Childhood Cancer Survivor Study
Analysis Concept Form

1. STUDY TITLE: Psychological, Behavioral, and Educational Outcomes in Pediatric Acute Myeloid Leukemia Survivors

2. WORKING GROUP AND INVESTIGATORS:

Working group: Psychology

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3. BACKGROUND AND RATIONALE:

As rates of pediatric cancer survivorship increase, a greater emphasis has been placed on reducing the late-effects of treatment and improving quality of life. This includes consideration of the long-term psychosocial impact of cancer and its treatment. Understanding the psychological, behavioral, and educational outcomes of childhood cancer survivors is an important first step in developing interventions that can improve quality of life in this population. The Childhood Cancer Survivor Study (CCSS) provides the opportunity to look at a large number of pediatric cancer survivors and has previously been used successfully to evaluate psychosocial outcomes in many diagnostic groups. Within the CCSS, one specific group that would benefit from additional evaluation of psychosocial outcomes is pediatric acute myeloid leukemia (AML) survivors.

AML is the second most common form of pediatric leukemia. It can be treated with chemotherapy alone or with chemotherapy followed by bone marrow transplantation (BMT). The choice of therapy depends on multiple considerations, including leukemia risk factors and availability of a donor for transplant. As a result of treatment, childhood AML survivors have an increased rate of chronic health problems,[1-3] with those who have been treated with an allogeneic BMT at the highest risk.[1] This population is important to study for two reasons: 1) Pediatric AML survivors are believed to be at high risk for late-effects that further analysis could help to more definitively describe, and 2) Pediatric AML survivors are a unique population that allows for the study of the effects of treatment stratified by BMT with and without total body irradiation (TBI) versus chemotherapy-alone in a single disease.

With its recent expansion, the Childhood Cancer Survivor Study provides the opportunity to evaluate 868 survivors of AML and allows for assessment of outcomes across 30 years of diagnostic time. It also affords the opportunity to understand more about the contribution of different treatments to the development of subsequent psychological late-effects by directly comparing outcomes of AML survivors treated with chemotherapy-only to those treated with bone marrow transplantation, including those treated with and without TBI. Determining the prevalence of and risk factors for psychological, behavioral, and educational difficulties may allow for improved screening and better identification of necessary services.

Previous studies of AML patients are limited by small sample sizes, use of different outcome measures and the exclusion of AML survivors treated with BMT. While higher levels of psychological distress have been reported in adolescent survivors of AML[4] as well as adult survivors of AML[5] when compared to physically healthy samples, other studies have shown no significant change in emotional and behavioral functioning in those treated with BMT at less than three years of age.[6] In regard to school outcomes, it has been reported that the proportion of pediatric AML survivors treated with chemotherapy alone needing special education services did not differ from that of their siblings.[7] However, when considering all therapies for AML, it was found that pediatric AML survivors treated with chemotherapy plus cranial radiation or chemotherapy plus total body irradiation and BMT were at higher risk of development of academic difficulties as compared to those treated with chemotherapy only.[8] It has also been reported that educational attainment in AML survivors is lower than what might be expected within an individual family unit.[2]

Prior studies of the CCSS cohort have indicated that most survivors of childhood cancers are psychologically healthy; however, there is a subset of survivors who are at increased risk for psychological distress including anxiety,[9,10] depression,[9,10] PTSD,[11] and other forms of psychological distress,[12-15] as well as poor behavioral outcomes.[9] Treatment-related risk factors cited include exposure to intensive chemotherapy,[9,11,16,17] cranial radiation,[9,17-19] and presence of medical late-effects, [12,18-21] which may be particularly relevant to AML survivors. Other factors associated with increased psychological distress in pediatric cancer survivors include low household income,[11,16,18,19] lower educational attainment,[11,16,18,19,21] and female gender.[12,16,18-21] Similarly, an increased need for special education services among pediatric cancer survivors has also been described.[22-24] Missed school and low test scores are reported as reasons survivors require special education services or repeat a grade.[22] Risk factors for special education service utilization include cranial radiation,[17,22-24] intrathecal methotrexate,[17,22] and younger age at diagnosis.[22] Given the vulnerability of AML survivors to medical late-effects of treatment and knowledge that certain subsets of childhood cancer survivors are at higher risk for psychological distress and poorer behavioral and education outcomes, it is clear that pediatric AML survivors are an important population to study in more detail. The aim of this study is to evaluate the long-term psychological, behavioral and educational outcomes in pediatric AML survivors. The large size of the CCSS population and the ability to stratify analyses based on transplant status in this study will overcome some of the limitations of previous studies described above. The CCSS also provides the opportunity to gain a better understanding of the contribution of different treatment types to the development of subsequent late-effects. Determining the prevalence of and risk factors for psychological, behavioral, and educational difficulties will allow for more targeted screening based on risk and earlier identification of necessary services with the long-term goal of improved quality of life for pediatric AML survivors.

