simulation Study with 100,000 Replications

Operating Characteristics for TRM for 1st Auto Tx, N = 600

True 3 Month Mortality	2.5%	5%	7.5%	10%
Probability Reject Null	0.003	0.10	0.71	0.99
Mean Month Stopped	36.9	34.0	19.5	8.5
Mean # Deaths in 3 Mo.	14.6	26.8	22.2	11.4
Mean # Patients Enrolled	598	551	320	141

Operating Characteristics for TRM for 2nd Allo Tx, N = 142

True 6 Month Mortality	15%	20%	25%	30%
Probability Reject Null	0.01	0.12	0.47	0.85
Mean Month Stopped	36.7	34.8	28.7	20.5
Mean # Deaths in 6 Mo.	18.3	22.9	22.8	17.8
Mean # Patients Enrolled	133.1	125.5	101.8	69.6

Operating Characteristics for TRM for 2nd Auto Tx, N = 214

True 6 Month Mortality	2.5%	5%	7.5%	10%
Probability Reject Null	0.005	0.11	0.50	0.86
Mean Month Stopped	36.9	34.8	27.9	19.9
Mean # Deaths in 6 Mo.	4.6	8.6	9.8	8.4
Mean # Patients Enrolled	201.6	189.2	148.4	101.1

Operating Characteristics for TRM for 1st and 2nd Auto Tx for Age ≥65, N = 42

True 9 Month Mortality	15%	20%	25%	30%
Probability Reject Null	0.02	0.09	0.27	0.53
Mean Month Stopped	36.7	35.5	32.9	28.8
Mean # Deaths in 9 Mo.	5.9	7.6	8.8	9.1
Mean # Patients Enrolled	41.6	40.4	37.6	33.2

TRM associated with the first transplant is monitored in all subjects (N = 600), from the initiation of conditioning for the first transplant, until the initiation of conditioning for the second transplant, or if a second transplant is not performed, until six months post first transplant. The SPRT rejects the null hypothesis in favor of the alternative 99% of the time when the true six-month TRM is 10%, 10% of the time when the true six-month TRM is 5%, and less than 1% of the time when the true rate is 2.5%. This corresponds to a type I error rate of $\alpha = 0.10$ and a type II error rate of $\beta = 0.01$. When the true six-month TRM rate is 10%, on average, the DSMB will be consulted 8.5 months after opening, when 11.4 deaths have been observed in 141 patients.

After the second transplant, six-month TRM will be monitored separately by intent-to-treat assignment to the auto-allo or two auto-auto arms. The calculation of power for the SPRT assumes that 5% of subjects will not receive a second transplant, and results presented for the SPRT are conditional on receipt of a second transplant.

After the allotransplant, the procedure rejects the null hypothesis in favor of the alternative 12% of the time when the true six-month TRM is 20%, and 85% of the time when the true rate is

30%. This corresponds to a type I error rate of $\alpha = 0.12$ and a type II error rate of $\beta = 0.15$. When the true six-month TRM rate is 30%, on average, the DSMB will be consulted 20.5 months after opening, when 17.8 deaths have been observed in 69.6 patients.

In each of the auto-auto arms, the procedure rejects the null hypothesis in favor of the alternative 118% of the time when the true six-month TRM is 5%, and 86% of the time when the true rate is 10%. This corresponds to a type I error rate of $\alpha = 0.11$ and a type II error rate of $\beta = 0.14$. When the true six-month TRM rate is 10%, on average, the DSMB will be consulted 19.9 months after opening, when 8.4 deaths have been observed in 101.1 patients.

For the 65 and over age group the monitoring starts with the initiation of conditioning for the first transplant. If a second transplant is performed, then the monitoring ends six months after the second transplant, otherwise it ends six months after the first transplant. The calculation of power for the SPRT assumes that 20% of subjects age 65 and older will not receive a second transplant.

In the age 65 and older cohort, the procedure rejects the null hypothesis in favor of the alternative 2% of the time when the true nine-month TRM is 15%, 9% of the time when the true nine-month TRM is 20%, and 53% of the time when the true rate is 30%. This corresponds to a type I error rate of $\alpha = 0.09$ and a type II error rate of $\beta = 0.47$. When the true nine-month TRM rate is 30%, on average, the DSMB will be consulted 28.8 months after opening, when 9.1 deaths have been observed in 33.2 patients age 65 or older.

Note that the SPRT procedure is adequately powered to distinguish between a six-month TRM rate of 5% and 10% in each of the auto-auto arms (86%), and from 20% to 30% in the auto-allo arm (85%), but not in the older age group (53%). These results reflect the assumptions of fewer available patients with HLA-matched siblings (25% of the total of 600 patients), and fewer older patients (7% of the total of 600 patients).

Regimen-related Toxicities

There are six stopping guidelines for regimen-related toxicity:

- 1) Grade III or higher DVT in the auto-auto maintenance arm
- 2) Grade III or higher DVT in the auto-auto observation arm
- 3) Grade III or higher sensory neuropathy in the auto-auto maintenance arm
- 4) Grade III or higher sensory neuropathy in the auto-auto observation arm
- 5) Grade III or higher hepatic toxicity in the auto-allo arm
- 6) Renal toxicity (use of dialysis) in the auto-allo arm

For the purpose of the stopping rule, any subject experiencing the toxicity is defined as an event, even if the condition later reverses, and subjects who die free of toxicity are censored.

The stopping guidelines were all derived from an SPRT contrasting 5% versus 15% twelve-month cumulative incidence rates, cumulated at twelve months post initiation of conditioning for

the second transplant. (Refer to Section 5.4.2 Transplant Related Mortality for a discussion of the statistical methodology used.) The parameters of the SPRT were adjusted so that the probability of stopping would be approximately 1%, 10%, and 95% at cumulative incidence of 5%, 10%, and 20%, respectively.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The actual operating characteristics of the truncated test, shown in Table 5.4.2b, were determined in a simulation study.

The simulation assumed exponential time to failure after the first transplant, and uniform accrual of 600 patients over a three-year time period, of whom 150 patients were assigned to the allograft arm, and 225 patients were assigned to each of the two autograft arms. The initiation of conditioning for the second transplant was assumed to occur uniformly between 60 to 120 days after the initial autotransplant, with monitoring of toxicities extending for up to twelve months post second transplant in the auto-allo arm and each of the auto-auto arms.

Table 5.4.2b
Operating Characteristics of Sequential Testing Procedure
Regimen-related Toxicity > 10%
from a Simulation Study with 100,000 Replications

Operating Characteristics for Auto-Allo Arm, N = 150

True 1 Year Incidence	5%	10%	15%	20%
Probability Reject Null	0.00	0.10	0.54	0.91
Mean Month Stopped	36.9	35.1	27.8	19.4
Mean # Events in 1 Year	5.8	10.9	12.0	9.2
Mean # Patients with Second Transplant	141.4	133.9	103.7	68.7

Operating Characteristics for Auto-Auto Arm, N = 225

True 1 Year Incidence	5%	10%	15%	20%
Probability Reject Null	0.00	0.10	0.61	0.97
Mean Month Stopped	36.9	34.9	25.7	16.5
Mean # Events in 1 Year	8.8	16.3	16.2	10.3
Mean # Patients with Second Transplant	212.2	199.4	142.4	84.5

In the auto-allo arm, the procedure rejects the null hypothesis in favor of the alternative 10% of the time when the true twelve-month event rate is 10%, and 91% of the time when the true rate is 20%. This corresponds to a type I error rate of $\alpha = 0.10$ and a type II error rate of $\beta = 0.09$. When the twelve-month event rate is 20%, on average, the DSMB will be consulted 19.4 months after opening, when 9.2 events have been observed in 68.7 patients in the twelve months following their second transplant.

In each of the auto-auto arms, the procedure rejects the null hypothesis in favor of the alternative 10% of the time when the true one-year event rate is 10%, and 97% of the time when the true rate is 20%. This corresponds to a type I error rate of $\alpha = 0.10$ and a type II error rate of $\beta = 0.03$. When the true one-year event rate is 20%, on average, the DSMB will be consulted 16.5 months after opening, when 10.3 events have been observed in 84.5 patients in the year following their second transplant.

5.5 Analysis Plan

All analyses are based on an intent-to-treat. In such an analysis, patients are considered as being in the auto-allo arm at the time of their initial autologous transplant if they have an HLA-matched sibling donor whether or not the allogeneic transplant takes place. Likewise, patients without an HLA-matched sibling donor randomized to maintenance therapy following their second autologous transplant are analyzed with this group whether or not they actually receive their second autologous transplant or maintenance therapy.

5.5.1 Analysis of the Primary Endpoint

The primary outcome of the trial is myeloma progression-free survival at three years following the initial autologous transplant. The primary null hypotheses of the study are: 1) that there is no difference in 3-year progression free survival between the two auto-auto arms; and, 2) that there is no difference between in 3-year progression free survival between the “best” auto-auto arm(s) and the auto-allo arm. The best auto-auto arm is either a pooled arm or the better of the two auto-auto arms depending on the results of the comparison of the auto-auto arms (maintenance therapy versus no maintenance therapy). The alternative hypotheses are: 1) PFS differs with use of maintenance therapy after tandem autologous transplantation; and, 2) PFS differs between auto-auto and auto-allo tandem transplant strategies.

In the final analysis, the endpoint of 3-year PFS will be estimated using the Kaplan-Meier product limit estimator, and compared between treatment arms using the modified Mantel-Haenszel test statistic stratified on clinical center⁷². The 2.5% significance level will be used to ensure that the chance of incorrectly deciding that one of the treatment plans is different from the other when there is no difference between the treatments is at most 5%. Standard confidence intervals will be computed for the measure. In the event that there are no significant differences between the arms, a *post-hoc* power analysis will be performed.

The primary analysis of myeloma progression-free survival at three years following the initial autologous transplant is described above. A secondary analysis of the primary endpoint will also be conducted. This secondary analysis complements the primary analysis, by permitting the clinical investigators to examine all pairwise comparisons of treatment arms, in a way that controls type I error. A two degree of freedom level .05 stratified weighted log-rank test will be performed comparing the three treatment arms. If any differences are found using the omnibus test, all pair-wise comparisons will be examined. It is not anticipated that there will be any differences in the results obtained from the primary and secondary analysis. However, if there are discrepancies, the primary analysis will be given precedence in report and publications.

5.5.2 Analysis of Secondary Endpoints

A number of secondary outcomes will be examined to compare the patient’s disease status over time between treatment arms.

Current Myeloma-Stable Survival:

Patients on either arm may progress and then be salvaged by more aggressive therapy, such as DLI on the allogeneic arm or dexamethasone and thalidomide on the auto-auto-maintenance arm. The “current myeloma-stable survival” distribution is an estimate of the likelihood that a patient will be alive with stable disease at any given point in time.

These survival curves will be compared between the two arms of the study across all time points using a technique found in Klein et. al⁷³.

We will also estimate for each arm the probability a patient is alive with stable disease at 2, 6, 9, 12, 18, 24, 30 and 36 months. In the analysis at K months, the numerator for this estimate counts

patients alive with at least stable disease, and the denominator counts all patients followed to K months, regardless of survival status. These probabilities will be compared using standard tests for binomial proportions.

Overall Survival:

The event is death from any cause. Patients alive at the time of the last observation are considered censored. Overall survival will be compared between treatment arms using a log-rank test, and the survival curves will be estimated using the Kaplan Meier Estimator.

Time to Progression:

The event is progression. Death without progression is considered a competing risk. Patients alive with no history of progression are considered as censored observations. Time to p will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

5.5.3 Analysis of Tertiary Endpoints

CR and CR+PR Proportion at Two and Twelve Months:

The numerator for the estimate of the CR rate counts patients who are alive and in CR at two (or twelve) months post first auto transplant, and the denominator counts patients who have been followed for two (or twelve) months, regardless of survival or remission status. The numerator for the estimate of the CR+PR rate counts patients who are alive and in CR or PR at two (or twelve) months. The proportion of patients in CR and PR will be compared between treatment arms using standard techniques for categorical data.

Time to CR and CR+PR:

The event is CR (CR or PR). The time to event is the time to CR (CR or PR). Patients who die in a state other than CR (CR or PR) are considered as failing from a competing risk. Patients alive and not in CR (CR or PR) at the time of last observation are considered as censored for this event. Time to CR (CR or PR) will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Time to Off-study Therapy:

The event is the initiation of any anti-myeloma therapy other than that defined by the protocol treatment arms. Patients who die without initiation of an off-study therapy will be considered as experiencing a competing risk. Patients who do not receive an off-study therapy but are alive at the end of the study will be considered censored. Time to off-study therapy will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Health Quality of Life:

Overview

The goal of the Health Quality of Life (HQL) component of this trial is to describe the HQL of study participants and to determine if there are differences in quality of life among recipients of the different treatment strategies in this protocol. All patients registered to the clinical trial are

potentially eligible for the study, and consent for participation will be obtained as part of consent for the clinical trial. Patients who cannot communicate in English or Spanish, can not complete HQL questionnaires due to cognitive, linguistic or emotional difficulties, will be excluded from the study. We anticipate that 90% of registered patients will be eligible, and that compliance will be roughly 80% among surviving patients, based on experiences with The Unrelated Donor Marrow Transplantation Trial [TCD Trial] (formerly the T Cell Depletion Trial) and other studies of HQL conducted for the NHLBI in bone marrow transplant recipients.

Instruments, Administration and Scoring Methods

In order to minimize response burden and increase the chance of complete response, the selection of instruments has been limited to the FACT-BMT⁷⁴ and the SF-36^{70, 71}. The FACT-BMT is comprised of a general core questionnaire, the FACT-G, evaluates the Quality of Life (QOL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The MOS SF-36 is a general assessment of health quality of life that has been widely applied in a variety of outcome studies and is being used in this trial as a generic measure of QOL.

HQL will be assessed through a self-administered questionnaire distributed to patients at clinic visits. The assessments will be conducted at baseline prior to the initiation of the conditioning regimen for the first transplant, again within two weeks prior to the initiation of the second transplant, and at yearly intervals from baseline. The protocol permits administration within a 2 week window before the target date for the first two interviews, and within a +/- 2 week window centered on the target date for the subsequent yearly interviews. The HQL instruments will be scored according to standard methods for these tools. Specifically, the FACT-BMT will be scored using software provided in the FACIT Manual Version 4.0⁷⁴, and the MOS SF-36 will be scored using software provided in the SF-36 Health Survey Manual and Interpretation Guide⁷⁰ and the SF-36 Physical and Mental Health Summary Scales: A User's Manual⁷¹.

Analysis and Interpretation of Results

While descriptive analyses will consider all HQL outcomes, following the lead of David Cella in the analysis of ECOG Study 5592⁷⁵, the primary HQL endpoint for hypothesis testing will be the Trial Outcome Index (TOI). The FACT-BMT TOI is derived by adding the scores on the Physical Well-Being and Functional Well-Being subscales of the FACT-BMT, to the BMT symptoms module score. At two years post-transplant, it is anticipated that the TOI, which contains relevant questions about physical functioning and BMT symptoms, will be most sensitive to long term differences in HQL attributable to differences in treatment strategy.

The initial analysis of the questionnaire data will focus on describing and reporting the HQL of study participants, through tables, graphs, and summary statistics characterizing the HQL scores over time in each treatment arm. Differences in QOL between the two auto-auto strategies and between the auto-auto and auto-allo strategies will be assessed in several ways. First, the marginal QOL scores given that the patient is alive will be compared at the specific time points described above using simple T-tests. Second, the Integrated Quality Adjusted Survival⁷⁶ will be compared. This latter approach aggregates QOL over the entire period of observation, and accounts for potential differences in survival rates. If an examination of patterns of missing data indicates that there is substantial informative censoring due to causes other than death,

techniques for joint modeling of survival and longitudinal data developed by Schluchter⁷⁷, and extended by Ibrahim et. al⁷⁸, will be considered.

