CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. **TITLE:** Psychosocial and cognitive outcomes in pediatric cancer survivors diagnosed in infancy (birth-1 year of age) compared to those diagnosed in toddlerhood (1-3 years), preschool age (3- <6 years) and school age (6-<15).

2. INVESTIGATORS AND WORKING GROUP

2.1.1. Investigators

2.1.1.1. Emily Walling, MD, MPHS
2.1.1.2. Robert Hayashi, MD
2.1.1.3. Jennifer Harman, PhD
2.1.1.4. Kevin Oeffinger, MD
2.1.1.5. Rebecca Howell, PhD
2.1.1.6. Deo Kumar Srivastava, PhD
2.1.1.7. Gregory T. Armstrong. MD, MSCE
2.1.1.8. Kevin Krull, PhD

2.1.2. Working Group

2.1.2.1. Psychology (Primary), Chronic Disease (Secondary)

3. BACKGROUND AND SIGNIFICANCE

Infancy is a critical stage of growth and development, representing a unique time of attachment formation, exploration and milestone attainment.[1–3] This period is recognized as distinct from toddlerhood (1-3 years), preschool age (3-6 years) and school age (6-15) and requires close developmental monitoring by pediatricians.[3–5] This phase of life may be particularly vulnerable to disruptions, such as those imposed by a serious illness like cancer. Hospitalizations may necessitate prolonged separation from care givers as parents tend to their other family responsibilities. Hospital care can result in repetitive and prolonged exposures to noxious stimuli, disruption to sleep cycle, and restriction of physical movement. These experiences have the potential to be particularly impactful in infancy when security, routine and unrestricted mobility are critical.[1,2,6,7] Additionally, the demands of treatment likely disrupt the routine developmental surveillance provided by primary physicians. Thus, delays in development may go unrecognized and patients may not receive early interventions.[8] Research in preterm infants supports the hypothesis that infancy is a vulnerable time to be diagnosed with and treated for a chronic illness. A review of newborns and infants provided evidence that early experiences with pain may lead to lasting morbidity by altering pain perception and early stressors may impact neuroendocrine and immune systems.[9] Growth retardation as well as motor and neurologic impairment have been observed in pre-term and term infants treated with corticosteroids, even if the duration of treatment is limited to three days.[10–12]

Prior investigations have revealed that survivors of childhood cancer are significantly impacted in psychosocial and cognitive realms of functioning, particularly those receiving

high intensity central nervous system directed therapy with younger age identified as risk factors for long term morbidity.[13–21] With subsequent follow-up investigators have shown that chronic health conditions in young children contribute to psychosocial and cognitive deficits.[22] However, only certain diagnoses have been examined and the data are confounded by merging infants with children in older age groups. Further, the long-term effect of cancer treatment on infants has not been carefully examined.

An investigation reporting higher likelihood of special education needs among survivors of childhood acute lymphoblastic leukemia (ALL) treated with cranial irradiation and intrathecal chemotherapy had a median age at diagnosis of 4 years and 5 months.[18] A Childhood Cancer Survivorship Study (CCSS) study corroborated the finding that survivors diagnosed at younger ages had higher utilization of special education services and included infants but stratified their data with children up to the age of 5 years.[19] A report of the impact of ALL treatment on IQ scores found that those less than 5 years of age were more likely to have lower IQ scores at three years of follow up.[20] Similarly, age in this study was dichotomized to those greater or less than 5 years of age, so those treated as infants were not analyzed separately from older children diagnosed beyond the first year of life. Furthermore, reports of depression among survivors of pediatric leukemia, lymphoma or brain tumors failed to identify age at diagnosis as a significant contributor however, survivors diagnosed in infancy were not closely examined.[13,14]

The few available studies specific to infants have detailed significant CNS directed treatment related morbidity and mortality.[23,24] An investigation of patients treated for infant leukemia found survivors experienced a range of physical and cognitive impairments. The greatest impact was observed among those requiring cranial radiation in addition to chemotherapy and the effect was more pronounced the younger the age when cranial radiation therapy was administered.[25] The recognition that younger children, in particular infants, are particularly vulnerable to the effects of cranial radiation has led to efforts to avoid cranial radiation completely or delay until a later age.[26–28] This change in practice highlights the need to specifically examine survivors treated in infancy.