4. SPECIFIC AIMS AND RESEARCH HYPOTHESES:

The objective for the proposed project is to evaluate the psychological, behavioral, and educational outcomes in pediatric AML survivors, and to compare outcomes based on treatment exposures as well as to a sibling control group. We will classify all AML survivors into three groups based on treatment exposure, as follows:

1- AML survivors treated with chemotherapy-only (no BMT)
2- AML survivors treated with chemotherapy followed by BMT
3- AML survivors treated with chemotherapy and TBI followed by BMT

Evaluating this population of survivors who may be at higher risk for difficulties in these areas may allow for more targeted screening and identification of necessary services. Using the CCSS dataset, we will

assess the prevalence and predictors of psychological and behavioral difficulties as well as special education service utilization.

4.1. **AIM 1:** To evaluate psychological distress among pediatric AML survivors based on treatment group, and to compare all groups of AML survivors to sibling controls using self-reported symptoms of psychological distress on the Brief Symptom Inventory 18 (BSI-18) for all participants completing this measure for the first time at baseline or on a follow up survey.

4.1.1. **Hypothesis 1:** Symptoms of psychological distress will be highest in AML survivors treated with BMT including chemotherapy and TBI, followed by AML survivors treated with BMT including chemotherapy, followed by those treated with chemotherapy-only, with the sibling control group showing the lowest levels of psychological distress.

4.2. **AIM 2:** To compare behavioral problems in pediatric AML survivors based on treatment group, and to compare all groups of AML survivors to sibling controls using parent-reported symptoms on the Behavior Problem Index (BPI) (for participants less than 18 years old at baseline.)

4.2.1. **Hypothesis 2:** Behavior problems, especially internalizing behavior problems, will be highest in AML survivors treated with BMT including chemotherapy and TBI, followed by AML survivors treated with BMT including chemotherapy, followed by those treated with chemotherapy-only, with the sibling control group showing the lowest levels of behavior problems.

4.3. **AIM 3:** To examine special education service utilization in pediatric AML survivors based on treatment group, and to compare all groups of AML survivors to sibling controls.

4.3.1. **Hypothesis 3:** AML survivors treated with chemotherapy and TBI followed by BMT will have higher rates of special education service utilization, followed by those treated with chemotherapy then BMT and then those treated with chemotherapy-alone, with the sibling control group showing the lowest rate of special education service utilization.

5. ANALYSIS FRAMEWORK:

5.1. **Population**: Pediatric AML survivors included in the overall cohort (i.e. original and expansion, n= 868), provided they completed the BSI-18 at baseline (for those $\geq$ 18 years old) or at follow up (first completed measure to be used), or their parent/guardian completed the BPI (for those <18 years of age). Pediatric AML survivors who died prior to administration of the baseline survey but for whom a BPI was completed by a parent or proxy will be included.

5.1.1. Exclusion criteria: Pediatric AML survivors who received a BMT $\geq$ 5 years after initial diagnosis of AML (for relapse or other indication); patients with genetic conditions known to be associated with developmental delays, intellectual disability or learning disabilities, including Down syndrome, Turner syndrome, Klinefelter syndrome, fragile X syndrome, Fanconi anemia, Bloom syndrome, neurofibromatosis type 1, and severe congenital neutropenia.