Statistical Power and Sample Size Considerations

The trial is not designed to be powered for a primary endpoint of detecting differences in QOL between the different treatment strategies. The HQL analysis in the study will be primarily descriptive. We can, however, estimate the power of the study to detect differences between the groups based on expected survival and prior HQL studies. The TCD Trial observed a baseline mean FACT-BMT TOI score of 67.2, with a standard deviation of 13.8 units, and a mean SF-36 Physical Component Score of 41.6, with a standard deviation of 10.2 units. These data are consistent with published norms for the FACT-BMT in transplant recipients, and the SF-36 in cancer patients, respectively^{70, 74}.

Formal hypothesis testing for the FACT-TOI endpoint will proceed according to the plan described previously for the PFS endpoint. The null hypotheses of the HQL study are: 1) that there is no difference in 3-year FACT-TOI between the two auto-auto arms; and, 2) that there is no difference in the 3-year FACT-TOI between the "best" auto-auto arm(s) and the auto-allo arm. The best auto-auto arm is either a pooled arm or the better of the two auto-auto arms depending on the results of the comparison of the auto-auto arms (maintenance versus no maintenance). The alternative hypotheses are that the treatments have different long term HQL as measured by the FACT-TOI.

To illustrate the statistical power available, consider a comparison of the FACT-TOI at the three-year time point between the tandem autograft patients randomized to observation and maintenance. Assuming 150 auto-allo patients, and 450 auto-auto patients, 90% of whom will be eligible for HQL study, a 45% survival rate at 3 years, and an 80% response rate, approximately 146 auto-auto patients will complete the third year interview. The estimated sample size of 73 per arm is sufficient to detect, with statistical power of 80%, a difference in the FACT-TOI score of 7.1 units, and a difference in the SF-36 PCS score of 5.3 units, using a two-sided level .025 test.

Incidence of Toxicities Grade ≥ 3 According to the CTCAE Version 3.0

For both arms, toxicities that occur over the course of time will be tabulated.

Grade ≥ 3 toxicities will be tabulated for each patient at set intervals over the course of the study. The proportion of patients developing toxicity will be compared between treatment arms.

Incidence of Infections

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each patient according to criteria in the BMT CTN Manual of Operations. The proportion of patients developing infections will be compared between treatment arms.

5.5.4 Analyses within Each Treatment Arm

A number of outcomes are specific to only one of the study arms. Between treatment arm comparisons will not be performed, but descriptive statistics will be computed.

Drop Out Rate and Duration of Maintenance Therapy

For patients in the tandem autologous transplant arm randomized to receive maintenance therapy after the second autograft, the proportion of patients complying with the maintenance therapy at 2, 6, 9, and 12 months, and the duration of maintenance therapy will be estimated.

Incidence of Primary and Secondary Graft Failure

Engraftment is defined as reaching $\geq 5\%$ donor chimerism. Median time to engraftment will be estimated from the cumulative incidence of engraftment, treating death as a competing risk.

The rate of Primary Graft Failure will be estimated as the number of patients who have failed to engraft by Day 56 post-allograft transplant, divided by the total number of patients who receive an allograft transplant.

The rate of Secondary Graft Failure will be estimated as the number of patients who engraft (at any time prior to one year), and subsequently lose chimerism ($< 5\%$) in the first year post-engraftment, divided by the total number of patients who engraft in the first year.

Incidence and Severity of Graft-versus-Host Disease

GVHD will be graded according to criteria in the BMT CTN MOP. The cumulative incidence curves for acute and chronic GVHD will be estimated treating death as a competing risk.

APPENDIX A

DURIE AND SALMON CRITERIA FOR THE INITIAL DIAGNOSIS AND STAGING OF MULTIPLE MYELOMA

INITIAL DIAGNOSIS

- Major criteria:
 - i) Plasmacytoma on tissue biopsy.
 - ii) Bone marrow plasmacytosis with > 30% plasma cells.
 - iii) Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for IgG peaks or 2.0 g/dL for IgA peaks, > 1.0 g/24h of kappa or lambda light chain excretion on urine electrophoresis in the absence of amyloidosis.

- Minor criteria
 - a) Bone marrow plasmacytosis with 10% to 30% plasma cells.
 - b) Monoclonal globulin spike present, but less than the levels defined above.
 - c) Lytic bone lesions.
 - d) Normal IgM < 50 mg/dL, IgA < 100 mg/dL, or IgG < 600 mg/dL.

- Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b:
 - a) i + b, i + c, i + d (i + a not sufficient).
 - b) ii + b, ii + c, ii + d.
 - c) iii + a, iii + c, iii + d.
 - d) a + b + c, a + b + d.

STAGING

The Durie and Salmon classification uses three multiple myeloma stages.

Stage I

All of the following:

- Hemoglobin greater than 10 g/dL
- Serum calcium less than 12 mg/dL
- Normal bone structure or solitary plasmacytoma on radiographs
- Low M component
 - IgG less than 5 g/dL
 - IgA less than 3 g/dL
 - Urine light chains less than 4 g/24 hr

Stage II

Fitting neither Stage I nor Stage III

Stage III

One or more of the following:

- Hemoglobin less than 8.5 g/dL
- Serum calcium greater than 12 mg/dL
- Advanced lytic bone lesions
- Hyper M component
 - IgG greater than 7 g/dL
 - IgA greater than 5 g/dL
 - Urinary light-chain excretion greater than 12 g/24 hr

Subclassification

A: serum creatinine less than 2.0 mg/dL

B: serum creatinine equal to or greater than 2.0 mg/dL

APPENDIX B
CONSENT FORMS

PATIENT INFORMED CONSENT

DONOR INFORMED CONSENT

Informed Consent to Participate in Research



You are being asked to take part in a large research study. About 800 patients will take part in this study at many centers around the country. Your participation in this study is expected to last approximately 3 and a half years.

This consent form tells you about the study. The Principal Investigator (the person in charge of this research) or a co-worker of the Principal Investigator will also describe this study to you and answer all of your questions. Furthermore, throughout your treatment your care will be discussed with you and questions answered as needed. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Taking part in this study is entirely your choice.

1. Name of the Subject (“Study Subject”)

2. Title of Research Study

A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by HLA-Matched Sibling Non-Myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma

3a. Principal Investigator Contact Information

Insert name, affiliation and contact information.

3b. Contact information for emergencies after hours or on weekends or holidays

Call (###) ###-####, the in-patient Bone Marrow Transplant Unit. Ask to speak to the Charge Nurse.

4. Sponsor and Source of Funding or Other Material Support

The sponsor of this study, The National Institutes of Health (NIH), is providing financial support for the coordination of this study through the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN).

5. What is the purpose of this study?

You are being asked to take part in this research study because you have multiple myeloma (MM), a cancer of the bone marrow. The study described in this consent form is designed to test different treatment strategies for patients with multiple myeloma. Multiple myeloma is considered incurable with chemotherapy (drugs that kill cancer) given at usual doses. This standard chemotherapy sometimes produces remission (absence of disease) in some individuals, but the disease recurs in all patients. Past studies have shown that high-dose chemotherapy can improve the survival of myeloma patients. However, this intensive therapy damages the special cells in the bone marrow called blood stem cells. Blood stem cells are cells found in the bone marrow and blood stream that produce all of the body's blood cells. Without healthy blood stem cells, a person cannot produce white blood cells (which fight infection), red blood cells (which transport oxygen to cells) or platelets (which help blood clot). Blood stem cells can be collected before chemotherapy to be returned intravenously (through a vein) after high-dose chemotherapy is given. This procedure is called autologous **stem cell transplantation** (SCT). Autologous transplantation is accepted standard therapy for patients with multiple myeloma. Although high-dose chemotherapy with autologous SCT has significantly improved the survival of myeloma patients, it does not cure them and the potential to further improve treatment remains. One approach has been to kill myeloma cells left after the first autologous SCT with another course of high dose therapy and a second autologous SCT. Studies have shown that receiving two autologous transplants a few months apart (tandem autologous SCT) improves survival for patients with multiple myeloma. Unfortunately, this approach still does not cure myeloma. It is not known if additional drugs given after tandem autologous SCTs will further improve survival of patients with multiple myeloma. This study will test whether additional treatment after two autologous transplants (standard care) will further improve the disease control and survival of patients with multiple myeloma. This will be tested by randomizing patients without a sibling donor to receive additional treatment for one year or no further treatment after their second autologous transplant. Randomizing means assigning to a treatment by chance, like the flip of a coin.

Another type of transplant is an allogeneic stem cell transplant where the patient receives high doses of chemotherapy, with or without radiation, followed by an infusion of blood stem cells donated by a sibling (brother or sister) who has the same tissue type (genetically matched). As with an autologous SCT, the blood stem cells would rescue your bone marrow from the toxic effects of chemotherapy and radiation. However, because the stem cells come from a healthy donor, these blood stem cells also replace your immune system with the donor's immune system. This new immune system also helps fight your myeloma. This effect of an allogeneic SCT is called a graft-versus-tumor effect. Unfortunately, the traditional type of allogeneic SCT that

uses high doses of chemotherapy and radiation can have many serious side effects and a high-risk of treatment-related death, particularly in patients with multiple myeloma.

The inability of many myeloma patients to tolerate a traditional allogeneic SCT may relate to combining the toxic effects of high-dose therapy and the immune effects of the allogeneic SCT in a single procedure. Recent studies have shown that a less toxic type of allogeneic SCT, called a non-myeloablative SCT (also sometimes called a mini transplant or reduced intensity transplant), when done following recovery from an autologous SCT, can more safely be carried out and still control MM. In this study, a patient who has a matched sibling donor will receive an autologous SCT followed by a non-myeloablative transplant once he or she has recovered from the autologous SCT.

The purpose of this study is to look at two different treatment approaches that involve stem cell transplants to improve the outcome of patients with multiple myeloma and to compare them with a common current approach, tandem autologous SCT. The two new approaches being studied are: 1) the use of additional drugs after tandem autologous SCT; and, 2) the use of a non-myeloablative allogeneic SCT after a single autologous SCT. Patients who don't have a matched sibling who can donate blood stem cells will undergo tandem autologous SCT. They will also be randomized (assigned by chance, like the flip of a coin) to receive additional therapy (a combination of two medications given by mouth called dexamethasone and thalidomide) or observation (disease will be watched with no more treatment) after recovery from the second autologous SCT.

Patients with a matched sibling donor who can donate stem cells will undergo a single autologous SCT and upon recovery will receive a non-myeloablative SCT from their sibling after first receiving low dose radiation therapy.

The two main purposes of this study are to determine:

1. For MM patients without a matched sibling donor, whether additional therapy after tandem autologous SCTs improves disease control and survival.
2. For MM patients with a matched sibling donor, whether tandem autologous transplants (with or without additional therapy) or a single autologous transplant followed by a non-myeloablative SCT from their matched sibling improves disease control and survival.

The study may find that patients who have different treatments for MM have similar results.

6. What will be done if you take part in this research study?

If you decide to take part in this study and have signed the informed consent, you and your matched sibling, if you have one, will be evaluated to make sure it is safe for you to participate in the study. Before starting treatment in this study, your doctor will check your general health.

You will have the following tests and evaluations to find out if you can participate:

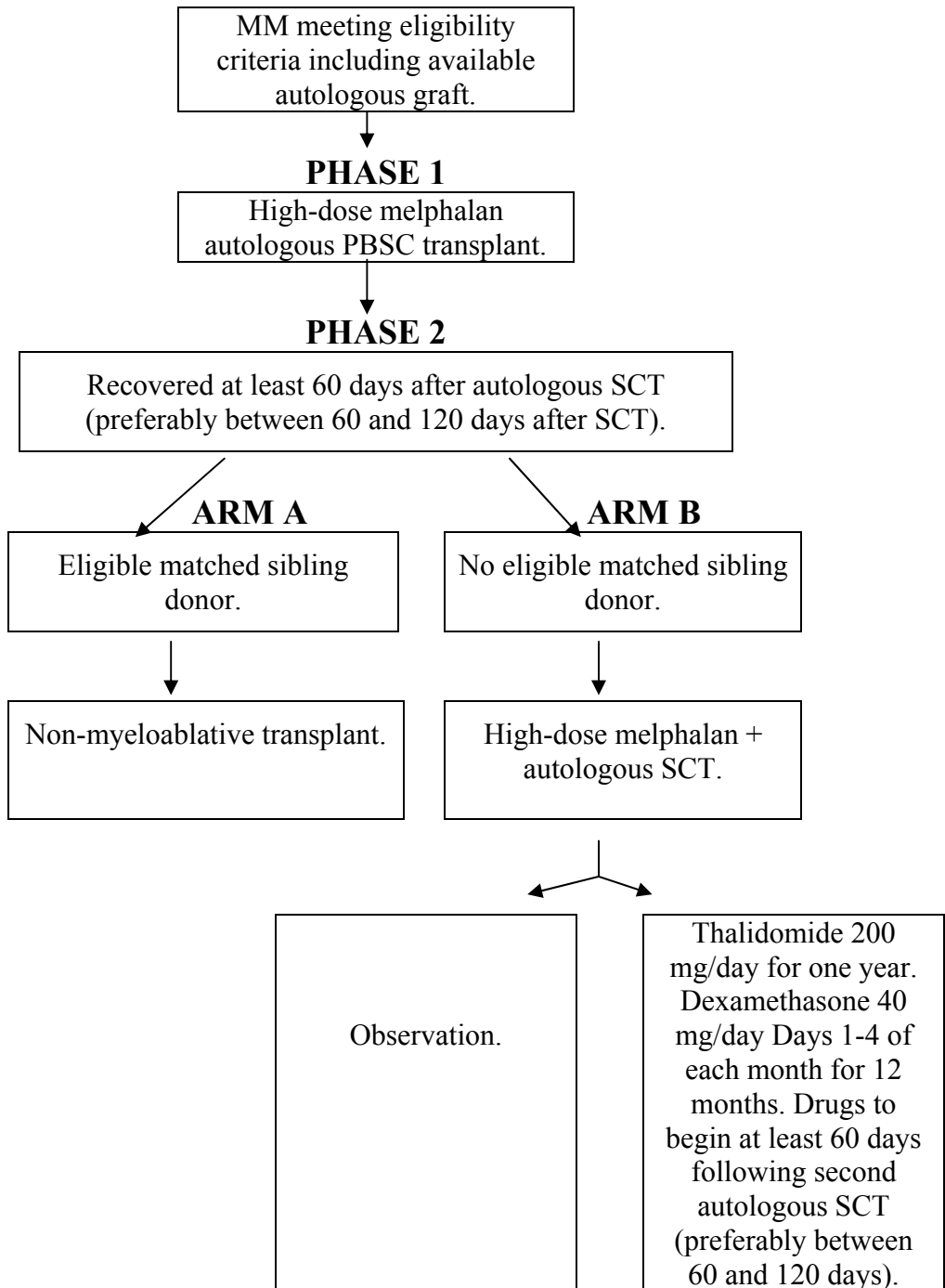
- Medical history and physical examination, including height and weight.
- Blood tests (approximately 4 – 5 tablespoons)
- Urine tests
- Electrocardiogram (ECG or EKG), a picture of the electrical action of the heart)
- Echocardiogram (a picture of the heart in motion made using ultrasound or sound waves) or MUGA scan (a picture of your heart after a small amount of radioactive material is injected into the bloodstream through a vein) to evaluate your heart function
- Pulmonary Function Test (PFT), which is a breathing test that tells how your lungs are working, measures the amount of air taken into your lungs and exhaled as you breath)
- Bone marrow biopsies and aspirates. A bone marrow aspiration is a procedure in which an area of the hipbone is numbed, and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through the needle.
- If you are a woman able to have children, a serum pregnancy test will also be performed. If you are pregnant, you will not be able to take part in this study.

