

1. STUDY TITLE: Psychosocial and physical factors influencing fatigue in survivors of childhood Hodgkin Lymphoma

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Group: Psychology

2.2. Investigators:

Amanda Rach	amanda.rach@stjude.org
Valerie Crabtree	valerie.crabtree@stjude.org
Tara Brinkman	Tara.brinkman@stjude.org
Les Robison	les.robison@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Kevin Krull	kevin.krull@stjude.org
Wendy Leisenring	wleisnr@fhcrc.org
Jordan Gilleland	jordan.gilleland@choa.org
Lonnie Zeltzer	lzeltzer@mednet.ucla.edu
Jin-Shei Lai	js-lai@northwestern.edu
Dan Mulrooney	Daniel.Mulrooney@st.jude.org

3. BACKGROUND AND RATIONALE:

Long term follow-up studies of childhood Hodgkin Lymphoma (HL) survivors find that they are susceptible to developing a number of physical and psychological late effects as a result of their cancer and its associated treatment. Specifically, CCSS cohort studies indicate that HL survivors report more emotional distress and physical functioning limitations as well as increased amounts of fatigue and disrupted sleep (Mulrooney et al., 2008; Ness et al., 2005; Zeltzer et al., 2008) in comparison to both sibling controls and survivors of other cancers. Additionally, survivors of HL frequently endorse pain sensations in various bodily regions including the head and chest (Adams et al., 2004; Lu et al., 2011).

Fatigue and reduced sleep quality are frequent complaints of cancer survivors across ages (Bower et al., 2000; Fosså, Dahl, & Loge, 2003; Meeske, Siegel, Globe, Mack, & Bernstein, 2005) with extant research suggesting both syndromes negatively impact survivors' health related quality of life (HRQoL) (Langeveld, Stam, Grootenhuis, & Last, 2002). In particular, fatigued survivors have been found to report lower levels of general, physical, and psychosocial functioning compared to non-fatigued survivors, who report levels of HRQoL similar to those of healthy controls (Hjermstad et al., 2006; Jóhannsdóttir et al., 2012; Meeske, Patel, Palmer, Nelson, & Parow, 2007). As such, understanding the factors that contribute to pediatric cancer survivors' levels of fatigue and sleepiness is of importance.

Within the population at large, pain, emotional distress, and physical functioning have been found to influence the development and maintenance of fatigue and poor sleep quality (Lavigne, Nashed, Manzini, & Carra, 2011; Manu et al., 1989; O'Sullivan & McCarthy, 2007) with similar relationships found in survivor cohorts as well. Meeske et al., (2007)

observed reduced sleep quality to be associated with increased risk for poor physical functioning in survivors with a variety of childhood cancers, and results of Mulrooney et al., (2008) indicate that depression is associated with increased risk for both fatigue and sleepiness. In addition, childhood cancer survivors' exposure to intensive treatments is a risk factor for late effects. Survivors treated with radiation only or radiation plus chemotherapy are at an increased risk for depressive symptoms (Zeltzer, et al., 2008) and physical functioning limitations (Hudson et al., 2003; Ness, et al., 2005) compared to survivors treated with surgery only.

The mechanism by which pain, emotional distress, and physical functioning limitations influence fatigue, sleepiness, and reduced sleep quality in survivors of childhood HL is largely unknown. We propose to investigate associations between these factors in adult survivors of childhood HL. Results of this investigation will offer researchers and care providers information regarding areas of potential points of intervention to reduce fatigue and improve sleep quality and by extension improve HRQOL.

#### 4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

##### 4.2 Primary Aims:

- 4.2.1 To investigate concurrent associations between levels of pain, emotional distress, and physical functioning and fatigue, sleepiness, and sleep quality in survivors of childhood Hodgkin Lymphoma after controlling for relevant demographic characteristics.
- 4.2.2 To determine whether treatment characteristics mediate or moderate the relationships between pain, emotional distress, and physical functioning on fatigue, sleepiness, and sleep quality in survivors of childhood Hodgkin Lymphoma after controlling for relevant demographics using the sequence of steps outlined by (Baron & Kenny, 1986).

##### 4.3 Secondary Aims:

- 4.3.1 To investigate the degree to which pain, emotional distress, and physical functioning predict group membership for survivors who score in the clinical range on fatigue, sleepiness, and poor sleep quality.

