CCSS Analysis Concept Proposal
April 19, 2007

1. Title: Physical activity patterns and predictors of sedentary lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study

2. Working group investigators:

Kiri Ness	kiri.ness@stjude.org	901-495-5157
Wendy Leisenring	wleisen@fhcrc.org	206-667-4374
Melissa Hudson	Melissa.hudson@stjude.org	901-495-3445
Jim Gurney	jamegurn@umich.edu	734-615-9748
Kim Whelan	kwhelan@peds.uab.edu	205-939-6127
Wendy Hobbie	hobbie2@pobox.upenn.edu	
Jenny Lanctot	jenny.lanctot@stjude.org	901-495-5916
Greg Armstrong	greg.armstrong@stjude.org	901-495-5892
Les Robison	les.robison@stjude.org	901-495-5817
Kevin Oeffinger	oeffingk@mskcc.org	212-639-8649

3. Background and rationale:

In the U.S. population, a certain proportion of chronic diseases, including some cancers, heart disease, obesity, metabolic syndrome, and type II diabetes can be attributed to or influenced by poor lifestyle choices. Others, like osteoporosis, depression and anxiety are associated with aging, genetics, or environmental influences. Chronic health problems are a public health challenge in the U.S., fueled by ready access to an abundant food supply and an environment that offers few opportunities for daily physical activity. Chronic health problems are an even bigger challenge for childhood cancer survivors, whose medical and psychosocial late effects not only contribute to disease, but also prevent them from participation in life activities that may modify their risk for future disease.

As the prevalence of childhood cancer survivors continues to increase, the need for long term medical follow-up and interventions to address or prevent late effects and to remediate activity limitations becomes more important. Individualized medical follow-up for long-term survivors of childhood cancer is encouraged by at least three pediatric professional medical organizations: the American Society of Pediatric Hematology and Oncology, the International Society of Pediatric Oncology, and the American Academy of Pediatrics.[1] Risk-based, treatment-specific screening guidelines have been established by the Children's Oncology Group (COG), and are intended for asymptomatic survivors of childhood, adolescent, or young adult cancer presenting for routine medical follow-up. The COG Long Term Follow-Up Guidelines are connected to "Health Links" that provide information and encourage survivors to take action for health..[2]

Healthy behaviors, such as physical activity,[3] are supported by evidence for the rest of the population, including persons with chronic disease,[3-12] and may have the potential to ameliorate some of the long-term problems experienced by childhood cancer survivors, including functional loss.[13-18] The COG guidelines include a general physical activity health link; however, it is not yet directed to diagnosis, treatment-related risk factors, or late effects that specifically interfere with the ability of the cancer survivor to participate in physical activity necessary for long-term health. Because of the heterogeneous nature of histologies and treatments experienced by childhood cancer survivors, and because of the well documented, treatment-related medical late effects, there is a need for specific, risk-based guidelines that address health behaviors, including physical activity. There is a need to provide a comprehensive documentation of physical activity patterns in the entire CCSS cohort. In addition, we may identify risk factors helped by interventions that modify lifestyle choices or that are amenable to existing programs designed to improve physical health, like those that target persons with obesity,[19], diabetes, [20, 21] or cardiovascular disease [22]. Finally, this analysis will provide a foundation for the eventual

development of evidence-based, risk-based guidelines and interventions for physical activity promotion among long-term childhood cancer survivors.

4. Purpose/aims:

The purpose of this manuscript is to document physical activity patterns in the CCSS cohort, to compare physical activity patterns between survivors and siblings, and to evaluate the association between diagnosis, treatment, demographic/personal and chronic disease outcomes and risk for sedentary lifestyle. We acknowledge that an analysis similar to this has been done for the ALL survivors in this cohort. We propose to conduct overall analyses of these outcomes in the cohort, limiting our examination of treatment to broad categories of surgery, chemotherapy and radiation. Future analyses of these outcomes could focus on disease specific populations where the treatment effects could be examined in more detail.

Hypothesis #1: Adult survivors of childhood cancer will report less than the nationally recommended guidelines for physical activity (30 minutes of moderate intensity physical activity on 5 or more days of the week or 30 minutes of vigorous physical activity on 3 or more days of the week) and will report lower levels of any, moderate or vigorous physical activity when compared to siblings or to a nationally representative group of individuals from the behavioral risk factor surveillance survey (BRFSS).

