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## Childhood Cancer Survivor Study (CCSS) Analysis Concept Proposal

### 1. Title: Epidemiology and Correlates of Posttraumatic Responses to Cancer Treatment in Young Adult Childhood Cancer Survivors

### 2. Working Group and Investigators:

Margaret L. Stuber, M.D.	<a href="mailto:mstuber@mednet.ucla.edu">mstuber@mednet.ucla.edu</a>	310-825-5213
Brad Zebrack, Ph.D.	<a href="mailto:zebrack@usc.edu">zebrack@usc.edu</a>	213-821-3111
Sebastian Uijtdehaage, PhD	<a href="mailto:bas@mednet.ucla.edu">bas@mednet.ucla.edu</a>	310-794-9009
Gretchen Guiton, PhD	<a href="mailto:gguiton@mednet.ucla.edu">gguiton@mednet.ucla.edu</a>	310-267-2798
Ann Mertens, Ph.D.	<a href="mailto:mertens@epi.umn.edu">mertens@epi.umn.edu</a>	612-626-9689
Les Robison, Ph.D.	<a href="mailto:Robison@epi.umn.edu">Robison@epi.umn.edu</a>	612-825-0731
Lonnie Zeltzer, M.D.	<a href="mailto:Lzeltzer@mednet.ucla.edu">Lzeltzer@mednet.ucla.edu</a>	310-825-0731

### 3. Background and Rationale

Psychological distress in childhood cancer survivors in response to cancer treatment has been the topic of study for an increasing number of investigators over the past decade. Several studies of children and adolescents have found a small but possibly clinically significant number of cancer survivors who report symptoms of posttraumatic stress. These symptoms include

1. intrusion of unwanted memories, such as nightmares or flashbacks,
2. avoidance of reminders of the events, such as doctors or hospitals, and
3. increased startle response to sudden noise, and constant monitoring for danger.

In the largest study of posttraumatic stress symptoms in pediatric cancer survivors, 309 childhood cancer survivors, 8 to 20 years old and an average of almost six years after concluding cancer treatment, were compared to 219 healthy children. Almost 20% of the cancer survivors reported symptoms of posttraumatic stress. However, the rates of symptoms severe enough to meet the formal psychiatric criteria for a diagnosis of posttraumatic stress disorder (PTSD) were not statistically different in the cancer and comparison groups (Kazak, et. al. 1997).

Very different results emerged in a study of young adults who were survivors of childhood cancer. Of 78 young adult (age 18 to 37) survivors of childhood cancer, approximately 20% of the young adult survivors reported symptoms meeting diagnostic criteria for PTSD (Hobbie, et al, 2000). These young adult survivors who met criteria for PTSD appeared to have a number of differences from those who did not. They

1. were less likely to be married (none, compared to 23% of the non-PTSD group),
2. reported more psychological distress, and
3. reported poorer quality of life across all domains.

[to incorporate # 04-06, 04-07, 04-08]

The greatest differences between those who met diagnostic criteria for PTSD and those who did not meet criteria for PTSD were in social functioning, emotional well-being, and role limitations due to emotional health and pain. Survivors who did not meet criteria for PTSD (even though many of them reported some posttraumatic stress symptoms) as a group did not differ from population norms in social functioning, emotional well-being, and role limitations due to emotional health and pain (Meeske, et al, 2001).

Not all of the emotional responses to pediatric cancer reported by survivors are negative, however. Posttraumatic Growth, defined as the experience of finding meaning in a traumatic experience, is also reported by pediatric cancer survivors. In a study of quality of life in 176 childhood cancer survivors (age 16-28), survivors attributed experiences of happiness, feeling useful, life satisfaction and ability to cope as a result of having had cancer. This was not that they were saying that they were happier than before the cancer, but that they felt the cancer experience was responsible for positive changes in their perspective on life. The results of this study suggested that survivors who reported feeling a sense of purpose in life and perceiving positive changes as a result of cancer were more likely to report a positive quality of life (Zebrack & Chesler, 2002).

