

## CHILDHOOD CANCER SURVIVOR STUDY Analysis Concept Proposal

1. **Title:** Long-term Neurologic Sequelae in Adult Survivors of Childhood Acute Lymphoblastic Leukemia.

2. **Working Group and Investigators:**

Proposed investigators:

Robert Goldsby  
Paul Nathan  
Daniel Bowers  
Yeaton-Massey, Amanda  
Aimee Szniewajs  
Les Robison  
John Whitton  
Lonnie Zeltzer  
Greg Armstrong  
Roger Packer

3. **Background and Rationale:**

Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. Although ALL was almost uniformly fatal prior to the 1970's, among patients receiving current multi-agent therapy, including treatment directed the central nervous system (CNS), the overall 5-year survival rate is more than 85%. With the growing numbers of children surviving ALL, there is increasing recognition of long-term sequelae. Adverse neurologic outcomes following ALL therapy are an important and somewhat controversial topic.

One of the major advances in treatment of ALL arose from the recognition that leukemic cells can invade the CNS and, there, reside protected by the blood-brain barrier and untouched by therapeutic concentrations of systemically administered antileukemic drugs. In attempt to treat this sanctuary site, children with leukemia were originally treated with cranial radiation. Although cranial radiation was effective in improving the survival of this population, evidence suggested a link with neurologic complications. . Because of these concerns, subsequent therapeutic regimens attempted to reduce or eliminate the use of cranial radiation by substituting intensified intrathecal and systemic chemotherapy for CNS prophylaxis. A number of factors may impact the risk for neurologic sequelae including age at the time of treatment, gender, extent of CNS involvement at diagnosis, radiation dose, chemotherapy utilized and the time from therapy. <sup>1-8</sup>.

Brain abnormalities (leukoencephalopathy), seizures, altered intellectual and psychomotor function as well as neurosensory dysfunction, such as hearing loss or vision disturbance, have been described in the literature following cranial radiation and chemotherapy directed at the CNS. Although the mechanism is poorly understood, young children treated with CNS-directed therapies are at risk for neurologic late-effects because of the theorized damage to their developing neurologic system.

The large group of ALL survivors in the CCSS cohort provides an excellent opportunity to evaluate the long-term neurologic effects of ALL therapy. The CCSS cohort includes 4151 children with ALL treated between 1970 and 1986 who survived at least 5 years after diagnosis. The size of this cohort may help define the risks of neurologic sequelae associated leukemia therapy. We propose a study to assess neurologic outcomes in adult survivors of childhood ALL identified in the CCSS cohort.

#### 4. Specific Aims/Research Hypotheses:

##### **Aims:**

1. Determine the incidence of adverse neurologic conditions, stratified by the time period in which the outcome was reported to first occur.
2. Compare late-onset (>5 years postdiagnosis) adverse neurologic conditions among survivors to that of a group of participating siblings.
3. Evaluate the effect of treatment on the risk of developing a late adverse neurologic condition.

##### **Hypothesis:**

1. Survivors of childhood ALL will have an increased risk of adverse neurologic conditions compared to sibling controls.
2. Late-onset adverse neurologic conditions will be increased compared to siblings.
3. Age at diagnosis and treatment will impact risk of developing a late neurologic adverse condition.

#### 5. Analysis Framework:

- A. Subject population: 4151 survivors of childhood leukemia in the CCSS cohort. Survivors of AML will be excluded. 3846 siblings of childhood cancer will serve as controls.
- B. Analysis: The analysis will be essentially the same as the analysis done for survivors of brain tumors.
- C. Variables:
  - I. Explanatory Variables: Original diagnosis (age at diagnosis – [age>10, age 1-<10, Infant <1yo], gender, treatment of original diagnosis (radiation [dose], alkylator score, methotrexate dose [total dose, IV dose, IM dose, IT dose] vincristine discontinued due to toxicity, asparaginase discontinued due to toxicity and, cytarabine dose, intrathecal chemotherapy utilized [IT single vs triples]), leukemia relapse, bone marrow transplant and time from original diagnosis to questionnaire.
  - II. Outcome variables: Three types of neurologic outcomes will be considered: neurosensory deficits, focal neurologic dysfunction, and seizures.

Neurosensory deficits: hearing loss requiring a hearing aid, deafness in one or both ears not completely corrected by hearing aid, complete deafness in either ear, tinnitus, persistent dizziness, legally blind in one or both eyes, and

cataracts. Hearing loss, deafness, or complete deafness will be aggregated into the “yes” or “no” variable for “any hearing problem.”

Focal neurologic dysfunction: Focal neurologic dysfunction include deficits related to problems with balance, tremors, or movements, as well as the weakness or inability to move arm(s) or leg(s). An aggregate variable for “any coordination problem” will be derived from balance problems or tremors. Similarly, a variable for “any motor problem” will be derived from weakness or inability to move arms(s) or leg(s).

Seizures: “Any seizure disorder” will be composed of responses for epilepsy, or repeated seizures, convulsions, or blackouts.

