1. STUDY TITLE: *An examination of the association between fatigue, vitality and sleep disturbance, and neurocognitive functioning in adult survivors of childhood cancer.*

2. WORKING GROUP AND INVESTIGATORS:

   2.1. Working Groups: Psychology

   2.2. Investigators:

Nancy R. Clanton	nrclanto@texaschildrenshospital.org
Lonnie Zeltzer	lzeltzer@mednet.ucla.edu
Dan Mulrooney	mulro006@umn.edu
Kumar Srivastava	kumar.srivastava@stjude.org
Brannon Morris	brannon.morris@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Les Robison	les.robison@stjude.org
Kevin R. Krull	kevin.krull@stjude.org

3. BACKGROUND AND RATIONALE:

As enhanced medical treatments have contributed to an increase in the number of adult survivors of childhood cancer, a good deal of research has been devoted to medical and psychosocial late effects.[1-4] Two of the common quality of life late effects include neurocognitive impairment and cancer-related fatigue. This study aims to examine the association between these two outcomes by examining the impact of fatigue and vitality, as well as sleep quality, on neurocognitive functioning; an area that has yet to receive much attention in adult survivors of childhood cancer.

Among the neurocognitive effects associated with childhood cancer, research has shown common impairment in specific domains including, but not limited to, processing speed, attention, and memory.[1-3] However, reduced sleep quality and fatigue alone are also thought to impact some of the same aforementioned neurocognitive skills. For example, among adults who were diagnosed with chronic fatigue syndrome, specific neurocognitive deficits such as slow processing speed, impaired working memory, and poor memory and learning of new information has been reported.[5,6] Moreover, the presence of significant fatigue has been associated with poor neuropsychological functioning in adults following acute medical conditions.[7,8] However, other studies have failed to find an association between fatigue and neuropsychological test performance in adults chronic medical disease such as Multiple Sclerosis (MS)[9] and HIV/AIDS.[10]

As fatigue and reduced sleep quality have been associated with long-term survivors of cancer,[11-14] the impact of fatigue and vitality on neurocognitive skills is an area that warrants examination. It is estimated that up to 45% of the general population report symptoms of fatigue,[15] while rates as high as 90% have been reported in adult cancer survivors.[14] In fact, the only group to report more frequent sleep and fatigue problems than cancer survivors is psychiatric patients.[16] Fatigue has also been reported as a problem in adult survivors of childhood cancer. Using the Childhood Cancer Survivor Study (CCSS) database,

Mulrooney and colleagues found slightly higher rates of fatigue among adult survivors compared to a sibling cohort.[17] No significant differences were reported between siblings and survivors on levels of sleepiness and poor sleep quality.[17] Although the differences between the CCSS survivor and sibling cohorts were small, differential sensitivity of fatigue and poor sleep quality on neurocognitive functions may exist. Sleep is important for neural recovery following brain injury.[18] Furthermore, sleep deprivation in individuals with brain injury exacerbates the degree of neurocognitive impairment.[19] Thus, although the rate of fatigue and poor sleep quality may not be clinically significant between the CCSS survivors and their siblings, the impact of the fatigue and sleep loss on neurocognitive performance may be more substantial in the survivors who have experienced reduced cognitive reserve following neurotoxic cancer therapy.

Understanding the impact of fatigue and vitality on functional behavior is important from a research perspective to help evaluate cancer treatments. However, it is also important from a clinical perspective because it is prevalent in so many oncology patients and because the impact of fatigue and vitality on the quality of life of cancer patients is poorly understood.[20] As discussed previously, although some research has examined the relation between fatigue and neurocognitive effects associated with chronic illnesses such as MS, HIV/AIDS, and chronic fatigue syndrome among others, little is known about this association among adult survivors of childhood cancer.