Hypothesis #2: Survivors diagnosed with CNS malignancies, bone tumors and Hodgkin's Lymphoma will report the lowest levels of physical activity.

Hypothesis #3: Treatment modalities associated with the lowest levels of physical activity will include younger age at diagnosis, lower extremity amputation, chest radiation, and anthracycline based chemotherapy.

Hypothesis #4: Demographic and personal factors associated with the lowest levels of physical activity will include female gender, baseline obesity (defined as body mass index greater than or equal to 30 at baseline (or 95th percentile for age and gender if younger than 18 at baseline)), baseline depression (defined as depression index on the baseline Brief Symptom Inventory of 63 or greater/Behavior problem index depression scale in lowest 10^{th} percentile for those under 18 at baseline), current cancer related pain, current cancer related anxiety, less than High School Education and annual household income less than $20,000 per year.

Hypothesis #5: Participants who report grade 3 –severe or grade 4 – disabling or life threatening, or who report the presence of 2 or more chronic conditions will report the lowest levels of physical activity

5. Analysis framework:

Sample
Survivor and sibling participants who completed the baseline and the second follow-up questionnaire are eligible for these analyses. For the analyses of treatment effects, those who consented to and had a medical record abstraction will be included.

Outcomes of interest
Physical activity levels: Questions D1 – D7 from the second follow-up questionnaire:

- The average number of minutes per day (or week) of moderate physical activity
- The average number of minutes per day (or week) of vigorous physical activity
- A binary variable for whether subjects meet the nationally recommended guidelines for physical activity (30 minutes of moderate intensity physical activity on 5 or more days of the week or 30 minutes of vigorous physical activity on 3 or more days of the week).
- A binary variable indicating if subjects reported no physical activity over the past month

Independent (exploratory) variables

A. Diagnosis and treatment variables
- Cancer diagnosis and diagnosis group
- Age at diagnosis (Date of diagnosis and date of birth), explored as:
  - specific categories
    - 0-4 years
    - 5-9 years
    - 10-14 years
    - 15-20 years
  - continuous
- Treatment
  - Surgery not amputation (reference)
  - Surgery including amputation
  - Cranial radiation
  - Chest radiation
  - Anthracyclines (explored as yes/no or cumulative dose)

B. Demographic and personal factors
- BMI at baseline and the second follow-up (weight in kilograms/height in meters squared) (A10-A11)
- Age at second follow-up (Completion date second follow-up and date of birth)
  - specific categories
  - continuous
- Gender (A.2 – baseline)
- Race/ethnicity (A4 and A4a baseline)
  - White not Hispanic (reference)
  - Black
  - Hispanic
  - Other
- Household income at second follow-up (S1)
  - <$40,000/year
  - $40-59,999/year
  - 60+/year
  - Not indicated
- Education at second follow-up (1)
  - < high school
  - High school graduate
  - College graduate
- Marital status at second follow-up (2)
  - Single
  - Widowed
  - Divorced/separated
  - Married/living as married
- Employment status at second follow-up (4-6)
  - Unemployed
  - Student
  - Employed or caring for home/family
- BSI questions/BPI from baseline (J16-J36 adult/J16-J21 under 18)
  - Depression T-score from BSI
  - Depression scale score from behavioral problem index
- Pain and anxiety question from second follow-up (G19-G20)
  - None or mild vs. moderate or greater for both variables
- Smoking/tobacco (L1-6 second follow-up)
  - Never user, current user, former user
- Participation in physical activity at baseline (N 15)
  - Yes/no

C. Chronic disease variables using the scoring rubric used by Oeffinger et al., [23] based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3 and the scoring system developed through the National Cancer Institute.[24] We will use four grades: grade 1 - mild; grade 2 - moderate; grade 3 - severe; grade 4 - life-threatening or disabling; omitting grade 5 – death, as participants no longer alive are not eligible for these analyses. As in the study by Oeffinger et al,, [23] a total of 137 health conditions will be scored.
explored as:

- Any condition in grades 0- 4
- Number of conditions
- Grades 0,1,2 vs. grade 3or 4

