



# **Assessment of Allogeneic Hematopoietic Cell Transplantation in Medicare Beneficiaries with Multiple Myeloma: A Study to Develop Evidence of Effectiveness for the Centers for Medicare and Medicaid Services (CMS)**

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## **Study Plan**

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## 1.0 BACKGROUND AND RATIONALE

### Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in adults.<sup>1</sup> There are approximately 30,000 new cases annually in the United States with a prevalence of 95,700 cases in 2016.<sup>2</sup> It is slightly more common in men than in women, and is twice as common in African-Americans than in Caucasians.<sup>3</sup> It is a disease of an aging population with a median age at diagnosis of 69 years; 26% of MM patients are between the ages of 65 and 74 years.

Overall survival (OS) in MM has improved significantly in the last 15 years with the emergence of novel therapies such as thalidomide, bortezomib and lenalidomide. More recent additions to the list of effective anti-MM drugs include carfilzomib, pomalidomide, panabinostat, ixazomib, elotuzumab and daratumumab, all of which are approved by the Food and Drug Administration to treat relapsed MM. Despite these drugs, MM remains incurable and over 75% of patients die from relapsed, refractory MM.

The median life expectancy of patients with MM treated in the current era is more than 6 years, while SEER data from a slightly earlier time period (2008-12) estimated the 5 year survival at 48.5%.<sup>4</sup> However, prognosis is not uniform and varies considerably based on a presenting features and response to therapy. Using cytogenetic risk stratification, median life expectancy is 10+ years for standard risk patients but only 3-4 years for high risk patients. However, there are no plateaus on the progression-free survival (PFS) curves for either group, indicating the lack of cures.

### Prognostic factors

Several prognostic factors classify MM patients into groups with distinct outcomes (PFS and OS).<sup>5-8</sup> These markers consider host factors (performance status, comorbidities such as renal failure, advanced age); tumor burden (international staging system) and tumor biology [presence of high risk molecular markers detected by cytogenetics or interphase fluorescent in-situ hybridization (FISH), high LDH, high plasma cell proliferative rate and high-risk signature on gene expression profiling].<sup>9</sup>

### Risk Stratification Schemes:

Modern prognostic risk-stratification schemas define a high-risk group of MM patients with substantially worse prognosis who should be managed differently from standard-risk patients. Multiple classification systems exist and continue to evolve.<sup>9</sup> The International Myeloma Workshop 2011 consensus suggested that patients with cytogenetic detection of chromosome 13 or 13q deletion and cytogenetic or FISH detection of t(4;14), t(14;16), and del (17p) should be considered high risk.<sup>10</sup> The International Myeloma Working Group (IMWG) 2014 consensus defined a combined high risk model incorporating International Staging System (ISS) II or III and del (17p) or t(4;14). Using this model, high-risk patients are predicted to survive a median of 2 years despite novel agents, compared to more than 10 years for low-risk patients.<sup>11</sup> Other

cytogenetic/FISH abnormalities associated with worse outcomes in some studies include t(14;16)<sup>12,13</sup> and chromosome 1 abnormalities (1q21 amplification, 1p deletion)<sup>12,14</sup>, although the data regarding their prognostic significance are conflicting. Emerging data show that outcomes of patients with t(4;14) are not uniformly poor. If accompanied by a low beta 2-microglobulin and high hemoglobin at diagnosis, prolonged survival after tandem hematopoietic cell transplantation (HCT) is achievable.<sup>12</sup>

In 2015, Palumbo, et al. published, on behalf of the IMWG, a 'revised ISS' (R-ISS) based on data from 4,445 newly diagnosed MM patients enrolled on 11 international clinical trials. This system incorporated serum LDH (above or below normal), cytogenetic abnormalities [del 17p, t(4;14) and t(14;16) versus other or none] and ISS.<sup>6</sup> At a median follow up of 46 months, the five-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups. A designation of "ultra high-risk MM" was also recently defined to characterize a group of patients with a median OS of  $\leq 24$  months.<sup>15</sup> This includes patients presenting with ISS III disease in addition to del 17p, t(4;14) or t(14;16) and  $>3$  copies of chromosome 1q21 amplification, and high LDH at diagnosis.<sup>6,15</sup>

Finally, gene expression profiling provides an additional tool to identify high-risk MM. The University of Arkansas Medical Sciences Myeloma Institute identified a high-risk subset with a median OS of 3 years based on a 17-gene set.<sup>16</sup> The French group has a model based on 15 genes that identifies 25% of MM patients as high-risk with OS of 47% at 3 years.<sup>17</sup> The HOVON/GMMG group generated a prognostic gene expression signature of 92 genes, confirmed in sets of newly diagnosed and relapsed patients, and were able to identify about 20% patients with OS of  $< 2$  years in both transplant-eligible and non-transplant-eligible groups.<sup>18</sup>

It is estimated that 10-20% of MM patients are high-risk as defined by any of these criteria.<sup>6,18,19</sup>

