CIBMTR Studies under CED:
What has happened and where are we headed next?

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A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

CMS Background

- Centers for Medicaid and Medicare Services (CMS) is the US government agency that manages Medicare
- Medicare – primary insurer for most persons 65 and older in the US as well as younger adults with disabilities (including those related to sickle cell disease)
- CMS decisions often influence policies of private insurers and Medicaid programs

CMS Background

- Through National Coverage Decisions (NCDs), CMS can specifically mandate or prohibit coverage for specific procedures in specific indications
- For many procedures, CMS is “silent”, i.e. it has not issued a pertinent NCD – decisions about coverage are then made by local Medicare Administrative Contractors

CMS Background

- Standard Medicare does not allow for prior authorization – i.e. advance approval of a procedure
- For ‘silent’ indications, the transplant program and patient take on the financial risk for the procedure
- Resulted in an access barrier for patients with indications other than those on the covered list

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Background – CED for MDS

- Allogeneic hematopoietic stem cell transplantation (SCT) remains the only curative therapy for patients with MDS.
- Historically, patients 65 and older with Medicare did not have coverage for HCT.
- On August 4th 2010, the Centers for Medicare and Medicaid services (CMS) established coverage for HCT for MDS through coverage with evidence development (CED).
- A Center for International Bone Marrow Transplant Research (CIBMTR) study comparing outcomes of patients 55-64 vs. 65 and older was approved in December 2010.

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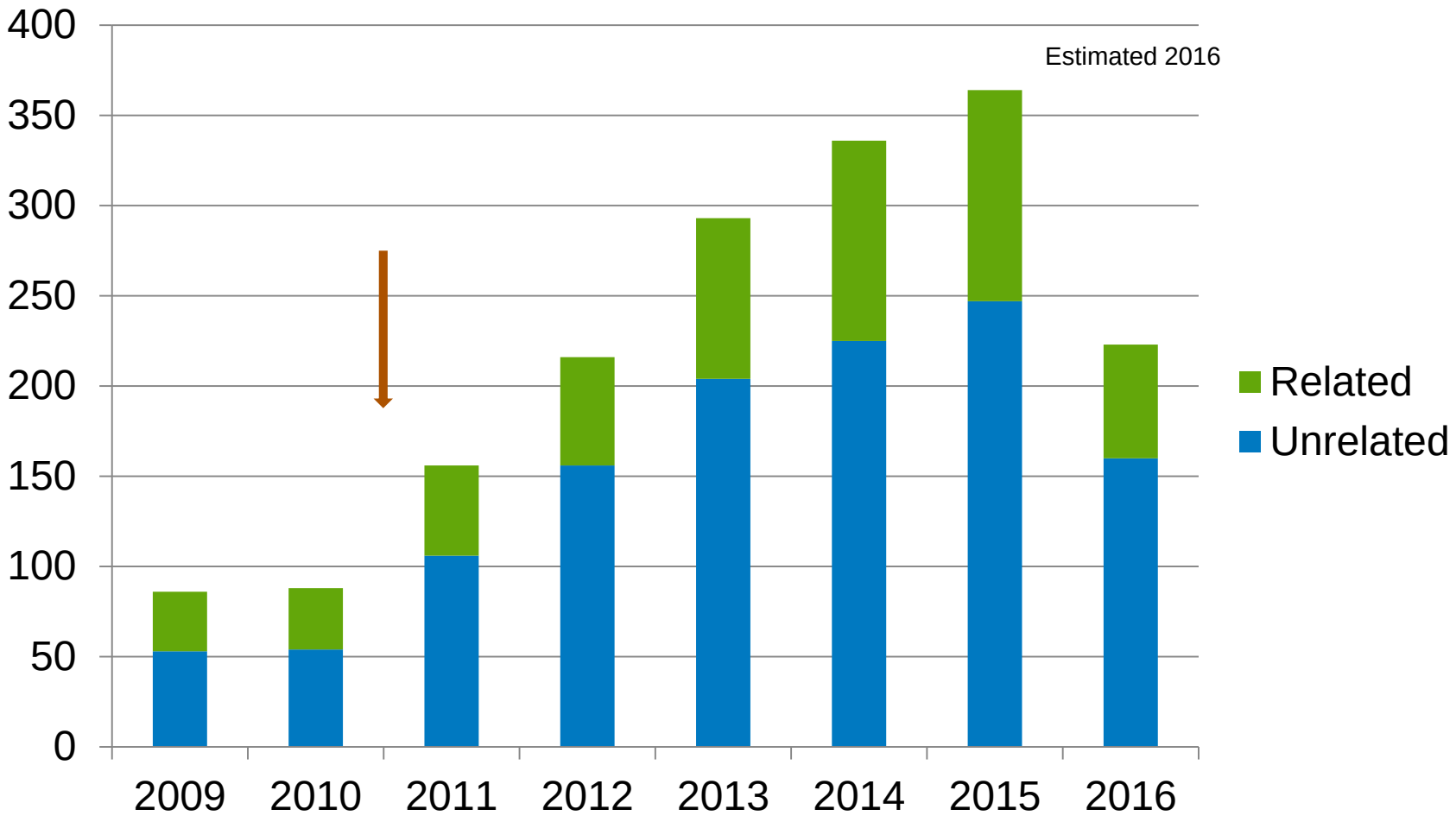
What if you remove insurance barriers?