Some additional x-rays will be done to evaluate your disease. These tests will help your doctor determine the amount of disease you have at the start of treatment and to follow the status of your disease throughout your treatment.

This study is divided into two phases and is explained in detail below. All patients will undergo the Phase I treatment portion of this study, using high-dose melphalan followed by an autologous SCT. Under the Phase II treatment portion of this study, if you have a matched sibling donor, you will receive a non-myeloablative allogeneic SCT using your sibling's stem cells (referred to as Treatment Arm A). If you do not have a matched sibling who can serve as your donor, you will receive a second autologous SCT (referred to as Treatment Arm B) using the same high-dose melphalan chemotherapy as described in this consent under Phase I. Patients in Treatment Arm B will be randomized (like the tossing of a coin) to receive or not receive two additional medications (dexamethasone and thalidomide) given by mouth following their second autologous SCT. Your doctor will tell you which Treatment Arm you will be treated on and, if treated on Arm B, whether or not you are to receive the additional drug therapy.

One of the objectives of this study is to evaluate how the treatment affects the quality of the patient's life and whether there is a difference between the two treatment arms. Therefore, all English and Spanish speaking patients will be asked to complete questionnaires asking about their quality of life before the first and second transplant, and at 6 months, 1, 2 and 3 years after the second transplant. It will take you approximately half an hour to complete the questionnaires.

Outline of Treatment Plan



Phase I Treatment (All Study Participants)

Central Venous Catheter: You will need to have central venous catheter (CVC) placed to participate in the study. A central venous catheter is a flexible sterile tube that will be placed into a large vein that runs under your collarbone so that blood can be withdrawn and medications given to you more easily and with less discomfort. This tube is usually placed under local anesthesia. There is a lot of experience with the use of these catheters. Complications include blood clots and infection. Clotting may require removal of the catheter or treatment of the clot by instilling a medicine that dissolves blood clots into the line. If you develop an infection you will require treatment with antibiotics and your catheter may need to be replaced. Other uncommon side effects may include swelling of the face and arm and/or lung collapse. If the lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand.

Mobilization and Leukapheresis: You will receive chemotherapy to release your blood stem cells from your bone marrow into your circulating blood (mobilization) so that they can be collected. Your doctor will explain the side effects, benefits and type of the chemotherapy you will receive to mobilize your blood stem cells. Following chemotherapy for stem cell mobilization, you will receive a bone marrow stimulating medication called granulocyte-colony stimulating factor (G-CSF) by injection under your skin daily for approximately 10 days. G-CSF will help to move your stem cells out of the bone marrow into the bloodstream. You or someone who agrees to be responsible may be taught how to give you the G-CSF, so you can receive it at home. Once the number of stem cells in your blood stream is high enough, they will be collected over 2-5 days, while you are still receiving the G-CSF injections. A procedure called Leukapheresis will be done to collect your stem cells. During this procedure, your blood will be collected either through your central venous catheter or from a vein in one arm, processed through a machine to remove the white blood cells (stem cells), and then the rest of the blood will be returned to you through your catheter or a vein in the other arm. The leukapheresis procedure will last approximately several hours each time. **You will be asked to sign a separate consent form for the leukapheresis procedure.** Enough stem cells will be collected from you for two autologous SCTs in case you do not have a matched sibling donor to donate stem cells. Your stem cells will be frozen (cryopreserved) until the time when they will be given back to you.

Autologous Stem Cell Transplant: A couple of weeks after your stem cells have been collected, you will undergo an autologous SCT using high-dose chemotherapy with a drug called melphalan given over 15 to 20 minutes through your central venous line. Since this high-dose treatment destroys the normal bone marrow in addition to the myeloma cells, your blood stem cells (blood cells able to repopulate the bone marrow) must be given back to you. Your previously collected stem cells will be unfrozen and given back to you through your central venous catheter, similar to a blood transfusion, two days after you received the melphalan. Starting on the fifth day after you received your stem cells, you will be given the drug G-CSF, subcutaneously (under the skin). The G-CSF helps to stimulate the bone marrow to produce cells and will continue until your white blood count returns to normal.

Table -- High-Dose Melphalan / Autologous SCT

Day	-2	-1	0	+5 to Engraftment
Melphalan (200 mg/m ² /IV)	X			
Stem cell infusion			X	
G-CSF (5 µg/kg/day) SQ or IV until white cells recover				X

After your stem cells have been reinfused, it will take about two weeks before adequate numbers of blood cells are made. During this time you may not be making any blood cells and therefore may require several red blood cell and platelet transfusions. Because your immune system is very weak, you may develop serious infections. You will be watched closely and receive antibiotics at the earliest sign of infection. During the time that your blood counts will be low, you may have mouth sores and feel very tired. You will receive medications to lessen these symptoms as much as possible. You will probably have a poor appetite during this time and may need to be given feedings through the central venous catheter. You may also receive pain medications as needed to minimize and control discomfort and pain. Once you begin to make new blood cells, the risk of serious infections will gradually be reduced. You should gradually come to the point where you will no longer require red cell and platelet transfusions. You should gradually regain your appetite. Although it is possible that the entire process may be done in the outpatient setting, it is also possible that a hospital stay of approximately 3 to 4 weeks will be necessary.

After completion of the transplant process, you will be followed in the outpatient clinic facility at least weekly, or as clinically indicated, until you are ready for your second SCT.

Phase II Treatment

Approximately 60 to 120 days after your autologous SCT, you will receive one of two therapies. If one of your siblings is a match and is able and willing to serve as your stem cell donor, you will receive a non-myeloablative SCT using your sibling's stem cells (referred to as Treatment Arm A). If you do not have a matched sibling who can donate stem cells, you will receive a second autologous SCT using the same high-dose melphalan chemotherapy (referred to as Treatment Arm B).

Treatment Arm A (allogeneic NMSCT)

Table – Allogeneic Non-myeloablative Stem Cell Transplant Schedule

	Day -3	Day 0	Day +1	Day +27	Day +84	Day +114	Day +180
TBI 200 cGy		X					
Cyclosporine twice a day	Start				Initiate taper	Off if not in PR* or CR* and no GVHD on Day +84	Off if CR or PR and no GVHD on Day +84
Mycophenolate Mofetil (MMF) twice a day		First dose 20:00hrs		Last dose			
Stem cell infusion		X	X				

* CR complete remission; PR partial remission.

If you have a matched sibling donor who is able and willing to donate stem cells for your transplant, he or she will have stem cells collected from his/her bloodstream by leukapheresis after treatment for several days with G-CSF. In most cases, the leukapheresis of the donor is done using the veins in the arms. Occasionally, if the donor’s veins are not large enough, a central vein catheter may be required.

Your treatment will start three days before you are to receive your sibling’s stem cells. You will begin taking an anti-rejection drug called cyclosporine, by mouth, twice daily for three days. On the fourth day you will receive a low dose of total body irradiation (TBI). The purpose of TBI is to allow your body to accept the donor cells without rejecting them. After the TBI is completed, your sibling’s stem cells will be given to you through your central venous catheter. This is called a non-myeloablative allogeneic transplant (mini-transplant or reduced intensity transplant).

After the allogeneic non-myeloablative SCT you will continue to receive cyclosporine (CSA) and will start taking another medication, mycophenolate mofetil (MMF). The evening of your transplant, you will receive one dose of mycophenolate mofetil (MMF) by mouth. Starting the day after your transplant, you will be given MMF twice a day for a total of 27 days. MMF and CSA are given to prevent your body from rejecting your sibling’s stem cells and to help decrease the risk of developing a complication called graft-versus-host-disease (GVHD). GVHD is a condition where your donor’s immune cells attack your skin, liver, intestines and potentially other organs. Most patients transplanted with stem cells from a matched donor develop only a mild or moderate case of GVHD. However, some patients develop very severe GVHD, which can be fatal.

Because the chance of developing GVHD can persist many months after an allogeneic NMSCT, you will continue to receive cyclosporine for 84 days after your transplant. After 84 days, the cyclosporine dose will be gradually reduced based on how your disease has responded to the allogeneic NMSCT and whether you have developed GVHD. If there is no evidence that your multiple myeloma is worse and you do not have active GVHD, CSA will be stopped approximately 6 months after your non-myeloablative transplant. Patients with active GVHD may require CSA or other drugs that control GVHD for a longer period of time, as long as they have active GVHD. While you are taking CSA, blood tests to monitor the amount of CSA in your blood will be done at least weekly for the first several months and your dose of CSA will be adjusted if necessary to maintain the proper level in your blood.

Blood tests will be performed frequently to evaluate your response to treatment and possible side effects of treatment. If necessary, platelet and red cell transfusions will be given to maintain adequate levels and antibiotics will be given to treat or prevent infection. You may also require intravenous nutritional support and pain medications during or after transplantation. You will be monitored closely for any signs and symptoms of GVHD.

The medications cyclosporine and mycophenolate mofetil, although approved for sale by the Food and Drug Administration (FDA) and used commonly in stem cell transplantation, are not specifically approved by the FDA for use in stem cell transplantation. However, studies have shown that CSA and MMF have been successful in preventing and controlling GVHD.

Discharge and Follow up

After completion of your allogeneic non-myeloablative SCT, you will visit the outpatient clinic facility at least weekly for the first 2 to 3 months and then at least monthly until 6 months after your allogeneic non-myeloablative SCT. If you were referred from another doctor in order to undergo this procedure, you may return to the care of the referring doctor approximately six months after your allogeneic non-myeloablative SCT. You will need to return to the _____ (medical facility performing transplant) at least every 6 months until 3 years after your allogeneic non-myeloablative SCT for evaluations. Most patients regain their strength and are able to return to their previous level of activity approximately 6 months after their allogeneic non-myeloablative SCT. However, each patient is different and your recovery may take longer or may even be a shorter period of time. Your ability to fight off infections may be weakened for at least one year or longer after the transplant and it may take you longer to recover from an infection or cold. Therefore, you will need to be careful and call your doctor if you have any symptoms of an infection or cold (e.g. fever, chills, cough, shortness of breath, sore throat or just not feeling well) during the first several months after transplant. If you are not sure, you may contact your doctor anytime and let him/her know how you are feeling and they will advise you on what to do. You should also call your doctor if you experience a skin rash, diarrhea, nausea, vomiting, jaundice (yellow skin), dry mouth, dry eyes, weight loss or difficulty breathing. These symptoms could be due to GVHD and require further evaluation.

Treatment Arm B (Second Autologous SCT)

If you do not have a matched sibling that can donate stem cells, you will have a second autologous SCT using the same procedure that is described under Phase I. You also will be randomized (like the tossing of a coin) between observation and receiving maintenance therapy (two anti-myeloma medications - dexamethasone and thalidomide) to begin once you recover from your second autologous transplant. The reason for this randomization is to determine whether or not receiving additional therapy will improve the outcome after tandem autologous SCT. Results from two recent studies show that thalidomide may slow the rate of relapse after autologous transplantation. These studies show that time to worsening disease may be longer in patients who get thalidomide. In these studies, thalidomide did not prolong survival, and did increase the number of side effects. The dose and timing of thalidomide was different in these reported studies than in this study. We do not know if it is better to wait until a relapse occurs to use this drug. We also do not know whether thalidomide will significantly affect quality of life.

If you were randomized to receive maintenance therapy with dexamethasone and thalidomide, you will receive these two drugs beginning at least 60 days after your second autologous SCT. You will receive 40 mg of the drug dexamethasone for four days a month (once a day by mouth), for a total of 12 months. The drug thalidomide will be given every day for 12 months. You will start thalidomide 50 mg a day by mouth and the dose will be increased each week if you are tolerating it, until you reach a maximum dose of 200 mg per day.

Table -- Dexamethasone and Thalidomide Treatment Schedule

	Months 1-12
Thalidomide 200 mg/day PO	Start 50 mg/day and increase 50 mg/day each week as tolerated to target dose of 200 mg/day
Dexamethasone 40 mg/day PO	Days 1-4 of each month

You will be seen in the clinic at least weekly, or as clinically indicated, for the first several months, regardless of whether you were randomized to observation or maintenance therapy with dexamethasone and thalidomide. After three months you will be seen at least every month until 6 months after transplant and then you will be seen at least every 6 months until three years. If necessary, you may require more frequent follow-up.

Additional assessments: If you are a female patient that has any chance of becoming pregnant, you must have a serum pregnancy test performed. The test will be performed within 24 hours of starting thalidomide, weekly for the first four weeks of taking thalidomide, and then every four weeks if your periods are regular or every two weeks if they are not, until you have finished taking thalidomide (12 months).

7. Will You Provide Blood Samples for Research?

Research Blood Samples

Genetic material is any sample of tissue, blood, fluid, etc. obtained from you during the study. With your permission, 20 samples of your blood (2 teaspoons for each sample) will be collected during the course of the study and stored to be used solely for research purposes. The samples will be stored for future studies that will look at responses to treatment based on factors not yet known. These factors may relate to characteristics of your MM or to how your body tolerated the study treatments. Usually these blood samples can be drawn from you at the time of routine blood collections. Your confidentiality will be maintained because no identifying markers (name, etc.) will remain with the sample.

All BMT CTN research samples will be paired with the respective donor or recipient sample and given unique bar code designations that cannot be linked back to the donor or the recipient. All research samples will become property of the NHLBI after conclusion of the BMT CTN Protocol #0102 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If an Investigator request for these samples is approved by the committee, the NHLBI may provide a panel of the specimens requested using unique code numbers. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the main protocol. Samples sent to researchers cannot be linked with any remaining sample at the repository.

If you agree to allow your blood to be kept for research, you are free to change your mind at any time. We ask that you contact [Principal Investigator] in writing and let him/her know you are withdrawing your permission for your blood to be used for research. His/her mailing address is on the first page of this form.

You are free not to take part in this additional future research. There will be absolutely no change in your care as a result of your refusal to give these additional samples. Please indicate your choice below:

- I agree to provide blood for future research.
- I do not agree to provide blood for future research.

Signature

Date

8. What are the possible discomforts and risks?

The treatment used in this study may cause all, some, or none of the side effects listed below. Also, there is always the chance of unexpected new side effects.

ALL PATIENTS

Central Venous Catheter: There has been considerable experience with the use of central venous catheters. The most common complications are clotting and local infection which sometimes lead to a generalized infection in the blood. Clotting may require the removal of the catheter or treatment of the clot by a fibrinolytic agent (medicines that dissolve blood clots). Infections will be treated with antibiotics, and sometimes, removal of the catheter may be required. Occasionally, there has been skin redness at the catheter exit site, which may require treatment with an antibiotic. There is also a small risk of puncturing the lung at the time of the catheter insertion. If this occurs, placement of a temporary chest tube to reinflate the lung may be required and there are no long-term effects once it has resolved.

G-CSF: G-CSF may cause local pain and burning at the injection site and some patients experience pain in their bone when treated with this drug. The bone pain is generally mild to moderate in severity and controllable in most patients with oral medication. The growth factor may cause your white count to become very high, which could affect your blood flow. Your white blood cell count will be measured, and if it becomes too high, the dose of the growth factor will be reduced or stopped. Less common possible side effects include headaches, body aches, upset stomach, skin rash, fatigue and trouble sleeping. Local inflammation and rarely an infection at the G-CSF injection site may also occur.