##### 4.5 Primary Hypothesis:

- 4.5.1 Pain and emotional distress will be positively associated with both fatigue and sleepiness.
- 4.5.2 Physical functioning will be negatively associated with both fatigue and sleepiness.
- 4.5.3 Pain and emotional distress will be negatively associated with sleep quality.
- 4.5.4 Physical functioning will be positively associated with sleep quality.
- 4.5.5 Treatment characteristics will moderate the influence of pain, emotional distress, and physical functioning on sleep outcomes (fatigue, sleepiness, and sleep quality).

#### 4.6 Secondary Hypothesis:

- 4.6.1 Higher levels of pain and emotional distress and decreased physical functioning will significantly predict group membership in significant fatigue, sleepiness, and poor sleep quality.

### 5. ANALYSIS FRAMEWORK:

#### 5.1.1. Population:

Childhood Hodgkin Lymphoma survivors who completed the Sleep Survey in 2002 will be used to address the study aims.

Number of survivors who completed the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and Functional Assessment of Chronic Illness Therapy-Fatigue = 995.

#### 5.1.2. Exclusion criteria:

- Not completing the Follow-up 2003 survey
- Paralysis
- Mental Retardation

### 5.2. Outcomes of interest:

The primary outcomes of interest (dependent variables): 1) fatigue, 2) sleepiness, and 3) sleep quality as measured by the Sleep Survey.

#### 5.2.1. **Fatigue** will be measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT fatigue) (13 items). The FACIT fatigue ranges from 0-52

- In the last seven days how often would you describe yourself as...
  - a. I feel fatigued
  - b. I feel weak all over
  - c. I feel listless (“washed out”)
  - d. I feel tired
  - e. I have trouble stating things because I am tired
  - f. I have trouble finishing things because I am tired
  - g. I have energy
  - h. I am able to do my usual activities
  - i. I need to sleep during the day
  - j. I am too tired to eat
  - k. I need help doing my usual activities
  - l. I am frustrated by being too tired to do the things I want to do
  - m. I have to limit my social activity because I am tired
- With the following response options
  - Not at all
  - A little bit
  - Somewhat

- Quite a bit
- Very much

5.2.2. **Sleepiness** will be measured using the Epworth Sleepiness Scale (ESS) (8 items). The ESS ranges from 0-24.

- How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?
  - a. Sitting and reading
  - b. Watching TV
  - c. Sitting, inactive in a public place, for example, a theater or a meeting
  - d. As a passenger in a car for an hour without a break
  - e. Lying down to rest in the afternoon when circumstances permit
  - f. Sitting and talking to someone
  - g. Sitting quietly after a lunch without alcohol
  - h. In a car, while stopped for a few minutes in traffic
- With the following response options
  - Would never doze
  - Slight chance of dozing
  - Moderate chance of dozing
  - High chance of dozing

5.2.3. **Sleep quality** will be measured using The Pittsburgh Sleep Quality Index (PSQI) (items 5 to 13). The PSQI ranges from 0-21.

- During the past month, how often have you had trouble sleeping because you...
  - a. Cannot get to sleep within 30 minutes
  - b. Wake up in the middle of the night or early morning
  - c. Have to get up to use the bathroom
  - d. Cannot breathe comfortably
  - e. Cough or snore loudly
  - f. Feel too cold
  - g. Feel too hot
  - h. Had bad dreams
  - i. Have pain
- With the following response options
  - Not during the past month
  - Less than once a week
  - Once or twice a week
  - Three or more times a week
- During the past month, how would you rate your sleep quality overall?
  - Very good
  - Fairly good
  - Fairly bad
  - Very bad

- During the past month...
  - a. How often have you taken medicine (prescribed or “over the counter”) to help you sleep?
  - b. How often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
- With the following response options
  - Not during the past month
  - Less than once a week
  - Once or twice a week
  - Three or more times a week
- During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
  - No problem at all
  - Only a very slight problem
  - Somewhat of a problem
  - A very big problem
- Do you use anything to help you get to sleep (for example, melatonin, yoga, meditation)?
  - Yes
  - No
- Do you use anything to help you stay awake (for example, coffee, other caffeinated drinks, exercise, pills?)
  - Yes
  - No
- On a typical day, how much of the following caffeinated beverages do you drink?
  - Cups (8 oz) of coffee
  - Cups of tea
  - Cans (12 oz) of soda
  - Bottles (20 oz) of soda
- Do you have a bed partner or roommate?
  - No bed partner or roommate
  - Partner/ roommate in other room
  - Partner in same room, but not same bed
  - Partner in same bed
- If you have a roommate or bed partner, ask **him or her** how often in the past month you have had...
  - a. Loud snoring
  - b. Long pauses between breaths while asleep