Statistics

The primary outcome is the difference in physical activity levels between survivors, siblings and a nationally representative sample of individuals from the BRFSS. Four specific physical activity outcomes will be used; 1) the average number of minutes per day (or week) of moderate or 2) vigorous physical activity and 3) a binary variable for whether subjects meet the nationally recommended guidelines for physical activity (30 minutes of moderate intensity physical activity on 5 or more days of the week or 30 minutes of vigorous physical activity on 3 or more days of the week) 4) a binary variable for whether subjects report no physical activity over the past month. The average number of minutes per day (or week) of moderate and vigorous physical activity will be compared between survivors (overall and by diagnosis) and siblings in age and gender adjusted generalized linear mixed models to allow for correlation between survivors and siblings from the same family. The proportion of survivors (overall and by diagnosis) and siblings meeting the nationally recommended guidelines for physical activity will be calculated and compared with age and gender adjusted generalized estimating equations. The proportion of survivors (overall and by diagnosis) and siblings who report no physical activity over the past month will be calculated and compared with age and gender adjusted generalized estimating equations. Siblings and survivors will be compared to a nationally representative sample of individuals from the BRFSS on each physical activity outcome in similar models. Univariate analyses will be performed to assess the association between each treatment, demographic/personal, and chronic disease variable and each physical activity level outcome. As part of the analyses, physical activity will be expressed as a continuous variable (minutes per day or week) and as a binary variable (meets or does not meet recommended physical activity guidelines). Separate multivariable models will be constructed using linear and logistic regression to estimate the relative risk for a sedentary lifestyle by treatment, personal/demographic, and chronic disease variables. Specific personal/demographic variables will be included in treatment and chronic disease models (e.g. age, gender, etc.) as appropriate.

6. References

1. National Cancer Institute. Late effects of treatment for childhood cancer (PDQ) Health Professional Version. Available at: www.cancer.gov/cancertopics/pdq/treatment/lateeffects. Accessed April 3, 2006.
2. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Available at: http://www.survivorshipguidelines.org/. Accessed April 3, 2006.
3. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med.* Jan 17 2006;144(2):73-81.
4. Fletcher B, Berra K, Ades P, et al. Managing abnormal blood lipids: a collaborative approach. *Circulation.* Nov 15 2005;112(20):3184-3209.
5. Mears S. The importance of exercise training in patients with chronic heart failure. *Nurs Stand.* Apr 12-18 2006;20(31):41-47.
6. Pais PS. Early intervention and prevention of myocardial infarction. *J Hypertens.* Apr 2006;24 Suppl 2:S25-S30.
7. Kohut ML, McCann DA, Russell DW, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun.* May 2006;20(3):201-209.
8. Streuber SD, Amsterdam EA, Stebbins CL. Heart rate recovery in heart failure patients after a 12-week cardiac rehabilitation program. *Am J Cardiol.* Mar 1 2006;97(5):694-698.
9. Ries AL, Make BJ, Lee SM, et al. The effects of pulmonary rehabilitation in the national emphysema treatment trial. *Chest.* Dec 2005;128(6):3799-3809.
10. Foy CG, Wickley KL, Adair N, et al. The Reconditioning Exercise and Chronic Obstructive Pulmonary Disease Trial II (REACT II): Rationale and study design for a clinical trial of physical activity among individuals with chronic obstructive pulmonary disease. *Contemp Clin Trials.* Apr 2006;27(2):135-146.
11. Konhilas JP, Watson PA, Maass A, et al. Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. *Circ Res.* Mar 3 2006;98(4):540-548.
12. Barbour KA, Blumenthal JA. Exercise training and depression in older adults. *Neurobiol Aging.* Dec 2005;26 Suppl 1:119-123.
13. Berk DR, Hubert HB, Fries JF. Associations of changes in exercise level with subsequent disability among seniors: a 16-year longitudinal study. *J Gerontol A Biol Sci Med Sci.* Jan 2006;61(1):97-102.
14. Nash MS. Exercise as a health-promoting activity following spinal cord injury. *J Neurol Phys Ther.* Jun 2005;29(2):87-103, 106.
15. Hurwitz EL, Morgenstern H, Chiao C. Effects of recreational physical activity and back exercises on low back pain and psychological distress: findings from the UCLA Low Back Pain Study. *Am J Public Health.* Oct 2005;95(10):1817-1824.
16. Tak E, Staats P, Van Hespen A, Hopman-Rock M. The effects of an exercise program for older adults with osteoarthritis of the hip. *J Rheumatol.* Jun 2005;32(6):1106-1113.
17. White LJ, Dressendorfer RH. Exercise and multiple sclerosis. *Sports Med.* 2004;34(15):1077-1100.
18. Cooper RA, Quatrano LA, Axelson PW, et al. Research on physical activity and health among people with disabilities: a consensus statement. *J Rehabil Res Dev.* Apr 1999;36(2):142-154.

