Childhood Cancer Survivor Study
Study Proposal: Male Health Questionnaire (MHQ) and CED
February 2015

1. **STUDY TITLE:** Cyclophosphamide Equivalent Dosing and Male Health Late Effects – Infertility, Erectile Dysfunction, Sexual Function and Testosterone Replacement Therapy in Survivors diagnosed from 1970-1986: A report from the Childhood Cancer Survivor Study

2. **WORKING GROUP AND INVESTIGATORS:** This proposed publication will be within the Chronic Disease Working Group. Proposed investigators will include:

Lillian Meacham	Lillian_meacham@oz.ped.emory.edu
Daniel Green	Daniel.Green@stjude.org
Wendy Leisenring	wleisenr@fhcrc.org
Kristy Seidel	kseidel@fhcrc.org
Jordan Gilleland	jgillel@emory.edu
Karen Wasilewski-Masker	karen.wasilewski@choa.org
Chad Ritenour	Chad.ritenour@emoryhealthcare.org
Marilyn Stovall	mstovall@mdanderson.org
Greg Armstrong	Greg.Armstrong@stjude.org
Chuck Sklar	sklarc@mskcc.org
Les Robison	Les.robison@stjude.org
Ann Mertens	Ann.mertens@choa.org

3. **BACKGROUND AND RATIONALE**

As the percentage of childhood cancer patients who are long term survivors increases, a focus of post cancer therapy care is on improving awareness in patients of the need for life-long survivorship care [1]. Many patients are eager to understand what the future holds for them, anxious to learn what specific late effects for which they are at risk and interested in obtaining a surveillance plan for early recognition and treatment for late effects of their cancer therapy. Particularly sensitive issues are future reproductive potential, normalcy of sexual function and adequacy of sex hormone production [2-4] [5, 6]. It is important to be able to stratify the level of risk for male health late effects when counseling patients in clinic. Thresholds for doses of radiation that effect spermatogenesis and androgen production have been established and these doses have been incorporated into the Children's Oncology Group Long-Term Follow-Up Guidelines (COG LTFUG) [7, 8]. This information is used regularly in clinics to counsel patients about their level of risk for male health late effects. Levels of risk based on chemotherapy exposure have been quantified by alkylating agent dose (AAD) score in CCSS papers prior to 2014. Alkylating agent dose score was derived by analysis of each alkylator's dose distribution within a population and the establishment of tertiles. For each alkylator a patient receives they are assigned a score of 1,2 or 3 based on the tertile of their dose and the tertile scores were then summed and the value was the AAD for that patient. Use of AAD scores is very cohort and era specific and importantly, not very useful when counseling patients in survivor clinic. In 2014, the CCSS developed a method for converting the cumulative doses of various alkylating agents to a cyclophosphamide equivalent dose (CED) [9]. The stratification of risk based on CED will be important for key late effects specifically infertility, adult testosterone replacement therapy, erectile dysfunction and sexual dysfunction.

In the 2007 CCSS Follow-Up Questionnaire, male survivors and siblings were asked if they would complete an additional questionnaire aimed to better understand fertility and sexual

function and those that agreed were sent the Male Health Questionnaire (MHQ). The MHQ would be used to assess key areas of male health including: infertility, perceptions of individual risk for infertility, erectile dysfunction and sexual dysfunction and adult testosterone replacement therapy. All of these men's health topics discussed with at-risk male patients in long-term follow-up. Analyses have been completed and published in regard to infertility as assessed in the MHQ and its association with AAD. In this study we propose to analyze the infertility data based on CEDs. Analysis of associations of CEDs and erectile dysfunction based on the international index of erectile dysfunction (IIEF) which was embedded in the CCSS- MHQ have been completed [10, 11]. Analysis of CEDs and sexual dysfunction as measured by the sexual function questionnaire (SFQ) are planned. Lastly, analysis of the final men's health late effect, the frequency of testosterone replacement therapy (TRT) in adults, and demographic and treatment variables associated with TRT will be done as a part of this concept. CEDs will be used for the analysis of treatment associated adult TRT..