- c. Legs twitching or jerking while you sleep
- d. Episodes of disorientation or confusion during sleep
- e. Other restlessness while you sleep
- With the following response options
  - Not during the past month
  - Less than once a week
  - Once or twice a week
  - Three or more times a week

Secondary outcomes include prediction of group membership. For this, we will analyze fatigue, sleepiness, and sleep quality as dichotomous variables based on whether the survivor exceeds published cutoffs on each of the scales. We will use a FACIT fatigue score > 30 (Mallinson, Cella, Cashy, & Holzner, 2006), an ESS score > 10 (Johns, 1991), and a PSQI score > 5 (Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989).

### 5.3. Primary Predictors:

- Emotional Distress will be measured by the Brief Symptom Inventory 18 (BSI-18; CCSS Long-term Follow-up Study 2003 survey, items G.1 to G.18). The BSI-18 is composed of three subscales<sup>21</sup> including depression (items G 4, 6-8, 13, 18), somatization (items G 2-3, 10-12, 14), and anxiety (items G 1, 5, 9, 15-17). The scale also provides a Global Severity Index. Emotional distress will be characterized by the total and factor scores of the BSI-18.
- Pain will be measured by three items (Short Form Health Survey; SF-36; CCSS Long-term Follow-up Study 2003 survey, bodily pain items E. 21, E.22 & CCSS Long-term Follow-up Study 2003 survey, item G.19). Pain will be characterized by summing survivors' responses on the three items to create a total score.
  - How much body pain have you had during the past 4 weeks?  
With the following response options:
    - None
    - Very mild
    - Mild
    - Moderate
    - Severe
  - During the past 4 weeks, how much did body pain interfere with your normal work (including both work outside the home and house work)? With the following response options:
    - Not at all
    - A little bit
    - Moderately
    - Quite a bit
    - Extremely

- Do you currently have pain as a result of your cancer or similar illness, or its treatment? With the following response options:
      - No pain
      - Small amount of pain
      - Medium amount of pain
      - A lot of pain
      - Very bad, excruciating pain
- Physical Functioning will be measured by the Short Form Health Survey 36 (SF-36; CCSS Long-term Follow-up Study 2003 survey, items E.3 to E.12). Physical Functioning will be characterized by a total score summing survivors' responses to each item to create a total score.
  - The following items are about activities you might do during a typical day. **Does your physical health now limit you** in these activities? If so, how much?
    - **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports
    - **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
    - Lifting or carrying groceries
    - Climbing **several** flights of stairs
    - Climbing **one** flight of stairs
    - Bending, kneeling, or stooping
    - Walking **more than a mile**
    - Walking several blocks
    - Walking **one block**
    - Bathing or dressing yourself
 With the following response options:
    - Yes, limited a lot
    - Yes, limited a little
    - No, not limited at all
- Chemotherapy Variables (dichotomous: yes/no)
  - Anthracycline
  - Alkylating Agents
  - Bleomycin
  - Vinca Alkaloids & Heavy Metal
  - None
- Chest Radiation
  - < 30 Gy
  - ≥ 30 Gy

#### 5.4. Covariates:

- Sex (categorical)
  - Male
  - Female
- Age at diagnosis, years (continuous, but will be examined as the groups below)
  - 7-10
  - 11-15
  - 16-20
- Age at Sleep Survey, years (continuous, but will be examined as the groups below)
  - 18-24
  - 25-29
  - 30-34
  - $\geq 35$
- Education (categorical)
  - < High School
  - High School & Some College
  - College/ Postgraduate
- Household Income (continuous, but will be examined as the groups below)
  - < \$19, 999
  - \$20,000 - \$39, 999
  - \$40,000 - \$59, 999
  - > \$60,000
- Employed in last year (dichotomous)
  - Yes
  - No