5.1.2. Pediatric AML Survivor Categorization: Within the original cohort, The CCSS Radiation Dosimetry Center at MD Anderson has abstracted TBI from the radiation records and chemotherapy is available from the Medical Records Abstraction Form (MRAF) data. Within the expansion cohort, reliable data is available via the MRAF on treatment regimen, including BMT status. It is proposed that pediatric AML survivors be categorized as receiving chemotherapy-only, chemotherapy followed by BMT, or chemotherapy and TBI followed by BMT as follows:

5.1.2.1. Original cohort: There are known difficulties identifying BMT status within the original cohort as specific MRAF data is not available; however, Dr. Leisenring and her group have developed a schema for assigning BMT status within the original cohort as

definitely, probably or indeterminate and previous CCSS studies have reported on BMT status.[25] AML survivors treated with chemo-alone vs. chemotherapy followed by BMT vs. chemotherapy and TBI followed by BMT will be identified as outlined below:

5.1.2.1.1. AML survivors who have total body irradiation (TBI) reported in the medical record will be classified as having received a bone marrow transplant based on the previously established assignment schema.

5.1.2.1.2. AML survivors previously confirmed by Dr. Leisenring's team as definitely having received a BMT will be assigned to the BMT group

5.1.2.1.3. AML survivors with no medical record of TBI who were not previously identified and confirmed as having a BMT will be categorized as having received chemotherapy-only

5.1.2.2. Expansion cohort: MRAF data is available and reliable, including BMT status. MRAF data will be used to identify AML survivors who were treated with chemotherapy alone versus bone marrow transplantation

5.1.2.3. Data Checks on BMT Status: Due to possible inconsistency of BMT coding within the original cohort, AML survivors treated with BMT in the original cohort (n=70) will be compared with those in the expansion cohort (n=230) on demographic and treatment variables to determine whether any critical and unexpected differences are identified prior to combining both groups and moving forward with analyses. Additionally, a sensitivity analysis will be performed after full analyses to examine the possible impact of incorrect ascertainment of BMT status. Lastly, a sensitivity analysis repeating the analysis in the expansion cohort alone will be performed. If the results for the expansion cohort alone are the same as the overall analysis (original + expansion cohorts), then the overall analysis will be used.

5.2. **Outcomes of Interest:**

5.2.1. **Psychological Distress:** Psychological distress as measured by the Brief Symptom Inventory 18. The BSI-18 provides measures of anxiety, somatization, depression, and a global severity index. Increased levels of psychological distress on the BSI-18 will be defined as a T score $\geq$ 63.

Original baseline >18, items J16-24, J26-27, J29-35
Expansion baseline >18, items K1-18
Sibling baseline >18 (original and expansion), items J16-24, J26-27, J29-35
2003 follow up, items G1-18 *
2003 sibling follow up with psychosocial, items G1-18
2003 sibling follow up, items E1-18
2007 follow up, items L1-18
2007 sibling follow up, items L1-18

5.2.2. **Behavior Problems:** Behavioral functioning as measured by the Behavior Problem Index. The BPI provides measures of attention deficit, depression/anxiety, headstrong behavior, social withdrawal, antisocial behavior and immature/dependency (for those age 4-11). Increased levels of behavior problems on the BPI will be defined as a score $\geq$ 90th percentile for age and gender based on normative data from the National Longitudinal Survey of Youth.[26]

Original baseline <18, items J19-21
Expansion baseline <18, items K4-6
Sibling baseline <18 (original and expansion), items J19-21

* For all follow up surveys, BSI-18 to be used only when BPI was completed at baseline. Only first BSI-18 completed to be used in analysis.

5.2.3. **Special Education Service Utilization:** Special education service utilization as reported in the school history.