Leukapheresis: If you have a central venous catheter, this procedure will be done through the catheter and not through a vein. If done through a vein, the needle insertion used for the Leukapheresis procedure may cause local bruising and infection in the vein or on the skin around the vein. The bruising resolves on its own and has no additional risks. The infection in the vein or of the skin around the vein would be treated with antibiotics.

Your blood will be thinned with citrate during the Leukapheresis procedure. Citrate decreases the calcium in the blood sometimes causing temporary numbness or tingling of the fingertips or around the mouth. Should you experience any numbness, you must tell the nurse operating the machine. You will be given a dose of calcium to reverse this side effect, before the problem becomes severe. Other possible side effects of the collection procedure include lightheadedness, nausea or more rarely, fainting due to temporary lowering of the blood pressure. Stopping the procedure and giving additional intravenous fluids can correct this. Occasionally, the filtering process also removes platelets (the cells that help the blood to clot). If your platelet count falls low enough to place you in danger of bleeding, any further collection will be postponed until a replacement transfusion is given.

AUTOLOGOUS STEM CELL TRANSPLANT

Melphalan: The most common side effect in patients who have received melphalan has been nausea and vomiting (mild to moderate), loss of appetite (mild), diarrhea and skin rash. Your doctor will prescribe drugs to prevent and lessen these side effects should they occur. Melphalan will irritate your skin if it leaks outside of the vein while being given. Let your doctor or nurse know if you feel any burning, stinging or pain while you are receiving this drug. Notify your doctor right away if the area around the injection becomes red or swollen after you receive the drug. Side effects that occur several days or a week later include low blood count, mouth sores, temporary hair loss, fatigue and poor appetite. You may need blood and platelet transfusions while your counts are low and/or antibiotics to fight infections. Mouth sores which sometimes extend into the throat or esophagus can be painful, and some patients may require 7 to 10 days of morphine or a similar medication to control the discomfort. Mouth sores can also make eating difficult. If this occurs, patients will receive their nutrition intravenously until the problem resolves. In rare instances, melphalan can cause lung damage or a secondary cancer (a cancer caused by prior cancer treatment). Secondary cancers are often very difficult to treat and can be fatal.

Infusion of Autologous Stem Cells: The stem cell infusion is given similar to a blood transfusion. It is given through your central venous catheter. You will be given pre-medications just prior to the infusion to decrease the risk of a reaction. There is a very slight risk of infection due to contamination of the stem cell products during their storage or drawing. Some patients react to the preservative called DMSO, which is used in the freezing process of your stem cells. You may notice a garlic taste or smell from the DMSO. Common, less serious reactions for patients receiving an autologous SCT include mild wheezing, mild shortness of breath, back or chest pain or lightheadedness. In rare instances, a severe allergic reaction called anaphylaxis can occur leading to a drop in blood pressure or extreme difficulty in breathing. You will be monitored very closely during the infusion and afterwards to look for these reactions and given medications and/or intravenous fluids to correct these side effects. These complications are reversible with treatment.

Risk of Infection and Other Complications of Low Blood Counts: After any of the therapies in this study, but before the stem cells have begun to make new blood cells, your ability to fight infections will be very low. During that time you will be very susceptible to serious infections and will need to take extra precautions to limit your exposure to infectious agents. Bacteria, fungi and viruses that can easily be destroyed by a healthy person's immune system can cause a serious, and sometimes fatal infection in patients with low white blood cell counts. You will be given medications to prevent infections and to treat them if you develop one as determined by your doctor.

After transplantation you may not be able to make red blood cells or platelets for approximately two to three weeks until the stem cells start growing in your bone marrow. If your red blood cell count is very low, you may have severe fatigue or shortness of breath. If your platelet count is low, there is a small chance of serious bleeding. Therefore, you may need red blood cell and platelet transfusions.

The risk of dying from the complications of an autologous transplant is less than 5%. This means that for every hundred patients who have an autologous transplant for multiple myeloma, up to 5 of them may die from complications of the treatment. It is not possible to know before your transplant if you will die from complications of treatment.

NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANT (Allogeneic NMSCT)

Total Body Irradiation (TBI): The immediate effects of irradiation may include nausea, vomiting, diarrhea, loss of appetite, painful swelling of the salivary gland under the jaw for a few days, and temporary hair loss. TBI may lower your blood counts. The dose of TBI used in this protocol is approximately one-sixth of that used in conventional transplant protocols, and severe side effects are not expected and have not been seen in other patients receiving this dose of TBI. TBI has been associated with causing sterility; however, it is expected that the risk of infertility will be lower than the risk after transplants that use higher doses of TBI. Although TBI can theoretically cause abnormalities in children born to transplant survivors, the incidence of genetic abnormalities has not been reported to be greater than the general population. However, this is a potential risk and birth control should be used for at least one year after transplant to minimize risks of conceiving. In addition, there may be a small increased risk of you developing other cancers in the future as a consequence of having received chemotherapy and TBI. Cancers that are caused by treatment with chemotherapy or radiation are often fatal.

Infusion of Allogeneic Stem Cells: The infusion of your donor's stem cells into you is generally well tolerated. There is a very slight risk of infection due to contamination of the stem cell products. There is a slight risk that the stem cells will not grow after they are infused. If this occurs, you would be expected to recover your blood counts with your own blood cells, if they were relatively normal prior to this treatment. There is a very small chance that if your donor's cells do not grow, your blood counts would not recover. If this were to happen, you could die from this problem.

Risk of Infection and Other Complications of Low Blood Counts: It is possible but not likely that you will develop low blood counts after your allogeneic stem cell transplant. However, even if your blood counts are normal your ability to fight infections is decreased after allogeneic transplant. Therefore, you will be very susceptible to serious infections for a period of time after your transplant and will need to take extra precautions to limit your exposure to infectious agents. You will be given medications to prevent infections and to treat them if one develops.

After transplantation you may not be able to make red blood cells or platelets for a few weeks and may need red blood cell and platelet transfusions.

The risk of dying from the complications of an allogeneic transplant as described in this consent are estimated to be less than 20%. This means that for every hundred patients who undergo a non-myeloablative allogeneic transplant for multiple myeloma, up to 20 of them may die from

complications of the treatment. It is not possible to know before your transplant whether you will die from complications of treatment.

Mycophenolate Mofetil (MMF): MMF is a recently approved drug used for suppressing the immune system and has not been extensively used in stem cell transplantation. Preliminary studies indicate that this drug is reasonably well tolerated in the transplant setting. There are a small number of patients who have received transplants and had reversible decreases in their red cell or white cell count while receiving MMF. Your blood counts will be monitored closely and if significant decrease is noted, lowering your dose or stopping your MMF may be indicated. Other uncommon side effects include nausea, vomiting, diarrhea, and abdominal discomfort. Occasional cases of gastrointestinal bleeding have also been reported in transplant patients. Your MMF dose may also be decreased if you have severe gastrointestinal (gut) side effects.

Cyclosporine: The immediate effects of this drug may include nausea or vomiting when given orally. Other possible side effects include developing high blood pressure (hypertension), shaking of the hands (tremor), increased facial hair growth, headache, and an effect on mental function. These effects are generally reversible upon decreasing the dose of the drug. An occasional patient has had a seizure but it is unclear whether cyclosporine, other drugs, or a combination of drugs was responsible. Some patients given intravenous cyclosporine for the treatment of GVHD have experienced a painful sensation in the hands or feet or both. The pain went away after the GVHD improved or when the cyclosporine was switched from the intravenous to the oral form.

The dose of cyclosporine may need to be reduced or possibly withheld if routine blood tests show a change in kidney function. This effect on the kidneys seems to increase when other drugs, which might cause kidney problems, are given at the same time, especially certain antibiotics. Occasionally, the kidney damage is severe enough to require the use of an artificial kidney machine (hemodialysis). During treatment, cyclosporine blood levels will be monitored periodically to determine if there are increased risks of side effects that warrant adjusting the dose.

Graft-Versus-Host-Disease: Graft-versus-host-disease (GVHD) is a known complication of allogeneic stem cell transplantation. This is a process where the donor's stem cells cause inflammation of your skin, liver, gastrointestinal system and/or other organs. About 50% of patients who have undergone a non-myeloablative allogeneic stem cell transplant have developed GVHD. Your risk of developing GVHD is thought to be about the same. Cyclosporine and mycophenolate mofetil will be given to you in this study to minimize the risk of developing GVHD.

GVHD is called acute GVHD when it starts during the first one hundred days after your transplant. It can cause a skin rash, inflammation of the liver and nausea, vomiting and/or diarrhea. Graft-versus-host-disease starting later on, more than 100 days after your transplant, is called chronic GVHD. It may cause mouth sores, diarrhea, inflammation of the liver, weight loss, joint pain, dry eyes, dry mouth, skin thickness and joint problems, and, rarely, lung damage. You may develop acute, chronic or both. If you develop GVHD, several medications to control the severity of GVHD are available and are usually successful in getting rid of or controlling the symptoms. Your doctor will discuss with you the different types of treatment available to treat

GVHD. Both acute GVHD and chronic GVHD are usually mild to moderate in severity. However, severe GVHD or complications of its treatment can be fatal.

LOW RISK PATIENTS

Multiple myeloma does not behave the same in all patients. There are lab tests that can, in general, identify patients who have a better survival after autologous transplantation than other MM patients. These lab tests include a blood test called beta-2 microglobulin and a standard bone marrow test called cytogenetics or chromosome study. As a group, patients with normal cytogenetics in the bone marrow and a low beta 2 microglobulin level in their blood have a better outcome than other MM patients after autologous SCT. On average this low risk group of patients have a survival of greater than 7 years following either single or tandem autologous SCT. These patients, however, are not cured of their MM and eventually they will succumb to their disease. It is possible that for this low risk group of patients, there is a greater risk of complications and dying from the allogeneic non-myeloablative SCT in the first few years after the transplant than if they had tandem autologous SCT. It is possible though that in the long-term, the benefit of a graft versus myeloma effect may result in a better outcome for the patients who received allogeneic non-myeloablative SCT. For low risk patients, this short term risk must be considered when considering participating in the study.

MAINTENANCE THERAPY (ARM B OF PHASE II)

Dexamethasone: This medication may temporarily increase blood pressure and blood sugar levels. Some patients require medication to control their blood sugar. Steroid medications have also been known to cause insomnia (difficulty sleeping), personality changes and depression. Dexamethasone may also cause nausea, vomiting, increased appetite, stretch marks, weight gain, fluid retention, gas and heartburn. These symptoms usually go away once the medication is stopped. Gas and heartburn can be treated with medications. Call your doctor if you experience these symptoms. Dexamethasone can also cause thinning and weakening of the bones.

Thalidomide: Thalidomide may very likely cause sleepiness, decreased alertness, constipation, increased appetite, weight gain, loss of sex drive, nausea, skin rash, dry skin, numbness and tingling of the hands and/or feet, dry mouth and temporary hair loss. Less likely side effects of thalidomide include slowing of the heart, depression, swelling of the face, hands, or feet, irregular menstrual periods, and milky like fluid leaking from the nipples. Your thalidomide dose will be adjusted to try and minimize these symptoms.

Reproductive Risks: Thalidomide causes severe birth defects in unborn babies if females who are pregnant take the drug. The risk of thalidomide causing damage to the embryo is up to 50% for females taking thalidomide during the “sensitive period” which is estimated to range from 35-50 days after the last menstrual period. It is not known whether thalidomide may cause birth defects in unborn babies if it is taken after the “sensitive” period. **A single dose of thalidomide, however, may cause birth defects.**

Birth defects observed in babies exposed to thalidomide during pregnancy include absent or abnormal legs and arms; spinal cord defects; cleft lip or palate; absent or abnormal external ear; heart, kidney and genital abnormalities; and, abnormal formation of the digestive system, including blockage of necessary openings. An association between thalidomide and autism has also been proposed.

Because of the severity of these abnormalities, it is extremely important that pregnancies do not occur while you are taking thalidomide.

You should discuss with your doctor what the best methods of birth control are for you. Remember, however, that no method of birth control besides complete abstinence provides 100% protection from pregnancy.

If you are a female patient taking thalidomide, you must either abstain from all reproductive sexual intercourse or use two methods of birth control or at least one highly active method (e.g., intrauterine device [IUD], hormonal [birth control pills, injections or implants], tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), for at least four weeks before starting thalidomide therapy, during therapy, and for at least four weeks after discontinuing thalidomide therapy even when there has been a history of infertility, unless due to hysterectomy or because you have been post-menopausal or have had no menses (that is no menstrual period) for at least 24 continuous months.

If you are a female patient and have any chance of becoming pregnant, you must have a serum pregnancy test performed. The test will be performed within 24 hours of beginning thalidomide, weekly for the first four weeks of treatment, and then every four weeks if the patient's periods are regular or every two weeks if they are not, until you have finished taking thalidomide (12 months).

If you are a male patient, you will be counseled that thalidomide may be present in your semen. You must use a latex condom every time you have sexual intercourse with a woman during therapy and for four weeks after discontinuing thalidomide, even if you have had a successful vasectomy. You should request that female partners use a second method of birth control in addition to using a male condom.

You must be willing and able to participate in the FDA mandated System for Thalidomide Educational Prescribing and Safety (S.T.E.P.S.TM) if you are to receive thalidomide. Hence, you will be asked to sign a separate mandatory consent form (as part of the S.T.E.P.S.TM system). Also, all doctors and pharmacists will be registered to prescribe or dispense thalidomide.

ALL PATIENTS

Blood Drawing: The risks of drawing blood from a vein include discomfort at the site of puncture (where the needle is placed in the vein); possible bruising and swelling around the puncture site; rarely, an infection; and uncommonly, faintness from the procedure. If you have a central line or catheter, these risks will not apply to you and the risks of the central line were explained to you at the time you had the line or catheter placed. Occasionally even if you have a central catheter, you may require blood draws from a vein requiring a needle stick.

Bone Marrow Aspiration and Biopsy: A bone marrow aspiration is a procedure in which an area of the hip (buttock area) is numbed with local anesthetic, and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through the needle. When the local anesthesia is given, you may initially feel a burning sensation in your skin and bone surface for several seconds. During the actual procedure itself, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely an infection can develop.

Bone marrow aspirates and biopsies will be used to check how your disease is responding to the study treatments.

Unexpected Organ Damage and Other Side Effects: Although your major organs function well, it is possible that unexpected heart, lung, kidney, or liver damage may occur as a result of this therapy, which are rarely life-threatening and usually reversible with treatment. You will be informed if problems arise and the measures being taken to help you. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal despite intensive medical management. Other unpredictable side effects can occur and will be explained to you and treated by your physicians should unforeseeable problems arise.

Late Effects: These may include gland problems resulting in poor growth and sterility. There may be poor function of the thyroid gland, requiring thyroid hormone supplementation. There is also a risk of second cancers as a result of the chemotherapy and/or underlying disease. The risk of developing and dying from a secondary cancer is far less than the risk of dying from your disease without treatment. The long-term effects upon heart, lung, and brain are unknown.

Risk to the Unborn: The treatments in this study have not been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant must use some effective method of birth control. Effective birth control would be defined as the following: 1) refraining from all acts of vaginal intercourse (ABSTINENCE); 2) consistent use of birth control pills; 3) injectable birth control methods (Depo-Provera, Norplant); 4) tubal sterilization or male partner who has undergone a vasectomy; 5) placement of an IUD (intrauterine device); and, 6) use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.