#### 5.5 Statistical Modeling

- 5.5.1. Frequency distributions will be used to categorize relevant outcome variables, predictors, and covariates according to reasonable groupings and consistent with previous CCSS manuscripts.
- 5.5.2. Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percentiles will be calculated for the primary outcomes of interest (fatigue, sleepiness, and sleep quality) as well as for the primary predictors (pain, emotional distress, physical functioning, and treatment characteristics) and all covariates (Table 1).
- 5.5.3. To address the primary aims, the analysis procedure outlined below will be conducted three times for each dichotomous outcome variable (clinically elevated versus non-clinically elevated levels of fatigue, sleepiness, and sleep quality). To control for all relevant demographic variables, they will be entered in the first step of each logistic regression analysis. First, the predictive ability of pain, emotional distress (depression, anxiety, somatization), and physical functioning on the dichotomous sleep outcomes (fatigue, sleepiness, and sleep quality) will be tested. A second logistic regression will examine the relation between pain, emotional distress, and physical functioning and the proposed moderator of treatment



characteristics. Third, logistic regressions with fatigue, sleepiness, and sleep quality predicted by pain, emotional distress, and physical functioning and treatment characteristics simultaneously will be conducted.

- 5.5.4. To address the secondary aim, using elevated scores of pain, emotional distress, and physical functioning to predict survivors with clinical levels of fatigue, sleepiness, and poor sleep quality we will use logistic regression. A median split analysis will be used to divide the sample into survivors who are high or low on pain. Cutoffs published with the measures of emotional distress, physical functioning, sleep, and fatigue will be used to categorize participants as clinically elevated.

Table 1. Survivor Descriptive Statistics\*

Variable	Survivors	
	N	%
Sex Male Female		
Age at 2003 Sleep Survey 18-24 25-29 30-34 ≥ 35		
Radiation Therapy Chest		
Chemotherapy Anthracycline Alkylating Agents Bleomycin Vinca Alkaloids & Heavy Metals None		
Age at diagnosis 7-10 11-15 16-20		
Employment within the last year Yes No		
Education < High School High School & Some College College/Postgraduate		
Household Income < \$19,999 \$20,000-\$39,999 \$40,000-\$59,999 > \$60,000		
Cancer related pain None Small amount Medium amount Very bad, excruciating		

Table 2.  
*Correlations Between Pain, Emotional Distress, and Physical Functioning with Fatigue and Sleep Disturbance Variables*

	<i>M</i>	<i>SD</i>	1	2	3	4	5	6
1. Pain			–					
2. Emotional Distress				–				
3. Physical Functioning					–			
4. Fatigue						–		
5. Sleepiness							–	
6. Sleep Quality								–

Table 3.  
*Summary of Hierarchical Regression Analysis Predicting Fatigue or Sleep Disturbances*

	<i>B</i>	<i>SE B</i>	$\beta$	$R^2$	$\Delta R^2$
<b>Fatigue</b>					
Step 1					
Demographic Variables					
Step 2					
Pain					
Emotional distress					
Physical functioning					
<b>Sleepiness</b>					
Step 1					
Demographic Variables					
Step 2					
Pain					
Emotional distress					
Physical functioning					
<b>Sleep quality</b>					
Step 1					
Demographic Variables					
Step 2					
Pain					
Emotional distress					
Physical functioning					

Table 4.  
*Summary of Hierarchical Regression Analysis Predicting Fatigue or Sleep Disturbances with Treatment Characteristics*

	B	SE B	$\beta$	$R^2$	$\Delta R^2$
<b>Fatigue</b>					
Step 1					
Demographic Variables					
Step 2					
Treatment Characteristics					
Step 3					
Pain					
Emotional distress					
Physical functioning					
<b>Sleepiness</b>					
Step 1					
Demographic Variables					
Step 2					
Treatment Characteristics					
Step 3					
Pain					
Emotional distress					
Physical functioning					
<b>Sleep quality</b>					
Step 1					
Demographic Variables					
Step 2					
Treatment Characteristics					
Step 3					
Pain					
Emotional distress					
Physical functioning					