Given the rapid developmental changes that occur during infancy and prior studies documenting acute toxicities among the youngest children receiving cancer therapy, it is reasonable to postulate that infant cancer survivors may be particularly at risk for long term effects on cognitive and psychosocial functioning compared to higher age groups. The goal of this proposal is to achieve a more granular assessment of how a diagnosis of cancer in infancy impacts social, cognitive and psychological outcomes, and how the prevalence and severity of chronic health conditions may impact these outcomes, compared to survivors also diagnosed at a young age; toddlerhood (1- <3 years), pre-school ages (3- <6 years) and school age (6-15). An awareness of such vulnerabilities will ultimately facilitate the advancement of strategies to provide enhanced services to these respective groups and to develop new therapies to minimize the risk of morbidity to future patients. The breadth of the CCSS database will allow us to examine this issue in detail and characterize what other variables may influence the psychological and cognitive

outcomes of patients diagnosed in these discrete age groups so that we can better refine our management of these patients.

4. SPECIFIC AIMS AND OBJECTIVES

4.1. Primary aim:

4.1.1. To describe the neurocognitive outcomes in long term cancer survivors diagnosed in infancy (≤ 1 year) compared to toddlers (1 to <3 year-olds), preschool age children (3 to <6 year-olds), school age children (6 to <15 year-olds) and sibling controls.

4.1.2. To describe the psychosocial functioning (emotional and health-related quality of life) in long term cancer survivors diagnosed in infancy compared to toddlers, preschool age children, school age children and their healthy sibling controls.

4.1.3. To describe the social attainment of cancer survivors diagnosed in infancy compared to toddlers, preschool age children, school age children and their healthy sibling controls.

4.2. Secondary aims:

4.2.1. To identify diagnostic and treatment variables associated with neurocognitive, psychosocial and social attainment outcomes in survivors diagnosed as infants and older children.

4.2.2. To examine the impact of chronic health conditions on neurocognitive, psychosocial and social attainment outcomes in survivors diagnosed as infants and older children.

5. Hypotheses:

5.1. Survivors of childhood cancer diagnosed in infancy will have higher prevalence of neurocognitive impairment associated with higher rates of special education and lower rates of education and job attainment compared to survivors diagnosed later in childhood and to healthy controls

5.2. Survivors of childhood cancer diagnosed in infancy will have higher prevalence of depression and anxiety and lower health-related quality of life compared to survivors diagnosed later in childhood and to healthy controls

5.3. Survivors of childhood cancer diagnosed in infancy will have lower social attainment compared to survivors diagnosed later in childhood and to healthy controls.

5.4. Survivors of childhood cancer treated in infancy are more susceptible to treatment related morbidity and this will disproportionally impact their functional outcomes compared to those diagnosed later in childhood.

5.5. Cardiac, pulmonary, endocrine and neurologic chronic conditions will be related to neurocognitive and psychosocial outcomes and will moderate the effect of treatment exposures on functional outcomes.

6. ANALYSIS FRAMEWORK

6.1. Population: All CCSS participants diagnosed with cancer requiring chemotherapy or radiation therapy at ages <1 year of age compared to survivors diagnosed at 1 to <3 years, 3 to <6 years, 6 to <15 years and sibling controls in both the original and expansion CCSS cohorts.

6.2. Outcomes of Interest: Neurocognitive, emotional, HRQoL and social attainment from Follow-up 2 (FUP2) for the original cohort and Follow-up 5 (FUP5) for the expansion cohort.