### **Current Standard of Care for Transplant-Eligible patients with MM**

The current standard of care for MM patients fit to undergo high dose conditioning chemotherapy is an autologous HCT (autoHCT). Typically, patients receive three to four cycles of induction therapy prior to stem cell harvest. These induction regimens include combinations of alkylators (cyclophosphamide, C) and novel agents such as bortezomib (V) and lenalidomide (R), including VRD, VCD, VD, RD. Autologous HCT improves PFS and OS in MM by at least 12 months.<sup>20-22</sup> There is controversy regarding the timing of autoHCT after initial novel therapy induction with randomized trials showing similar OS whether done early or delayed to time of relapse as salvage therapy.<sup>23,24</sup> However, more recent trials comparing early versus delayed transplant support the benefit of early upfront autoHCT. Two of these trials have published outcomes demonstrating superior PFS and OS in the early transplant group who received novel agent induction therapy.<sup>22,25</sup> Preliminary data presented from the other two trials also show superior PFS with early transplantation. The latter trials include the IFM 2009 phase 3 study of 700 patients comparing early versus delayed autoHCT in patients treated with VRD

followed by R maintenance. The IFM trial found a significant improvement in PFS with early autoHCT.<sup>26</sup> The European Myeloma Network also compared early versus late transplant and showed superior PFS.<sup>27</sup> At this early time point, neither of these two trials show an OS difference but prior trials demonstrating early PFS advantages eventually showed OS advantages with longer follow-up, particularly in high-risk MM.<sup>28</sup>

Post-autoHCT, patients are considered for consolidation and then placed on maintenance therapies with novel agents such as lenalidomide<sup>22,29,30</sup>, bortezomib<sup>31,32</sup> and combinations thereof, particularly for high-risk MM.<sup>33</sup> However, among patients with high-risk MM survival remains poor (median survival 2-4 years) despite autoHCT and aggressive therapy incorporating almost every available drug class and schedule.<sup>9</sup>

### **Outcomes after Allogeneic HCT in MM**

Allogeneic HCT (alloHCT) is the only potentially curative therapy available to patients with MM. However, the significant morbidity and mortality of this procedure historically limited its application in older patients. Allogeneic HCT with myeloablative conditioning was initially explored in the late 1980s and the 1990s.<sup>34-36</sup> In these early reports, transplant-related mortality (TRM) was high at 20-60%. Two prospective clinical trials studied alloHCT with myeloablative conditioning. A US Intergroup trial (S9321) of early versus late autoHCT had a third arm that allowed patients <55 years with matched siblings to undergo alloHCT. The 3 month TRM of ~53% in the alloHCT arm resulted in closure of this arm of the study.<sup>23</sup> Among the surviving patients, a plateau was seen at 2 years with a 7-year actuarial OS of 39%.<sup>23</sup> The HOVON-24 trial studied T-cell depleted myeloablative alloHCT after cyclophosphamide and total body irradiation and showed a TRM of over 30% in the upfront alloHCT setting.<sup>37</sup> With improved patient selection, optimized timing of transplantation and newer conditioning regimens, these rates of TRM improved significantly in recent years.<sup>38</sup> Current data from the Center for International Blood and Marrow Research (CIBMTR) show TRM rates of 23 (20-26)% at 5 years with myeloablative conditioning.

The development of less toxic, reduced intensity conditioning regimens offered the ability to further minimize TRM. Among ≤ 65 year old patients with newly diagnosed MM treated with induction chemotherapy followed by sequential autologous HCTs (tandem autoHCT) versus autoHCT followed by allogeneic HCT with non-myeloablative conditioning (auto-alloHCT), Bruno, et al. showed a TRM rate of 10% at 2 years with superior survival in the auto-alloHCT arm compared to tandem autoHCT.<sup>39</sup> At a median follow up of over 7 years, the median OS had not been reached in the auto-alloHCT arm.<sup>40</sup>

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0102 multicenter clinical trial in the United States compared tandem autoHCT versus auto-alloHCT randomized based on matched sibling donor availability.<sup>41</sup> High-risk MM in this study was defined as an elevated beta2-microglobulin >4 mg/dl and karyotypic chromosome 13 deletion. Non-myeloablative conditioning with 2 Gy TBI was used for alloHCT. A total of 710 patients were enrolled: 625 standard-risk (436 tandem autoHCT and 189 auto-alloHCT) and 85 high-risk (48 tandem autoHCT and 37 auto-alloHCT) patients. The

dropout rate between first and second transplantation was 16% in the tandem autoHCT group and 17% in the auto-alloHCT group. In the standard-risk cohorts, the two arms were similar for the primary end point of 3-year PFS (46% vs 43%,  $P=0.67$ ) and for OS (80% vs 77%,  $P=0.19$ ) with tandem autoHCT vs auto-alloHCT, respectively. Corresponding TRM rates were 4% and 11%, respectively. Similarly, in the high-risk cohort, no benefit was observed between groups: 3-year PFS (33% vs 40%,  $P=0.74$ ) and 3-year OS (67% vs 59%,  $P=0.46$ ) with tandem autoHCT vs auto-alloHCT, respectively. The cumulative incidence of graft-versus-host disease (GVHD) was high with 26% grade 3–4 acute and 47% chronic GVHD at 1 year after alloHCT. There was a trend towards improved PFS (6 months,  $P=0.012$ ) in patients who developed chronic GVHD.