HCT in US for MDS over age 65 and CMS coverage



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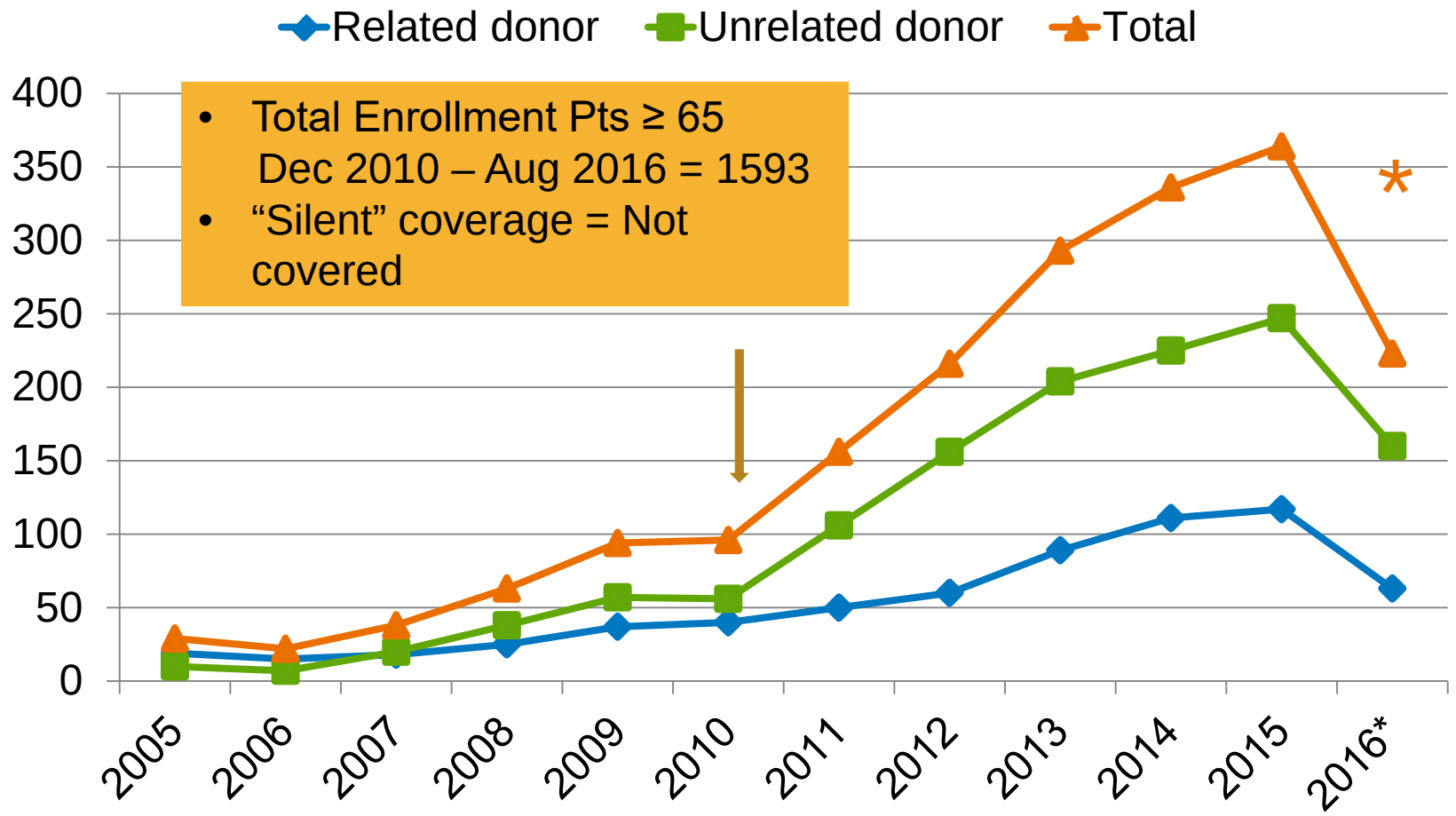
US Allogeneic Transplants for MDS in Patients Older than 65 y, 2005-2016