6.2.1. Neurocognitive Function: Assessed by the Neurocognitive Questionnaire (NCQ) domains; Task Efficiency, Emotional Regulation, Organization and Memory. Scores will be reported as a continuous variable with impaired performance defined as ≥ 90th percentile based on norms obtained in the sibling cohort.
(FUP2 J1-25 FUP5 section Q1-33).

6.2.2. Emotional Function: Assessed with Brief Symptom Inventory (BSI) Scales; Anxiety, Depression, Somatization. Scores will be reported as a continuous variable. Impairment will be defined as performance ≥ 90th percentile based on norms.
(FUP2 G1-18 FUP5 L1-18).

6.2.3. Health Related Quality of Life (HRQoL): Assessed by the Medical Outcomes Study SF-36. Tool; general health, physical function, pain, vitality, role limitation due to physical and emotional function, social function and mental health. Scores will be reported as continuous variables with impairment defined as scores falling 1 standard deviation below the mean. (FUP2 E1-22, F1-14, FUP5 O1-8, P1-3)

6.2.4. Demographic and Social Factors: educational attainment (FUP 2 1), employment status (FUP2 4), marital status (FUP2 2), living arrangement (FUP2 2, FUP5 M1) and household income (FUP2 S1-S3; FUP5 A7-A9). All variables will be dichotomously defined consistent with previous CCSS publications.

6.3. Explanatory variables:

6.3.1. Age at diagnosis
6.3.2. Sex
6.3.3. Race/Ethnicity
6.3.4. Primary diagnosis
6.3.5. Age at Baseline Questionnaire
6.3.6. Age at Follow up 2 (Original cohort) or 5 (Expansion cohort)

Treatment obtained from Medical Record Abstraction Form:

6.3.7. Chemotherapy (yes/no)
6.3.8. Cumulative dose of chemotherapy agents: Methotrexate, Anthracyclines, Alkylators, Vinca Alkaloids, Epipodophyllotoxin
6.3.9. Intrathecal chemotherapy (Cytosine Arabinoside-IT, Methotrexate-IT, Hydrocortisone-IT)
6.3.10. Radiation Therapy (yes/no)
  6.3.10.1. CNS dose
  6.3.10.2. Chest/neck maximum target dose (maxTD)
  6.3.10.3. Abdomen/pelvis maxTD
6.3.11. Surgery (yes/no)
6.3.12. Chronic health conditions graded according to CTCAE criteria.
6.3.13. Anti-depressant and anti-anxiety medications

1

6.4. Analysis:

Descriptive statistics will be used to describe demographic characteristics for survivors and siblings and treatment variables for survivors. Frequency distributions will be used to summarize the outcome variables, predictors and covariates according to reasonable groupings consistent with previous CCSS manuscripts.

6.4.1. Primary aims:

6.4.1.1. To compare the neurocognitive outcomes in long term cancer survivors diagnosed in infancy (≤ 1 year), as toddlers (1 to <3 year-olds), in preschool age children (3 to <6 year-olds), and school age children (6 to <15 year-olds) using norms obtained from the sibling controls.

The primary focus of this objective is to assess if there are differences in neurocognitive functioning with age of diagnosis (diagnosed in infancy ≤1 year, diagnoses as toddlers (>1 to ≤3 years), diagnosed as preschool age (>3 to ≤6 years) and those diagnosed as school children (>6 to <15 years)). This will be assessed with the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ). Participants rated 19 items on a Likert scale with three possible responses: "Never a problem" (score=1), "Sometimes a problem" (score=2) and "Often a problem" (score=3). Four factor scores were derived from these items, including Task Efficiency, Emotional Regulation, Organization and Memory. A survivor would be classified as "impaired" on a particular factor if the factor z-scores ≥ 1.28, corresponding to ≥ 90th percentile of the sibling cohort. The prevalence of neurocognitive impairment across the four diagnosis age group will be compared using chi-square test. In addition, a log-binomial model, adjusting for the covariates (current age, sex, and length of follow-up) will be used to model the relationship between neurocognitive impairment and four levels of age at diagnosis.
If a clear monotonic relationship between neurocognitive measures and age groups is observed then we will evaluate that using Cochran-Armitage trend test. Once again, log-binomial model will be utilized and adjusted for the aforementioned covariates and using equal interval scores (1,2,3,4) for the four age groups.