In contrast, the European Blood and Marrow Transplantation (EBMT) Network showed superior results for alloHCT in a similarly designed clinical trial comparing auto-alloHCT (N = 91) with autoHCT (single, N = 145 or tandem, N = 104). Conditioning for alloHCT was TBI 2 Gy, as in the BMT CTN study, but also included fludarabine 30 mg/m<sup>2</sup> for 3 days.<sup>42</sup> The actuarial PFS was significantly better for the auto-alloHCT group compared to the autoHCT group, 35% compared to 18% ( $P=0.001$ ) at 60 months and 22% vs 12% ( $P=0.03$ ) at 96 months respectively, by intention-to-treat analysis. The incidence of relapse/progression was 49% for auto-alloHCT and 78% for the autoHCT groups. Cumulative TRM at 24 and 60 months was 12% and 16% for auto-alloHCT and 3% and 4% for the autoHCT groups ( $P<0.001$ ). Among the 91 patients who received the alloHCT, acute GVHD developed in 37% (9% grade 3 and 2% grade 4) and chronic GVHD in 54% (limited 31% and extensive 23%). Long-term OS was significantly superior in the auto-alloHCT group with a low hazard of death after 3 years ( $P=0.047$ ).<sup>42,43</sup> Additionally, this study also showed superior post-relapse OS among those who relapsed after alloHCT compared to autoHCT. At 8 years, 64 patients in the auto-alloHCT group and 205 patients in the autoHCT group progressed; intention-to-treat analysis showed that OS at 60 months from progression was 50% in the auto-alloHCT group compared to 27% in the autoHCT group ( $P=0.003$ ).<sup>43</sup>

There are a few studies evaluating the role of allogeneic HCT in treating relapse after autoHCT. In a single-arm, prospective multicenter EBMT study conducted in 2000–2002, Kroger, et al. used fludarabine (90 mg/m<sup>2</sup>), melphalan 140 mg/m<sup>2</sup> and rabbit anti-thymocyte globulin prior to unrelated donor transplantation in 21 patients with a 1 year TRM of 25%, a 5-year PFS of 20% and 5-year OS of 26%.<sup>44</sup> Patriarca et al. analyzed 169 consecutive patients who had relapsed after an autograft and underwent HLA-typing immediately after relapse.<sup>45</sup> The 2 year TRM was 22% among the patients who had an identified HLA compatible donor (donor group, N = 75) versus 1% for those without a donor (no donor group, N = 94). The 2-year PFS was 42% in the donor group and 18% in the no-donor group ( $P<0.0001$ ) with 2 year OS of 54% and 53%, respectively. In another small donor *versus* no-donor comparison, de Lavallade et al. showed that patients with relapsed MM and an HLA-identical sibling, (N = 19) who underwent reduced-intensity alloHCT had a significantly better event-free survival than patients without a HLA-identical sibling, N = 13 (46% *versus* 8% at 3 years).<sup>46</sup>

**AlloHCT in high-risk MM:** In a prospective study of 73 patients treated with sequential autoHCT followed by alloHCT, remission, PFS, OS and relapse rates were similar in patients with and without del(17p)/t(4;14) non-del(17p)/t(4;14) patients; achievement of molecular complete remission was the major predictive factor for outcome.<sup>47</sup> In a prospective randomized study by Knop *et al.*,<sup>48</sup> 126 patients with newly diagnosed MM were randomized to either tandem auto-allo-HCT from HLA-matched related, N = 52, or unrelated donors, N = 74, (with fludarabine/melphalan conditioning) or tandem autoHCT, N =73. At 49 months of follow-up, median PFS ( $P=0.002$ ) and OS were superior ( $P=0.011$ ) with alloHCT in the highest risk subgroup with del 17p and del 13q abnormality but not in others.

Thus, although potentially curative, standard risk MM patients have excellent prognoses in the era of novel therapies which reduces the overall benefit of alloHCT. However, because the outcomes for high-risk MM remain poor despite the best available standard therapies (OS of 24–36 months), initial data suggest that alloHCT should be explored in this subset.<sup>38,49</sup>

### **Patient Selection for AlloHCT in MM:**

AlloHCT is most appropriate in MM patients whose risk of disease progression and death from MM is sufficiently high to balance the risk of TRM from an alloHCT<sup>50</sup>. “Ultra-high risk MM” is a term that characterizes patients who have a predicted median OS of 24 months or less<sup>15</sup>. The presence of chromosomal abnormalities [Ig heavy chain gene translocations [t(4:14), t(14:16)], +1q21 (1q21 amplification; >3 copies), deletion 17p by FISH; deletion 13q by karyotyping or high-risk gene expression profiling] are the conventional high risk markers.<sup>51,52</sup> Similarly, in the R-ISS system that incorporates myeloma burden and biology, stage III carries the highest risk (predicted 5-year OS and PFS of 40% and 24%, respectively)<sup>6</sup>. Regardless of initial risk category, relapse within 18-24 months of an upfront autoHCT is also a negative prognostic marker.<sup>53,54</sup> Effective treatment which establishes long-term disease control in these subsets of high-risk MM patients is an unmet need and alloHCT should be a consideration for biologically fit patients regardless of age.

*We hypothesize that: With alloHCT, patients with high-risk MM will have superior 5-year OS than with autoHCT, despite a higher initial risk of TRM. Similarly, patients who relapse early after an autoHCT will have improved 5-year OS with salvage alloHCT compared to autoHCT.*

### **Centers for Medicare and Medicaid Services (CMS) National Coverage Determination**

With the development of reduced intensity conditioning (RIC) regimens over the last two decades, the applicability of alloHCT in older patients expanded considerably. Several studies indicate the efficacy of RIC alloHCT in older patients with other hematologic malignancies such as acute leukemia or myelodysplastic syndrome, but there are no large studies evaluating outcomes of alloHCT in patients with MM older than 65 years. This is of vital importance because the median age at diagnosis of MM is 69 years (26%

are 65-74 years). A major impediment to performing such studies in the United States is the lack of Medicare coverage for the procedure.

