

**CCSS Concept Proposal**  
**Working Group: Biostatistics and Epidemiology**

**Draft date:** June 26, 2010

**Title:** Conditional Survival in Pediatric Malignancies: A Comparison of CCSS and SEER Data

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**Background and Rationale:**

Conditional survival (CS) is the likelihood of not having an event (death) after a cohort of patients has actually survived for specific interval after diagnosis[1-5]. This measurement of survival is more clinically relevant because the likelihood of survival changes after a patient has survived for a period of time[1-5]. In addition, CS is a more accurate and practical reflection of future patient outcome as compared to conventional 5 and 10-yr survival estimates[2-4] [2-4]. As patients transition to long-term follow-up settings, they often want to know their chance of recurrence as the time from diagnosis increases. In survivors of high-risk diseases, having “beaten the odds” to date, it is important to determine the chance of a late recurrence or death[6-8] .

There is emerging data in the adult literature analyzing conditional survival in large population databases such as the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) as well as in some individual adult clinical trials[2-5, 9-13]. In the pediatric literature little is published on conditional survival. The Childhood Cancer Survivor Study (CCSS) in essence has described survival in this way. Mertens et al originally reported on late mortality in five-year survivors of childhood cancer from the CCSS in 2001 with an update of this data recently completed in 2008[6, 7]. In this analysis there was a decrease in the standardized mortality rate (SMR) with increasing survival time after diagnosis. All-cause 30-year cumulative mortality was 18.1% (95% CI = 17.3 to 18.9) for 5-year survivors, 12.4% (95% CI = 11.6 to 10.3) for 10-year survivors, 9.5% (95% CI = 8.7 to 10.3) for 15-year survivors, and 7.0% (95% CI = 6.3 to 7.8) for 20-year survivors [6].

The CCSS report on late recurrences described conditional event-free survival in 5, 10, 15, and 20 year survivors of childhood cancer [8]. While late recurrences were rare, 10-year survivors of CNS tumors, Hodgkin lymphoma, soft tissue sarcomas and Ewing sarcoma still had a greater than 3% risk of recurrence, with survivors of CNS tumors having a persistent risk even after 15-20 years of recurrence-free survival[8].

Bleyer et al. used the SEER database to determine the conditional survival of 15- to 29-year olds diagnosed with cancer during 1975-2000 compared with younger and older patients [14, 15]. It was found that although adolescents and young adults had a better prognosis at diagnosis, their probability of survival thereafter did not increase as rapidly as younger and older patients, particularly for relative survival [14, 15]. In fact, AYAs had a lower conditional survival improvement than any other age group, including infants and the elderly [15]. The explanation for this is not known, but may certainly be due to the types of cancers seen in this age group.

To investigate conditional survival further we propose a comparative analysis of conditional survival in the original CCSS cohort and the Surveillance, Epidemiology and End Results (SEER) database (SEER-9). The SEER 9 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah[9]. Data is available from 1975-2007. There will be some acknowledged overlap, specifically in the populations from Atlanta and Seattle. To address this issue, sensitivity analyses will be performed, with restriction to the geographical locations where the overlap is considered minimal.

This comparison will serve two purposes. First, comparison of CCSS to SEER data will serve as a surrogate comparison of patients likely treated in an academic/pediatric cooperative group setting (i.e. Children's Oncology Group - COG) with patients from a large population dataset, SEER, which is more likely to contain information on patients treated at non-academic and adult institutions. Likewise, the CCSS cohort is more likely to contain patients treated on clinical trial versus the SEER database. Secondly, this analysis will provide insight into the representativeness of CCSS data compared to the population data from SEER, a more ethnically and institutionally diverse sample.

In addition this study will allow for a more detailed analysis of conditional survival than was performed in the previous late mortality and late recurrence studies. In the updated mortality paper, conditional survival curves were shown overall, and by recurrence and other deaths. In this new manuscript, we plan to expand the CS plots for different subsets of populations within both CCSS and SEER, such as diagnosis, ethnicity, age at diagnosis, and treatment era.. An additional option for analysis is to look at census data for both CCSS and SEER (SEER county attributes variables) and use as a covariate approximating SES.

Clinically, this data will be useful to individual patients who want to know their chance of survival after having survived for a period of time already. Conditional survival is particularly useful for malignancies with a relatively high initial mortality or relapse rate that then tapers off [4]. For oncologists, as with survivors, this information is clinically important in counseling patients on their conditional survival. The additional detailed analyses of subgroups planned in this proposal will be more clinically relevant than general conditional survival curves. Information on who has the better outcome as measured by conditional survival will provide insight into the role of treatment location. It may also provide some indirect information as to the advantages and disadvantages with regard to academic versus non-academic centers. Lastly, as CCSS is the premier source of data on long-term outcomes in pediatric cancer survivors, and survival is

arguably the most important outcome measure, it is important to compare the CCSS data to population data from SEER to assess the representativeness of the data.

