

OS-14
revised

Childhood Cancer Survivor Study Analysis Concept Proposal

Resubmitted June 2006

1. Title: The Long-Term Outcomes of Childhood Acute Lymphoblastic Leukemia (ALL) survivors: A Report from the Childhood Cancer Survivor Study

2. Working Group and Investigators:

This proposed publication will be within the **Chronic Disease Working Group (Leukemia)**.

Proposed Investigators (name/e-mail/fax) will include:

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Others may be added later

3. Background and Rationale:

Acute Lymphoblastic Leukemia (ALL) is the most common cancer of childhood. Since 1970s, the rate of cure of ALL in children has increased dramatically from less than 30 percent to an estimated 5 year overall survival of about 80-86% with current therapeutic protocols. This success has been achieved by improvement in both laboratory and clinical sciences. Some of the highly effective therapeutic strategies include, stratifying patients into risk groups based on their risk for relapse and biology, intensified treatment protocols for higher risk patients, and using preventive intrathecal chemotherapy. Although highly effective, most studies have indicated an excess mortality and morbidity in these long term survivors of childhood ALL. If cure is defined as restoration of normal health, attainment of "cure" is only possible when the adverse effects associated with disease and therapy are well understood for childhood cancer survivors. The current medical literature on long term medical, socioeconomic and psychological outcomes in childhood ALL survivors only contains few small, single institution studies and there is a real need for a large multinstitutional study which includes heterogeneous patient population and covers different treatment era.

In February 2004 the CCSS steering committee set forth objectives to evaluate the survivorship issues for each original cancer diagnosis in CCSS. This manuscript will address the survivorship issues in ALL survivors.

Our primary objective for this publication is to provide a comprehensive description of the physical and social health of ALL survivors. Included in this will be the overall survival, late mortality, and second malignancy (SMN) in this population compared to entire sibling cohort and age/sex matched US population. The publication will also look at the overall health status, late medical complications including cardiovascular, endocrine disorders and various socioeconomic outcomes including marriage, employment and health insurance coverage in this population as compared to the sibling cohort as well as age/sex matched US population.

4. Specific Aims/ Objectives/ Research Hypotheses:

This study will use data from the Childhood Cancer Survivor Study (CCSS). Our analysis will include all ALL survivors including survivors of ALL relapse and survivors who have received BMT, although we will not perform any detailed analysis based on TBI. This is designed out of practical consideration of avoiding any overlap with Dr. Baker's current manuscript describing the status of leukemia survivors who underwent a BMT.

Hypotheses:

- 1) Overall survival will be significantly lower among survivors of childhood ALL compared to the U.S. population.
- 2) Survivors of childhood ALL will have higher prevalence and severity of late morbidities (as defined by CTCAE 3.0), when compared to siblings (i.e. cardiovascular disease, endocrine disorders, second cancers, etc.)
- 3) Survivors of childhood ALL will be less educated, will have lower insurance coverage rates, and are less likely to be married as compared to siblings and US general population.
- 4) Childhood ALL survivors who have survived a relapse, will experience significantly more late mortality and SMN as compared with survivors who have not experienced any relapse of their ALL.
- 5) Childhood ALL survivors who have survived a relapse, will have higher prevalence and severity of late morbidities (as defined by CTCAE 3.0), as compared to survivors who have not experienced any relapse of their ALL. (i.e. cardiovascular disease, endocrine disorders etc.)
- 6) Childhood ALL survivors who have survived a relapse, will be less educated, will have lower insurance coverage rates, and are less likely to be married as compared to survivors who have not experienced any relapse of their ALL.

Analysis Framework:

A. Outcomes of interest:

1. Survival rates

2. Medical Complications:

a. Baseline: medical conditions, sections C,D,E, F, G, H, I, J

- b. Follow-up 1: medical conditions, questions: 9, 10, 11, 12
- 3. Second Cancers / Recurrence of ALL:
 - a. Baseline: section K
 - b. Follow-up 1: question 17
 - c. Follow-up 2: section R
- 4. Education:
 - a. Baseline: section O, questions 1-4
 - b. Follow-up 1: question 1
 - c. Follow-up 2: question 1
- 5. Employment:
 - a. Baseline: section O, questions 5-11, section Q, questions 8, 9
 - b. Follow-up 2: question 3
 - c. Follow-up 3: questions 4, 5, 6
- 6. Insurance:
 - a. Baseline: section Q, questions 1-6
 - b. Follow-up 1: question 16
 - c. Follow-up 2: section M
- 7. Marriage:
 - a. Baseline: section L
 - b. Follow-up 1: question 2
 - c. Follow-up 2: questions 2 and 3
- 8. Pregnancy history: (Number and Outcome)
 - a. Baseline: section M
 - b. Follow-up 1: question 8
 - c. Follow-up 2: section N

For radiation related outcomes following RT cutoff dates will be used:

- 1. SMN: all the RT delivered up to 5 years prior to diagnosis of SMN will be included.
- 2. Infertility: all the RT delivered till the diagnosis of infertility will be included.
- 3. Education: all the RT delivered up to high school graduation date will be included.
- 4. Cardiac outcomes: all the RT delivered up to the cardiac event (CHF, MI) will be included.