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***Data for 2016 are incomplete**

Outcome of Patients 65 Years and Older with Myelodysplastic Syndrome (MDS) Receiving Allogeneic Hematopoietic Stem Cell Transplantation Compared to Patients 55-64 Years of Age

There are no conflicts of interest to disclose.

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MDS CED: 3 ???

- Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes?
  - NRM, PFS, Relapse, Overall Survival
- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do IPSS score, patient age, cytopenias and comorbidities predict outcomes?
- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, what treatment facility characteristics predict meaningful clinical improvement in outcomes?

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Study Population

- Patients >65 years old (or <65 years of age and a CMS beneficiary) compared to a cohort of patients 55-64
- Diagnosis of MDS and related disorders, including chronic myelomonocytic leukemia (CMML)
- Eligible to receive an allogeneic HCT from either an HLA-identical sibling or unrelated donor in a US transplant center
- Eligibility for HCT according to local institutional practices

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Outcomes

- Primary Outcome:
  - 100-day mortality
- Secondary Outcomes:
  - Acute GVHD / chronic GVHD
  - Relapse / progression
  - Disease-free survival
  - Overall survival
  - Prognostic value of patient and disease characteristics upon the outcome of SCT

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Study Design

- Hypothesis: 100-day mortality in age 65 year old cohort is not significantly greater than that in patients ages 55-64, which is approximately 20%.
- Target accrual was 240 patients age 65. This provided 80% power to detect 6.5% or greater increase in 100-day mortality compared to the 55-64 age group.
- In June 2012, target accrual was increased to determine the prognostic value of patient and disease characteristics upon the outcomes of SCT.

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Baseline Characteristics

Variable	65 + (n=688)	55-64 (n=592)
Median age, years	68 (65-79)	61 (55-64)
65-69	523 (76)	0
70-74	151 (22)	0
75-79	14 (2)	0
Male gender	476 (69)	371 (63)
KPS ≥90	145 (78)	311 (63)
Caucasian / White	624 (91)	536 (91)
HCT-CI		
0	156 (23)	119 (20)
1-2	187 (27)	159 (27)
3	127 (18)	129 (22)
4+	218 (32)	185 (31)
Interval from diagnosis to SCT	9 (<1-266)	8 (<1-173)

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Baseline Characteristics

Variable	65 + (n=688)	55-64 (n=592)
Disease subtype at diagnosis (WHO)		
MDS not otherwise specified	121 (18)	106 (18)
RA / RARS / RCMD / RCMD-RS	206 (30)	151 (26)
Chronic myelomonocytic leukemia	66 (10)	43 (7)
RAEB-1	140 (20)	103 (17)
RAEB-2	147 (21)	141 (24)
5q-syndrome	3 (<1)	9 (2)
MDS / MPN-U	3 (<1)	3 (<1)
Missing	2 (<1)	10 (2)