Original baseline for those <18 and ≥18, items O3-4
Expanded baseline for those <18 and ≥18, items R3-4
Sibling baseline <18 and >18 (original and expansion), items O3-4

5.2.4. **Predictors/Covariates/Effect Modifiers:**

5.2.4.1. Demographics: Age at survey completion, sex, race, ethnicity
5.2.4.2. Treatment factors:
Age at diagnosis (continuous and categorical <3 and ≥3 years old)
Chemotherapy (specific doses, unless otherwise noted)
Anthracyclines
Total anthracycline dose
Daunorubicin, Doxorubicin, Idarubicin, Actinomycin-D
Alkylating Agents
Total alkylating agent/cyclophosphamide equivalent dose
Carmustine, Busulfan, Lomustine, Cisplatinum, Cyclophosphamide, DTIC, Ifsofamide, Melphalan, Nitrogen Mustard, Procarbazine
Antimetabolites
Cytosine Arabinoside (IV, IT), Methotrexate (IT)
Steroids, plant alkyloids, epipodophyllotoxins (yes/no)
Etoposide
Radiation (specific doses)
TBI Dose
CNS Radiation: From body region dosimetry data maximum treatment dose to brain, chest, abdomen, and pelvis regions
Bone marrow transplantation status (yes/no) as defined above
MRAF
Stem cell source: autologous, related allogeneic, unrelated allogeneic
TBI exposure (proxy)
5.2.4.3. Medical conditions (grades 3-5): hearing/vision/speech, brain and nervous system
5.2.4.4. Medications: psychotropic medications
5.2.4.5. Psychosocial: insurance, income, marriage, employment
5.2.4.6. Special Education: Receipt of special education services prior to cancer diagnosis
5.2.3.7. Treatment era (1970-1975, 1976-1980, 1981-1985, 1986-1989, 1990-1995, 1996-1999)

5.3. **Proposed Analyses:**

5.3.1. **Aim 1:** To evaluate psychological distress among pediatric AML survivors based on treatment group, and to compare all groups of AML survivors to sibling controls using self-reported symptoms of psychological distress on the Brief Symptom Inventory 18 (BSI-18) for all participants completing this measure for the first time at baseline or on a follow up survey.

Methods: Our analysis will include baseline data from the original and expanded cohorts. Four study groups will be included in the analyses: 1) AML survivors who received chemotherapy only; 2) AML survivors who received chemotherapy followed by BMT; 3) AML survivors who received chemotherapy and TBI followed by BMT; and 4) Sibling controls with no history of AML. Baseline characteristics including, but not limited to, age at diagnosis, times since diagnosis,

race, ethnicity and gender, will be compared across study groups using descriptive statistics. Percent differences in categorical variables will be compared with a chi-square test or z-test of proportional differences. For each participant, only the first administration of the BSI-18 will be used as the outcome and the age at which it is administered will be adjusted for in the analyses. Univariate differences in domain specific outcomes from the BSI-18 will be summarized across groups using comparable descriptive statistics. To adjust for potential confounding factors, multivariate logistic regression will be employed to determine associations between group and domain specific outcomes from the BSI-18 dichotomized at the level of clinical significance. Potential covariates will be included in the models (e.g. age, gender, race/ethnicity) and additional variables, such as medical conditions (hearing, speech and vision impairments), will be explored as potential mediators of the association. Potential interactions will be tested using interaction terms in the multivariate models and if necessary, we will employ stratification.

5.3.2. **Aim 2:** To compare behavioral problems in pediatric AML survivors based on treatment group, and to compare all groups of AML survivors to sibling controls using parent-reported symptoms on the BPI.

Methods: Four study groups, as defined above, will be included in the analyses among subjects who were less than 18 years of age at the time of baseline data collection. Similar statistical methods to those used for Aim 1 will be employed; however outcomes, including attention deficit, depression/anxiety, headstrong behavior, social withdrawal, antisocial behavior and immature/dependency (for those age 4-11) will be derived from the Behavior Problem Index. Age and gender specific normative data from the National Longitudinal Study of Youth[26] will be used to identify those survivors in the top 10% of behavior problems.

5.3.3. **Aim 3:** To examine special education service utilization in pediatric AML survivors based on treatment group, and to compare all groups of AML survivors to sibling controls.