6.4.1.2. To compare the psychosocial functioning (emotional and health-related quality of life) in long term cancer survivors diagnosed in infancy compared to toddlers, preschool age children, school children.

Emotional functioning will be assessed using the Brief Symptom Inventory -18 (BSI-18). The BSI-18 assesses three factors (depression, anxiety, somatization) and a global severity index. Scores for each of the three domains will be operationalized as binary variables (distressed or not). Participants will be considered distressed if their score is ≥ the 90th percentile of published norm. Comparisons of each age group (<1, 1- <3, 3-<6, 6-<15 years at diagnosis) will be compared with the sibling control group, then between age groups to assess both whether a specific age group has inferior psychosocial functioning

compared to the sibling control and also whether the youngest age groups are most significantly impacted. Health-related quality of life (HRQoL) will be assessed using the Medical Outcomes Short Form (SF-36). The SF-36 includes questions on general health and quality of life. Eight specific domains of the SF-36 will be used in all aims: general health, physical function, physical role function, physical role limitation, pain, emotional role limitation, vitality, social functioning. Scores for each of the eight domains will be operationalized as binary variables (impaired vs not). Health scales will be converted into T-scores based on the norms in the standardization manual and scores falling below a T-score of 40 will be identified as being impaired. Comparisons of each age group (<1, 1- <3, 3-<6, 6-<15 years at diagnosis) will be compared with the sibling control group, then between age groups to assess both whether a specific age group has inferior HRQoL compared to the sibling control and also whether the youngest age groups are most significantly impacted.

6.4.1.3 To compare Social Attainment of cancer survivors diagnosed in infancy compared to toddlers, preschool age children, school children.

Once again the statistical approaches described above, such as chi-square test or log-binomial regression, will be used to compare social attainment, educational attainment, and employment across four diagnosis age groups. These models will be adjusted for sex, ethnicity, and race. Adjusted RR and 95% confidence intervals will be reported. (Table 1a). The evaluation of the educational attainment will be restricted to survivors who are at least 25 years of age as the expectation is that this will provide survivors with the opportunity to graduate from college.

6.4.2 Secondary aims

6.4.2.1 In addition of the effect of age groups we will conduct multivariable log binomial regression to identify the diagnostic and treatment variables associated with presence or absence of impairments in neurocognitive, psychosocial impairments, poor HRQoL and inferior social attainment outcomes. Chemotherapy parameters will focus on likely candidates including radiation exposure (site and dose), IT MTX dose (cumulative exposure); IV MTX (cumulative exposure); cytarabine (yes/no); anthracycline (yes/no); alkylating agents (yes/no); dexamethasone (yes/no) Epipodophyllotoxin (cum dose, vinca alkaloid (yes/no).

6.4.2.2 Similarly, in a separate log binomial regression model will be used to assess the relationship between diagnostic age groups, chronic conditions on neurocognitive, psychosocial, HRQoL and social attainment outcomes in childhood cancer survivors.

References

1. Johnson CP, Blasco PA. Infant Growth and Development. *Pediatr Rev*. 1997;18(7):224-242. doi:10.1542/pir.18-7-224

2. Scharf RJ, Scharf GJ, Stroustrup A. Developmental Milestones. *Pediatr Rev*. 2016;37(1):25-37; quiz 38, 47. doi:10.1542/pir.2014-0103

3. Kliegman R, Stanton B, St. Geme III J, Schor N, Behrman R. *Nelson Textbook of Pediatrics*. 19th ed. Elsevier/Saunders; 2011.