On January 27, 2016, CMS issued the Final National Coverage Decision Memorandum for Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, Sickle Cell Disease), Administrative File CAG-00444R. In this memorandum, CMS stated it will modify the existing National Coverage Determinations Manual to cover stem cell transplantation for these three indications as part of the Coverage with Evidence Development (CED) mechanism.<sup>55</sup>

Per the decision memo, CMS defines eligibility for Medicare beneficiaries to be limited to those with Durie-Salmon Stage II or III MM, or International Staging System Stage II or Stage III MM, while participating in an approved prospective clinical study. The study must address the following question:

*“Prospectively, compared to patients who do not receive alloHCT, do Medicare beneficiaries with MM who receive alloHCT have improved outcomes as indicated by: GVHD (acute and chronic); Other transplant-related adverse events; Overall survival; and Quality of life (optional)”*

## **2.0 PROPOSED STUDY**

The aim of this study is to prospectively determine outcomes of alloHCT in Medicare beneficiaries with Stage II and III MM and to compare those outcomes to similar patients receiving autoHCT, a standard therapy currently reimbursed by CMS. The study will further determine if these outcomes among  $\geq 65$  year old patients are similar to  $<65$  year old beneficiaries. Lastly, this study will also evaluate patient, disease and treatment factors which might modify transplant outcomes.

The hypothesis is that use of alloHCT will improve the 5-year OS in patients with advanced stage/high-risk MM when compared to autoHCT. This study will compare outcomes of prospectively enrolled patients on the alloHCT arm to outcomes of a cohort of age-matched historical autoHCT controls from the CIBMTR database.

The reason for using an historical autoHCT cohort for comparison is *to ensure that we have sufficient numbers of similarly high-risk MM patients for comparison*. We anticipate that many patients who will elect to have alloHCT under this protocol would previously have been treated with autoHCT for financial coverage reasons. Therefore, high risk patients will be under-represented in concurrent autoHCT controls. In other words, the availability of this protocol will change the risk profile of CMS beneficiaries receiving autoHCT by eliminating the highest risk patients who would now be preferentially represented in the study population (alloHCT). By using a historic cohort of patients who underwent autoHCT between 2010 and 2016 we will be able to capture a representative cohort treated in the modern era with novel therapies and autoHCT before this protocol was made available.

The rationale for focusing on a five-year endpoint is that we expect that early mortality (day 100 TRM) will be higher with alloHCT than with autoHCT, where it has been  $\leq 1\%$  in recent years. However, the early increased risk of TRM may be acceptable in return for improved long term disease control, though it will take time for this advantage to show an OS benefit. We will closely track early mortality between the 2 arms and propose stopping rules if there is an excess in expected day 100 TRM in the alloHCT arm (see Section 6.2).

### 3.0 STUDY POPULATION

This will be prospective cohort study of approximately 544 patients receiving allogeneic HCT for multiple myeloma in CIBMTR centers in the US. Each patient will be matched to a historical control patients treated with autoHCT between 2010 and 2016.

#### 3.1 Inclusion criteria

Eligible patients are:

- Medicare beneficiaries
- Have Stage II or III multiple myeloma
- Are eligible to receive an alloHCT from any suitable allogeneic donor (as determined by the transplant center) including umbilical cord blood
- Being treated in a US transplant center
- Provide informed consent to participate in the study

It is anticipated that most patients will be 65 or older and that almost all will be 55 or older. Eligibility for alloHCT will be limited to MM patients with Stage II or III MM per CMS guidelines. Further eligibility will be according to local institutional practices. GVHD prophylaxis will be per institutional practices. Patients who have received prior therapy on clinical trials or who are enrolled on clinical trials will be allowed. This will ensure the capture of the broadest range of high risk MM patients in whom the therapy will be used without exclusion based on race, gender or prior therapy.

### 4.0 STUDY ENDPOINTS

#### 4.1 Primary outcome

The primary outcome is to compare **five-year OS probabilities** between the alloHCT cohort and an age and disease risk matched cohort of autoHCT patients. OS is calculated for all patients from the date of transplant until death from any cause. Observation is censored at the date of the last follow-up for patients alive at last contact.

#### 4.2 Secondary outcomes

##### 4.2.1 PFS



We will compare five-year PFS probabilities between the alloHCT cohort and an age and disease risk matched cohort of autoHCT patients. PFS is calculated as the interval from the date of transplant to the date of relapse/progression of MM or death from any cause, whichever comes first. Observation is censored at the date of last follow-up for patients alive without relapse/progression of MM at last contact.

#### **4.2.2 Relapse/Progression**

Myeloma recurrence or progression will be defined per IMWG guidelines<sup>56</sup> and will be summarized by a cumulative incidence estimator with TRM as the competing risk.

#### **4.2.3 HCT-specific endpoints**

- TRM: defined as death from any cause within 28 days after alloHCT or death in the absence of progression/relapse of MM after day 28 post-transplant. This event will be summarized as a cumulative incidence estimate with relapse / progression as the competing risk.
- Incidence of acute GVHD: Occurrence of grade I, II and III/IV skin, gastrointestinal, or liver abnormalities fulfilling the Consensus criteria of Grades II-IV acute GVHD.<sup>57</sup> Patients are censored at last follow-up.
- Incidence of chronic GVHD: Occurrence of symptoms in any organ system fulfilling the criteria of chronic GVHD. Patients are censored at last follow-up or second transplant.

## **5.0 DATA COLLECTION**

Patients undergoing alloHCT will be reported to the CIBMTR and will be followed using standard CIBMTR reporting schedules and data collection forms. Data on the autoHCT controls will be obtained from patients reported to the CIBMTR using identical data schedules and data collection forms between 2010 and 2016 (**Appendix A**).