B. Subject population:

- 1. All de novo ALL survivors in the CCSS cohort who have survived 5 years from diagnosis (separate analysis will be performed analysis will be performed for 10 year ALL survivors) will be included for survival analysis and analysis of SMN.
- 2. For all other outcomes of interest we will exclude ALL survivors who have undergone BMT irrespective of relapse status.
- 3. Entire Sibling cohort will be used as a control group
- 4. U.S. Census Bureau data to obtain marital and employment status in the general population.
- 5. Medical Expenditure Panel Survey data for insurance rates in the general population.

C. Explanatory variables:

- 1. Age at cancer diagnosis
- 2. Age at response to CCSS questionnaire
- 3. Gender

4. Type of treatment (chemotherapy alone, chemotherapy and BMT, CNS radiation)
5. Cumulative doses of chemotherapy, specifically alkylator score and anthracycline cumulative dose
6. CNS radiation (y/n) and dose (18GY, 24 GY)
7. TBI (Y/N) for survival analysis and SMN
8. Recurrence of ALL

D. Analysis Plan:

1. Descriptive Epidemiology/Summary statistics:
 - a. Characteristics of ALL survivors will be described using means (SD) or medians (range).
2. Survival Analysis:
 - a. Overall survival survival will be analyzed from the entry into the cohort and compared to expected survival in the US population for an age and gender matched control with the Kaplan-Meier method.
 - b. Separate survival analysis will be performed for all ALL survivors and ALL survivor following a relapse.
 - c. Hazard ratios comparing survival between different treatment groups will be evaluated using Cox proportional-hazards/ Poisson regression models adjusted for age at diagnosis, sex, race, and treatment era.
 - d. Standardized mortality ratios (observed number of deaths divided by the expected number) and their 95% confidence intervals will be calculated by the Breslow and Day method for major sources of mortality including second cancers, cardiac disease, and external causes.
3. The overall health status of ALL survivors, will be established using the methodology of Hudson et al. (see JAMA. 2003 Sep 24; 290(12):1583-92). Comparison will be made by gender of survivor, age at diagnosis and therapeutic exposures.
4. The incidence and severity of chronic medical complications will be determined using the methodology of Oeffinger K et al. used in their CCSS MS "Incidence and severity of chronic medical complications in adult survivors of childhood cancers". Comparison will be made between ALL survivors as compared to sibling group and non relapsed ALL survivors compared to relapsed ALL survivors..
5. The chi-square test of independence (or Fisher's exact test if expected frequencies are less than 5) will be used to compare proportions of educational levels, employment status, insured status, marital status of ALL survivors, siblings, and the general population.
6. The chi-square test of independence (or Fisher's exact test if expected frequencies are less than 5) and logistic/poisson regression will be used to compare proportions of educational levels, employment status, insured status, marital status of non relapsed ALL survivors with relapsed ALL survivors.
7. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of educational levels, employment status, insured status, marital status of ALL survivors

with, siblings, and the general population adjusting for adjusted for age at study, gender, and race/ethnicity.

8. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of educational levels, employment status, insured status, marital status of non relapsed ALL survivors with relapsed ALL survivors, after adjusting for cumulative chemo dosing, radiation dosing (non-relapsed survivor as a reference), age at study, gender, and race/ethnicity.

E. Tables and Figures:

1. Demographic table of CCSS ALL cases:
 - sex
 - diagnosis
 - age at diagnosis
 - age at follow-up
 - type of treatment (chemotherapy, Radiation, BMT)
 - treatment era
 - medical complications
 - Relapse status (ALL)
2. Survival curves: overall survival and EFS: All Survivors, survival after a relapse
3. Cumulative incidence curves: late medical outcomes,,second cancers.
4. Tables: educational attainment, employment status, insurance status, marital/family status demonstrating frequencies and rates of each these social indicators in ALL compared to the sibling control group and population norms (SEE ATTACHED TABLES).
5. Tables: educational attainment, employment status, insurance status, marital/family status demonstrating frequencies and rates of each these social indicators in relapsed vs. non-relapsed survivors.