4. Dworkin PH. British and American Recommendations for Developmental Monitoring: The Role of Surveillance. *Pediatrics*. 1989;84(6):1000-1010.

5. Disabilities C on CW, Pediatrics S on DB, Committee BFS, Committee MHI for CWSNPA. Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening. *Pediatrics*. 2006;118(1):405-420. doi:10.1542/peds.2006-1231

6. Waitzman KA. The Importance of Positioning the Near-term Infant for Sleep, Play, and Development. *Newborn Infant Nurs Rev*. 2007;7(2):76-81. doi:10.1053/j.nainr.2007.05.004

7. Perry RE, Blair C, Sullivan RM. Neurobiology of infant attachment: attachment despite adversity and parental programming of emotionality. *Curr Opin Psychol*. 2017;17:1-6. doi:10.1016/j.copsyc.2017.04.022

8. First LR, Palfrey JS. The Infant or Young Child with Developmental Delay. *N Engl J Med*. 1994;330(7):478-483. doi:10.1056/NEJM199402173300708

9. Page GG. Are there long-term consequences of pain in newborn or very young infants? *J Perinat Educ*. 2004;13(3):10-17. doi:10.1624/105812404X1725

10. Tijsseling D, ter Wolbeek M, Derks JB, et al. Neonatal corticosteroid therapy affects growth patterns in early infancy. *PLoS ONE*. 2018;13(2). doi:10.1371/journal.pone.0192162

11. Shinwell ES, Karplus M, Reich D, et al. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. *Arch Dis Child - Fetal Neonatal Ed*. 2000;83(3):F177-F181. doi:10.1136/fn.83.3.F177

12. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr*. 2001;1:1. doi:10.1186/1471-2431-1-1

13. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2004;22(6):999-1006. doi:10.1200/JCO.2004.06.148

14. Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. *Pediatrics*. 2002;110(1 Pt 1):42-52. doi:10.1542/peds.110.1.42

15. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2009;27(14):2396-2404. doi:10.1200/JCO.2008.21.1433

16. Gurney JG, Krull KR, Kadan-Lottick N, et al. Social outcomes in the Childhood Cancer Survivor Study cohort. *J Clin Oncol Off J Am Soc Clin Oncol*. 2009;27(14):2390-2395. doi:10.1200/JCO.2008.21.1458

17. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2018;36(21):2181-2189. doi:10.1200/JCO.2017.76.4696

18. Kingma A, Rammeloo L a. J, Berg A van der D den, Rekers-Mombarg L, Postma A. Academic career after treatment for acute lymphoblastic leukaemia. *Arch Dis Child*. 2000;82(5):353-357. doi:10.1136/adc.82.5.353

19. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer. *Cancer*. 2003;97(4):1115-1126. doi:10.1002/cncr.11117

20. Halsey C, Buck G, Richards S, Vargha-Khadem F, Hill F, Gibson B. The impact of therapy for childhood acute lymphoblastic leukaemia on intelligence quotients; results of the risk-stratified randomized central nervous system treatment trial MRC UKALL XI. *J Hematol OncolJ Hematol Oncol*. 2011;4:42. doi:10.1186/1756-8722-4-42

21. Buizer AI, Sonneville LMJ de, Veerman AJP. Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: A critical review of the literature. *Pediatr Blood Cancer*. 2009;52(4):447-454. doi:10.1002/pbc.21869

22. Cheung YT, Brinkman TM, Li C, et al. Chronic Health Conditions and Neurocognitive Function in Aging Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. *JNCI J Natl Cancer Inst*. 2017;110(4):411-419. doi:10.1093/jnci/djx224

23. Brown P. Treatment of infant leukemias: challenge and promise. *Hematol Educ Program Am Soc Hematol Am Soc Hematol Educ Program*. 2013;2013:596-600. doi:10.1182/asheducation-2013.1.596