The purpose of the proposed study is to elucidate the association between fatigue and neurocognitive functioning in the adult survivors of the CCSS. For this purpose, performance on the Neurocognitive Questionnaire (CCSS-NCQ)[21] completed during the Follow-up 2003 survey will be compared to the fatigue and sleep quality assessments collected on the cohort previously reported by Mulrooney.[17] The CCSS-NCQ has been identified as comprising four primary factors: Task Efficiency, Emotional Regulation, Organization, and Memory. These factors provide a measure of executive functioning (e.g., Emotional Regulation and Organization factors), attention (e.g., Task Efficiency factor), and working and long-term memory (e.g., Memory factor).[21] The Medical Outcomes Short Form-36 (SF-36) was also collected during Follow-up 2003 to evaluate health related quality of life.[22] Within the SF-36, questions comprising a Vitality Scale will be used. This scale measured the degree of feeling energetic and full of life versus feeling tired and worn out.[22] Three rating scales were included in an ancillary sleep survey, collected at roughly the same time as Follow-up 2003. These additional rating scales assessed fatigue, sleepiness, and sleep quality. Fatigue was measured with the fatigue subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). This is a measure of the physical and functional consequences associated with fatigue, and results in a single score.[23] The Pittsburgh Sleep Quality Index (PSQI) was administered to assess sleep quality over the month prior to survey completion.[24] A number of sleep quality components are measured with the PSQI, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. Symptoms of daytime sleepiness were measured using the Epworth Sleepiness Scale (ESS).[25] Along with the SF-36 Vitality Scale, these three fatigue/sleep scales will be used as predictor variables, with the CCSS-NCQ considered the outcome measure.

Since emotional functioning has already been associated with sleep quality and fatigue,[17] as well as neurocognitive functioning, we propose to include a measure of emotional distress as a covariate. The Brief Symptom Inventory-18 (BSI-18) provided a measure of global distress, as well as subscales for anxiety, depression, and somatization. [26]

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aim:

4.1.1. To examine the impact of fatigue and vitality on neurocognitive outcome among adult survivors of childhood cancer.

4.2. Objectives:

4.2.1. To examine the impact of fatigue on task efficiency, emotion regulation, organization, and memory.

4.2.2. To examine the impact of vitality on task efficiency, emotion regulation, organization, and memory.

4.3. Hypothesis:

4.3.1. Patients with higher ratings of fatigue will report more problems related to task efficiency and memory.

4.3.2. Patients with lower ratings of vitality will report more problems related to task efficiency, emotion regulation, organization, and memory.

4.4. Secondary Aim:

4.4.1. To examine the impact of sleep quality and sleepiness on neurocognitive outcomes among adult survivors of childhood cancer.

5. PARTICIPANTS

5.1. CCSS Survivor Cohort only from the Follow-up 2 survey (i.e. Follow-up 2003)

5.2. Inclusion criteria

- Cancer survivors who completed CCSS-NCQ, FACIT, PSQI, ESS, SF-36, and BSI-18, questions. Based on a previous CCSS study using the FACIT, PSQI and ESS, 2,645 participants were available for inclusion. We expect the majority of these participants to have also completed the NCQ, SF-36, and BSI.

5.3. Exclusion criteria

- Mental Retardation (Baseline Survey item J.3)

5.4. Variables

- Cancer Diagnosis
- Cranial Radiation Therapy (Yes/No)
- CNS Chemotherapy (Yes/No)
- Medication Use (Follow-Up 2003 item Q8, psychoactive substances)
- Current Age
- Sex
- Household Income (Follow-Up 2003 item S1)
- CCSS- NCQ (Follow-Up 2003 section J)
- BSI-18 (Follow-Up 2003 section G items 1-18)

- FACIT-Fatigue (Fatigue survey)
- PSQI (Sleep survey)
- ESS (Daytime sleepiness survey)
- SF-36 - Vitality subscale (Follow-Up 2003 items F1, F5, F7, and F9)

6. ANALYSIS FRAMEWORK:
   6.1. Primary Outcomes Variables:
      6.1.1. CCSS-NCQ : Factors = Task Efficiency, Emotional Regulation, Organization, and Memory.

   6.2. Primary predictors: (Primary Aim)
      6.2.1. FACIT: Total fatigue subscale
      6.2.2. SF-36 Vitality subscale

   6.3. Secondary Predictors: (Secondary Aim)
      6.3.1. PSQI: Factors = Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbance, Use of Sleeping Medications, and Daytime Dysfunction
      6.3.2. ESS: Daytime sleepiness score

   6.4. Covariates:
      6.4.1. BSI-18: Anxiety, Depression, Somatization.
      6.4.2. Cancer Diagnosis
      6.4.3. Cranial Radiation Therapy (Yes/No)
      6.4.4. CNS Chemotherapy (Antimetabolites Yes/No; Corticosteroids Yes/No)
      6.4.5. Medication Use (mood stabilizers, anxiolytics, stimulants)
      6.4.6. Current Age
      6.4.7. Sex
      6.4.8. Household Income