Sterility and Future Childbearing Potential for Men and Women: Chemotherapy and /or irradiation may affect fertility. Male patients may become sterile (unable to produce sperm). Female patients may find that their menstrual cycle becomes irregular or stops permanently. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use some effective method of birth control. Damage to reproductive tissue may result in birth defects or permanent inability to father a child or become pregnant. You should discuss these risks and options in detail with your doctor before entering this study.

Other Information:

There may be some unknown or unanticipated discomforts or risks associated with this treatment in addition to those specified above, but every precaution will be taken to assure your personal safety and to minimize discomforts.

Throughout the study, the researchers will tell you of new information that might affect your decision to remain in the study.

If you wish to discuss the information above or any other discomforts you may experience, you may ask questions now or call your doctor _____, the Principal Investigator or contact person listed on the front page of this form.

9a. What are the possible benefits to you for taking part in this study?

Although this study cannot be guaranteed to be of benefit to you, it is hoped that your taking part may lead to the improvement or disappearance of your myeloma and prolongation of your life. However, no benefit is guaranteed.

9b. What are the possible benefits to others?

A possible advantage of this study is that benefit to others may result from the knowledge gained from your participation in this research study.

10. If you choose to take part in this study, will it cost you anything?

You are responsible for the costs of treatment for your disease on this protocol. Your insurance provider may not cover all or part of these costs. You are not required to pay for tests or research samples that are being performed or collected only for research purposes. You or your family will have to pay installments based on your verified ability to pay. If you have concerns or questions regarding coverage or potential charges, you should contact (contact person's name) at (###) ###-####, or the Principal Investigator of the study, to review the situation.

11. Will you receive payment for taking part in this research study?

No.

12. What if you are injured because of the study?

You agreed to take the risks listed above. If you experience an injury that is directly caused by this study, only the professional medical care you receive at the [participating clinical facility] will be provided without charge. Hospital expenses will be paid by you or your insurance provider. No other compensation is offered. By signing this form you have not waived any of your legal rights. If you have any questions about injuries, you may call [insert name] at (###) ###-####.

13. What other options or treatments are available if you do not want to be in this study?

Participation in this study is entirely voluntary. You are free to refuse to be in the study, and your refusal will not affect current or future health care you receive at this institution. You and your doctor will discuss any other treatment options available to you.

Current therapies for multiple myeloma include:

- Chemotherapy using single or combinations of drugs
- Single autologous transplants with or without additional drugs to prevent relapse after transplantation
- Double autologous transplants with or without additional drugs to prevent relapse after transplantation
- Allogeneic transplantation using a related or unrelated donor

You may also be eligible to receive other investigational treatment or you may decide not to receive any treatment. Your doctor will discuss these and other possible treatment approaches with you.

14a. How can you withdraw from this research study?

If you agree to be in this study, you are free to change your mind. At any time you may withdraw your consent to be in this study and for us to use your data. If you withdraw from the study, you will continue to have access to health care at [participating clinical facility]. If you decide to withdraw, we ask that you tell the [Principal Investigator] in writing; his/her mailing address is on the first page of this form. If you do withdraw your consent, there will be no penalty and you will not lose any benefits to which you are otherwise entitled.

Due to the nature of your illness and the study treatments, it is important to continue to receive medical follow-up even if you withdraw from the research study. If you have any questions about your rights as a study subject, you may call the Institutional Review Board (IRB) office at (###) ###-####.

14b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from the study, we ask that you agree that we can continue using all information about you that has already been collected as part of the study prior to your withdrawal, and to continue to allow your doctor to tell us about your progress until 12 months after your transplant. You may, of course, say no.

14c. Can the Principal Investigator withdraw you from this research study?

You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant as the study treatment could be harmful to the fetus.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the study treatment you are taking has been found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).
- Your myeloma returns.

15. How will your privacy and the confidentiality of your research records be protected?

Study records that have your name will be kept private as required by law. You will not be identified by name in the central study records. Your records will be given a unique code number. The key to the code will be kept in a locked file in the offices of the Coordinating Center for the study. Authorized persons from the [participating clinical facility], the hospital or clinic (if any) involved in this research, and the Institutional Review Board have the legal right to review your research records and will protect their confidentiality to the extent permitted by law. This research study is sponsored by and conducted with funds from the National Institutes of Health; therefore, the sponsor, the sponsor's agent, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the investigators conducting this study, Southwest Oncology Group, and the FDA also have the legal right to review your research records. Otherwise, your research records will not be shown to anyone without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your name will not be disclosed.

16. Expiration date for retention of records

The study results will stay in your research record at [insert Institution] for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your medical record will be destroyed or your name and other identifying information will be removed from such study results. Research information in your medical record will be kept indefinitely.

17. How will the researcher(s) benefit from your being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in scientific journals. In addition, the sponsor is providing funds to the Principal Investigator to facilitate the conduct of this study.

18. HIPAA¹ authorization to use and disclose individual health information for research purposes

- a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher’s staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by Matched Sibling Non-myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma*.
- b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work-up and after transplantation (e.g., bone marrow tests, blood tests, biopsy results).
- c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher’s staff may obtain my individual health information from (*list hospitals, clinics or providers from which health care information can be requested*).

- d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item “c.” above and information

¹ HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
 - Dr. David Maloney, Study Chairperson and staff/laboratories at Fred Hutchinson Cancer Research Center
 - Dr. Amrita Krishnan, Study Chairperson and staff/laboratories at City of Hope National Medical Center
 - National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
 - Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
 - Southwest Oncology Group (SWOG), clinical trials cooperative group
 - U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
 - U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
 - Celgene (the manufacturer of thalidomide) and the S.T.E.P.S.TM Survey Coordinating Center (Slone Epidemiology Unit of Boston University School of Public Health)
- e. Right to Refuse to sign this Authorization: I do not have the sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.
- f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.
- g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.
- h. This authorization does not have an expiration date.

Patient Consent

IRB #

19. Further Information

If you have further questions concerning this project at any time, you are free to ask them of Dr. _____, who will be available to answer them. His/her telephone number is located on the first page of the consent.

20. Consent Instructions

To voluntarily become a participant in this research study I must confirm the following and sign below.

- * I have read all of the information in the Informed Consent and I have had time to think about it.
- * All of my questions have been answered to my satisfaction. If I did not understand any of the words or parts of this study, I asked the study doctor or the research staff to explain what I did not understand.
- * I voluntarily agree to be part of this research study and to follow the study procedures as directed. I agree to keep the research staff informed of my current contact information.
- * I have been informed that I may discontinue my participation in this study at any time.
- * Signing this consent form is not a waiver of my legal rights.
- * I have received a signed copy of this Informed Consent to keep for my reference.

Subject Name (please print)

Subject Signature or Legal Representative (relationship)

Date & Time

Name of Individual Conducting Informed Consent Discussion
(please print)

Signature of Individual Conducting Informed Consent Discussion

Date

Signature of Witness (where Applicable)

Date

Patient Consent

IRB #

I have fully explained the research study to the subject and answered all of the subjects questions.

Name of Principal Investigator or Authorized Representative
(please print)

Signature of Principal Investigator or Authorized
Representative

Date

THALOMID™ (thalidomide) Informed Consent Forms

Important Information and Warnings for ADULT MALES

WARNING: SEVERE, LIFE THREATENING HUMAN BIRTH DEFECTS.
IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50, 100 OR 200 MG)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

CONSENT FOR MEN:

- INIT: _____ 1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my doctor that any unborn baby will almost certainly have severe birth defects or can even die if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide).
- INIT: _____ 2. I have been told by my doctor that I must NEVER have unprotected sexual contact with a woman who can become pregnant. Because THALOMID® (thalidomide) is present in semen, my doctor has explained that I must either completely abstain from sexual contact with women who are pregnant or able to become pregnant, or I must use a latex condom EVERY TIME I engage in any sexual contact with women who are pregnant or may become pregnant while taking THALOMID® (thalidomide) -- and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.
- INIT: _____ 3. I know that I must inform my doctor if I have had unprotected sexual contact with a woman who can become pregnant; or if I think, FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call Celgene Drug Safety at 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception.
- INIT: _____ 4. I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must not share it with ANYONE, even someone who has similar symptoms to mine. It must be kept out of the reach of children and should NEVER be given to women who are able to have children.
- INIT: _____ 5. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene.
- INIT: _____ 6. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)." I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that I cannot donate blood or semen while taking THALOMID™ (thalidomide).
- INIT: _____ 7. I understand that I must participate in a telephone survey and patient registry while I am on THALOMID® (thalidomide).
- INIT: _____ 8. My doctor has answered any questions I have asked.
- INIT: _____ 9. I understand that I might be asked to participate in an additional voluntary survey by mail or telephone to evaluate this S.T.E.P.S.® program. My agreement or disagreement will not interfere with my ability to receive THALOMID® (thalidomide).
- INIT: _____ 10. I acknowledge I may be contacted by a Celgene representative in regards to following the rules of the S.T.E.P.S.® program.

AUTHORIZATION:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID® (thalidomide). I now authorize my doctor to begin my treatment with THALOMID® (thalidomide).

Patient Name (please print) Social Security No. (only last six digits required) Date of birth (mm/dd/yyyy) _____
Patient, Parent/Guardian Signature Date (mm/dd/yyyy)

Patient Consent

IRB #

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if he has any questions regarding his treatment with THALOMID[®] (thalidomide) and have answered those questions to the best of my ability. I will comply with all of my obligations and responsibilities as a prescriber registered under the *S.T.E.P.S.* restricted distribution program.

Physician Name (please print)

DEA No.

Physician Signature

Date (mm/dd/yyyy)

THALOMID™ (thalidomide) Informed Consent Forms

Important Information and Warnings for ADULT FEMALES OF CHILDBEARING POTENTIAL

WARNING: SEVERE, LIFE THREATENING HUMAN BIRTH DEFECTS.
IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50, 100 OR 200 MG)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

CONSENT FOR FEMALES OF CHILDBEARING POTENTIAL:

INIT: _____ 1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have severe birth defects or can even die if I am pregnant or become pregnant while taking THALOMID® (thalidomide).

INIT: _____ 2. I understand that I must not take THALOMID® (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.

INIT: _____ 3. If I am having sexual relations with a man, and I am less than 50 years of age, and/or menses stopped due to treatment of my disease, I understand that I am able to become pregnant. I must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME:

- | | | |
|---|------------|--|
| At least one highly effective method | AND | One additional effective method |
| - IUD | | - Latex condom |
| - Hormonal (birth control pills, injections, patch, implants) | | - Diaphragm |
| - Tubal ligation (tubes tied) | | - Cervical cap |
| - Partner's vasectomy | | |

These birth control methods must be used for at least 4 weeks before starting THALOMID® (thalidomide) therapy, all during THALOMID® (thalidomide) therapy, and for at least 4 weeks after THALOMID® (thalidomide) therapy has stopped. I must use these methods unless I completely abstain from heterosexual sexual contact. If a hormonal (birth control pills, injections, patch or implants) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

INIT: _____ 4. I know that I must have a pregnancy test done by my doctor within 24 hours prior to starting THALOMID® (thalidomide) therapy, even if I have not had my menses due to treatment of my disease, then every week during the first 4 weeks of THALOMID® (thalidomide) therapy. I will then have a pregnancy test every 4 weeks if I have regular and/or no menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID® (thalidomide).

INIT: _____ 5. I know that I must immediately stop taking THALOMID® (thalidomide) and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, FOR ANY REASON, that I may be pregnant. If my doctor is not available, I can call Celgene Drug Safety at 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception.

INIT: _____ 6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID® (thalidomide).

INIT: _____ 7. I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must not share it with ANYONE, even someone who has similar symptoms to mine. It must be kept out of the reach of children and should NEVER be given to women who are able to have children.

Patient Consent

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- INIT: _____ 8. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene.
- INIT: _____ 9. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)." I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that I cannot donate blood while taking THALOMID™ (thalidomide).
- INIT: _____ 10. I understand that I must participate in a telephone survey and patient registry while I am on THALOMID® (thalidomide).
- INIT: _____ 11. My doctor has answered any questions I have asked.
- INIT: _____ 12. I understand that I might be asked to participate in an additional voluntary survey by mail or telephone to evaluate this S.T.E.P.S® program. My agreement or disagreement will not interfere with my ability to receive THALOMID® (thalidomide).
- INIT: _____ 13. I acknowledge I may be contacted by a Celgene representative in regards to following the rules with the S.T.E.P.S® program.

AUTHORIZATION:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID® (thalidomide). I now authorize my doctor to begin my treatment with THALOMID® (thalidomide).

 Patient Name (please print) Social Security No. (only last six digits required) Date of birth (mm/dd/yyyy) Patient, Parent/Guardian Signature Date (mm/dd/yyyy)

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if he has any questions regarding his treatment with THALOMID® (thalidomide) and have answered those questions to the best of my ability. I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

 Physician Name (please print) DEA No. Physician Signature Date (mm/dd/yyyy)

THALOMID™ (thalidomide) Informed Consent Forms

Important Information and Warnings for ADULT FEMALES NOT OF CHILDBEARING POTENTIAL

WARNING: SEVERE, LIFE THREATENING HUMAN BIRTH DEFECTS.
IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50, 100 OR 200 MG)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

CONSENT FOR FEMALES NOT OF CHILDBEARING POTENTIAL:

- INIT: _____ 1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have severe birth defects or can even die if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide).
- INIT: _____ 2. I certify that I am not now pregnant, nor am I of childbearing potential as I have been in a natural menopause for at least 24 months (been through the changes of life); or I had my uterus/womb completely removed (hysterectomy).
- INIT: _____ 3. I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must not share it with ANYONE, even someone who has similar symptoms to mine. It must be kept out of the reach of children and should NEVER be given to women who are able to have children.
- INIT: _____ 4. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene.
- INIT: _____ 5. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)." I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that I cannot donate blood while taking THALOMID™ (thalidomide).
- INIT: _____ 6. I understand that I must participate in a telephone survey and patient registry while I am on THALOMID® (thalidomide).
- INIT: _____ 7. My doctor has answered any questions I have asked.
- INIT: _____ 8. I understand that I might be asked to participate in an additional voluntary survey by mail or telephone to evaluate this S.T.E.P.S® program. My agreement or disagreement will not interfere with my ability to receive THALOMID® (thalidomide).
- INIT: _____ 9. I acknowledge I may be contacted by a Celgene representative in regards to following the rules with the S.T.E.P.S® program.

AUTHORIZATION:

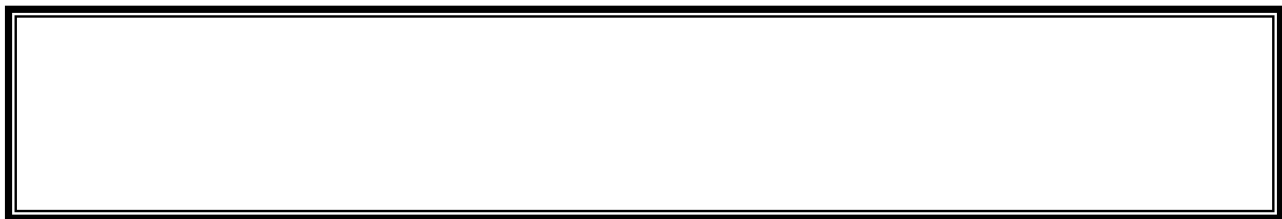
This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID® (thalidomide). I now authorize my doctor to begin my treatment with THALOMID® (thalidomide).