There have not been previous studies looking at the relationship between posttraumatic stress symptoms and posttraumatic growth in childhood cancer survivors. In adults it appears that an experience which is seen as life-threatening is the common denominator in posttraumatic stress and posttraumatic growth. A recent study compared self reports of depression, well-being, and posttraumatic growth from 70 breast cancer survivors with those of 70 age- and education-matched healthy comparison women. The two groups did not differ in depression or well-being. However, the survivor group showed a pattern of greater self-reports of posttraumatic growth, particularly regarding relating to others, appreciation of life, and spiritual change. Posttraumatic growth was unrelated to distress or well-being but was positively associated with perceived life-threat, income, time since diagnosis, and previous discussions about breast cancer (Cordova et al, 2001).

There are no currently published studies on posttraumatic growth in siblings of pediatric cancer survivors. There have been some initial reports that siblings of childhood cancer survivors do report an elevated level of symptoms of posttraumatic stress (Kazak, personal communication, 2004).

These findings indicate a need for a larger, more detailed examination of the prevalence, predictors and correlates of posttraumatic stress symptoms and posttraumatic growth in young adults who are childhood cancer survivors and in their siblings. Such information would allow clinicians to know if we should be concerned about individual symptoms or clusters of symptoms of posttraumatic stress, and if there are ways to encourage posttraumatic growth. For researchers, there is interest in understanding whether the current criteria for a diagnosis of posttraumatic stress disorder are useful in differentiating those with functional problems (a dichotomous or categorical approach), or if it would be more useful to simply evaluate the number and severity of symptoms (a continuous approach). These results would inform the committee now developing the new diagnostic criteria for the American Psychiatric Association.

## Specific Aims

1. To determine the
  - a. prevalence and distribution of symptoms of posttraumatic stress and
  - b. number reporting symptoms meeting criteria for PTSDin young adults who are childhood cancer survivors, and compare them to their siblings and results of previous smaller studies.
  
2. To examine the relationships between self-reported current posttraumatic stress symptoms, hypothesized cancer-related predictors (initial diagnosis, age at diagnosis, time since diagnosis), and demographic predictors (age, gender, ethnicity, total income and education) in young adults who are childhood cancer survivors.
  
3. To examine the correlation of categorical diagnosis of PTSD with
  - a. functional status (marital status, work status, years completed in school, general health status),
  - b. self-reported quality of life (as reported on the Short Form-36), and
  - c. emotional functioning (as reported on the Brief Symptom Inventory-18 at two time points).
  
4. To compare the relative strengths of the relationships of
  - a. categorical diagnosis of PTSD,
  - b. specific posttraumatic stress symptom clusters, and
  - c. continuous measures of PTSD symptom number and severity, with
    - 1) functional status (marital status, work status, years completed in school, general health status), and
    - 2) quality of life (as measured on the SF-36).
  
5. To determine the prevalence and distribution of reports of posttraumatic growth in young adults who are childhood cancer survivors, and compare them to those of their siblings.
  
6. To examine the relationships between self-reported posttraumatic growth and
  - a. hypothesized cancer-related predictors (initial diagnosis, age at diagnosis, intensity of treatment, time since diagnosis) and
  - b. demographic predictors (gender, ethnicity, current age) in young adults who are childhood cancer survivors.
  
7. To examine the relationship between posttraumatic growth and
  - a. functional status (marital status, work status, years completed in school, general health status),
  - b. self-reported quality of life (as reported on the Short Form-36), and
  - c. emotional functioning (as reported on the Brief Symptom Inventory-18 at two time points).

8. To examine the relationship between self-reported posttraumatic growth and self-reported current posttraumatic stress symptoms.

#### 4. Analysis Framework

##### a. Subject population

Subjects will be childhood cancer survivors participating in the Childhood Cancer Survivor Study (CCSS). This group includes children and adolescents (<21 years of age at time of diagnosis) diagnosed with cancer between 1970 and 1986 at 25 oncology centers in the United States and Canada. It is estimated that between 6,000 and 10,000 subjects will be included.

##### b. Comparison group

A comparison group of 500 randomly selected siblings of the childhood cancer survivor participants will be included for this study.