### **Specific Aims/Hypotheses:**

- 1) Compare conditional survival in the CCSS cohort versus SEER database
  - *Hypothesis 1:* Patients in the CCSS cohort (pediatric academic institutions) will have superior CS compared to comparable patients within the SEER-9 database (all-inclusive).
- 2) Estimate CS yearly, starting with 5-year survivors, in the SEER database and CCSS cohort
  - *Hypothesis 2:* Standardized mortality rates (SMRs) will decrease with increasing survival time
- 3) Determine patient characteristics that affect CS for sub-groups, including gender, race/ethnicity, age at diagnosis, treatment era, primary diagnosis, and institution (CCSS)/geographic location (SEER)
  - *Hypothesis 3:* Patients will have a more favorable CS profile if they have the following characteristics: male gender, black race, younger age at diagnosis (< 15 y.o vs. 15-20 y.o.), later treatment era, and diagnoses of neuroblastoma, kidney tumors and non-Hodgkin's lymphoma.

### **Significance:**

- 1) The proposed analysis has not been done
- 2) Patients and health care providers would benefit from having CS estimates as well as comparative data from SEER and CCSS cohorts. Once a patient has survived for a period of time, the chance of survival from that point on and not from initial diagnosis is what is most clinically relevant.
- 3) Patients and health care providers would benefit from having CS estimates on subgroups such as gender, race, age, diagnosis and institution/geographic area.
- 4) The results from this study will be relevant in that it is a very tangible way to help explain representativeness of the CCSS population. Whether or not the survival is better or worse, this analysis will help frame possible differences within some context, instead of not knowing the answer to the question of how CCSS might differ from other pediatric cancer survivors who do not participate in CCSS.

### **Analysis framework:**

- 1) Outcome of interest: Relative survival
  - a) Death (NDI through 2002)
    - i) No

- ii) Yes
- 2) Subject population
  - a) Age 0-20 years
  - b) Diagnosis between **1975-1986** (to have consistent diagnosis dates between CCSS and SEER-9)
  - c) Primary diagnosis
    - i) Leukemia (including MDS)
    - ii) CNS
    - iii) HD
    - iv) NHL
    - v) Kidney
    - vi) NBL
    - vii) STS
    - viii) Bone
  - d) Patients in the SEER-9 and CCSS databases
- 3) Exploratory variables:
  - a) Gender
    - i) Female
    - ii) Male
  - b) Race
    - i) White
    - ii) Black
    - iii) Other
  - c) Age at diagnosis
    - i) 0-4 years
    - ii) 5-9 years
    - iii) 10-14 years
    - iv) 15-20 years
  - d) Primary diagnosis:
    - i) Leukemia (including MDS)
    - ii) CNS
    - iii) HD
    - iv) NHL
    - v) Kidney
    - vi) NBL
    - vii) STS
    - viii) Bone
  - e) Treatment era
    - i) 1975-1980
    - ii) 1981-1986
  - f) Time at risk for event
    - i)
- 4) Table and Figures:
  - a) Table 1 – Patient characteristics

	CCSS		SEER	
	N	%	N	%

<b>Total patients</b>				
<b>Gender</b>				
Male				
Female				
<b>Race</b>				
White				
Black				
Other				
<b>Diagnosis</b>				
Leukemia				
ALL				
AML/MDS				
Other leukemia				
Lymphoma				
Hodgkin's				
NHL				
Bone Tumor				
Ewing's sarcoma				
Osteosarcoma				
Other bone tumor				
CNS				
Astrocytoma				
Medulloblastoma; PNET				
Other CNS				
Kidney tumor				
Neuroblastoma				
Soft tissue sarcoma				
<b>Age at Diagnosis</b>				
0-4				
5-9				
10-14				
15-19				
<b>Treatment Era</b>				
1975-1980				
1981-1986				

b) Table 2 – Fifteen-year relative survival conditional on already having survived 5, 10 and 15 years from diagnosis

	5-year Survivors		10-year Survivors		15-year Survivors	
	SEER	CCSS	SEER	CCSS	SEER	CCSS
<b>Total patients</b>						
<b>Gender</b>						
Male						
Female						
<b>Race</b>						
White						
Black						
Other						
<b>Age at Diagnosis</b>						
0-4						
5-9						
10-14						
15-19						
<b>Treatment Era</b>						

1973-1979						
1980-1986						

- c) Figure I: Survival Curves – Conditional survival curves for 5, 10, 15, and 20 years for gender, diagnosis, age at diagnosis, ethnicity – CCSS and SEER
- d) Table 3: Yearly conditional survival versus diagnosis: Years: 5,10,15,20,25 for CCSS and SEER; Years 1, 2, 3, 4, 5 for SEER only
- e) Table 4- Multivariate analysis - effect of the following variables on conditional survival: gender, ethnicity, age, treatment era, diagnosis, SES, location, and cohort (CCSS vs. SEER)

**Special Considerations:**

1. Statistical analysis: Due to acknowledged overlaps in the populations from Atlanta and Seattle, sensitivity analyses will be performed, with restriction to the geographical locations where the overlap is considered minimal.
2. Certain analyses for predictor variables such as race and primary diagnosis may be limited by the number of patients in each category.
3. It is likely there will be differences between CCSS and SEER - it is not clear, however in which direction these results will be. If we assume that the CCSS institutions see all the more difficult patients, it is probable these patients also died in the first 5 years, and would not be eligible for this analysis. However, we could think differently, and that at CCSS institutions most children were put on study or on the most recent protocol, so would likely do better than those SEER patients who were not seen at an academic institution.
4. Results will be reviewed before publication, to make sure they do not harm the reputation of CCSS. We envision that this analysis will be beneficial, and will aid in the interpretation of subsequent CCSS analyses. Les Robison will be involved at an early stage in reviewing the data to provided input on how the results will be presented in the manuscript.

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