Patient Name (please print) Social Security No. (only last six digits required) Date of birth (mm/dd/yyyy) Patient, Parent/Guardian Signature Date (mm/dd/yyyy)

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if he has any questions regarding his treatment with THALOMID® (thalidomide) and have answered those questions to the best of my ability. I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

Physician Name (please print) DEA No. Physician Signature Date (mm/dd/yyyy)

Donor Informed Consent to Participate in Research



This is a consent form for a research study. This clinical trial is a research study to determine better treatment for patients with Multiple Myeloma (MM).

We invite you to join this study because:

- Your brother or sister has multiple myeloma (mm)
- Your blood stem cells are a match for your brother or sister
- Their disease may be treated by a blood stem cell transplant, and
- They want to join the MM research study

It is very important for you to know your choices before you decide to join a research study.

Your sibling who has multiple myeloma may be helped by a blood stem cell transplant (SCT). Stem cells are cells found in the bone marrow and blood stream that rebuild your blood, bone marrow and the immune system.

This study uses two sources of blood stem cells for transplant: autologous and allogeneic.

- An **autologous transplant** uses blood stem cells collected from the **patient**
- An **allogeneic transplant** uses blood stem cells collected from a **brother** or **sister** who are a tissue match with the patient.

Doctors currently use both sources of blood stem cells for transplants. At present autologous transplants are considered standard therapy for multiple myeloma. Allogeneic transplants as planned in this study are considered investigational. Information from this study will help doctors understand the best treatment choices for MM.

Donor Consent

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We determined that you are a tissue-match to your sibling by testing your blood. We tested to see if your antigens matched your sibling's antigens. Since all of these antigens matched, your sibling is a tissue-match with you.

This consent describes the collection of stem cells from your blood to transplant into your sibling. The donation process for stem cells is not experimental. The treatment for your sibling is part of a research clinical trial.

Patients will first have a transplant using their own cells. A few months after they have recovered from their first transplant, patients with a matched sibling donor will receive blood stem cells from their matched sibling. Patients who do not have a matched sibling donor will have a second autologous transplant.

This consent form outlines the process, potential risks and benefits of donating your stem cells for transplantation into your sibling.

1. Name of the Donor

2. Title of the Research Study

A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by HLA-Matched Sibling Non-Myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma

3a. Principal Investigator Contact Information

Insert name, affiliation, and contact information

3b. Contact information for emergencies after hours or on weekends or holidays

Call (###) ### - ####, the in-patient Bone Marrow Transplant Unit. Ask to speak to the Charge Nurse.

4. Sponsor and Source of Funding

The National Institutes of Health (or NIH), provides financial support for this study through the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN).

5. What will be done if you take part in this research study?

You will undergo a brief medical evaluation and a series of blood tests to prepare for the possible stem cell donation. The following tests and procedures will be done:

- Medical history, physical examination
- Blood tests
- Urine tests
- If you are a woman able to have children, a blood test to check for pregnancy will be done. If you are pregnant, you cannot take part in this study.
- Other tests, such as a chest x-ray or electrocardiogram (ECG or EKG, a picture of the electrical action of the heart) will be done if your physician feels it is necessary.

If your medical evaluation shows any problems or concerns, you will be told about them. This will be kept private and not shared with your sibling unless you agree.

Procedures:

Only a small quantity of stem cells is normally present in the blood. A drug called G-CSF (granulocyte-colony stimulating factor) can increase the number of these stem cells in the blood. This drug allows enough stem cells to be collected from you for transplantation into your sibling.

If the medical exam and blood tests confirm that you are a suitable donor, you will receive injections of G-CSF into the skin (like an insulin injection) once a day for 5 days to stimulate the release of your stem cells into your blood. You must come to the donor center or clinic each day for the G-CSF injections unless these can be arranged at home.















On the fourth and fifth day of G-CSF injections (and possibly the sixth day) you will go to the donor center to have stem cells collected by a machine called a blood cell separator. The procedure of collecting stem cells is called apheresis. Each apheresis procedure takes about 4 to 6 hours. The procedure of collecting stem cells involves removing blood from a vein in one arm, passing the blood through the machine where stem cells are collected, and the rest of your blood cells and plasma (the liquid portion of your blood) are returned to you through a vein in your other arm. This procedure will involve placing a needle in each of your arms, collecting the cells over approximately four to six hours during which time you will be required to lie relatively still. If the veins in your arms are not large enough for the needles, you will need to have a temporary central venous catheter placed to collect your stem cells. A central venous catheter is a sterile flexible tube that will be placed into a large vein under local anesthesia. Your physician will explain this procedure to you in more detail and you will be required to sign a separate consent form for this procedure.

Sometimes, not enough stem cells are obtained with two aphereses. If this occurs, you will need to undergo a third apheresis procedure to try to collect enough stem cells.

This process will not deplete your blood and bone marrow of stem cells. Healthy people have sufficient stem cells following the collection (aphereses) to produce a normal level of blood cells and the body will replace the lost stem cells with new ones.

You will be weighed and have blood tests (1-2 teaspoons) including a complete blood count before each collection. We repeat the complete blood count after each apheresis procedure.

The following table summarizes the schedule and procedures you undergo when donating stem cells.

DONATION SCHEDULE					
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
 G-CSF (16 µg/kg/SQ) injection					You may need to do another day
			 Weight measured and blood tests done		You may need to do another day
			 (Apheresis) Blood stem cell collection		You may need to do another day
			 Blood cells counted		You may need to do another day

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6. How long will I be in the study?

You will be in the study for up to several months from the time you sign the consent until approximately one month after stem cell collection. The actual process of taking G-CSF and then collecting your stem cells though takes less than a week. You will be contacted by phone approximately 30 days after initiation of G-CSF. You will be asked to answer questions about your health since your stem cells were collected.

7. Will you provide blood samples for research?*Research Blood Samples*

Genetic material is any sample of tissue, blood, fluid, etc. obtained from you during the study. With your permission, 3-5 teaspoons from your blood stem cell collection will be collected and stored to be used solely for research purposes. The samples will be stored for future studies that will look at responses to treatment based on factors not yet known. Your confidentiality will be maintained because no identifying markers (name, etc.) will remain with the sample.

All BMT CTN research samples will be paired with the respective donor or recipient sample and given unique bar code designations that cannot be linked back to the donor or the recipient. All research samples will become property of the NHLBI after conclusion of the BMT CTN Protocol #0102 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If an Investigator's request for these samples is approved by the committee, the NHLBI may provide a panel of the specimens requested using unique code numbers. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the main protocol. Samples sent to researchers cannot be linked with any remaining sample at the repository.

If you agree to allow your blood stem cells to be kept for research, you are free to change your mind at any time. We ask that you contact {Principal Investigator} in writing and let him know you are withdrawing your permission for your blood to be used for research. His mailing address is on the first page of this form.

You are free not to take part in this additional future research. There will be absolutely no change in your care as a result of your refusal to give these additional samples. Refusal to participate does not affect your sibling's care. Please indicate your choice below:

- I agree to provide blood stem cells for future research.
- I do not agree to provide blood stem cells for future research.

Signature_____
Date

8. What are the possible discomforts and risks?

There may be side effects from taking G-CSF and donating stem cells. The G-CSF and apheresis may cause some, all or none of the side effects listed below. You should discuss these with your doctor. In addition, there is always the chance of new, unexpected or previously unknown side effects. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the G-CSF and apheresis is stopped, but in some cases side effects can be serious, long-lasting, permanent or life threatening. Death is very rare, but possible.

Your physician and the apheresis nurse will check you closely to see if any of these side effects are occurring and routine blood tests will be done to monitor the effects of treatment.

Risks and side effects include:

G-CSF: Less than ½ teaspoon (2 ml) G-CSF will be injected under your skin each day. Injection of G-CSF under the skin could cause some local pain or burning sensation at the injection site. Most people experience varying levels of pain in their bones when treated with this drug. The pain is usually relieved with acetaminophen (Tylenol™) or ibuprofen (Motrin™, Advil™). Aspirin or aspirin containing drugs must not be taken during G-CSF administration and for two weeks after your last apheresis collection procedure without physician approval. Other, less frequently reported side effects of G-CSF include skin rash, headaches, muscle aches, nausea, vomiting, muscle cramps and trouble sleeping. These symptoms usually go away within a few days after stopping the drug. Other rare potential side effects include signs of allergy such as a rapid heart rate, dizziness, shortness of breath, itching or rash. Temporary changes in laboratory values that monitor liver and bone changes can also occur. These return to normal after stopping the drug. Rarely, normal donors receiving G-CSF have experienced swelling of their spleen and on occasion, internal bleeding from rupture of the spleen. Symptoms of this side effect are pain in the upper left-side just below the rib cage, general fatigue and weakness, or loss of consciousness from low blood pressure. Rupture of the spleen can be very serious and is potentially life threatening. Management of this problem could require blood transfusions or surgery. G-CSF could cause your white count to be very high which will be monitored when your white blood cell count is measured. If it becomes too high, the dose of G-CSF will be reduced. Other, unanticipated side effects may occur which have not been reported before. If you have any unusual symptoms, you should report them immediately.

Long-term (beyond one year) safety data on G-CSF administered to normal, healthy people is limited, but so far has not identified any late problems for donors. Possible interactions of G-CSF with other drugs have not been fully evaluated; therefore, it is important that you report all drugs, both prescription and non-prescription to the donor center. There is a theoretical possibility that G-CSF can accelerate the growth of tumors or cancers, although currently there is no evidence of this effect, and therefore the possibility cannot be excluded.

Apheresis (collection of stem cells from the blood stream): If possible, apheresis will be done through your veins. The needle insertion used for the apheresis procedure may cause local

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bruising and infection in the vein or on the skin around the vein. The bruising resolves on its own and has no additional risks. An infection would be treated with antibiotics.

To prevent clotting, your blood will be thinned with citrate (an anticoagulant) during the apheresis procedure. Citrate decreases the calcium in the blood sometimes causing temporary numbness or tingling of the fingertips or around the mouth. Should you experience any numbness, you must tell the nurse operating the machine. If not corrected by replacing calcium, this complication could progress to severe muscle cramps while your calcium is low. Other possible side effects of the collection procedure include lightheadedness, nausea or more rarely, fainting due to temporary lowering of the blood pressure. Stopping the procedure and giving intravenous fluids can correct this. Occasionally, the filtering process also removes platelets (the cells that help the blood to clot). If your platelet count falls low enough to place you in danger of bleeding (less than 30,000 ml), any further collection will be postponed until a replacement transfusion is given.

You will also lose some platelets with the stem cells. If your platelet count drops low enough to place you in danger of bleeding any further collections will be delayed until your platelet count increases.

Central Venous Catheter: If your arm veins are too small to allow apheresis, you will require a central venous catheter to donate cells. A central venous catheter is a flexible sterile tube that will be placed into a large vein so that blood can be withdrawn more easily and with less discomfort. This tube is placed under local anesthesia. There is considerable experience with the use of central venous catheters. Complications include blood clots and infection. Clotting may necessitate removal of the catheter or treatment of the clot by injecting a medicine (streptokinase or urokinase) that dissolves blood clots. If you develop an infection you will require treatment with antibiotics and your catheter may need to be replaced. Other uncommon side effects may include swelling of the face and arm and/or lung collapse. If the lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand. There are no long-term effects once it has resolved.

Venipuncture: Drawing blood from a vein is painful (like a pin-prick) and may be associated with bleeding into the skin (bruising). Very rarely it may result in an infection.

Risks to the Unborn: Since the G-CSF and apheresis used in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. Since it is also not known how apheresis affects breast milk, you should not nurse your baby while on this study.

You can not be pregnant and be in this study

9a. What are the possible benefits to you for taking part in this study?

There is no direct medical benefit to you for taking part in this study.

9b. What are the possible benefits to others?

The possible benefit to your sibling may be improvement in the control of their multiple myeloma and possibly prolonged survival. We hope the information learned from this study will benefit other patients with multiple myeloma in the future.

10. If you choose to take part in this study, will it cost you anything?

There is no financial benefit to you by participating in this treatment protocol. Usually, the insurance policy of the stem cell recipient will cover the cost of the donor evaluation and stem cell collection. The transplant coordinator will help you identify insurance coverage before you incur charges for your evaluation and donation. If you have concerns or questions regarding coverage or potential charges, you should contact (contact person's name) at (###) ### - ##### to review the situation.

11. Will you receive compensation for taking part in this research study?

No.

12. What if you are injured because of the study?

You agree to take the risks listed above. If you experience an injury that is directly caused by this study, only the professional medical care you receive at the [participating clinical facility] will be provided without charge. Hospital expenses will be paid by you or your insurance provider. No other compensation is offered. By signing this form, you have not waived any of your legal rights. If you have any questions about injuries, you should contact [insert name] at (###) ###-####.

13. What other options or treatments are available if you do not want to be in this study?

Participation in this study is entirely voluntary. You are free to refuse to be in the study and your refusal will not influence current or future health care you receive at this institution.

Instead of being in this study, your sibling may have these options:

- Treatment with other drugs or combination of drugs.
- Autologous or allogeneic stem cell transplant.
- No therapy at this time, with care to help them feel more comfortable.

Your sibling may receive these treatments at this or other centers even if you or they choose not to take part in this study.

14a. How can you withdraw from this research study?

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor first. Your sibling will have chemotherapy and receive an autologous stem cell transplant approximately 60 to 120 days before your stem cells are needed. Leaving the study early may affect your sibling's treatment.

If you decide to withdraw, we ask that you notify [Principal Investigator] in writing; his/her mailing address is on the first page of this form.

If you have any questions regarding your rights as a donor, you may call the Institutional Review Board (IRB) office at (###) ###-####.

14b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from the study, we will ask your permission to continue using all information about you that has already been collected as part of the study prior to your withdrawal.

14c. Can the Principal Investigator withdraw you from this research study?

Your doctor may decide to take your sibling off this study if their condition becomes worse, side effects of their treatment are severe or life threatening, or the treatment is no longer in their best interest. If your sibling leaves the study there will be no need for you to donate stem cells.

Your doctor may also decide to take you off this study if the G-CSF or apheresis causes severe, unmanageable or life threatening side effects in you.

15. How will your privacy and the confidentiality of your research records be protected?

Study records that identify you will be kept confidential as required by law. You will not be identified by name in the study records. Your records will be assigned a unique code number. The key to the code will be kept in a locked file in the Data and Coordinating Center. Authorized persons from [Clinical Center Name], the hospital or clinic (if any) involved in this research, and the Institutional Review Board have the legal right to review your research records and will protect the confidentiality of them to the extent permitted by law. This research study is sponsored and conducted under the authority of the National Institutes of Health; therefore, the sponsor and the sponsor's agent also have the legal right to review your research records. Otherwise, your research records will not be released without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your identity will not be disclosed.

16. Expiration Date for Retention of Records

The study results will be retained in your research record for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your medical record will be destroyed or your name and other identifying information will be removed from such study results. Research information in your medical record will be kept indefinitely.

17. How will the researcher(s) benefit from your being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in scientific journals. In addition, the sponsor is providing funds to the Principal Investigator to facilitate the conduct of this study.

18. HIPAA¹ authorization to use and disclose individual health information for research purposes

- a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher’s staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by Matched Sibling Non-myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma*.
- b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment) and physical examination findings.
- c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher’s staff may obtain my individual health information from *(list hospitals, clinics or providers from which health care information can be requested)*.