Methods: Population will be limited to AML survivors <18 years of age at diagnosis given the lack of opportunity to obtain special education services after age 18 years. Four study groups, as defined about, will be compared combining survivors, regardless of age (including younger and older than 18 years at baseline,) participating in the original or expanded baseline survey. The proportion of subjects who had special education placement after cancer diagnosis will be compared across groups. Logistic regression will estimate the relative risk (by generating odds ratios) of special education placement based on treatment group, compared to sibling controls and adjusting for potential confounding factors, including receipt of special education services prior to cancer diagnosis.

The frequency of special education service utilization will be analyzed by year in the sibling control group. If changes in frequency are noted, special education service utilization will be stratified by era (1970-1975, 1976-1980, 1981-1985, 1986-1989, 1990-1995, 1996-1999) in all groups.

Table 1. Characteristics of AML survivors and sibling controls[†]

	ALL AML (1)		Chemo only (2)		BMT-Chemo (3)		BMT-Chemo + TBI (4)		Siblings (5)		P						
	N	%	N	%	N	%	N	%	N	%	1 v 2	2 v 3	2 v 4	2 v 5	3 v 4	3 v 5	4 v 5
Gender																	
Female																	
Male																	
Race																	
While																	
Black																	
Asian or Pacific Islander																	
Other																	
Unknown																	
Hispanic																	
Yes																	
No																	
Unknown																	
Household Income																	
<20,000																	
20,000-60,000																	
>60,000																	
Relationship Status																	
Single																	
Married/living as married																	
Divorced/separated/widowed																	
Employment																	
Employed																	
Student																	
Unemployed																	
Insurance Status																	
Insured																	
Noninsured																	
Age at AML Diagnosis																	
0-3 years																	
4-9 years																	
10-14 years																	
15-20 years																	
Age at Baseline Survey																	
<18 years																	
≥18 years																	
Time from Diagnosis at Baseline																	
5-10 years																	
10-15 years																	
15-20 years																	
20+ years																	
Treatment Era																	
1970-1975																	
1976-1980																	
1981-1985																	
1986-1989																	
1990-1995																	
1996-1999																	

[†] There are 868 AML survivors in the CCSS. In the original cohort, there are 356 AML survivors. 70 of those survivors were identified as having a BMT within 5 years of the primary cancer diagnosis and 43 of these 70 received TBI. In the expansion cohort, there are 512 AML survivors. 231 AML survivors in the expansion cohort were identified as having a BMT < 5 years after primary diagnosis. Of these 231 survivors, 96 received TBI.

	ALL AML (1)		Chemo only (2)		BMT-Chemo (3)		BMT-Chemo + TBI (4)		Siblings (5)		P						
	N	%	N	%	N	%	N	%	N	%	1 v 2	2 v 3	2 v 4	2 v 5	3 v 4	3 v 5	4 v 5
Treatment																	
BMT																	
No																	
Yes																	
Autologous																	
Allogeneic- related donor																	
Allogeneic-unrelated donor																	
Radiation‡																	
None																	
Cranial Radiation																	
>0-1 Gy																	
>1-5 Gy																	
>5-15 Gy																	
>15-25 Gy																	
>25 Gy																	
Cranial and Spine Radiation																	
>0-1 Gy																	
>1-5 Gy																	
>5-15 Gy																	
>15-25 Gy																	
>25 Gy																	
Total Body Irradiation																	
>0-1 Gy																	
>1-5 Gy																	
>5-15 Gy																	
>15-25 Gy																	
>25 Gy																	
Total CNS Radiation																	
>0-1 Gy																	
>1-5 Gy																	
>5-15 Gy																	
>15-25 Gy																	
>25 Gy																	
Chemotherapy																	
Epipodophyllotoxins																	
Etoposide																	
	Mdn	R	Mdn	R	Mdn	R	Mdn	R									
Anthracyclines																	
Total Anthracycline Dose																	
Daunorubicin																	
Doxorubicin																	
Idarubicin																	
Actinomycin-D																	
Alkylating Agents																	
Total Alk dose/Cyclophos equiv.																	
Carmustine																	
Busulfan																	
Lomustine																	
Cisplatinum																	
Cyclophosphamide																	
DTIC																	
Ifsofamide																	
Melphalan																	
Nitrogen Mustard																	
Procarbazine																	
Antimetabolites																	
Cytosine Arabinsode (IV)																	
Cytosine Arabinsode (IT)																	
Methotrexate (IT)																	

