Childhood Cancer Survivor Study
Analysis Concept Proposal

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Title: Longitudinal Evaluation of Chronic Disease and Health Status in Soft Tissue Sarcoma Survivors: A Report from the Childhood Cancer Survivor Study (CCSS).

Working Group and Investigators:

This proposal will be set within the Chronic Disease and Cancer Control Working Groups.

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1. **Background and Rationale**: Soft tissue sarcomas (STS), the fifth most common pediatric cancer, arise from connective tissues[1]. Amongst STS, rhabdomyosarcoma accounts for approximately 50% of diagnoses while the remainder is a heterogeneous group of diverse sarcomas[2]. Historically, the primary mode of therapy for rhabdomyosarcoma was surgical resection despite significant morbidity and extremely poor long-term outcomes. The advent of therapeutic radiation improved results, but disease recurrence remained high and was usually systemic. Therefore, chemotherapy became a mainstay of treatment and offered promise of a sustained cure. This has substantially improved 5-year survival rates, which were 25% in the 1960's using primarily local control measures[3]. The Children's' Oncology Group (COG) now estimates that current long-term failure free survival (FFS) for intermediate risk rhabdomyosarcoma is as high as 65%.

   Unfortunately, survivors of pediatric soft tissue sarcomas often experience serious long-term sequelae of their treatments[4]. These complications depend upon the location of disease, mode of treatment (surgery, radiation, chemotherapy), and types of chemotherapy. Recent studies of late effects of radiotherapy revealed that survivors may suffer from cataracts, dental abnormalities, orbital or bony hypoplasia, decreased stature, and neuroendocrine abnormalities[5-12]. Complications of surgical interventions include genitourinary problems

(incontinence, ejaculatory dysfunction) and bowel adhesions[13-14]. Chemotherapy can cause infertility, hearing loss, renal impairment and secondary malignancy. Learning disabilities and neurocognitive dysfunction are also found and are likely related to multiple factors during therapy[15]. Quality of life for soft tissue sarcoma survivors can be greatly influenced by all of these factors.

An evaluation of the CCSS baseline questionnaire revealed that rhabdomyosarcoma patients were at a substantially elevated risk for the development of visual, endocrine, cardiopulmonary, neurosensory, and neuromotor deficits[16]. Another CCSS study of all STS patients discovered that STS survivors showed higher rates of physical impairment as compared with both the sibling cohort and leukemia survivors[17]. No previous analyses of the CCSS data have investigated the longitudinal development of chronic medical conditions. As well, there is little data on the impact of self-reported chronic medical conditions on these survivors' health related quality of life (HRQoL).

2. Study Aims:

(1) Characterize mortality, second malignant neoplasms, and quantity and severity of self-reported chronic medical conditions in STS survivors, as a function of attained age.

Hypotheses:

i. There will be an increase in quantity and severity of chronic medical conditions as the STS population ages.
ii. STS patients treated with radiation to the head and neck will have increased number of chronic medical conditions compared with other tumor locations.
iii. Survivors treated with radiation, and those who received higher doses of anthracyclines or alkylating agents will be at increased risk for chronic health conditions.
iv. Survivors' risk for chronic medical conditions will be increased when compared to a sibling control group.

(2) Evaluate health status among STS survivors grouped by number and/or severity of chronic medical conditions, as a function of attained age.

Hypotheses:

i. Health status reported by survivors will be inversely proportional to the quantity and severity of their chronic conditions.
ii. The chronic medical conditions that will most significantly affect health status will be Grade 3-4 cardiovascular conditions.
iii. Survivors will report inferior health status when compared to a sibling control group.

3. Study Population:

a. Study participants will include individuals in the original CCSS survivor cohort with a diagnosis of soft tissue sarcoma (rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma). The analysis will be performed on all patients who completed the baseline questionnaire for whom we have medical record abstraction.
   i. Diagnosis category of "soft tissue sarcoma"
   ii. Patient data

	Eligible/Completed FU Survey	Lost to FU	Deceased after baseline	Participated with medical data
Baseline	1246	-	-	1096
FU2003	820	271	52	752
FU2007	650	142	29	650