4. Aims:

Testosterone Replacement Therapy (TRT)

Aim 1: To determine the prevalence of TRT based on reported testosterone therapy in the MHQ in adult male survivors of childhood or adolescent cancer in comparison to sibling controls

Aim 2: To determine associations of demographic factors and treatment factors including CED with TRT in adult cancer survivors

MHQ CED

Aim 3: Quantify the risk for each of the four male health late effects according to level of CED exposure:

i. Infertility
ii. Testosterone Replacement Therapy (TRT)
iii. Erectile dysfunction
iv. Sexual dysfunction

5. Data Analysis

Aim 1: Prevalence of Testosterone Replacement Therapy (TRT)

Population:

- Inclusion
  - All male survivors and siblings who responded to the MHQ
- Exclusion
  - Recurrence
  - SMN

Primary outcome variable:

- Yes to B6 (*Are you currently on testosterone*?)
  or
- Yes to B4 (*Have you ever been treated with testosterone?*) + B9 *(If you took testosterone and it was discontinued, at what age did you stop taking testosterone?)* must be older than 18 years when testosterone was discontinued

Demographic Variables

- Race / Ethnicity (Baseline)
- Age at assessment (date of MHQ – date of birth)
- General Health (MHQ D1)
- Physical activity (N15-21 CDC recommendations as used in C Ritenour analysis LTFU 2007)
- Education level (A3 – LTFU 2007)

- Insurance coverage (B9 – LTFU 2007)
- Marital status (M2 – LTFU 2007)
- Sexual Activity in lifetime (same as Chad's ED analysis for the MHQ)
- Sexual activity in last year (same as Chad's ED analysis for the MHQ)
- Depression (MHQ B1)
- Other major psychiatric illness (MHQ B1)

Treatment variables:

- Age at cancer diagnosis (MRAF)
- Cancer diagnosis (MRAF)
- Radiation to the testes (same as ED)
    - None
    - 1-399
    - 400-999
    - 1000-1999 cGy
    - ≥2000 cGy
- Radiation to the hypothalamus
    - None
    - 1-2999 cGy
    - ≥3000 cGy
- Alkylators
    - CED option 1 (first choice)
        - None
        - 1-3999
        - 4000-7999
        - 8000-11999
        - 12000-15999
        - 16000-19999
        - >20,000
- GU/prostate surgery (MRAF as used by Ritenour)

Statistical Methods Characteristics (demographic and treatment factors listed above) of participants in the MHQ will be compared to those of non-participants and any differences will be evaluated and considered as a source of potential bias.

Prevalence of testosterone treatment will be evaluated for survivors and siblings and compared in univariate using logistic regression models with robust variances to account for intra-family correlation. Adjusted models will also be fit; demographic factors listed above will be considered as confounders and included in the model if their inclusion modifies the comparison between survivors and siblings substantially (>10% change in odds ratio estimate).

Aim 2: demographic and treatment factors associated with Testosterone Replacement Therapy

Population:

- Inclusion
    - All male survivors who responded to the MHQ
- Exclusion
    - Recurrence
    - SMN

Primary outcome variable:

- Yes to B6 (*Are you currently on testosterone*?)
  or

- Yes to B4 (*Have you ever been treated with testosterone?*) + B8 (*At what age did you start testosterone*)> 18 year of age

Explanatory variables:

- Ethnicity (Baseline)
- Age at diagnosis (MRAF)
- Age at assessment (date of MHQ – dob)
- Carry forward factors found to be significant in survivor vs sibling comparison in Aim 1
- Radiation to the testes (same as ED)
  - None
  - 1-399
  - 400-999
  - 1000-1999 cGy
  - ≥2000 cGy
- Radiation to the hypothalamus
  - None
  - 1-2999 cGy
  - ≥3000 cGy
- Alkylators
  - CED option 1 (first choice)
    - None
    - 1-3999
    - 4000-7999
    - 8000-11999
    - 12000-15999
    - 16000-19999
    - >20,000
- Surgery on the GU tract
  - Yes
  - No
- Prostate disease or surgery
  - Yes
  - No

Statistical Methods: Using logistic regression models, among survivors, we will evaluate univariable and multivariable associations between testosterone replacement therapy (TRT) and the demographic and treatment variables listed above, with particular focus on exposure to CED. Particular care will be taken to evaluate correlations between treatment factors to determine whether they should be included in models simultaneously, or in separate adjusted models.