Table 1. Characteristics of the study population

| | ALL Survivors (N=X) | | Siblings (N=X) | | p-value |
|-----------------------------------|------------------------|-----|-------------------|-----|---------|
| | N | (%) | N | (%) | |
| Gender | | | | | |
| Female | | | | | |
| Male | | | | | |
| Age at diagnosis | | | | | |
| Mean (SD) | | | | | |
| 0-4 years | | | | N/A | |
| 5-9 years | | | | N/A | |
| 10-14 years | | | | N/A | |
| 15+ years | | | | N/A | |
| Age at questionnaire | | | | | |
| Mean (SD) | | | | | |
| 18-29 years | | | | | |
| 30-39 years | | | | | |
| 40-49 years | | | | | |
| 50+ years | | | | | |
| Survival time | | | | | |
| Mean (SD) | | | | | |
| 15-19 years | | | | | |
| 20-24 years | | | | | |
| 25-29 years | | | | | |
| 30+ years | | | | | |
| Highest level of education | | | | | |
| Grade school | | | | | |
| High school | | | | | |
| Technical school | | | | | |
| College | | | | | |
| Post graduate | | | | | |
| Not indicated | | | | | |
| Marital status | | | | | |
| Married or living as married | | | | | |
| Not married | | | | | |
| Not indicated | | | | | |
| Employment status | | | | | |
| Working full time | | | | | |
| Not working full time | | | | | |
| CNS involvement | | | | | |
| Yes | | | | N/A | |
| No | | | | | |
| CNS prophylaxis | | | | | |
| IT chemotherapy | | | | N/A | |
| CNS directed RT | | | | | |

Table 2. Relative risk and 95% confidence intervals for chronic health conditions in ALL survivors compared with siblings*

| Cancer Diagnosis or Treatment Exposure | Grade 1 - 4 | | Grade 3 or 4 | | ≥ 2 Conditions | |
|--|-------------|--------|--------------|--------|----------------|--------|
| | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| Siblings | 1.0 | Ref | 1.0 | Ref | 1.0 | Ref |
| All ALL Survivors | | | | | | |
| Chemotherapy | | | | | | |
| Any chemotherapy | | | | | | |
| Alkylating agent | | | | | | |
| Anthracycline | | | | | | |
| Radiation therapy | | | | | | |
| No radiation | | | | | | |
| Any radiation | | | | | | |
| Brain radiation | | | | | | |
| Craniospinal Radiation | | | | | | |
| Total body irradiation | | | | | | |
| Specific combinations | | | | | | |
| Any CT + Any RT | | | | | | |
| Any CT + Brain RT | | | | | | |
| Brain RT + Alkylating Agent | | | | | | |
| Chest RT + anthracycline | | | | | | |

Table 4 (continued)

* Each row represents an individual multivariate regression model, adjusted for age at study, gender, and race

Abbreviations: RT, radiation therapy;

Table 3. Frequencies, percents, odds ratios and 95% CIs comparing ALL survivors and siblings on medical complications*

| | ALL Survivors | | | | Siblings | | | |
|------------------------------|---------------|---|----|--------|----------|---|----|--------|
| | N | % | OR | 95% CI | N | % | OR | 95% CI |
| Medical complications | | | | | | | | |
| Relapse | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| SMN | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Cardiovascular | | | | | | | | |
| Congestive heart failure | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Ischemic Heart Disease | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Endocrine | | | | | | | | |
| Hypothyroid | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Infertility | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Pulmonary | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Neurosensory | | | | | | | | |
| Vision | | | | | | | | |
| Hearing | | | | | | | | |
| Abnormal sensation | | | | | | | | |
| Pain | | | | | | | | |

* Adjusted for age at interview, gender and ethnicity

Table 4. Rates of socioeconomic factors in ALL survivors compared to siblings and the general population

| <u>Marital Status</u> | | | | | | | | |
|---------------------------------|------------|------------|------------------------------|------------|------------|-----------------------------------|------------|------------|
| <u>Married</u> | | | <u>Separated or Divorced</u> | | | <u>Never Married</u> | | |
| Cases | Siblings | Population | Cases | Siblings | Population | Cases | Siblings | Population |
| % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |
| <u>Employment Status</u> | | | | | | | | |
| <u>Fulltime</u> | | | <u>Part-time</u> | | | <u>Unemployed</u> | | |
| % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |
| <u>Education</u> | | | | | | | | |
| <u>No High School Education</u> | | | <u>High School Graduate</u> | | | <u>Post High School Education</u> | | |
| % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |
| <u>Insurance</u> | | | | | | | | |
| <u>Private Insurance</u> | | | <u>Public Insurance</u> | | | <u>No Insurance</u> | | |
| % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |

Adjusted for gender, ethnicity and age at interview
 † Case rate differs from sibling rate (p<0.05)
 ‡ Case rate differs from population rate (p<0.05)

Table 5. Percent of ALL survivors* and siblings with a chronic physical health condition, with CTCAE v3 severity score

| | Survivors | | Siblings | |
|--------------------------------------|-----------|---|----------|---|
| | N | % | N | % |
| No condition | | | | |
| Grade 1, Mild | | | | |
| Grade 2, Moderate | | | | |
| Grade 3, Severe | | | | |
| Grade 4, Life-threatening | | | | |
| Grade 5, Death | | | | |
| Any Grade 1-4 health condition*** | | | | |
| Any Grade 3 or 4 health condition*** | | | | |
| Multiple health conditions | | | | |
| ≥ 2 health conditions | | | | |
| ≥ 3 health conditions | | | | |

Abbreviation: CTCAE v3, Common Terminology Criteria for Adverse Events version 3; NA, not applicable

* Survivor health conditions do not include any problems prior to the cancer diagnosis or acute problems prior to 5 years post cancer diagnosis.

** To be eligible, siblings had to be alive at time of enrollment. Survivors may have died in the interval between 5 years post cancer diagnosis and time of study. The composite percent for survivors with grade 3 or 4 conditions include conditions that were reported before the time of death in the 163 survivors who died.

***The number may not reflect the sum of Grade 1-Grade 4. Grade1-Grade5 was calculated by taking the maximum grade per subject. A subject with Grade 5 may have other lower grades.

Table 6. Severe, life-threatening or disabling chronic conditions or death (Grade 3-5) by organ system in ALL survivors*

| Organ System | N | Percent of all Grade 3-5 Conditions |
|---|---|-------------------------------------|
| All organ systems | | |
| Musculoskeletal | | |
| Endocrine | | |
| Second malignant neoplasms [†] | | |
| Cardiac | | |
| Pulmonary | | |
| Neurological | | |
| Vision | | |
| Hearing | | |
| Gastrointestinal | | |
| Renal | | |

* All chronic conditions grade 3-5 are included. Participants may have had more than one condition.

[†] Excluding non-melanoma skin cancer

Table 7. Frequencies, percents, odds ratios and 95% CIs comparing Relapsed vs. Non-Relapsed ALL survivors on medical complications

| | Non-Relapsed ALL Survivors | | | | Relapsed ALL Survivors | | | |
|------------------------------|----------------------------|---|----|--------|------------------------|---|----|--------|
| | N | % | OR | 95% CI | N | % | OR | 95% CI |
| Medical complications | | | | | | | | |
| SMN | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Cardiovascular | | | | | | | | |
| Congestive heart failure | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Ischemic Heart Disease | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Endocrine | | | | | | | | |
| Hypothyroid | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Infertility | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Pulmonary | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Neurosensory | | | | | | | | |
| Vision | | | | | | | | |
| Hearing | | | | | | | | |
| Abnormal sensation | | | | | | | | |
| Pain | | | | | | | | |

Adjusted for cumulative chemo, gender, age at interview and ethnicity
 Non-Relapsed survivor rate differs from Relapsed survivor rate (p<0.05)

Table 8. Rates of socioeconomic factors in Relapsed vs. Non-Relapsed ALL survivors*

| | Non-Relapsed ALL Survivors | | | Relapsed ALL Survivors | | |
|--------------------------|----------------------------|---|--------|------------------------|---|--------|
| | N | % | 95% CI | N | % | 95% CI |
| Marrital Status | | | | | | |
| Married | | | | | | |
| Divorced or separated | | | | | | |
| Never Married | | | | | | |
| Employment Status | | | | | | |
| Full Time | | | | | | |
| Part Time | | | | | | |
| Unemployed | | | | | | |
| Education | | | | | | |
| No High School | | | | | | |
| High School graduate | | | | | | |
| Post High School Edu. | | | | | | |
| Insurance Status | | | | | | |
| Private Insurance | | | | | | |
| Public Insurance | | | | | | |
| No Insurance | | | | | | |

* Adjusted for cumulative chemo, gender, age at interview and ethnicity
 Non-Relapsed survivor rate differs from Relapsed survivor rate (p<0.05)

References:

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