‡ Categories may be redefined once distribution of sample is known

Table 2a. Characteristics of AML survivors by treatment type and sibling controls, <18 years at baseline

	Chemo only (1)		BMT-Chemo (2)		BMT-Chemo + TBI (3)		Siblings (4)		P					
	N	%	N	%	N	%	N	%	1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Gender														
Female														
Male														
Race														
While														
Black														
Asian or Pacific Islander														
Other														
Unknown														
Hispanic														
Yes														
No														
Unknown														
Household Income														
<20,000														
20,000-60,000														
>60,000														
Relationship Status														
Single														
Married/living as married														
Divorced/separated/widowed														
Employment														
Employed														
Student														
Unemployed														
Insurance Status														
Insured														
Noninsured														
Age at AML Diagnosis														
0-3 years														
4-9 years														
10-14 years														
15-20 years														
Time from Diagnosis at Baseline														
5-10 years														
10-15 years														
15-20 years														
20+ years														
Treatment Era														
1970-1975														
1976-1980														
1981-1985														
1986-1989														
1990-1995														
1996-1999														
Treatment														
BMT														
No														
Yes														
Autologous														
Allogeneic- related donor														
Allogeneic-unrelated donor														
Radiation[§]														
None														
Cranial Radiation														
>0-1 Gy														
>1-5 Gy														

[§] Categories may be redefined once distribution of sample is known

>5-15 Gy														
>15-25 Gy														
>25 Gy														
Cranial and Spine Radiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														
>25 Gy														
Total Body Irradiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														
>25 Gy														
Total CNS Radiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														
>25 Gy														
Chemotherapy														
Epipodophyllotoxins														
Etoposide														
	Mdn	R	Mdn	R	Mdn	R								
Anthracyclines														
Total Anthracycline Dose														
Daunorubicin														
Doxorubicin														
Idarubicin														
Actinomycin-D														
Alkylating Agents														
Total Alk dose/Cyclophos equiv.														
Carmustine														
Busulfan														
Lomustine														
Cisplatinum														
Cyclophosphamide														
DTIC														
Ifsofamide														
Melphalan														
Nitrogen Mustard														
Procarbazine														
Antimetabolites														
Cytosine Arabinsode (IV)														
Cytosine Arabinsode (IT)														
Methotrexate (IT)														

Table 2b. Characteristics of AML survivors by treatment type and sibling controls, ≥ 18 years at baseline

	Chemo only (1)		BMT-Chemo (2)		BMT-Chemo + TBI (3)		Siblings (4)		P					
	N	%	N	%	N	%	N	%	1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Gender														
Female														
Male														
Race														
While														
Black														
Asian or Pacific Islander														
Other														
Unknown														
Hispanic														
Yes														
No														
Unknown														
Household Income														
<20,000														
20,000-60,000														
>60,000														
Relationship Status														
Single														
Married/living as married														
Divorced/separated/widowed														
Employment														
Employed														
Student														
Unemployed														
Insurance Status														
Insured														
Noninsured														
Age at AML Diagnosis														
0-3 years														
4-9 years														
10-14 years														
15-20 years														
Time from Diagnosis at Baseline														
5-10 years														
10-15 years														
15-20 years														
20+ years														
Treatment Era														
1970-1975														
1976-1980														
1981-1985														
1986-1989														
1990-1995														
1996-1999														
Treatment														
BMT														
No														
Yes														
Autologous														
Allogeneic- related donor														
Allogeneic-unrelated donor														
Radiation**														
None														
Cranial Radiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														