   6.5. Related to the specific hypotheses, the following analyses will be conducted:
      6.5.1. Frequency distributions will be examined to categorize relevant outcome variables and covariates according to reasonable groupings and consistent with previous CCSS manuscripts. The NCQ factor scores will be dichotomized based on whether the performance is considered "impaired" or not (Yes/No), with impairment defined as a performance falling $\geq 90^{th}$ percentile based on sibling group norms (i.e. higher scores reflect more neurocognitive problems). Scales from the SF-36 and BSI-18 will be dichotomized based on whether the performance is "impaired" or note (Yes/No), with impairment defined as a performance falling below a T-Score of 40 or above a T-score of 63 on national norms collected for the SF-36 and BSI-18, respectively. Scales from the FACIT, PSQI, and ESS will be dichotomized based on whether the performance is "impaired" or not (Yes/No), consistent with the approach used by Mulrooney.[17] That is, "impaired" performance will consist of scores falling $\leq 10^{th}$ percentile on the FACIT (i.e. low scores reflect more fatigue) and $\geq 90^{th}$ percentile based on

PSQI and ESS (i.e. high scores reflect more problems), with all comparisons made in reference to the sibling group norms from the CCSS.

6.5.2. Collinearity will be examined between the factors on the PSQI, as well as between the PSQI and ESS. Should collinearity be observed, individual scales will be selected that best reflect the construct of interest, and/or scores will be combined into a general factor score.

6.5.3. Descriptive statistics will be reported for all predictors, outcomes, and covariates.

6.5.4. Univariate logistic regression analyses will be conducted between the possible predictor variables and the outcome variables (with separate analyses conducted for each factor of the CCSS-NCQ). Those variables that are significant will then be used in the multivariate model, with care taken to not include predictors that demonstrate Collinearity (see 6.5.2 above).

6.5.5. Multivariate logistic regression analyses will then be conducted to identify which variables uniquely predict the CCSS-NCQ outcome variables. Analyses will be conducted for each outcome variable using dichotomized primary predictors and covariates as indicated above.

6.5.6. Multivariate generalized linear regression analyses will also be conducted for each outcome variable to estimate the amount of variance accounted for by the FACIT, PSQI, ESS, and Vitality Scale as primary predictors and covariates as indicated above. For these analyses, raw scores on the outcome and predictors will be used rather than dichotomized categories.

6.5.7. For each univariate and multivariate analyses, treatment variables (i.e. CRT and CNS Chemo) will be used as covariates in conjunction with BSI-18 factor scores, Medication Use, Current Age, Sex, and Household Income. The analyses will then be repeated to examine the contribution of Cancer Diagnosis, by substituting diagnostic groups for the treatment variables and including all other covariates.

6.6. Examples of specific tables and figures:

Descriptive Statistics at Follow Up 2

	No	**%**
Sex		
Female		
Male		
Age		
Categories TBD		
Income		
<20,000		
20,000-39,000		
40,000-59,999		
60,000-79,999		
80,000-99,999		
>100,000		
Diagnosis		
Leukemia		
CNS malignancy		
Hodgkin Disease		
Soft tissue sarcoma		
Bone cancer		
Cranial Radiation Therapy		
20-39 gy		
40-54 gy		
55 + gy		
CNS Chemotherapy		
Antimetabolite		
Corticosteroid		
Psychoactive Medication		
Depressants		
Anxiolytics		
Stimulants		

Odds ratios for the prediction of neurocognitive outcome by fatigue and vitality comparing survivors to the sibling comparison group

	NCQ Task Efficiency			*NCQ Emotion Regulation*			*NCQ Organization*			*NCQ Memory*		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
FACIT (score $\leq 10^{th}$ %ile)												
PSQI (score $\geq 90^{th}$ %ile)												
ESS (score $\geq 90^{th}$ %ile)												
SF-36 Vitality Scale (T score ≤ 40)												
BSI- Depression Scale (score $\geq 90^{th}$ %ile)												
BSI- Anxiety Scale (score $\geq 90^{th}$ %ile)												
BSI- Somatization Scale (score $\geq 90^{th}$ %ile)												
Sex: Female vs. Male												
Age												
Categories TBD												
Household Income												
<20,000 vs. ≥ 20,000												
Diagnosis												
Leukemia												
CNS malignancy												
Hodgkin Disease												
Soft tissue sarcoma												
Bone cancer												
CRT (Yes/No)												
CNS Chemotherapy (Yes/No)												
Psychoactive Medication												
Depressants												
Anxiolytics												
Stimulants												