##### c. Outcomes of interest

###### Functional status

Education status, employment, and marital status from the most recent data from the subjects will be used as individual and summed variables in analysis.

###### Quality of life

The Short Form-36 on the current survey measures 8 health status domains of quality of life (including general health, mental health, functional status, activity limitations, cancer-related pain, and cancer-related anxiety/fears). A total score and the 8 domain scores will be used.

###### Posttraumatic Growth

The Posttraumatic Growth Inventory (Tedeschi & Calhoun, 1996) will be used to assess posttraumatic growth. This 21-item scale includes factors of New Possibilities, Relating to Others, Personal Strength, Spiritual Change, and Appreciation of Life. A total score will be used.

###### Posttraumatic stress symptoms

The number and severity of each of the 17 DSM IV specific posttraumatic stress symptoms will be assessed, using the Foa PTSD Self-Report measure, included in the current survey. Two distinct outcome variables will be generated

- a. total score of individual symptoms, aggregated across number and intensity,
- b. presence or absence of the constellation of symptoms meeting criteria for a diagnosis of PTSD.

Each individual item and the three clusters (Re-experiencing, Avoidance and Arousal) will also be evaluated, for descriptive purposes.

#### **d. Definitions of independent variables**

##### **Cancer-related predictors**

Initial diagnosis, age at diagnosis, and time since diagnosis, will be evaluated independently for their impact on the dependent variables.

##### **Demographic predictors**

Gender, current age, and ethnicity will be evaluated for their independent contribution.

##### **Data analysis plan**

After screening data for missing data or invalid codes, data will be scored according to standard protocols. Frequencies of responses for gender, ethnicity, diagnosis, and age at initial diagnosis will be examined to evaluate the sample size in each category and in combinations. Categories will be collapsed as needed for additional analyses. Descriptive statistics will be computed for all groups of interest. Frequencies of each area of posttraumatic growth will be calculated.

For each research question, a corresponding analysis plan is described below:

1. Chi-square statistics will be calculated to compare the proportion of PTSD in young adults who are childhood cancer survivors with the proportion of their siblings and in previous studies of childhood cancer survivors with PTSD. For each PTSD symptom, the likelihood ratio will be calculated for young adults who are cancer survivors.
2. In young adults who are survivors of childhood cancer, logistic regression analysis will be conducted to examine the relationships between demographic predictors (current age, gender, and ethnicity), cancer-related predictors (initial diagnosis, age at diagnosis, time since diagnosis) and PTSD status diagnosed using current DSM IV guidelines.
3. The relationship between PTSD status as a dichotomous category, based on current DSM diagnostic criteria, and functional status (marital status, work status, years completed in school, general health status), self-reported quality of life, and emotional functioning will be estimated using appropriate measures of association (e.g., phi coefficient for PTSD and marital status, and eta for PTSD and quality of life).
4. PTSD will be determined using two methods in addition to the categorical diagnosis in DSM IV. First, posttraumatic stress symptom responses will be subjected to cluster analysis to classify individuals into groups. Second a PTSD measure will be calculated by summing posttraumatic symptoms weighted by their severity into a single continuous variable. Relationships between these two new measures of PTSD and functional status, emotional functioning, and quality of life as measured on the SF-36 will be investigated using measures of association appropriate to the nature of the variables being compared. The strength of the resulting relationships will be compared for the three methods of diagnosing PTSD.

### Aims 5 through 8, on Posttraumatic Growth

Statistical tests (chi-square, t-test, MANOVA) will be reported to evaluate group differences in incidence of effects. The primary groups of interest will be a comparison of posttraumatic growth in the siblings to the cancer survivors. Additional group comparisons will be by gender and by developmental level at the time of diagnosis and treatment (early childhood, school age, adolescents).

A sequential multiple regression analysis will be used to determine the contribution of the independent variables as potential predictors of posttraumatic stress and posttraumatic growth. These include demographic predictors and cancer-related predictors.

The relationships between posttraumatic stress, posttraumatic growth and quality of life, functional status and health will be analyzed using correlations for variables measured on a continuous scale.

## **5. References**

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