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Baseline Characteristics

Variable	65 + (n=688)	55-64 (n=592)
Cytogenetics (IPSS classification)		
Good	306 (44)	216 (36)
Intermediate	117 (17)	96 (16)
Poor	207 (30)	216 (36)
Missing / not tested / not evaluable	58 (8)	64 (10)
IPSS score at diagnosis		
Low risk	39 (6)	26 (4)
INT-1	228 (33)	162 (27)
INT-2	167 (24)	159 (27)
High risk	38 (6)	35 (6)
Missing	56 (8)	53 (9)
T-MDS	160 (23)	157 (27)

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Baseline Characteristics

Variable	65 + (n=688)	55-64 (n=592)
Therapy given prior to preparative regimen		
No therapy	57 (8)	73 (12)
(azacytidine or decitabine) only	346 (50)	289 (49)
(azacytidine or decitabine) + lenalidomide +/- others	71 (10)	44 (7)
(azacytidine or decitabine) +/- others	131 (19)	91 (15)
Revlimid +/- others	7 (1)	13 (2)
Chemotherapy	26 (4)	38 (6)
Blasts in BM prior to HCT		
<5%	443 (64)	406 (69)
5%-10%	134 (19)	93 (16)
11%-20%	75 (11)	45 (8)
Missing	36 (5)	48 (8)

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Baseline Characteristics

Variable	65 + (n=688)	55-64 (n=592)
Conditioning Regimen		
Myeloablative	**197 (29)**	**288 (49)**
RIC / NMA	**491 (71)**	**304 (51)**
Source of stem cells		
BM	78 (11)	68 (11)
PB+ / -BM	581 (84)	492 (83)
Single / double CB	29 (4)	32 (6)
Donor		
HLA-identical sibling	167 (24)	204 (34)
Other related	42 (6)	27 (5)
Unrelated donor 8/8 match	382 (56)	282 (48)
Unrelated donor 7/8 match	68 (10)	47 (8)