24. Salzer WL, Jones TL, Devidas M, et al. Modifications to Induction Therapy Decrease Risk of Early Death in Infants With Acute Lymphoblastic Leukemia Treated on Children's Oncology Group P9407. *Pediatr Blood Cancer*. 2012;59(5):834-839. doi:10.1002/pbc.24132

25. Leung W, Hudson M, Zhu Y, et al. Late effects in survivors of infant leukemia. *Leukemia*. 2000;14(7):1185-1190. doi:10.1038/sj.leu.2401818

26. Geyer JR, Sposto R, Jennings M, et al. Multiagent Chemotherapy and Deferred Radiotherapy in Infants With Malignant Brain Tumors: A Report From the Children's Cancer Group. *J Clin Oncol*. 2005;23(30):7621-7631. doi:10.1200/JCO.2005.09.095

27. Christie D, Leiper AD, Chessells JM, Vargha-Khadem F. Intellectual performance after presymptomatic cranial radiotherapy for leukaemia: effects of age and sex. *Arch Dis Child*. 1995;73(2):136-140.

28. Ater JL, Eys J van, Woo SY, III BM, Copeland DR, Bruner J. MOPP chemotherapy without irradiation as primary postsurgical therapy for brain tumors in infants and young children. *J Neurooncol*. 1997;32(3):243-252. doi:10.1023/A:1005744527443

6.5 Proposed Study Tables

Table 1a: Characteristics of study population

Characteristic	Survivor Age at diagnosis (yrs)				Siblings
	<1	1- <3	3- <6	6-15	
Gender, #, (%)					
Female					
Male					
Race, # (%)					
White					
Black					
Hispanic					
Other					
Ethnicity # (%)					
Hispanic					
Non-Hispanic					
Education					
1-8 years					
9-12 years but did not graduate					
High school graduate					
Training post high school					
Some college					
College graduate					
Post graduate level					
Employment					
Full-time					
Part-time					
Working in the home					
Unemployed & looking for work					
Unable to work due to disability					
Retired					
Student					
Other					
Marital Status					
Single					
Married					
Divorced					
Widow					
Separated					
Independent Living (yes/no)					

Table 1b: Diagnostic and treatment characteristics of survivors

Characteristic	**Survivor age at diagnosis (yrs)**			
	<1	**1- <3**	**3- <6**	**6-15**
Diagnosis				
Acute lymphoblastic leukemia				
Acute myeloid leukemia				
Other leukemia				
Astrocytoma				
Medulloblastoma, PNET				
Other CNS tumors				
Wilms tumors				
Soft tissue sarcoma				
Neuroblastoma				
Length of treatment (months)				
Treatment				
Surgery				
Chemotherapy				
IT chemotherapy				
Radiation				
Chemotherapy (cum dose)				
Methotrexate				
Anthracycline				
Alkylating agent				
Vinca Alkaloid				
Epipodophyllotoxin				
IT Chemotherapy (cum dose)				
Cytosine Arabinoside				
Methotrexate				
Hydrocortisone				
Surgery				
Number of surgical procedures				
Radiation				
CNS dosimetry				
Chest/neck dosimetry				
Abdomen/pelvis dosimetry				

Table 2. Neurocognitive, emotional functioning and health related quality of life for survivors vs siblings*

	Survivor age at diagnosis (yrs)				Siblings
	<1 No. (%)	**1- <3 No. (%)**	**3-<6 No. (%)**	**6-15 No. (%)**	
Neurocognitive					
Task efficiency					
Emotional Regulation					
Organization					
Memory					
Emotional function					
Depression					
Anxiety					
Somatization					
Global status index					
Health Related Quality of life					
General health					
Physical functioning					
Physical role functioning					
Emotional role functioning					
Social role functioning					
Vitality					
Pain					
Mental health					

*Adjusted for relevant factors from Table 1

Table 3A: Diagnostic predictors of neurocognitive impairment among infant versus older childhood cancer survivors