4. Analysis 1: Chronic Health Conditions Among Pediatric Soft Tissue Sarcoma Survivors

a. Analysis Framework for Aim 1

i. Outcomes of Interest

1. Mortality – death (date) and cause specific death (date) from the National Death Index
2. Second Malignant Neoplasms – validated SMNs from all questionnaires (items K1-K8 from baseline; R1-R2 from 2003; B1 from 2005 and P1 from 2007 questionnaire)
3. Chronic Conditions – CTCAE Grades completed by Oeffinger and Armstrong using baseline, 2003 and 2007 questionnaire data
    a. Severity of conditions is scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 3: grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening or disabling) or 5 (fatal).

ii. Independent Variables

1. Age at Time of Questionnaire
2. Treatment Variables:
    a. Chemotherapy
        i. Anthracycline score
        ii. Alkylating agent score
    b. Radiation – field (yes/no) and dose
        i. Head and neck
        ii. Chest
            1. Cardiac
            2. Pulmonary
        iii. Abdomen
        iv. Pelvis
        v. Limb
    c. Surgery
        i. Head & Neck resection (e.g., orbital)
        ii. Thoracotomy
        iii. Abdominal Surgery
        iv. Limb
            1. Amputation
            2. Resection

iii. Potential Confounders and Effect Modifiers

1. Gender
2. Race/ethnicity
3. Age at diagnosis
4. Education
5. Household Income

iv. Statistical Approach:

1. Outcomes will be utilized according to the following algorithm:
    a. Continuous variable
        i. Number of medical conditions
        ii. Level of severity of medical conditions
    b. Dichotomized variables:
        i. Quantity of conditions
            1. None
            2. Any One Condition Grades 1-4, no Grade 5
            3. ≥ 2 Conditions Grades 3-4
            4. ≥ 3 Conditions Grades 3-4
        ii. Severity of conditions
            1. Mild-Moderate: Grade 1-2
            2. Severe-Life Threatening: Grade 3-4
            3. Death: Grade 5
        iii. Chronic Medical Condition by Organ System
            1. Secondary Malignancy
            2. Cardiovascular
            3. Respiratory
            4. Gastrointestinal
            5. Renal
            6. Endocrine
            7. Musculoskeletal
            8. Hearing/Vision/Speech
            9. Central Nervous System
2. Demographic and treatment characteristics will be described for the Soft Tissue Sarcoma survivors who completed each questionnaire and non-cancer-related factors will be compared with siblings. (Table 1 and 2)
3. Overall and cause-specific mortality prior to December 31, 2007 will be determined for all CCSS eligible STS patients using the National Death Index and information from all follow-up surveys. Cause of death will be determined by examining both death certificates and survey responses[18]. Survival will then be estimated by the Kaplan-Meier method (Figure 1: Overall and cause specific mortality curves). Events will be counted from cohort entry and event time will be censored at the age of last contact or death. Standardized mortality ratios (SMR) will be computed for overall and cause-specific mortality by dividing the observed number of deaths among STS survivors by the expected number of deaths in the general population. Poisson regression models

will be used to calculate 95% confidence intervals for each SMR. Mortality rates will be evaluated as a function of chemotherapy received, radiation received and surgical exposure using Cox proportional hazards models, with attained age as the time scale.

4. Subsequent malignant neoplasms will be evaluated by assessing cumulative incidence estimations using death as a competing risk[19]. Descriptive statistics of SMNs will be presented in Table 3. Neoplasms present at baseline questionnaire will be considered prevalent at time of cohort entry in cumulative incidence curves. Standardized Incidence Ratios (SIRs) and Excess Absolute Risk (EAR) of overall and specific types of second and subsequent malignancies will be calculated in same manner as SMRs, using the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer incidence rates. (Figure 2: Cumulative Incidence of SMNs)
5. Descriptive statistics of presence and severity of chronic medical conditions will be presented as in Table 4. Chronic medical conditions will be evaluated using Cox regression models of time-to-first-onset of chronic medical condition. Event times will be censored at time of loss-to-follow-up or death. Cox proportional hazard ratios for the outcome event in STS survivors versus sibling controls will be estimated, along with the accompanying 95% confidence intervals, using age as the time scale. Robust estimation procedures will be utilized to account for any dependence among observations on subjects from the same family. (Figures will be created to demonstrate cumulative incidence curves of quantity, severity, and conditions according to organ system)
6. All of the analyses will be performed with the goal of comparing outcomes between survivors and siblings, with appropriate adjustment for demographic covariates, age, gender, and race.