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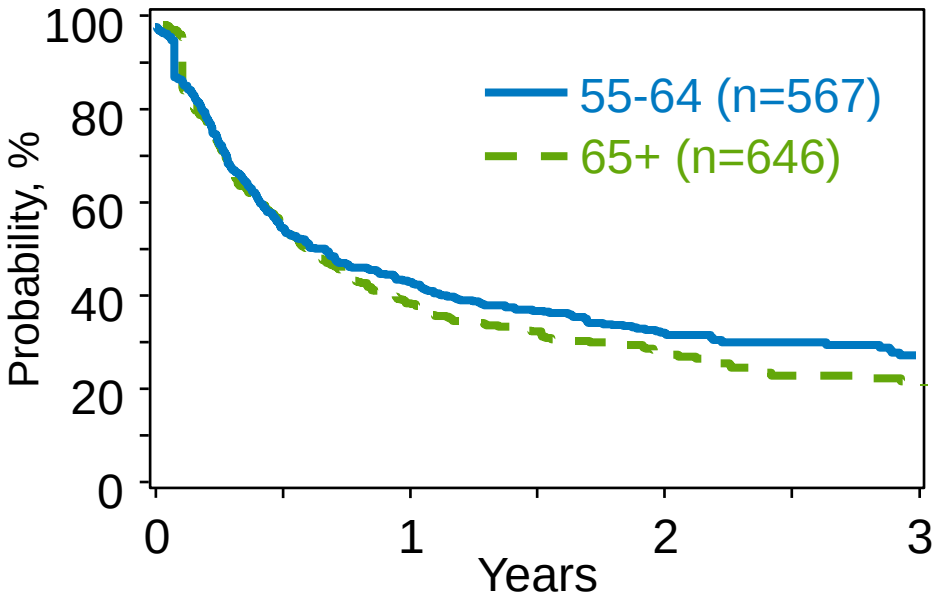
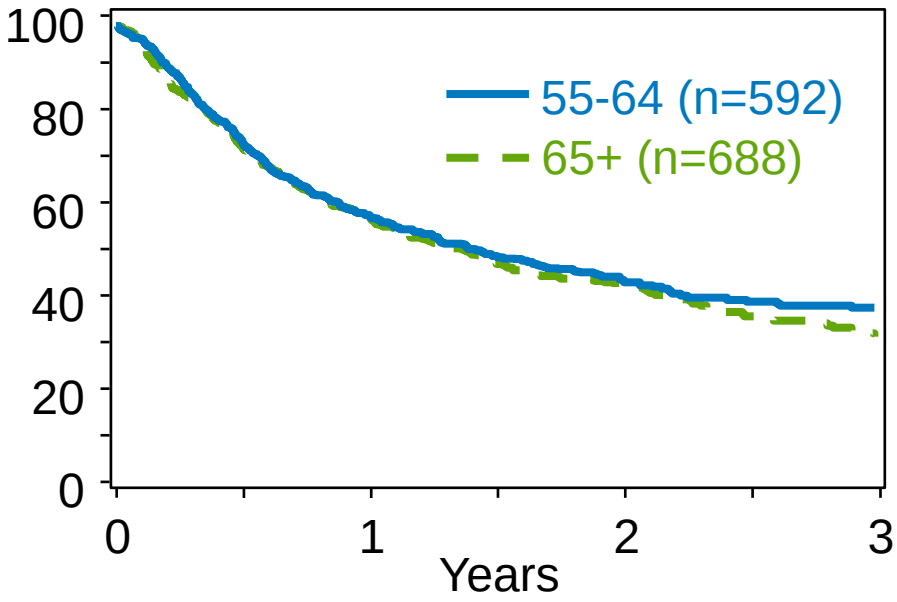
Disease-free Survival



Overall Survival



Outcomes	65+ (n=688)		55-64 (n=592)		P-value
	N Eval	(95% CI)	N Eval	(95% CI)	
Disease-free Survival	646		567		
@ 100-days		68 (65-72)%		73 (69-77)%	0.0590
@ 1-year		40 (36-44)%		45 (41-49)%	0.0564
@ 2-years		29 (25-33)%		34 (30-39)%	0.0780
Overall Survival	688		592		
@ 100-days		85 (23-87)%		87 (84-89)%	0.2468
@ 1-year		58 (54-62)%		59 (55-63)%	0.7518
@ 2-years		44 (40-48)%		44 (40-49)%	0.8355

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Multivariate Analysis

- Regression models were used to examine the association of patient and disease characteristics with mortality, and to examine the impact of age.
- Logistic regression was used for day 100 mortality, while Cox regression was used for overall mortality.
- Stepwise model building procedures were used to identify important prognostic factors, forcing age group into the model.
- Assessment of the proportional hazards assumption for the Cox model was performed using time-dependent covariate approaches and graphical methods.
- Adjusted survival curves were developed using a stratified Cox model after adjusting for significant covariates in the model.

Multivariate Analysis (day 100 mortality)

	Relative Risk (95% CI)	P-value
Age		0.1626
55-65	1.00	
65+	1.26 (0.91-1.75)	0.1626
Cytogenetics		0.0004
Good	1.00	
Intermediate	0.71 (0.42-1.23)	0.2231
Poor	1.85 (1.28-2.68)	0.0011
Unknown	1.03 (0.57-1.88)	0.9147
Disease Status		0.0238
Complete remission	1.00	
Hematological improvement	2.24 (0.98-5.15)	0.0570
No response / stable disease	3.35 (1.59-7.07)	0.0015
Progression / relapse	2.91 (1.13-7.51)	0.0270
Never treated	2.90 (1.17-7.21)	0.0217
Missing	1.83 (0.62-5.39)	0.2709
Platelets at diagnosis		0.0012
≥50	1.00	
<50	1.68 (1.17-2.43)	0.0052
Missing	2.14 (1.31-3.48)	0.0022