	Task efficiency		**Emotional Regulation**		**Organization**		**Memory**	
Variable	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref
<1								
1- <3								
3- <6								
6-15								
Gender		Ref		Ref		Ref		Ref
Male								
Female								
Diagnosis		Ref		Ref		Ref		Ref
Acute lymphoblastic leukemia								
Acute myeloid leukemia								
Other leukemia								
Astrocytoma								
Medulloblastoma, PNET								
Other CNS tumors								
Wilms tumors								
Soft tissue sarcoma								
Neuroblastoma								

3B. Treatment predictors of neurocognitive impairment among infant versus older childhood cancer survivors

Variable	Task Efficiency		Emotional Regulation		Organization		Memory	
	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref
<1								
1- <3								
3- <6								
6-15								
Chemotherapy (cum dose)*		Ref		Ref		Ref		Ref
Methotrexate								
Anthracycline								
Alkylating agent								
Vinca Alkaloid								
Epipodophyllotoxin								
IT Chemotherapy (cum dose)		Ref		Ref		Ref		Ref
Cytosine Arabinoside								
Methotrexate								
Hydrocortisone								
Surgery		Ref		Ref		Ref		Ref
Number of surgical procedures								
Radiation		Ref		Ref		Ref		Ref
CNS dosimetry								
Chest/neck dosimetry								
Abdomen/pelvis dosimetry								

*Will stratify treatment by diagnosis to adjust for confounding variables

3C. Chronic health predictors of neurocognitive impairment among infant versus older childhood cancer survivors

Variable	Task Efficiency		Emotional Regulation		Organization		Memory	
	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref
<1								
1- <3								
3- <6								
6-15								
Chronic health condition		Ref		Ref		Ref		Ref
Any grade 2-4								
Multiple grade 2-4								
Cardiac grade 2-4								
Pulmonary grade 2-4								
Endocrine grade 2-4								
Neurologic grade 2-4								

Table 4A: Diagnostic predictors of emotional function impairment among infant versus older childhood cancer survivors

	Depression		**Anxiety**		**Somatization**		**Global Status Index**	
Variable	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref
<1								
1- <3								
3- <6								
6-15								
Gender		Ref		Ref		Ref		Ref
Male								
Female								
Diagnosis		Ref		Ref		Ref		Ref
Acute lymphoblastic leukemia								
Acute myeloid leukemia								
Other leukemia								
Astrocytoma								
Medulloblastoma, PNET								
Other CNS tumors								
Wilms tumors								
Soft tissue sarcoma								
Neuroblastoma								

4B. Treatment predictors of emotional function impairment among infant versus older childhood cancer survivors*

	Depression		Anxiety		Somatization		Global Status Index	
	No. (%)	**OR (95%)**	**No. (%)**	**OR (95%)**	**No. (%)**	**OR (95%)**	**No. (%)**	**OR (95%)**
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref
<1								
1- <3								
3- <6								
6-15								
Chemotherapy (cum dose)*		Ref		Ref		Ref		Ref
Methotrexate								
Anthracycline								
Alkylating agent								
Vinca Alkaloid								
Epipodophyllotoxin								
IT Chemotherapy (cum dose)		Ref		Ref		Ref		Ref
Cytosine Arabinoside								
Methotrexate								
Hydrocortisone								
Surgery		Ref		Ref		Ref		Ref
Number of surgical procedures								
Radiation		Ref		Ref		Ref		Ref
CNS dosimetry								
Chest/neck dosimetry								
Abdomen/pelvis dosimetry								

*Will stratify treatment by diagnosis to adjust for confounding variables

4C. Chronic health predictors of emotional function impairment among infant versus older childhood cancer survivors*

Variable	**Depression**		**Anxiety**		**Somatization**		**Global Status Index**	
	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)	No. (%).	OR (95% CI)
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref
<1								
1- <3								
3- <6								
6-15								
Chronic health condition		Ref		Ref		Ref		Ref
Any grade 2-4								
Multiple grade 2-4								
Cardiac grade 2-4								
Pulmonary grade 2-4								
Endocrine grade 2-4								
Neurologic grade 2-4								