Data collection on alloHCT recipients will follow standard CIBMTR policies and procedures. The most recent versions of the CIBMTR study forms can be found at [www.cibmtr.org](http://www.cibmtr.org). Transplant centers pre-register all transplant recipients within two weeks of starting pre-transplant conditioning. The Pre-Transplant Essential Data Form (PreTED) captures information regarding primary disease, type of graft, conditioning regimen, and GVHD prophylaxis. For the purposes of this study, centers will be asked to complete Comprehensive Report Forms (CRF) for each transplant patient.

Within the transplant cohort, initial follow-up forms are due three months post-transplant and include a 100 Days Post-HSCT Data Form, Pre and Post-HSCT Disease Insert, and a Product Form. These forms capture demographics; details of the patient's pre-

transplant disease course and treatment; the transplant regimen, including graft characteristics; and post-transplant supportive care and outcomes, including disease control, GVHD, infections, organ dysfunction, and survival. Follow-up report forms will be required annually through year six post-transplant and include a general follow-up form and a disease-specific follow-up form. Follow-up forms will be required biannually after year six post-transplant and include a general follow-up form and a disease-specific follow-up form.

Reminders of forms due for preregistered patients and patients requiring follow-up report forms are sent to participating centers monthly. Standard CIBMTR procedures require that all contact with patients be done by the transplant center. **Appendix B** describes the CIBMTR procedures governing Institutional Review Board (IRB) oversight, consent, and privacy as they relate to the transplant centers and this study.

## 6.0 STATISTICAL ANALYSIS PLAN

Based on previous experience, we expect an annual lost to follow-up (LTF) rate of 1%, such that the estimated total LTF at the end of the study will be 10%. We plan to accrue 544 patients over a 5-year accrual period; therefore we will have approximately 500 evaluable patients (cases) at the end of the study.

**Table 1. Projected accrual number of patients over 5-year accrual period.**

Year 1	Year 2	Year 3	Year 4	Year 5	Total
111	110	109	108	107	544

### 6.1 Matched controls

At the end of accrual time, we will obtain our historical controls from autoHCT patients transplanted between 2010 and 2016 from the CIBMTR database and will obtain comprehensive data for analysis from 500 1-1 matched controls.

The following variables will be used to match cases and controls:

1. Age within 2 years between case and matched control
2. Creatinine at transplant, < 2 mg/dl versus ≥ 2 mg/dl
3. High risk cytogenetics, yes versus no
4. For patients who have never relapsed/never had autoHCT: Time from diagnosis to alloHCT; For patients who have had prior autoHCT: Time from autoHCT to relapse.

Matching will be performed among all possible cases and controls. We will select one final matched control with the smallest age difference with a given case.

## **6.2 Early Stopping Guidelines**

AlloHCT is an aggressive therapy with known risks of early mortality. Published CIBMTR data showed that among patients with MM who underwent alloHCT from either a matched sibling or unrelated donor with any conditioning regimen between 2001-2005, the 100-day TRM was 16.4%.<sup>58</sup> Day 100 mortality after allogeneic transplant in older adults  $\geq 65$  years is 19 (10-30)%.<sup>59</sup> We have thus created a stopping rule for this study based on the null hypothesis: 100-day mortality is  $<20\%$ . The alloHCT arm will stop if there are  $> 16$  early deaths in the first 50 cases,  $> 28$  deaths in the first 100 cases,  $>40$  deaths in the first 150 cases,  $> 51$  deaths in the first 200 or  $>74$  deaths in the first 300 patients. If the true TRM at 100 days is 20%, there is a 4% chance of triggering this stopping rule; if the true TRM at 100 days is 30%, there is an 82% chance of triggering this stopping rule (this stopping rule was calculated by **toxbdry** function in **R-clinfun** package).

## **6.3 Interim and Final Analyses**

Since the primary endpoint is five-year OS, no interim efficacy analysis will be done until year 7, since the number of patients who have completed five-year follow up will be too short. At each scheduled interim analysis time (at year 7 and at year 9), and final analysis at year 10, analysis will be performed as described below for the primary endpoint of OS. First, the probability of OS will be calculated by Kaplan-Meier estimator and the probability with its 95% confidence interval will be reported. Second, the log-rank test for overall mortality will be performed. In order to preserve the overall type I error rate at 5%, the critical value for the test statistics will be inflated above 1.96, the value that would be used if no repeated testing were used. Equivalently, the nominal p-value at which an observed difference is declared significant will be reduced below 0.05. The actual critical values and nominal p-values will be computed based on the primary outcome of overall mortality and using statistical methods for group sequential testing with O'Brien Fleming boundaries. We plan to examine overall mortality rates at the seventh, ninth and tenth years of the study. Current CIBMTR data indicate that for the patient population in this proposal, the cumulative overall mortality rates are 0.11, 0.22, 0.35, 0.42, 0.49, 0.54, 0.61, 0.73, 0.80, 0.86 at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 years after transplant, respectively. Consequently, the expected deaths at each planned analysis time are 211, 257 and 297, respectively. The critical value and nominal type I error are calculated based on these data using R-GrpSeqBnds function.