Multivariate Analysis (Overall Survival)

	Relative Risk (95% CI)	P-value
Age		0.100
55-65	1.00	
65+	1.14 (0.98-1.33)	0.100
Blasts in BM at HCT		0.000
<5%	1.00	
5%-10%	1.06 (0.85-1.31)	0.613
11%-20%	1.58 (1.24-2.03)	0.000
Missing	1.62 (1.2 -2.18)	0.001
Cytogenetic risk		0.000
Good	1.00	
Intermediate	1.02 (0.8-1.29)	0.876
Poor	1.68 (1.4-2.01)	0.000
Unknown	1.28 (0.96-1.71)	0.088
Sorror score		0.001
0	1.00	
1-2	1.25 (0.99-1.57)	0.063
3	1.27 (0.99-1.64)	0.062
4+	1.59 (1.27-1.99)	0.000

Conclusion

- Since approval of the CED, the number of alloHCTs for patients 65+ in the US has increased fourfold.
- In patients who are eligible for alloHCT, there was no difference in 100 day mortality or overall survival for patients 55-64 compared to patients 65 years and older.
- Age alone should not be a determinant for alloHCT eligibility.

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What are the impacts?

- Considerable effort for transplant centers to provide data on CRF forms
- Considerable effort for CIBMTR to manage study, reimburse for CRF forms, provide reports and updates to CMS

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MDS CED: 3 ???

- Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes? Ongoing BMT CTN 1102
  - NRM, PFS, Relapse, Overall Survival
- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do IPSS score, patient age, cytopenias and comorbidities predict outcomes?
- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, what treatment facility characteristics predict meaningful clinical improvement in outcomes?

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A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Intermediate-2 and High Risk Myelodysplastic Syndrome

BMT CTN Protocol 1102
Version 1.0

BMT CTN 1102: Biologic Assignment Trial

- As of Aug 31:
  - 207 enrolled of 338 expected
  - At 99% of accrual projection timeline
- Accrual projected to end February 2018
- Additional time for follow-up necessary before analysis can be completed
  - Anticipated for second half of 2019

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What is next for MDS?

- Finalize multivariate analysis and publish findings from observational study
- Sufficient numbers have accrued to address scientific questions addressable through the observational study
- Complete the biologic assignment trial through the BMT CTN
- Guidance needed from CMS regarding next steps

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Coverage limitations for patients 65 and older remain in other indications

New CMS Policy Reimbursement for Allogeneic Hematopoietic Stem Cell Transplantation (HCT) for Myeloma, Sickle Cell Disease and Myelofibrosis

January 2016

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New CMS on Reimbursement for HCT in Myeloma, Sickle Cell Disease, Myelofibrosis

- Prior to January 2016, CMS specifically prohibited coverage of alloHCT for multiple myeloma and was silent on allogeneic HCT for sickle cell disease and myelofibrosis
  - **No** Medicare reimbursement for allogeneic HCT in myeloma
  - **Variable** coverage for allogeneic HCT for sickle cell disease and myelofibrosis across the country

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New CMS Policy on Reimbursement for HCT in Myeloma, Sickle Cell Disease, Myelofibrosis

- NMDP, CIBMTR, ASBMT petitioned CMS to reconsider coverage for these diseases early 2015
- January 27, 2016, CMS issued NCD to cover allogeneic HCT for some beneficiaries with myeloma, sickle cell disease, myelofibrosis under its Coverage with Evidence Development (CED) paradigm
  - Reimbursement provided only if the patient is enrolled in a **CMS-approved clinical trial** designed to evaluate benefit in the Medicare population

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New CMS Policy on Reimbursement for HCT in Myeloma, Sickle Cell Disease, Myelofibrosis

Patients eligible

- Patients with **Stage II or III** (Durie-Salmon or IPSS) symptomatic multiple myeloma
- Patients with **Intermediate-2 or High DIPSS plus score** primary or secondary myelofibrosis
- Patients with **severe symptomatic** sickle cell disease