19. **Graffagnino CL, Falko JM, La Londe M, et al. Effect of a community-based weight management program on weight loss and cardiovascular disease risk factors. *Obes Res.* Feb 2006;14(2):280-288.**
20. **Schulz AJ, Zenk S, Odoms-Young A, et al. Healthy eating and exercising to reduce diabetes: exploring the potential of social determinants of health frameworks within the context of community-based participatory diabetes prevention. *Am J Public Health.* Apr 2005;95(4):645-651.**
21. **Norris SL, Zhang X, Avenell A, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database Syst Rev.* 2005(2):CD004095.**
22. **Matson-Koffman DM, Brownstein JN, Neiner JA, Greaney ML. A site-specific literature review of policy and environmental interventions that promote physical activity and nutrition for cardiovascular health: what works? *Am J Health Promot.* Jan-Feb 2005;19(3):167-193.**
23. **Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* Oct 12 2006;355(15):1572-1582.**
24. **CTCAE. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. *DCTD, NCI, NIH, DHHS*. Available at: http://ctep.cancer.gov. Accessed March 10, 2007.**

Examples of proposed tables

Table 1. Characteristics of the study population

	Survivors (N=)		Siblings (N=)		
	N	%	N	%	p-value*
Gender					
Male					
Female					
Race/ethnicity					
Asian/pacific islander					
Black – non Hispanic					
Hispanic					
White – non Hispanic					
Other					
Age group at second follow-up					
18-29 years					
30-39 years					
40-49 years					
50+ years					
Marital status					
Married/living as married					
Single					
Widowed					
Divorced/separated					
Educational attainment					
< High school					
High School graduate					
College graduate					
Employment					
Working/caring for home or family					
Student					
Unemployed/looking for work					
Unable to work					
Annual household income					
< $20.000					
$20-39,000					
$40-59,000					
$60-79,000					
$80-99,000					
$100,000+					
Current BMI					
Underweight					
Normal weight					
Over weight					
Obese					
Baseline BMI					
Underweight					
Normal weight					
Over weight					
Obese					
Baseline Depression					
Yes					
No					
Baseline exercise/sports (20					

minutes)
0-2 days/week
3+ days per week
Current smoking status
Never smoker
Ever smoker
Current smoker
Diagnosis
Acute lymphoblastic leukemia
Acute myeloid leukemia
Other or unspecified leukemia
Astrocytomas
Medulloblastoma, PNET
Other CNS tumors
Hodgkin's Disease
Non-Hodgkin's Lymphoma
Wilm's Tumor
Neuroblastoma
Soft tissue sarcoma
Ewings sarcoma
Osteosarcoma
Other bone
Age at diagnosis
0-3 years
4-9 years
10-14 years
15-20 years
Survival time
<20 years
20-24 years
25-29 years
30+ years
Surgery
Amputation of lower limb
Other surgery
No surgery
Chemotherapy
Anthracyclines
Other chemotherapy
No chemotherapy
Radiation
Cranial radiation
Chest radiation
Other radiation
No radiation

---

*From generalized estimating equations with a binomial distribution and a logit link to allow for intra-family correlation

Table 2.

	Moderate physical activity		Vigorous physical activity		Meets national guidelines for physical activity		Sedentary for the past month	
	Mean (SD)	p-value[t]	Mean (SD)	N (%)	p-value[#]	p-value[t]	N (%)	p-value[#]
Nationally representative group from BRFSS*								
Siblings								
Survivors (overall)								
Leukemia								
Acute lymphoblastic leukemia								
Acute myeloid leukemia								
Other or unspecified leukemia								
CNS Malignancies								
Astrocytomas								
Medulloblastoma, PNET								
Other CNS tumors								
Hodgkin's Disease								
Non-Hodgkin's Lymphoma								
Wilm's Tumor								
Neuroblastoma								
Soft tissue sarcoma								
Bone tumors								
Ewings sarcoma								
Osteosarcoma								
Other bone								

*Reference group

[t] From age and gender adjusted generalized linear mixed models

[#] From age and gender adjusted generalized estimating equations