**Table 2. Table of critical values and cumulative type I error for the interim analysis (with 2 interim analyses and one final analysis)**

Scheduled Interim Analysis	Critical Value	Nominal Type I Error
Year 7	2.4175	0.0156
Year 9	2.1982	0.0279
Final analysis	2.0580	0.0396

#### **6.4 Sample Size Considerations**

All patients will have at least five years of follow up. Current CIBMTR data indicate that, for the patient population targeted in this proposal, the five year probability of survival is 51%. Assuming an estimated annual LTF of 1%, the estimated total LTF at the end of the study will be 10%. Since we plan to accrue 110, 110, 109, 108 and 107 cases during the first, second, third, fourth and fifth year of the study period, respectively, and select an equivalent number of historical controls from CIBMTR database with similar patient characteristics, we will have a total of 1,088 patients followed until death or the end of the study period. With this population, the study will have 80% power (with alpha 0.05) to detect a 9% difference in OS with a 2-sided test:

#### **6.5 Covariates**

Since this is not a randomized study, it is possible that patients receiving alloHCT may differ from the controls for one or more baseline characteristics, even though the subjects are matched on key characteristics. The following patient, disease and treatment-related variables will be examined and adjusted for in multivariate analysis as necessary. Some possible covariate groupings are listed. They will be fully specified when the study population is determined.

##### 6.5.1 Patient related:

- Age – continuous variable
- Gender: male versus female
- Race-ethnicity: Caucasian, non-Hispanic versus African American versus Caucasian, Hispanic versus Asian versus Pacific Islander
- Karnofsky performance status: <90 versus ≥90
- HCT-CI: 0 vs 1-2 vs ≥3

##### 6.5.2 Disease related:

- Serum Creatinine at diagnosis: <2 mg/dl vs ≥2 mg/dl
- LDH at diagnosis: Normal vs ≥ ULN
- Stage – Durie Salmon or ISS Stage III versus II
- R-ISS stage at diagnosis: R-ISS I vs R-ISS II vs R-ISS III
- Cytogenetics and/or FISH: high-risk versus non-high-risk
- Induction therapy prior to transplant: novel triplet vs novel doublet
- Interval from diagnosis to transplant: <6 months vs 6-12 months vs

> 12 months

- Prior transplant: no prior transplant vs prior autoHCT
- Upfront alloHCT versus after relapse
- Lines of therapy prior to first transplant
- Disease status prior to allotransplant: stringent complete response (sCR)/CR vs very good partial response (VGPR) vs PR vs <PR

#### 6.5.3 Transplant related:

- Type of transplant: HLA-identical sibling versus matched other related versus mismatched other related versus 8/8 locus (HLA- A, B, C, DRB1) MUD versus 7/8 locus MMUD versus  $\leq 6/8$  MMUD versus single cords 6/6 match versus single cords 5/6 match versus single cords 4/6 match versus double cords  $\geq 5/6$  match versus double cords 4/6 match
- Stem cell source: bone marrow versus peripheral blood versus cord blood
- Donor age: continuous and by decade
- Donor-recipient sex match: male-male versus male-female versus female-male versus female-female
- Donor-recipient cytomegalovirus serostatus: -/- versus -/+ versus +/- versus +/+
- Year of transplant
- Conditioning regimen: TBI vs Busulfan-based, no TBI vs Melphalan-based, no TBI, versus Other
- Conditioning regimen density: Myeloablative versus RIC
- GVHD prophylaxis:  
T-cell depletion/CD34 selection versus tacrolimus (FK506)+mycophenolate mofetil (MMF)+/- others versus FK506+methotrexate (MTX)+/-others versus FK506 +/- others versus cyclosporine (CSA) +MMF +/- others (except FK506) versus CSA+MTX +/- others(except FK506, MMF) versus CSA +/- others(except FK506, MTX, MMF) versus post-transplant cyclophosphamide
- Transplant center characteristics: Average AlloHCT volume, years of operation

## 6.6 Analysis Plan

Patient-, disease- and transplant- related factors will be compared between treatment groups using the Chi-square test for categorical variables and the Wilcoxon two sample test for continuous variables. The primary outcome of the trial is OS at five years after transplant. Matched pair analysis of cases and controls will be conducted. Because this is not a randomized trial, there is a potential for bias resulting from the non-randomized comparison. The

comparison of OS will be therefore be adjusted for the aforementioned covariates. We will conduct a multivariate analysis using multivariate regression to adjust for any potential imbalance of risk factors which are associated with the clinical outcome. Marginal Cox proportional hazards regression will be used to compare the two treatment groups. The variables to be considered in the multivariate models are listed above. The assumption of proportional hazards for each factor in the Cox model will be tested using time-dependent covariates. When the test indicated differential effects over time (non-proportional hazards), appropriate adjustment (e.g. stratification or time-dependent covariates) will be considered. A stepwise model selection approach will be used to identify all significant risk factors. Each step of model building will retain the main effect of treatment group (alloHCT versus autoHCT). Other factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested. Adjusted probabilities of OS will be generated from the final Cox models stratified on treatment and weighted averages of covariate values using the pooled sample proportion as the weight function. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors. A 95% confidence interval for the difference in adjusted OS at five years will be constructed.

## **7.0 RELEVANCE TO CMS BENEFICIARY POPULATION**

### **7.1 CMS CED Requirements**

***a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.***

The principal purpose of the study is to determine whether HCT meaningfully improves health outcomes for Medicare beneficiaries with Stage II and III multiple myeloma. This study will compare the five-year OS probabilities from transplant between the two study arms: alloHCT and autoHCT. Further information regarding study objectives is provided in **Section 2**.

We will include patients under the age of 65 as many patients with newly diagnosed MM are CMS beneficiaries. Additionally, if there is no difference in OS between younger and older patients, we can combine the two cohorts to increase the power of our secondary analyses.