Table 5A: Diagnostic predictors of impairment of quality-of-life measures among infant versus older childhood cancer survivors

Variable	General Health %	OR	Physical Functioning %	OR	Emotional Role Functioning %	OR	Social Role Functioning %	OR	Physical Role Functioning %	OR	Bodily Pain %	OR	Vitality %	OR	Mental health %	OR	PCS %	OR	MCS %	OR
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
<1																				
1- <3																				
3- <6																				
6-15																				
Gender		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Male																				
Female																				
Diagnosis		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Acute lymphoblastic leukemia																				
Acute myeloid leukemia																				
Other leukemia																				
Astrocytoma																				
Medulloblastoma, PNET																				
Other CNS tumors																				
Wilms tumors																				
Soft tissue sarcoma																				
Neuroblastoma																				

Table 5B: Treatment predictors of impairment of quality-of-life measures among infant versus older childhood cancer survivors*

Variable	General Health %.	OR	Physical Functioning %.	OR	Emotional Role Functioning %.	OR	Social Role Functioning %.	OR	Physical Role Functioning %.	OR	Bodily Pain %.	OR	Vitality %.	OR	Mental Health %.	OR	PCS %.	OR	MCS %.	OR
Age at diagnosis (yrs)		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
<1																				
1- <3																				
3- <6																				
6-15																				
Surgery		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Number of surgical procedures																				
Chemotherapy (cum dose)		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Methotrexate																				
Anthracycline																				
Alkylating agent																				
Vinca Alkaloid																				
Epipodophyllotoxin																				
IT Chemotherapy (cum dose)		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Cytosine Arabinoside																				
Methotrexate																				
Hydrocortisone																				
Radiation		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
CNS dosimetry																				
Chest/neck dosimetry																				
Abdomen/pelvis dosimetry																				

*Will stratify treatment by diagnosis to adjust for confounding variables

Table 5C. Chronic Health predictors of impairment of quality-of-life measures among infant versus older childhood cancer survivors*

Variable	General Health %. OR	Physical Functioning %. OR	Emotional Role Functioning %. OR	Social Role Functioning %. OR	Physical Role Functioning %. OR	Bodily Pain %. OR	Vitality %. OR	Mental Health %. OR	PCS %. OR	MCS %. OR
Age at diagnosis (yrs)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
<1										
1- <3										
3- <6										
6-15										
Chronic health condition	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Any grade 2-4										
Multiple grade 2-4										
Cardiac grade 2-4										
Pulmonary grade 2-4										
Endocrine grade 2-4										
Neurologic grade 2-4										

Table 6. Risk of neurocognitive and psychosocial impairment associated with chronic health conditions among survivors diagnosed as infants

	CCSS NCQ				BSI			
	Task Efficiency	**Emotional regulation**	**Organization**	**Memory**	**Anxiety**	**Depression**	**Somatization**	**Global**
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
Any grade 3-4								
Any grade 2								
Any grade 0-1	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)
Grade 2+ cardiac (vs grade 0-1)								
Grade 2+ pulmonary (vs grade 0-1)								
Grade 2+ endocrine (vs grade 0-1)								
Grade 2+ neurologic (vs grade 0-1)								
	SF-36							
	General health	**Physical function**	**Physical role limitation**	**Pain**	**Emotional role limitation**	**Vitality**	**Social role function**	**Mental health**
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
Any grade 3-4								
Any grade 2								
Any grade 0-1	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)	Ref (1.0)
Grade 2+ cardiac (vs grade 0-1)								
Grade 2+ pulmonary (vs grade 0-1)								
Grade 2+ endocrine (vs grade 0-1)								
Grade 2+ neurologic (vs grade 0-1)								