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New CMS Policy on Reimbursement for HCT in Myeloma, Sickle Cell Disease, Myelofibrosis

Trial Requirements

- Prospective
- Have as **principal objective** to test whether alloHCT improves health outcomes of affected beneficiaries (no pathogenesis or toxicity studies)
  - Compare **survival** with non-alloHCT therapy
  - Adequately control for **selection bias** and potential confounding by **specific prognostic factors**
  - Address **GVHD and transplant-related adverse events**

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New CMS Policy on Reimbursement for HCT in Myeloma, Sickle Cell Disease, Myelofibrosis

Differences from Myelodysplasia CED:

- Requirement to address ALL questions (including comparison to non-alloHCT therapy) for approval
- Restriction to specific subpopulations of each disease (which requires that we assess eligibility beyond disease at time of enrollment)
- Three different diseases that will require three separate studies

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Planning for CED-Compliant Trials

- All of these differences, but particularly the requirement for formal comparison to non-alloHCT controls will make rapid development and implementation of a CED-compliant protocol more difficult
- Another important difference for sickle cell disease and myelofibrosis: in some locales, HCTs were being covered and **now they are not** (MDS and myeloma were specifically not covered before the CED) – so there is urgency to proceed so that path to transplant is not interrupted for affected patients

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Planning for CED-Compliant Trials: CIBMTR Assets

- Already **prospectively** captures data on all alloHCT recipients in the US
- Existing data collection and analysis protocol meets CMS's requirements for study quality (consent, CFR 45 compliance, listed on ClinicalTrials.gov, etc.)
- Disease experts involved with Working Committees
- Positive relationship with CMS from MDS CED

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Planning for CED-Compliant Trials: Additional challenges

- Substantial methodologic complexities must be addressed to design appropriate transplant and non-transplant comparisons
  - Selection of patients and risk factors by physicians
  - Historical control bias based on access (coverage)
  - Handling time to procedure; lead time bias
- Access to registries/databases for non-transplant patients with sufficient data to match cohorts and perform risk adjustment

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CED for Sickle Cell Disease

- BMT CTN 1503: A study to compare BMT to Standard of Care for Adolescents and Young Adults with Sickle Cell Disease STRIDE2
  - NCT02766465
- CMS determined fulfills the NCD criteria: June 14, 2016
- 44 centers anticipated to participate
- Protocol Activation: Late Sept/Early October

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CED for Myelofibrosis

- Compare the five-year survival probabilities from DIPSS assessment between:
  - alloHCT recipients (arm 1)
  - ruxolitinib / best supportive care (arm 2).
- Targeted accrual of 650 alloHCT recipients
  - About 225 receiving myeloablative conditioning.
- Non-HCT historical control cohort (2000 – 12)
  - Approximately 2,400 patients
- Descriptive Haploidentical donor cohort

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CED for Myelofibrosis

- Primary myelofibrosis or post-essential thrombocythemia / polycythemia vera
- DIPSS intermediate-2 or high risk disease
- Aged ≥55 at the time of DIPSS assessment
- HLA-Matched Donor HCT Study
  - 6/6 HLA-matched related donor
  - Peripheral blood stem cells and bone marrow
  - All conditioning regimen intensities and GVHD prophylaxis regimens are allowed.

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CED for Myelofibrosis

- Draft protocol in final preparation stages

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CED for Multiple Myeloma
Specific Aims

- To prospectively determine the outcomes of allogeneic HCT for MM in Medicare beneficiaries, ≥65 years, compared with patients ≥65 years who underwent autologous HCT for similar risk MM between 2010-2015.
- To prospectively determine disease- or patient-related factors that predict outcomes of alloHCT for MM in Medicare beneficiaries
- To prospectively determine disease- or patient-related factors that predict outcomes of alloHCT for MM in Medicare beneficiaries

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CED for Multiple Myeloma

- Draft protocol should be finalized by end of the calendar year

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Questions

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