5. Analysis 2: Longitudinal Changes in Health Status Among Soft Tissue Sarcoma Survivors

a. Analysis Framework for Aim 2
   i. Outcomes of Interest
      1. <u>Health Status</u>
         a. General Health Status (BL N15; FU2003 E1; L19 FU2007)
         b. Health Status:
            i. Mental Health (BL J16-24, J26, J27, J29-35; FU2003 G1-18; FU2007 L1-18)
            ii. Physical Impairment (BL N10-N12; FU2003 E12, E15, E16; FU2007 N22-N24)
            iii. Activity Limitations (BL N14 b,c,e; FU2003 E4-E6, E11; FU2007 N26 b,c,e)
            iv. Anxiety from Cancer (Survivors Only: BL J37; FU2003 G20; FU2007 L20)
            v. Pain from Cancer (Survivors Only: BL J36 ; FU2003 G19; FU2007 L21)

ii. Independent Variables

1. Age at Time of Questionnaire
2. Domains of Chronic Health Conditions
    a. Chronic medical conditions as determined in Analysis 1.
        i. No conditions
        ii. One condition (grades 1-4)
        iii. One condition (grade 3-4)
        iv. Greater than 2 conditions (grades 1-4)
        v. Severe or life-threatening condition (grades 3-5)
        vi. By organ system
3. Potential Confounders and effect modifiers
    a. Gender
    b. Race/ethnicity
    c. Age at diagnosis
    d. Time from diagnosis to questionnaire completion
    e. Household income
    f. Health Insurance
    g. Marital status
    h. Education
    i. Employment status
    j. Presence of depression/anxiety

iii. Statistical Approach:

1. Outcomes will be utilized according to the following algorithm:
    a. Dichotomized variables:
        i. General health: Answers fair or poor vs good, very good or excellent
        ii. Mental health: T-score of 63 or higher vs score of less than 63 on any subscale of the brief symptom inventory (BSI-18)
            1. Same T-score algorithm will be applied to each subscale: depression, anxiety, and somatization
        iii. Functional Impairment: Answers yes vs no to any of the three questions listed in 5.a.i.1.b.ii
        iv. Activity Limitation: Answers limited for more than three months over the past two years or limited a lot (FU2003) vs limited for 3 months or less/not limited at all or limited a little/not limited at all (FU2003) to any questions in 5.a.i.1.b.iii
        v. Anxiety: Answers of a lot/very many, extreme anxiety/fears vs other answers
        vi. Pain: Answers of very bad/a lot of pain or severe/very severe vs other answers
2. Using observations from all time points, univariate logistic regression analysis will be performed to assess the association between each dependent variable of health status and the independent variables of presence of chronic health conditions. Multivariate models will be

constructed using logistic regression to estimate impact on reduced health status for each independent variable when controlled for confounding. Models will include a repeated statement and utilize robust variance estimates with independence correlation matrix to account for within participation correlation. Model diagnostics will be used to evaluate the appropriate functional form required for the age variable in the model. Table 5 will depict the percentage of adult survivors of STS with adverse health status including unadjusted and adjusted for age at diagnosis, current age, sex, as well as presence of chronic medical conditions.

3. Models will be adjusted for potential confounders and effect modifiers, including but not limited to age, sex, and ethnicity.
4. The analysis of association between health status and chronic medical conditions is similarly being performed on the entire cohort of CCSS patients by Kiri Ness and Melissa Hudson. We will coordinate our analyses such that methods will be consistent between studies.
5. Figures will be developed to depict the change in predicted prevalence over time dependent upon presence of chronic medical conditions.

6. Special Consideration:

a. The proposed project will fulfill masters' program requirements for Emily Mueller, who will be receiving statistical support from Dr. Matthew Davis, MD, MAAP. The masters' program requires that Emily Mueller perform her own secondary data analysis.