For each of these three outcome variables, a “yes” response to any component of an aggregate variable will constitute a “yes” for that variable. If a “yes” response was recorded without an accompanying age at first occurrence, the age at first occurrence will be imputed using multiple imputation methodology employed for event-time imputations and appropriate methods for incorporating imputed values into the analyses will be used.<sup>9, 10</sup>

Three separate outcome variables are defined based on aggregate variables as described below. Poisson regression will be used to calculate incidence rates for these outcomes. Cox proportional hazard models will be used to estimate hazard ratios for the comparison of survivors to siblings and to evaluate the impact of the explanatory variables on each outcome. Both univariable and multivariable models will be evaluated, with multivariable models incorporating factors which have significant impact on outcome or which markedly influence the effect of another variable in the model (confounder). The 3,418 siblings who agreed to participate will be included as controls. Sandwich variance estimates will be utilized to account for the intra-family correlation between siblings and survivors included in the analysis.<sup>11</sup> Formal statistical analyses will focus on events occurring during the time period more than 5 years after diagnosis since the survivor cohort is defined from this time point forward. Summary numbers of events occurring prior to the 5 year post diagnosis time point may also be presented.

#### D. Specific Tables and Figures:

- I. Patient characteristics: age at interview, gender, race, ethnicity, age at diagnosis, CNS treatment (Craniospinal XRT, Cranial XRT, XRT+IT, ITMTX alone, IT other alone, HD MTX IV (dosing >500 mg/m<sup>2</sup>), or none), leukemia relapse, bone marrow transplant.
- II. Incidence rates by time period of onset [1) Those occurring from diagnosis to end of therapy, 2) Those occurring from end of therapy to 5 years post diagnosis and 3) Those occurring greater than 5 years after diagnosis].
- III. Late-onset neurologic outcomes by leukemia grouping: ALL by age (Age > 10, Age 1-10, Age <1).
- IV. Late-onset neurologic outcomes by cranial radiation exposure: >1800 cGy, <1800 cGy >0, or none.
- V. Late-onset neurologic outcomes by cumulative chemotherapy exposure: Vincristine d/c, MTX dose, Asparaginase d/c, Cytarabine dose

#### E. Preliminary data and test of feasibility:

To determine if this proposal was feasible, we did a preliminary evaluation of the total number of neurologic events. Below are the numbers of events for survivors as a whole, those reported at least five years after diagnosis for survivors, and the number reported by siblings of the subjects for the entire cohort. This data shows that there are approximately twice the number of reported neurologic events in survivors of ALL compared to sibling control population. This may be even greater when age of survivors and siblings are factored into the analysis. However, there were fewer late neurologic events. When time and age are factored into the analysis we may be able to see if there is a difference in late events. Regardless, even without a difference in late events, the findings will be interesting. Finally, comparing neurologic outcomes based on therapy may be more relevant than comparison with siblings from the cohort as a whole.

Survivors:	Events	Cumulative Percentage
Neurosensory deficits:	557	(13.4%)
Focal neurologic dysfunction:	791	(19.1%)
Seizures:	291	(7.0%)
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Any of the above:	1283	(30.9%)

Survivors <b>First occurrence more than five years after diagnosis:</b>	Events	Cumulative Percentage
Neurosensory deficits:	265	(6.7%)
Focal neurologic dysfunction:	357	(8.9%)
Seizures:	116	(2.9%)
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Any of the above:	597	(15.7%)

Siblings:	Events	Cumulative Percentage
Neurosensory deficits:	290	(7.4%)
Focal neurologic dysfunction:	361	(9.3%)
Seizures:	90	(2.3%)
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Any of the above:	628	(16.1%)

## References

1. Cousens P, Waters B, Said J, Stevens M. Cognitive effects of cranial irradiation in leukaemia: a survey and meta-analysis. *J Child Psychol Psychiatry* 1988;29(6):839-52. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=3069852](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3069852).
2. Chessells JM, Cox TC, Kendall B, Cavanagh NP, Jannoun L, Richards S. Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation. *Arch Dis Child* 1990;65(4):416-22. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=2346334](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2346334).
3. Moore IM, Kramer JH, Wara W, Halberg F, Ablin AR. Cognitive function in children with leukemia. Effect of radiation dose and time since irradiation. *Cancer* 1991;68(9):1913-7. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=1913542](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1913542).
4. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. *J Clin Oncol* 1991;9(8):1348-56. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=2072138](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2072138).
5. Waber DP, Tarbell NJ, Kahn CM, Gelber RD, Sallan SE. The relationship of sex and treatment modality to neuropsychologic outcome in childhood acute lymphoblastic leukemia. *J Clin Oncol* 1992;10(5):810-7. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=1569453](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1569453).
6. Jannoun L. Are cognitive and educational development affected by age at which prophylactic therapy is given in acute lymphoblastic leukaemia? *Arch Dis Child* 1983;58(12):953-8. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=6197936](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6197936).
7. Lansky SB, Cairns NU, Lansky LL, Cairns GF, Stephenson L, Garin G. Central nervous system prophylaxis. Studies showing impairment in verbal skills and academic achievement. *Am J Pediatr Hematol Oncol* 1984;6(2):183-90. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=6465470](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6465470).
8. Robison LL, Nesbit ME, Jr., Sather HN, Meadows AT, Ortega JA, Hammond GD. Factors associated with IQ scores in long-term survivors of childhood acute lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1984;6(2):115-21. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=6589968](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6589968).

9. Rubin D. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, 1987.

10. Taylor JM, Munoz A, Bass SM, Saah AJ, Chmiel JS, Kingsley LA. Estimating the distribution of times from HIV seroconversion to AIDS using multiple imputation. Multicentre AIDS Cohort Study. *Stat Med* 1990;9(5):505-14. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=2190287](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2190287).

11. Therneau M, Grambsch P. Modeling Survival Data Extending the Cox Model. New York, NY: Springer, 2000.