** Categories may be redefined once distribution of sample is known

>25 Gy														
Cranial and Spine Radiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														
>25 Gy														
Total Body Irradiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														
>25 Gy														
Total CNS Radiation														
>0-1 Gy														
>1-5 Gy														
>5-15 Gy														
>15-25 Gy														
>25 Gy														
Chemotherapy														
Epipodophyllotoxins														
Etoposide														
	Mdn	R	Mdn	R	Mdn	R								
Anthracyclines														
Total Anthracycline Dose														
Daunorubicin														
Doxorubicin														
Idarubicin														
Actinomycin-D														
Alkylating Agents														
Total Alk dose/Cyclophos equiv.														
Carmustine														
Busulfan														
Lomustine														
Cisplatinum														
Cyclophosphamide														
DTIC														
Ifsofamide														
Melphalan														
Nitrogen Mustard														
Procarbazine														
Antimetabolites														
Cytosine Arabinsode (IV)														
Cytosine Arabinsode (IT)														
Methotrexate (IT)														

AIM 1[††] [‡‡]

Table 3. Frequency comparisons of self-reported elevated levels of psychological distress (T score ≥ 63)

	AML- chemo only (1)		AML- chemotherapy + BMT (2)		AML- Chemo/TBI + BMT (3)		Siblings (4)		P Value					
	N	%	N	%	N	%	N	%	1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
BSI-18 domains														
Depression														
Anxiety														
Somatization														
Global Severity Index														

Table 4. Multivariate analyses of those >18 years: association between treatment and psychological distress on BSI-18

	Depression OR (95% confidence interval)	**Anxiety** OR (95% confidence interval	**Somatic Distress** OR (95% confidence interval	**Global Severity Index** OR (95% confidence interval)
Siblings	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
AML chemo- only				
AML chemo + BMT				
AML chemo/TBI + BMT				

* Variables adjusted for: Age at diagnosis, gender, possible others identified in preliminary analyses as differing between groups.

AIM 2

Table 5. Frequency comparisons of parent-reported elevated levels of behavior problems (score ≥ 90th percentile for age and gender)

	AML- chemo only (1)		AML- chemo + BMT (2)		AML- Chemo/TBI + BMT (3)		Siblings (4)		P Value					
	N	%	N	%	N	%	N	%	1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Total BPI Score														
BPI Domains														
Attention Deficit														
Depression/Anxiety														
Headstrong Behavior														
Social Withdrawal														
Antisocial Behavior														
Immature/Dependency														

[††] Propose to look at cumulative chemotherapy, dose of radiation exposure and BMT status (including stem cell source in the expansion cohort) with plan to further explore outcomes in aims 1-3 based on specific therapies once frequency data is available.

[‡‡] For aims 1-3, propose to examine univariate associations between treatment era (1970-1989 vs. 1990-1999) and outcomes to determine whether treatment era needs to be included in modeling

Table 6. Multivariate analyses of those <18 years looking at treatment predicting behavioral outcomes

	Attention deficit OR (95% confidence interval)	**Depression / anxiety** OR (95% confidence interval)	**Headstrong behavior** OR (95% confidence interval	**Social withdrawal** OR (95% confidence interval)	**Antisocial behavior** OR (95% confidence interval)	**Immature/ Dependency** OR (95% confidence interval)
Siblings	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
AML chemo- only						
AML chemo + BMT						
AML chemo/TBI + BMT						

*Variables adjusted for: Age at diagnosis, gender, possible others identified in preliminary analyses as differing between groups

AIM 3

Table 7. Frequency comparisons of special education utilization in those <18 and ≥18 years old

	AML-chemo only (1) N=		**AML-chemo + BMT (2) N=**		**AML-chemo/TBI + BMT (3) N=**		**Siblings (4) N=**		**P Value**					
	N	%	N	%	N	%	N	%	1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Special education services utilization														
Reason for service utilization														
Missed school														
Low scores on tests														
Problems learning or concentrating														
Emotional or behavioral problems														

Table 8. Multivariate analyses of those < 18 y and 18+: association between treatment status and special education utilization

	Special Education Utilization OR (95% confidence interval)
Siblings	1.00 (ref)
AML chemo-only	
AML- chemo + BMT	
AML- chemo/TBI + BMT	

*Variables adjusted for: Age at diagnosis, gender, special education service utilization prior to diagnosis, possible others identified in preliminary analyses as differing between groups

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