***b. The rationale for the study is well supported by available scientific and medical evidence.***

AlloHCT is currently the only potentially curative therapy for MM. Based on similar studies, and as reviewed in **Section 1**, age alone is not expected to be a major factor in outcomes.

***c. The study results are not anticipated to unjustifiably duplicate existing knowledge.***

To the best of our knowledge, there has not been a prospective study of similar methodology applied to the age-group cohort being studied in this protocol.

***d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.***

This study has an 80% power to detect a 9% improvement in five-year OS in the alloHCT arm compared to the autoHCT depending on the number of patients enrolled in the alloHCT. The methods are described in detail in the Statistical Analysis section 6.0. The CIBMTR has a long standing history of successfully using these methods in conducting similar large data analysis.

Although a randomized trial might be preferred, such a study was not deemed feasible for a rare subset which comprises 10-20% of MM. This has been specified in the following sections in greater detail:

- Introduction – **Section 1**
- Hypothesis to be tested – **Section 2**
- Specific aims – **Section 2**
- Background and significance – **Section 1**
- Trial design – **Sections 3, 4 and 5**
- Target population and recruitment target – **Sections 4 and 7**
- Inclusion and exclusion criteria – **Section 4**
- Power calculations – **Section 7**

***e. The study is sponsored by an organization or individual capable of completing it successfully.***

This study will be performed through the CIBMTR, which has performed hundreds of similar analyses during its >40 year history. The CIBMTR is a clinical research program that receives HCT outcomes data from a network of approximately 420 treatment centers worldwide. Data are collected and analyzed by the Coordinating Center, located at the Medical College of Wisconsin (MCW) in Milwaukee, WI, and the National Marrow Donor Program in Minneapolis, MN. The CIBMTR Research Database includes information for more than 440,000

transplant recipients and receives information for about 18,000 new transplants annually. CIBMTR data and statistical and scientific expertise have resulted in over 1000 peer-reviewed publications

([www.cibmtr.org/ReferenceCenter/PubList/index.html](http://www.cibmtr.org/ReferenceCenter/PubList/index.html)).

In 2010, the CIBMTR launched the CMS-approved study, “Assessment of Stem Cell Transplantation in Medicare Beneficiaries with Myelodysplastic Syndrome and Related Disorders.” In this study, >100 centers are participating, and approximately 1,300 patients  $\geq 65$  years old, >800 patients 55-64 years old, and >200 patients <54 years old are enrolled.<sup>60</sup> A follow-up study to this ongoing CMS study of HCT outcomes is now collecting comparison data for a cohort of patients receiving non-HCT therapy for myelodysplastic syndrome.

As of December 2007, all US transplant centers are required to report data on their related and unrelated donor transplants to the CIBMTR. Computerized checks for errors, review of submitted data by physicians, and on-site audits of participating centers are used to monitor the quality of the data. The CIBMTR collects data on two levels. All centers register basic data (PreTED) for all patients. Centers provide comprehensive data (CRF) for a subset of registered patients. Patients are selected for comprehensive data reporting using a randomization program that weights cases for selection in order to provide adequate numbers of cases for current and future studies and to ensure adequate representation of all transplant types and indications. The selection program is modified, as needed, to select cases for specific studies, such as the one described in this document. CIBMTR centers are asked to provide follow-up on all patients for as long as they are able to maintain contact. Completeness rates for five year survival data are >90%. These data sets have been used to conduct numerous studies of transplant outcomes, including comparisons of transplant to best supportive care. The most recent versions of the CIBMTR study forms can be found on the CIBMTR website

([http://www.cibmtr.org/DATA/Data\\_Mgmt\\_Forms/index.html](http://www.cibmtr.org/DATA/Data_Mgmt_Forms/index.html)).

The CIBMTR will utilize its existing center network and data collection infrastructure to obtain data for this study.

Additionally, the CIBMTR has assembled a team of HCT and multiple myeloma experts to guide development, implementation, and completion of this study.

Curriculum vitae for the study team members, listed below, are included in

**Appendix C.**

- Anita D’Souza, MD, MS (Medical College of Wisconsin, Milwaukee, WI) – Study Chair



- Parameswaran Hari, MD (Medical College of Wisconsin Milwaukee, WI) – Study Co-Chair
- Mei-Jie Zhang, PhD (Medical College of Wisconsin, Milwaukee, WI)
- Mary M Horowitz, MD, MS (Medical College of Wisconsin, Milwaukee, WI)
- Sergio Giralt, MD (Memorial Sloan Kettering Cancer Center, New York, NY)
- Gunjun Shah, MD (Memorial Sloan Kettering Cancer Center, New York, NY)
- Stephanie Farnia, MPH (NMDP/Be The Match)
- Patricia Steinert, PhD, MBA (CIBMTR, Milwaukee, WI)
- Keren Osmen, MD (Mount Sinai Medical Center, New York, NY)
- David H Vesole, MD, PhD (Hackensack Medical Center, New Jersey, NJ)
- Natalie Callander, (University of Wisconsin, Madison, WI)

***f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.***

The data collection and analyses for this study will be done in full compliance with the specified Federal regulations (**Appendix D**). Data from patients who have signed an informed consent for data collection and to research conduct will be used.

The most recent approval of the CIBMTR Research Database Protocol v7.5 occurred in February 2017 (**Appendix E**). The NMDP Institutional Review Board will review this Study Plan when final. The approved Study Plan will be released to clinical sites for review for compliance with all applicable Federal regulations concerning the protection of human subjects as detailed in 45 CFR Part 46 at their respective Institutional Review Boards. As approval is granted, we will provide the list of sites to CMS. All aspects of the study will be conducted according to appropriate standards of scientific integrity.