## References

- Adams, M. J., Lipsitz, S. R., Colan, S. D., Tarbell, N. J., Treves, S. T., Diller, L., . . . Lipshultz, S. E. (2004). Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *Journal of Clinical Oncology*, *22*(15), 3139-3148. doi: 10.1200/jco.2004.09.109
- Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychology research: Conceptual, strategies, and statistical considerations. *Journal of Personality and Social Psychology*, *51*(6), 1173-1182.
- Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology*, *18*(4), 743.
- Buyse, D. J., Reynolds Iii, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193-213. doi: [http://dx.doi.org/10.1016/0165-1781\(89\)90047-4](http://dx.doi.org/10.1016/0165-1781(89)90047-4)
- Fosså, S. D., Dahl, A. A., & Loge, J. H. (2003). Fatigue, anxiety, and depression in long-term survivors of testicular cancer. *Journal of Clinical Oncology*, *21*(7), 1249-1254. doi: 10.1200/jco.2003.08.163
- Hjermstad, M. J., Oldervoll, L., Fosså, S. D., Holte, H., Jacobsen, A. B., & Loge, J. H. (2006). Quality of life in long-term Hodgkin's disease survivors with chronic fatigue. *European journal of cancer (Oxford, England : 1990)*, *42*(3), 327-333.
- Hudson, M. M., Mertens, A. C., Yasui, Y., Hobbie, W., Chen, H., Gurney, J. G., . . . Oeffinger, K. C. (2003). Health status of adult long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *JAMA: The Journal of the American Medical Association*, *290*(12), 1583-1592. doi: 10.1001/jama.290.12.1583
- Jóhannsdóttir, I. M. R., Hjermstad, M. J., Moum, T., Wesenberg, F., Hjorth, L., Schrøder, H., . . . Loge, J. H. (2012). Increased prevalence of chronic fatigue among survivors of childhood cancers: A population-based study. *Pediatric Blood & Cancer*, *58*(3), 415-420. doi: 10.1002/psc.23111
- Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, *14*(6), 540-545.
- Langeveld, N. L., Stam, H. S., Grootenhuis, M. G., & Last, B. L. (2002). Quality of life in young adult survivors of childhood cancer. *Supportive Care in Cancer*, *10*(8), 579-600. doi: 10.1007/s00520-002-0388-6
- Lavigne, G. J., Nashed, A., Manzini, C., & Carra, M. C. (2011). Does sleep differ among patients with common musculoskeletal pain disorders? *Current Rheumatology Reports*, *13*(6), 535-542.
- Lu, Q., Krull, K. R., Leisenring, W., Owen, J. E., Kawashima, T., Tsao, J. C. I., . . . Zeltzer, L. K. (2011). Pain in long-term adult survivors of childhood cancers and their siblings: A report from the Childhood Cancer Survivor Study. *PAIN*, *152*(11), 2616-2624.
- Mallinson, T., Cella, D., Cashy, J., & Holzner, B. (2006). Giving meaning to measure: Linking self-reported fatigue and function to performance of everyday activities. *Journal of Pain and Symptom Management*, *31*(3), 229-241. doi: <http://dx.doi.org/10.1016/j.jpainsymman.2005.07.012>

- Manu, P., Matthews, D. A., Lane, T. J., Tennen, H., Hesselbrock, V., Mendola, R., & Affleck, G. (1989). Depression among patients with a chief complaint of chronic fatigue. *Journal of Affective Disorders, 17*(2), 165-172.
- Meeske, K. A., Patel, S. K., Palmer, S. N., Nelson, M. B., & Parow, A. M. (2007). Factors associated with health-related quality of life in pediatric cancer survivors. *Pediatric Blood & Cancer, 49*(3), 298-305. doi: 10.1002/psc.20923
- Meeske, K. A., Siegel, S. E., Globe, D. R., Mack, W. J., & Bernstein, L. (2005). Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. *Journal of Clinical Oncology, 23*(24), 5501-5510. doi: 10.1200/jco.2005.03.210
- Mulrooney, D. A., Ness, K. K., Neglia, J. P., Whitton, J. A., Green, D. M., Zeltzer, L. K., . . . Mertens, A. C. (2008). Fatigue and sleep disturbance in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *SLEEP, 31*(2), 271-281.
- Ness, K. K., Mertens, A. C., Hudson, M. M., Wall, M. M., Leisenring, W. M., Oeffinger, K. C., . . . Gurney, J. G. (2005). Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Annals of Internal Medicine, 143*(9), 639-647.
- O'Sullivan, D., & McCarthy, G. (2007). An exploration of the relationship between fatigue and physical functioning in patients with end stage renal disease receiving haemodialysis. *Journal of Clinical Nursing, 16*(11c), 276-284. doi: 10.1111/j.1365-2702.2007.01965.x
- Zeltzer, L. K., Lu, Q., Leisenring, W., Tsao, J. C. I., Recklitis, C., Armstrong, G., . . . Ness, K. K. (2008). Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: A report from the Childhood Cancer Survivor Study. *Cancer Epidemiology Biomarkers & Prevention, 17*(2), 435-446. doi: 10.1158/1055-9965.epi-07-2541