References:

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Table 1. Characteristics of Adult Survivors of Pediatric Soft Tissue Sarcomas

	STS Survivors	Siblings
	Number (N)/Percent (%)	
Age (Current)		
25-34 years		
35-44 years		
45-54 years		
Sex		
Female		
Male		
Race/Ethnicity		
White		
Black		
Hispanic		
Other		
Household Income (annual)		
<$20,000		
$20-59,999		
$60-99,999		
$1,000,000+		
Unknown		
Education		
<HS		
HS		
College graduate		
Unknown		
Marital Status		
Married or living as married		
Single		
Divorced or separated		
Unknown		
Employment		
Employed or caring for the home		
Looking for work or unable to work		
Student		
Current Health Insurance		

Table 2. Diagnosis and Treatment Characteristics

	Number (N)	Percentage (%)
Age at diagnosis		

<5 years		
6-14 years		
>15 years		
Survival Time		
15-20 years		
21-25 years		
26-30 years		
31-35 years		
Treatment modalities		
Chemotherapy		
Radiation		
Surgery		
Treatment Regimen		
Surgery alone		
Chemotherapy +/- surgery		
Radiation +/- surgery		
Chemotherapy and radiation +/- sx		
Anthracycline received		
Alkylating agents received		
Radiation therapy site		
Head or cranial		
Neck		
Chest		
Abdomen		
Pelvic		
Limb		
Total body		
Treatment Era		
1970-1979		
1980-1986		

Table 3. Cause of Death and Rates of SMN for STS survivors

(Will include all causes of deaths and types of SMN in STS patients)

	Number of STS patients (n)
Cause of Death	
Relapse	
SMN	
Cardiac	
Pulmonary	
Renal	
Relapse	
SMN	

Example figures:

Figure 1. Cumulative Cause-Specific Mortality

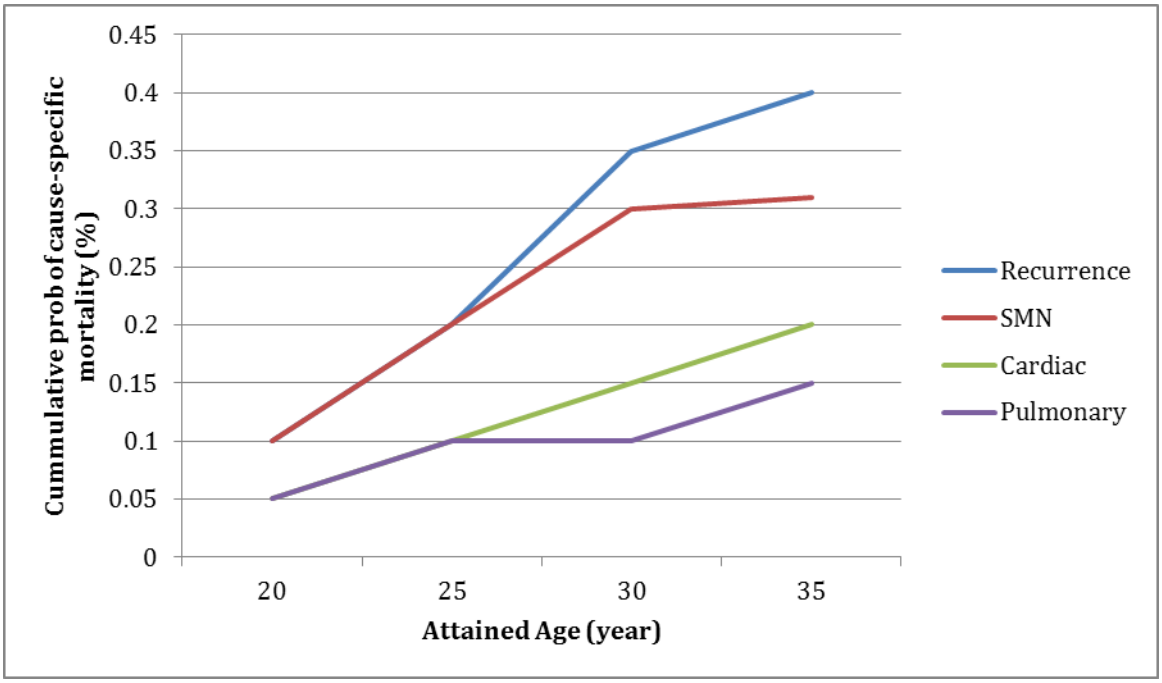

Figure 2. Cumulative Incidence of Chronic Medical Conditions

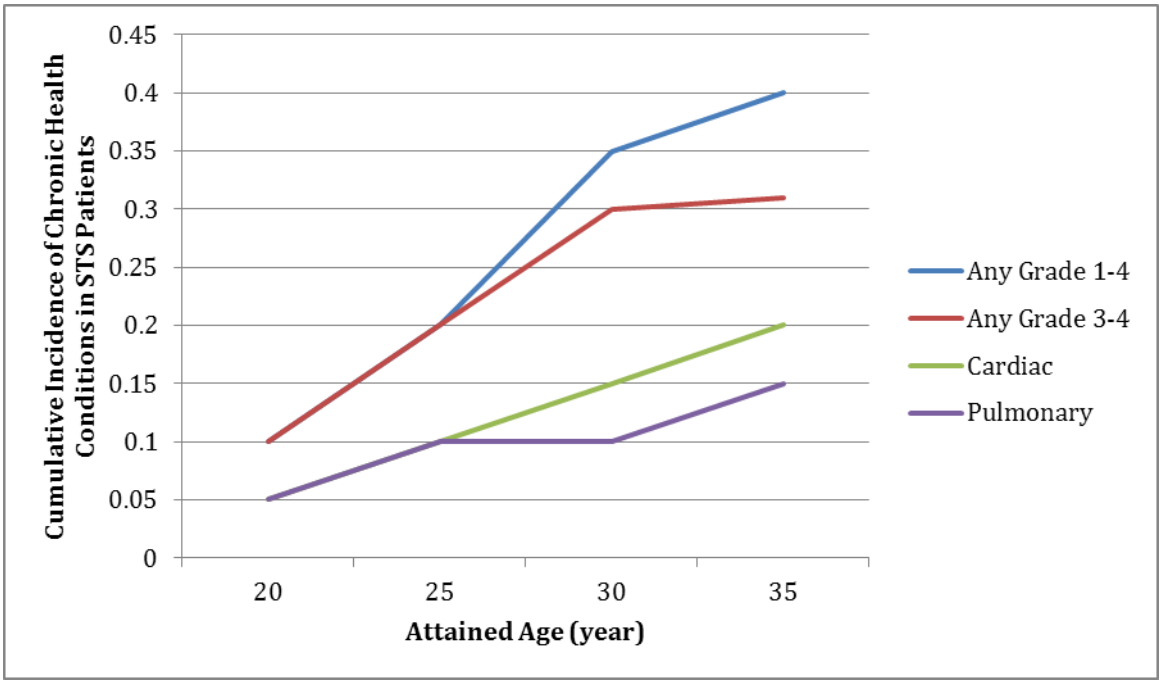

Table 4. Soft Tissue Sarcoma Survivor and Siblings with a Chronic Health Condition, According to the Severity Score

Health Condition	STS Survivors	Siblings
	No. (%)	
No condition		
Grade 1		
Grade 2		
Grade 3		
Grade 4		
Grade 5		
Any Condition		
Grade 1-4		
Grade 3-4		
Multiple health conditions		
≥2		
≥3		

Table 5. Percentage of Adult Survivors of Pediatric Soft Tissue Sarcoma with Adverse Health Status, by Diagnosis, Cancer Treatment and Presence of Chronic Medical Conditions

	General Health		Mental Health		Activity Limitations		Physical Impairment		Pain		Anxiety		Any domain	
	Unadj	Adj*	Unadj	Adj*	Unadj	Adj*	Unadj	Adj*	Unadj	Adj*	Unadj	Adj*	Unadj	Ad
Attained Age														
25-34 years														
35-44 years														
45-54 years														
Age at diagnosis														
<5 years														
6-14 years														
>15 years														
Sex														
Female														
Male														
Medical Conditions														
None														
Any One Grade 1-4														
Any One Grade 3-4														
> 2 conditions														
Secondary Malignancy														
Medical Condition by Organ System														
Cardiovascular														
Respiratory														
Gastrointestinal														
Renal														
Endocrine														
Hearing/Vision/Speech														
Central Nervous System														

*Adjusted for all variables in chart, as well as presence of depression or anxiety and sociodemographic factors including education, annual household income, employment, marital status.