The CIBMTR adheres to all appropriate standard of scientific integrity. An interim monitoring procedure for this study is described in Section 6.3. A stopping mechanism is described in section 6.2. At the time of each interim analysis, the interim analysis, and summary data on patient demographics, all secondary

outcomes and causes of death will be reviewed by the CIBMTR Data Monitoring Board. The primary function of the Monitoring Board is to perform ongoing assessment and monitoring of CIBMTR prospective studies relative to scientific merit/validity, safety and efficacy. The Monitoring Board is comprised of an interdisciplinary membership with expertise in hematopoietic stem cell transplantation, biostatistics, ethics and the conduct of clinical trials.

Key responsibilities of the Monitoring Board are to:

- Offer advice concerning the continued scientific merit and/or validity of each ongoing study.
- Provide continual assessment and monitoring of study participant safety; particularly with respect to the magnitude and impact of any adverse or severe adverse events.
- Provide ongoing assessment and monitoring of all study specific prescribed treatment protocols.
- Review and assess study specific site performance data such as study recruitment and accrual, protocol adherence and data quality.
- Recommend the continuation, amendment or termination of each ongoing study based upon regularly scheduled review of interim data results.
- Ensure study subject confidentiality as well as that of all study data and the conclusions reached as a result of the monitoring process

The Monitoring Board can recommend stopping the study if warranted by their review of the interim data.

***h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.***

This study clearly demonstrates adherence to the standard Medicare requirements, as explained in study rationale (**Section 1**) and design of the study (**Section 2**). This document serves as a written study plan, which in combination with the master protocol, A Database Study for Hematopoietic Stem Cell Transplantation and Marrow Injuries (NCT01166009) (**Appendix A**) addresses, or incorporates by reference, the standards listed.

***i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.***

Not applicable to this study.

***j. The clinical research studies and registries are registered on the [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) website by the principal sponsor / investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).***

This study is registered on the ClinicalTrials.gov website NCT03127761, titled Assessment of Allogeneic Hematopoietic Cell Transplantation in Medicare Beneficiaries with Multiple Myeloma.

***k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started / completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessible manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as [ClinicalTrials.gov](http://ClinicalTrials.gov), or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).***

Regardless of the outcomes, the results of this study will be incorporated into a primary manuscript and submitted to a peer-reviewed journal within 12 months of receipt of the 500<sup>th</sup> patient's 5-year follow-up data. Results will be made public via an abstract, submitted to the American Society of Hematology Annual Meeting, the BMT Tandem Meetings, or a similar, appropriate international meeting.

***l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment***

***or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.***

Multiple myeloma is a disease that disproportionately affects African Americans and older people and traditionally these groups are underrepresented in MM studies. Our protocol does not limit the inclusion of underrepresented groups and increases access to alloHCT for older patients who are CMS beneficiaries. In fact, the inclusion of all patients transplanted at all US transplant centers is a strength of this proposal. Centers reporting data to the CIBMTR must report data on all HCT recipients at their center regardless of gender, race, or age. All patients meeting the broad eligibility criteria (HCT recipient, MM, CMS beneficiary, informed consent) in **Section 2** will be included. Specifically:

- **Inclusion and exclusion criteria.** All Medicare beneficiaries with high-risk MM are eligible. As the study is comparing survival and other outcomes after alloHCT to standard of care autoHCT, study eligibility requires all patients enrolled on the study meet functional and organ function criteria that would allow them to proceed to transplantation if a suitable donor is identified.
- **Gender.** Both women and men are eligible.
- **Minorities.** The study allows the use of alternative donor sources such as haploidentical donors, which promotes increased participation by ethnic minorities as these subpopulations have decreased numbers of fully matched donors available.
- **Medicare beneficiaries.** Most, if not all, enrolled individuals will be Medicare beneficiaries, particularly those aged 65 and above.
- **Retention of study participants.** Transplant centers will follow study participants using standard CIBMTR forms and follow-up schedule. This schedule includes follow-up visits at regular intervals post-transplantation: three months, six months, annually during years one through five and every other year starting in year six. More than 95% of data collected by the CIBMTR is submitted electronically via FormsNet, a comprehensive electronic data submission system containing >240 forms related to capturing clinical outcomes. The system's flexible ID assignment form allows the CIBMTR to collect data on patients who receive treatment other than HCT. Robust data collection is critical to the success of the CIBMTR. The CIBMTR has in place a Continuous Process Improvement (CPI) program to ensure timeliness and completeness of data submission. Treatment centers receive CPI reports three times per year (January, May, and September), listing the number of follow-up forms that were due in the previous trimester. A form is not officially submitted until all errors are resolved and all applicable information is submitted and approved.

***m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.***

The study design targets an older adult population with high-risk MM. We expect the study results to be generalizable to those beneficiaries that are clinical candidates for alloHCT based on their overall health and disease status. This does not preclude generalizability to the subpopulations described previously.

## 8.0 List of Appendices

- **Appendix A.** CIBMTR Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries, version 7.4 (NCT01166009)
- **Appendix B.** CIBMTR procedures governing human subjects research and HIPAA compliance
- **Appendix C.** NIH Bio-sketches for study team members
- **Appendix D.** Patient level informed consent required for all CMS patient transplant data collected by the CIBMTR and stored in the Research Database
- **Appendix E.** Institutional Review Board approval of CIBMTR Research Database Protocol, version 7.4 (July 2016)

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