- d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item “c.” above and information disclosed by me during the course of the research may be received and used by the following parties:
 - Principal Investigator and the researcher’s staff

¹ HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

- Dr. David Maloney, Study Chairperson and staff/laboratories at Fred Hutchinson Cancer Research Center
 - Dr. Amrita Krishnan, Study Chairperson and staff/laboratories at City of Hope National Medical Center
 - National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
 - Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
 - Southwest Oncology Group (SWOG), clinical trials cooperative group
 - U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
 - U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- e. Right to Refuse to sign this Authorization: I do not have the sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.
- f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.
- g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.
- h. This authorization does not have an expiration date.

19. Further Information

If you have further questions concerning this project at any time, you are free to ask them of Dr. _____, who will be available to answer them. His/her telephone number is located on the first page of this consent.

Donor Consent

IRB #

20. Consent Instructions

To voluntarily become a participant in this research study I must confirm the following and sign below.

*I have read all of the information in the Informed Consent and I have had time to think about it.

*All of my questions have been answered to my satisfaction. If I did not understand any of the words or parts of this study, I asked the study doctor or the research staff to explain what I did not understand.

*I voluntarily agree to be part of this research study and to follow the study procedures as directed. I agree to keep the research staff informed of my current contact information.

*I have been informed that I may discontinue my participation in this study at any time.

*Signing this consent form is not a waiver of my legal rights.

*I have received a signed copy of this Informed Consent to keep for my reference.

Subject Name (please print)

Subject Signature or Legal Representative (relationship)

Date & Time

Name of Individual Conducting Informed Consent Discussion
(please print)

Signature of Individual Conducting Informed Consent Discussion

Date

Signature of Witness (where Applicable)

Date

Donor Consent

IRB #

I have fully explained the research study to the subject and answered all of the subjects questions.

Name of Principal Investigator or Authorized Representative
(please print)

Signature of Principal Investigator or Authorized
Representative

Date

APPENDIX C

LABORATORY PROCEDURES

1. HLA TYPING

HLA typing will be performed for all patients and sibling(s) as soon as possible after initial evaluation to determine the availability of an HLA-matched sibling donor. If possible, this testing will be complete prior to the first autologous transplant but it is expected that full donor evaluations will not always be possible to complete by this time. Patient samples for HLA-testing MUST be drawn prior to the first autologous transplant and potential donor samples must be drawn no later than three weeks after the first autologous transplant.

HLA typing of heparinized peripheral blood can be done by either serologic or DNA methods for HLA-A, -B. DNA methods must be utilized for DRB1.

The specimens for HLA typing will be:

- a) Donor – 5 ml peripheral blood sample(s) from sibling/family member, and
- b) Patient – 5 ml peripheral blood sample from the recipient.

2. CHIMERISM – Autologous/Allogeneic Transplant Patients Only

A heparinized peripheral blood sample from patient and donor is required for chimerism studies 2 weeks pre-allogeneic transplant to subsequently determine the host or donor origin of ANC recovery. All pre-transplant samples will be stored for future evaluation of post-transplant chimerism.

A 10 ml heparinized peripheral blood sample must also be obtained from the patient at weeks 4, 8, and 12, then at 6 months and one year post allogeneic transplant.

3. PATHOLOGY/CYTOGENETICS STUDIES

Unilateral bone marrow biopsies and aspirates are required for pathology analysis and aspirates are required for cytogenetic analysis prior to the first transplant (baseline) and yearly following the second transplant. Other bone marrow assessments as summarized in the schedule of evaluations (Chapter 4) do not require the inclusion of bone marrow pathology/cytogenetics unless the original diagnostic marrow or the baseline marrow documented abnormal pathology/cytogenetics.

Cytogenetic studies by standard metaphase karyotype analysis will be conducted per institutional guidelines.

4. FLOW CYTOMETRY

According to the BMT CTN Graft Evaluation MOP, the hematopoietic stem cell content of the product (graft) should be determined using CD45-FITC and CD34-PE staining to identify stem cells within the WBC component of the product.

Allogeneic donor products will also be analyzed to determine the B, T and NK cell content using CD3, CD4, CD8, CD19 and CD56 expression as detected by flow cytometry. Autologous grafts require CD34 enumeration at a minimum.

Flow cytometry will be done in keeping with the BMT CTN MOP and local institutional practice, and will be performed prior to infusion of the graft.

5. RESEARCH SPECIMENS

All BMT CTN research samples will be paired with the respective donor or recipient sample and given unique bar code designations that cannot be linked back to the donor or the recipient. All research samples will become property of the NHLBI after conclusion of the BMT CTN Protocol #0102 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If an Investigator's request for these samples is approved by the committee, the NHLBI may provide a panel of the specimens requested using unique code numbers. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the main protocol. Samples sent to researchers cannot be linked with any remaining sample at the repository.

For Donors Only:

Five vials, each containing 2-5 x 10⁶ nucleated cells (~1ml per cryovial) from the donor blood stem cells must be obtained prior to the allogeneic transplant. Transplant Centers should follow controlled-rate freezing SOPs for cryopreserving research samples as for product storage. Samples will be shipped annually to the NHLBI Repository in compliance with the shipping procedures specified in the BMT CTN MOP and the BMT CTN 0102 Laboratory Sample Information Guide.

Christine DeMasco
NHLBI Repository
SeraCare BioServices
217 Perry Parkway
Gaithersburg, MD 20877
Phone: (301) 208-8100, x196
Fax: (301) 208-8829

For Patients Only: Peripheral blood samples (one 10ml serum sample and one 10ml nucleated cell sample) will be collected for future testing at the time of disease staging and shipped quarterly to the Repository in compliance with the shipping procedures specified in the BMT CTN MOP.

Peripheral blood samples will be collected prior to the first autologous transplant and prior to the second transplant (auto or allo), and at 8 weeks, 6 months, 9 months and every 6 months until 3 years after the second transplant.

SCHEDULE OF LABORATORY EVALUATIONS

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
HLA Typing	5 ml peripheral blood or according to institutional practice	Store according to institutional practice	Prior to the 1 st autologous transplant	N/A	Transplant Center
Chimerism	10 ml heparinized peripheral blood or according to institutional practice	Store according to institutional practice	≤ 2 weeks prior to the allogeneic transplant for patient and donor. Weeks 4, 8 and 12, 6 months and one year post allogeneic transplant for patient	N/A	Transplant Center
Cytogenetic Studies	Volume of bone marrow aspirate determined according to institutional practice	Store according to institutional practice	Prior to the 1 st autologous transplant and yearly following the second transplant. Bone marrow aspirates must be done prior to the second transplant, prior to initiation of maintenance therapy (if applicable) and at 8 weeks and 6 months post second transplant only if previously documented abnormal cytogenetics.	N/A	Transplant Center
Flow Cytometry	Volume of graft determined according to institutional practice	Store according to institutional practice	Prior to 1st autologous transplant and prior to allo transplant .	N/A	Transplant Center
Donor Research Specimen Nucleated Cells	5 vials each containing 2 – 5 x 10 ⁶ nucleated cells collected from <u>allograft</u> (1mL cryovial)	Follow controlled-rate freezing SOPs for crypreserving research samples as for product storage at -150°	Prior to allogeneic transplant (at time of donation)	Liquid nitrogen shipment annually to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD
Patient Research Specimen Disease Assessments (Serum)	10 ml peripheral blood	Let sample sit for 30 minutes. Centrifuge for 10 minutes. Remove serum, aliquot into cryovials and freeze at -70°	Prior to first autologous transplant, prior to second transplant (auto or allo) and at 8 weeks, 6 months, 9 months, 12 months and then every 6 months until 3 years post second transplant	Frozen shipment quarterly to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
Patient Research Specimen Disease Assessments (Nucleated Cells)	10 ml peripheral blood	Obtain white blood cell pellet (by ficoll) and freeze in cryovial at -70°	Prior to first autologous transplant, prior to second transplant (auto or allo) and at 8 weeks, 6 months, 9 months, 12 months and then every 6 months until 3 years post second transplant	Frozen shipment quarterly to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD

APPENDIX D

SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (S.T.E.P.S.[™]) AND DOSAGE AND ADMINISTRATION PROCEDURES

This appendix is an excerpt (pages 27-39) of the S.T.E.P.S.[™] document found at

[http://www.celgene.com/images/pdf/\\$FILE/Balancing.pdf](http://www.celgene.com/images/pdf/$FILE/Balancing.pdf)

System for
Thalidomide
Education and
Prescribing
Safety

THALOMID™ (thalidomide)

Balancing the Benefits and the Risks

DOSAGE AND ADMINISTRATION

THALOMID™ (THALIDOMIDE) MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE *S.T.E.P.S.*™ PROGRAM. THALOMID™ (THALIDOMIDE) MAY ONLY BE PRESCRIBED BY PRESCRIBERS REGISTERED WITH THE *S.T.E.P.S.*™ PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS REGISTERED WITH THE *S.T.E.P.S.*™ PROGRAM.

Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.

Acute ENL Reaction

For an acute episode of cutaneous ENL, THALOMID™ (thalidomide) dosing should be initiated at 100 to 300 mg/d, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kg should be started at the low end of the dose range.

Severe ENL Reaction

In patients with a severe cutaneous ENL reaction or in those who have previously required higher doses to control the reaction, THALOMID™ (thalidomide) may be initiated at higher doses, up to 400 mg/d. THALOMID™ (thalidomide) should be administered once daily at bedtime or in divided doses with water, and should be taken at least 1 hour after meals. In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be initiated concomitantly with THALOMID™ (thalidomide). Corticosteroid usage can be tapered and discontinued when the neuritis has ameliorated.¹

THALOMID™ (thalidomide) should be usually continued until signs and symptoms of active reaction have subsided, usually at least 2 weeks.¹ The daily THALOMID™ (thalidomide) dose can then be tapered in 50-mg decrements every 2 to 4 weeks. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who experience a flare during tapering should be maintained on the minimum dose necessary to control the reaction.¹ Tapering of THALOMID™ (thalidomide) and discontinuation of the drug should be attempted every 3 to 6 months in 50-mg decrements every 2 to 4 weeks.¹

Summary of Dosage and Administration for Cutaneous ENL

- For an episode of cutaneous ENL, THALOMID™ (thalidomide) 100 to 300 mg/d should be administered once daily and continued until signs and symptoms have subsided, usually at least 2 weeks.
- For severe reactions, THALOMID™ (thalidomide) doses as high as 400 mg/d may be needed.
- After signs and symptoms have subsided, the daily THALOMID™ (thalidomide) dose should be tapered in 50-mg decrements every 2 to 4 weeks. Patients with a documented history of requiring prolonged maintenance treatment to prevent ENL recurrence or who experience a flare during tapering should be maintained on the minimum dose necessary to control the reaction. In these patients, a THALOMID™ (thalidomide) tapered withdrawal should be attempted every 3 to 6 months.
- In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids should be started concomitantly with THALOMID™ (thalidomide). Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (*S.T.E.P.S.*TM)

Description

The System for Thalidomide Education and Prescribing Safety, *S.T.E.P.S.*TM, is a multicomponent system designed to help ensure that fetal exposure to THALOMIDTM (thalidomide) does not occur. The system also creates awareness of other potential side effects that can occur during therapy with THALOMIDTM (thalidomide). *S.T.E.P.S.*TM requires that **all** prescribers and pharmacies register to prescribe or dispense THALOMIDTM (thalidomide) and all patients complete an informed consent process and participate in a **mandatory and confidential** surveillance registry.

Program Process

Prescriber Registration Process

All prescribers interested in treating patients with THALOMIDTM (thalidomide) must register in the THALOMIDTM (thalidomide) Prescriber Registry via a Prescriber Registration Card that is located in every *S.T.E.P.S.*TM folder.¹

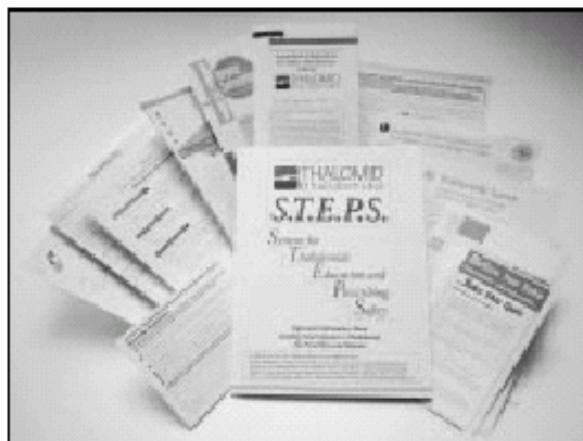
Prescribers must complete, sign, and return the Prescriber Registration Card; by doing so, prescribers agree to prescribe THALOMIDTM (thalidomide) in accordance with all the terms listed on the card.

Prescribers must wait for registration confirmation prior to prescribing THALOMIDTM (thalidomide).

All materials that are necessary to comply with *S.T.E.P.S.*TM program requirements are contained in the *S.T.E.P.S.*TM folder (Figure 3). The contents of **ONE FOLDER** should be used with **ONE PATIENT**, and kept with the patient's medical record. Additional *S.T.E.P.S.*TM folders can be obtained from a Celgene

Immunology Specialist or by calling 1-888-4-CELGENE. The *S.T.E.P.S.*TM folder contains the following information and materials to help ensure that fetal exposure to THALOMIDTM (thalidomide) does not occur:

Figure 3. *S.T.E.P.S.*TM materials for prescribers and patients.



- Prescriber Registration Card: **All prescribers must register.**
- Thalidomide Victims Association of Canada letter: A cautionary message to the prescriber and patient from thalidomide victims.
- *Information for Men and Women Taking THALOMID™ (thalidomide)*: This brochure should be used for patient counseling regarding the teratogenic risks as well as other side effects and precautions associated with THALOMID™ (thalidomide) therapy. A video presentation of this information will be provided to the prescriber's office upon registration.
- *Your Contraceptive Choices*: This brochure is provided to assist in counseling patients on choosing two appropriate contraceptive methods.
- *Emergency Contraception*: This brochure should be used to assist patients in the event they have unprotected heterosexual sexual intercourse while taking THALOMID™ (thalidomide).
- Patient Referral Form: A form that must be used if another health-care professional is chosen to provide contraceptive counseling for the patient.
- Patient Quiz: The quiz is provided to verify patient understanding of the risks and requirements of therapy.
- Consent Form (Figure 4): This informed consent document **must be understood and signed** before any patient can receive THALOMID™ (thalidomide).
- Thalidomide Survey Forms: These mandatory and confidential enrollment and follow-up surveys must be completed by the patient and prescriber. Men must participate, as well as women, because fetal exposure to THALOMID™ (thalidomide) could occur as a result of the presence of the drug in semen or through sharing the medication. Included are forms for patients aged 18 or older. ***Forms for patients under 18 years of age are available by calling 1-888-4-CELGENE.***

Important Information for Men and Women Taking THALOMID™ (thalidomide), the Consent Form, Patient Quiz, and Survey Forms are available in 14 languages and can be obtained through a Celgene Immunology Specialist or by calling 1-888-4-CELGENE.

S.T.E.P.S.™ program requirements differ for male and female patients. Both male and female patients must receive:

- Information regarding the general guidelines for taking THALOMID™ (thalidomide).

Figure 4. THALOMID™ (thalidomide) informed consent form.