Multivariate regression analyses

	NCQ Task Efficiency			*NCQ Emotion Regulation*			*NCQ Organization*			*NCQ Memory*		
	Beta	Std B	p	Beta	Std B	p	Beta	Std B	p	Beta	Std B	p
FACIT												
PSQI												
ESS												
SF-36 Vitality Scale												
BSI- Depression Scale												
BSI- Anxiety Scale												
BSI- Somatization Scale												

7. SPECIAL CONSIDERATION:

7.1. The analyses for this proposal will be conducted at St. Jude Children's Research Hospital under the direction of Dr. Kumar Srivastava and Dr. Kevin Krull. All analyses will be reviewed and approved by Dr. Wendy Leisenring.

8. REFERENCES:

1. Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol* 2000; 1 5(7): 603-30.

2. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychologic performance of children surviving leukemia who received 1 8-Gy, 24-Gy, or no cranial irradiation. *J Clin Oncol* 1991; 9(8):1348-56.

3. Butler RW, Haser JK. Neurocognitive effects of treatment for childhood cancer. *Ment Retard Dev Disabil Res Rev* 2006; 12(3): 184-91.

4. Campbell LK, Scaduto M, Sharp W, Dufton L, Van Slyke D, Whitlock JA, et al. A meta- analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer* 2007; 49(1): 65-73.

5. Majer,M, Wellberg LA, Capuron L, Miller AH, Pagoni G, Reeves WC. Neuropsychological performance in persons with chronic fatigue syndrome: Results from a population-based study. *Psychosom Med* 2008; 70(7): 829-36.

6. Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: A review. *Acta Psychiatr Scand* 2001; 103(2): 84-93.

7. Bruno RL, Galski T, DeLuca J. The neuropsychology of post-polio fatigue. *Arch Phys Med Rehab* 1993; 74: 1061-1065.

8. Ravdin LD, Hilton E, Prieau M, Clements C, Barr WB. Memory functioning in Lyme borreliosis. *J Clin Psychiat* 1996; 57: 282-286.

9. Archibald CJ, Fisk JD. Information processing efficiency in patients with multiple sclerosis. *J Clin Exp Neuropsyc* 2000; 22: 686-701.

10. Millikin CP, Rourke SB, Halman MH, Power C. Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. *J Clin Exp Neuropsyc* 2003; 25(2): 201-215.

11. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000; 18: 743-53.

12. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999; 17: 253-61.

13. Fossa SD, Dahl AA, Loge JH. Fatigue, anxiety, and depression in long-term survivors of testicular cancer. *J Clin Oncol* 2003; 21: 1249-54.

14. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. *Support Care Cancer* 2001; 9: 11-17.

15. Lewis G, Wessely S, The epidemiology of fatigue: More questions than answers. *J Epidemiol Community Health* 1992; 46: 92-7.

16. Anderson KO, Getto CJ, Mendoza TR, Palmer SN, Wang XS, Reyes-Gibby CC, et al. Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. *J Pain Symptom Manage* 2003; 25(4): 307-18.

17. Mulrooney DA, Ness KN, Neglia JP, Whitton JA, Green DM, Zeltzer LK et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *Sleep* 2008; 31(2): 271-81.

18. Parcell DL, Ponsford JL, Redman JR, Rajaratnam SM. Poor sleep quality and changes in objectively recorded sleep after traumatic brain injury: a preliminary study. Arch Phys Med Rehabil 2008;89:843-50.

19. Gomez Beldarrain M, Astorgano AG, Gonzalez AB, Garcia-Monco JC. Sleep improves sequential motor learning and performance in patients with prefrontal lobe lesions. Clin Neurol Neurosurg 2008;110:245-52.

20. Flechtner H, Bottomley A. Fatigue and quality of life: Lessons from the real world. *Oncologist* 2003; 8: 5-9.

21. Krull KR, Gioia G, Ness KK, Ellenberg L, Recklitis C, Leisenring W, et al.

Reliability and validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. *Cancer* in press.

22. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

23. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63-74.

24. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

25. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.

26. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med 1983;13:595 – 605.