Important Information and Warnings for All Patients Taking THALOMID™ (thalidomide)

WARNING: SERIOUS HUMAN BIRTH DEFECTS
IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

CONSENT FOR WOMEN:

- INIT: _____ 1. I understand that I must not take THALOMID™ (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.
- INIT: _____ 2. I understand that severe birth defects can occur with the use of THALOMID™ (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or maybe even die if I am pregnant or become pregnant while taking THALOMID™ (thalidomide).
- INIT: _____ 3. I understand that if I am able to become pregnant, I must use at least one highly effective method and one additional effective method of birth control contraception AT THE SAME TIME:
- | | | |
|--|-------------------|---|
| <p>At least one highly effective method</p> <ul style="list-style-type: none"> - IUD - Hormonal (birth control pills, injections, or implants) - Tubal ligation - Partner's vasectomy | <p>AND</p> | <p>One additional effective method</p> <ul style="list-style-type: none"> - Latex condom - Diaphragm - Cervical cap |
|--|-------------------|---|
- These birth control methods must be used for at least 4 weeks before starting THALOMID™ (thalidomide) therapy, all during THALOMID™ (thalidomide) therapy, and for at least 4 weeks after THALOMID™ (thalidomide) therapy has stopped. I must use these methods even if I am infertile, unless I have had a hysterectomy or because I have been postmenopausal for at least 24 months (been through the changes of life). The only exception is if I completely avoid heterosexual sexual intercourse. If a hormonal (birth control pills, injections, or implants) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.
- INIT: _____ 4. I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID™ (thalidomide) therapy, then every week during the first 4 weeks of THALOMID™ (thalidomide) therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID™ (thalidomide).
- INIT: _____ 5. I know that I must immediately stop taking THALOMID™ (thalidomide) and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, FOR ANY REASON, that I may be pregnant. If my doctor is not available, I can call (XXX)-XXX-XXXX for information on emergency contraception.
- INIT: _____ 6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID™ (thalidomide).
- INIT: _____ 7. I understand that THALOMID™ (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.
- INIT: _____ 8. I have read the THALOMID™ (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)." I understand the contents, including other possible health problems from THALOMID™ (thalidomide), so-called "side effects." I know that I cannot donate blood while taking THALOMID™ (thalidomide).
- INIT: _____ 9. My doctor has answered any questions I have asked.
- INIT: _____ 10. I understand that I must participate in a survey and patient registry while I am on THALOMID™ (thalidomide), which will require completing additional forms.

CONSENT FOR MEN:

- INIT: _____ 1. I understand that I must not take THALOMID™ (thalidomide) if I cannot avoid unprotected sex with a woman, even if I have had a successful vasectomy.
- INIT: _____ 2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy.
- INIT: _____ 3. I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID™ (thalidomide) and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.
- INIT: _____ 4. I also know that I must inform my doctor if I have had unprotected sex with a woman or if I think, FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call (XXX) XXX-XXXX for information on emergency contraception.
- INIT: _____ 5. I understand that THALOMID™ (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.
- INIT: _____ 6. I have read the THALOMID™ (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)." I understand the contents, including other possible health problems from THALOMID™ (thalidomide), so-called "side effects." I know that I cannot donate blood or semen while taking THALOMID™ (thalidomide).
- INIT: _____ 7. My doctor has answered any questions I have asked.
- INIT: _____ 8. I understand that I must participate in a survey and patient registry while I am on THALOMID™ (thalidomide), which will require completing additional forms.

AUTHORIZATION:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID™ (thalidomide). I now authorize my doctor to begin my treatment with THALOMID™ (thalidomide).

Patient Name (please print) Social Security No. (only last six digits required) Date of birth (mm/dd/yyyy) Patient, Parent/Guardian Signature Date (mm/dd/yyyy)

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ (thalidomide) and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed. In addition, I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

Physician Name (please print) DEA No. Physician Signature Date (mm/dd/yyyy)

- Comprehensive counseling on the risk of birth defects, other side effects, and important precautions associated with THALOMID™ (thalidomide) therapy as outlined in the brochure entitled *Important Information for Men and Women Taking THALOMID™ (thalidomide)* and in the informed consent form.
- **Mandatory** contraception and emergency contraception counseling.

In addition, female patients also must receive:

- Specific contraceptive counseling on the TWO methods of birth control they must use before, during, and after therapy.
- Pregnancy testing.

Pharmacy Registration Process

All retail and hospital pharmacies must be registered to dispense THALOMID™ (thalidomide). A registration card (Figure 5) outlining the terms for dispensing must be signed by the head pharmacist or director of pharmacy and returned to Celgene Corporation. When the registration information is received, the pharmacy's eligibility to dispense THALOMID™ (thalidomide) will be activated. Pharmacies must agree to:

- Refuse prescriptions written more than 7 days prior to presentation.
- Collect and retain on file a signed informed consent form with an initial prescription for THALOMID™ (thalidomide). Telephone prescriptions are not permitted.
- Register THALOMID™ (thalidomide) patients via facsimile or phone.
- Dispense blister packs intact.
- Dispense a maximum prescription of a 4-week (28-day) supply of THALOMID™ (thalidomide) therapy with no automatic refills.
- Dispense subsequent prescriptions only if fewer than 7 days of therapy remain on the previous prescription.
- Verify patient registry and record subsequent prescriptions via on-line transmission or phone.
- Educate all staff pharmacists about the dispensing procedures for THALOMID™ (thalidomide).
- Accept unused THALOMID™ (thalidomide) returned by patients.

Failure to comply with all requirements of the *S.T.E.P.S.*™ program may result in the pharmacy's not being permitted to dispense THALOMID™ (thalidomide).

Figure 5. Pharmacy registration card.

System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)

Pharmacy Registration

All retail and hospital pharmacies must be registered to dispense THALOMID™ (thalidomide). Please review the steps that must be followed with every patient and return this card to Celgene Corporation. Registration must be signed by the Head Pharmacist or Director of Pharmacy.

Before dispensing THALOMID™ (thalidomide), I accept responsibility to:

- Refuse prescriptions written more than 7 days prior to presentation
- Collect and file a signed informed consent form with initial prescriptions (telephone prescriptions are not permitted)
- Register patients via fax or phone
- Dispense blister packs intact
- Dispense a maximum of a 4-week (28-day) supply of THALOMID™ (thalidomide) therapy, with no automatic refills
- Dispense subsequent prescriptions only if fewer than 7 days of therapy remain on the previous prescription
- Verify patient registration and record subsequent prescriptions via on-line transmission or phone
- Educate all staff pharmacists about the dispensing procedure for THALOMID™ (thalidomide)
- Accept unused THALOMID™ (thalidomide) returned by patient

I understand that if I fail to comply with all requirements of the S.T.E.P.S. program, my pharmacy may not be permitted to dispense THALOMID™ (thalidomide).

Pharmacist Name _____ Title _____

Signature _____ Pharmacy Name _____

Address _____

City _____ State _____ Zip _____

Phone _____ Fax _____

Pharmacy No. _____ NABP No. _____ Preferred wholesaler _____

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Prescribing Procedures for THALOMID™ (thalidomide)*Initial Visit*

When considering THALOMID™ (thalidomide) therapy for a patient, the prescriber must do the following:

- **Establish appropriateness of THALOMID™ (thalidomide) therapy versus therapeutic alternatives:**
 - THALOMID™ (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe ENL. THALOMID™ (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. THALOMID™ (thalidomide) also is indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.
- **Provide comprehensive counseling on the risks and benefits of THALOMID™ (thalidomide) therapy:**
 - Patients must be counseled on the risk of birth defects, other side effects, and important precautions associated with THALOMID™ (thalidomide) therapy.
 - Men must be instructed to use a latex condom every time they have sexual intercourse with a woman, even if they have undergone a successful vasectomy.
 - Utilize the patient education materials provided.
- **Determine if patient has childbearing potential:**
 - If patient has undergone a hysterectomy, been postmenopausal, or had no menses for at least 24 months, continue with the instructions provided in the INITIATING THALOMID™ (thalidomide) THERAPY section.
 - **If patient is sexually mature and does not meet the above criteria, provide contraceptive counseling, including counseling on emergency contraception.**
- Female patients must thoroughly understand the need for two forms of contraception to be used AT THE SAME TIME, beginning 4 weeks before therapy, throughout therapy, and for 4 weeks after stopping therapy with THALOMID™ (thalidomide).
- Contraceptive methods must include one highly effective method (eg, IUD, hormonal [birth control pills, injections, or implants], tubal ligation, or partner's vasectomy) and one additional effective method (eg, latex condom, diaphragm, or cervical cap).

- If IUD or hormonal contraception is medically contraindicated, another highly effective method or two barrier methods must be used **AT THE SAME TIME**.
- Utilize the patient education materials provided.
 - **Prescribers may refer patients to another health-care professional for contraceptive counseling using the Patient Referral Form.**
- **Continue selected birth control options for 4 weeks prior to initiating THALOMID™ (thalidomide).**

Initiating THALOMID™ (thalidomide) Therapy

The following steps must be completed prior to initiating THALOMID™ (thalidomide) therapy:

- **Repeat patient counseling.**
- **Perform pregnancy test (female patients), even if continuous abstinence is the chosen method of birth control.**
 - Test must satisfy a sensitivity of least 50 mIU/mL.
 - Test must be performed on female patients of childbearing potential, **with negative results in written form**, within the 24 hours prior to initiating THALOMID™ (thalidomide) therapy.
 - Women of childbearing potential also must receive a pregnancy test every week for the first 4 weeks, then every 4 weeks thereafter if their menstrual cycles are regular.
 - If the menstrual cycle is irregular, female patients must receive a pregnancy test every 2 weeks thereafter.
 - Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.
 - **If pregnancy does occur during treatment, the drug must be immediately discontinued.** Any suspected fetal exposure to THALOMID™ (thalidomide) must be reported immediately to the FDA via the MedWATCH number at 1-800-FDA-1088 and also to Celgene Corporation. The patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

- **Administer the THALOMID™ (thalidomide) patient quiz.**
 - Gauge patient understanding of the requirements for taking the drug.
 - If the patient cannot answer all of the questions correctly, review the material that he or she does not understand.
 - Readminister patient quiz. Repeat until the patient satisfactorily understands all risks and correctly answers all questions or reconsider the appropriateness of THALOMID™ (thalidomide) therapy.
- **Complete the informed consent form.**
 - The consent form must be read to the patient and/or parent/legal guardian in the language of his or her choice. Each statement must be initialed by the patient and/or parent/legal guardian to indicate understanding, and the form must be completed and signed by the prescriber and patient and/or parent/legal guardian.
 - If the patient is under 18 years of age, his or her parent or legal guardian must read this material, sign the form, and agree to ensure compliance.
 - Retain “Prescriber” copy with patient record.
 - Mail “Survey Coordinators” copy (via self-mailing format).
 - Instruct patient to retain “Patient” copy and to present “Pharmacist” copy with prescription to pharmacist.
- **Complete the mandatory and confidential survey enrollment form.**
 - Instruct patients to complete the confidential section, seal the survey, and return it to you.
 - Complete prescriber section and return survey in the envelope provided to the Slone Epidemiology Unit of Boston University School of Public Health.
 - Men must complete the survey, as well as women, because failure to use a latex condom during sexual intercourse with a woman or drug-sharing could result in fetal exposure to thalidomide.
- **Provide prescription.**
 - Prescriptions cannot be issued by telephone.
 - Prescribe **no more than 4 weeks (28 days) of therapy**, with no automatic refills.
 - Inform patients that all prescriptions must be filled within 7 days.
 - It is recommended that female patients initially receive no more than a 1-week supply for each of the first 4 weeks to coincide with weekly pregnancy testing requirements.

Female Patient Monitoring During First 4 Weeks of Therapy

During the first 4 weeks of therapy, the following must be performed:

- **Repeat patient counseling.**
- **Perform pregnancy tests every week for the first 4 weeks of therapy.**
 - It is recommended that the tests be performed within the 24 hours before providing subsequent prescriptions.
 - Pregnancy tests must be performed even if continuous abstinence is the chosen method of birth control.
- **If pregnancy test is negative, provide prescription for a 1-week supply of THALOMID™ (thalidomide).**

Subsequent Patient Visits

On subsequent patient visits (after the first 4-week period) the following must be conducted:

- **Repeat patient counseling.**
- **Perform pregnancy test (female patients) every 4 weeks if patient's menstrual cycles are regular, every 2 weeks if cycles are irregular.**
 - It is recommended that the tests be performed within the 24 hours before providing subsequent prescriptions.
 - Pregnancy tests must be performed even if continuous abstinence is the chosen method of birth control.
- **If pregnancy test is negative or if the patient is male, provide prescription for no more than a 4-week (28-day) supply of THALOMID™ (thalidomide) therapy.**
- **Complete the follow-up survey form.**
 - Forms are included in the *S.T.E.P.S.*™ folder.
 - Female patients must complete the form every month. Men must complete the follow-up survey at each visit or at least every 3 months.

Filling a THALOMID™ (thalidomide) Prescription

The patient must present the pharmacy copy of the completed consent form along with the initial prescription to the pharmacist. The pharmacist must then:

- Ensure that the prescription was written within 7 days of presentation.
- Collect and retain the pharmacy copy of the signed informed consent form.
- Complete a patient registration form and enroll the patient in the *S.T.E.P.S.*™ Patient Registry by telephone or facsimile.
- Dispense blister packs intact.
- Dispense no more than a 4-week (28-day) supply of THALOMID™ (thalidomide), with no automatic refills.

When subsequent prescriptions are presented to the pharmacy, the pharmacist must:

- Ensure that the prescription was written within 7 days of presentation.
- Verify patient registration and record subsequent prescriptions in the THALOMID™ (thalidomide) Patient Registry via on-line transmission or telephone.
- Ensure that fewer than 7 days remain on the previous prescription.
- Dispense blister packs intact.
- Dispense no more than a 28-day supply of THALOMID™ (thalidomide).

HOW SUPPLIED AND DISPENSED

THALOMID™ (thalidomide) is supplied in 50-mg white, opaque, hard gelatin capsules imprinted with “Celgene” and a “DO NOT GET PREGNANT” logo.¹ Boxes contain six blister packages containing 14 capsules each (84 capsules total).¹

THALOMID™ (thalidomide) should be dispensed in no more than a 1-month supply and only on presentation of a new prescription written within the previous 7 days.¹ Informed consent and compliance with the mandatory patient registry and survey are required for both men and women prior to dispensing.¹ THALOMID™ (thalidomide) prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.¹ Prescriptions cannot be telephoned to the pharmacy.

THALOMID™ (thalidomide) must not be repackaged.¹ Packages of THALOMID™ (thalidomide) should be stored at 59 °F to 86 °F (15 °C to 30 °C) and protected from light.¹

Further information about THALOMID™ (thalidomide) and *S.T.E.P.S.*™ can be obtained by calling Celgene Corporation at 1-888-4-CELGENE.

¹ Manson JM. 1986. Teratogenicity. Cassarett and Doull's Toxicology: The Basic Science of Poisons. Third Edition. Pages 195-220. New York: MacMillan Publishing Co.

APPENDIX E

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient, donor and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principle investigator or other designated physician. All potential risks associated with the use of high-dose melphalan, TBI, and immunosuppressive drugs should be discussed as objectively as possible. It should be explained that patients offered this protocol have advanced MM with life expectancy of no more than several years with conventional treatments. Furthermore, it should be explained that the patient would be likely to benefit in terms of disease control and prolongation of survival from an autologous transplant alone, but would likely relapse from the disease. In addition, the risk of conventional allogeneic transplant for MM should be described.

The procedure for collecting peripheral blood mononuclear cells and toxicities of G-CSF will be explained to the donor. The donor should be counseled as to the risks of treatment with G-CSF and be informed that leukapheresis at several time points will be necessary. Informed consent from the donor and patient will be obtained using a form approved the Institutional Review Board of the institution enrolling the patient.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relating the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the IBMTR and from published data on incidence of MM in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

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