MHQ CED

- Aim 3 CED and Male Health outcomes
  Population:
    - Inclusion
        - All male survivors completing the MHQ based on outcome specific criteria (see primary outcome variables).
    - Exclusion
        - Recurrence
        - SMN

  Primary outcome variable:
    - Infertility (Wasilewski study) respond yes to C6 and C7
    - ED (Ritenour)- IIEF≤ 25
    - SFQ (Gilleland) > 2 SDs below the sibling mean

  Exposure variables:
    - Ethnicity (Baseline)
    - Age at diagnosis (MRAF)
    - Age at assessment (date of MHQ)
    - Alkylators
        - CED
            - None
            - 0-3999
            - 4000-7999
            - 8000-11999
            - 12000-15999
            - 16000-19999
            - ≥20,000
    - Radiation to the testes (same as ED)
        - None
        - 1-399
        - 400-999
        - 1000-1999 cGy
        - ≥2000 cGy
    - Radiation to the hypothalamus
        - None
        - 1-2999 cGy
        - ≥3000 cGy
    - Bleomycin
        - Yes
        - no
    - Platinums (combined)
        - Yes
        - No
    - Surgery
        - GU/pelvic surgery as defined in ED paper
            - Yes
            - no
        - prostate disease surgery as defined in the ED paper
            - yes
            - no

- spinal surgery as defined in the ED paper
  - yes
  - no

Statistical Methods: For each of the following outcomes: Infertility, erectile dysfunction and sexual dysfunction, we will examine CED as a risk factor, with care taken to adjust models for other known risk factors. In logistic regression models, dose response relationships will be examined using categorized CED. We will explore the effects of CED within stratum defined by RT dose, with the caveat that we may not be able to estimate much among those with high dose RT. If stratifying doesn't affect the CED associations, then we can revert to unstratified analyses.
We will report odds ratios (and 95% confidence intervals). The option to report relative risk ratios (estimated via models utilizing a log link function) will also be considered if any of the outcomes examined in this aim have a prevalence above 10% among survivors. In addition, we will plot predicted prevalence of the outcomes as a function of CED to illustrate both the magnitude of risk and the shape of the dose response curve. Initial categorization of CED is proposed above, but depending on the frequency of the outcome variable we may need to collapse some categories, or choose different cut points. The analysis of CED as a risk factor for testosterone replacement therapy is covered under Aim 2 and those results will be incorporated into the CED male health risks manuscript along with the Aim 3 results.

Table 1: Comparison of Respondents vs Non Respondents to the MHQ

Characteristic	**Survivors** MHQ	**Survivor Non Respondents**	p	Siblings MHQ	Sibling Non respondents	p
	Number (%)	Number (%)		N (%)	N (%)	
Race/ethnicity						
White (non-Hispanic)						
Black (non-Hispanic)						
Hispanic						
Other						
Age at MHQ completion						
20-29 years						
30-39 years						
40-49 years						
50+ years						
Mean age in years (SD)						
Primary Cancer Diagnosis						
Leukemia						
CNS tumors						
Hodgkin's Disease						
Non-Hodgkin's lymphoma						
Kidney (Wilm's tumor)						
Neuroblastoma						
Soft tissue sarcoma						
Bone cancer						
Age at Cancer Diagnosis						
0-4 years						
5-9 years						
10-14 years						
15-21 years						
Testicular Radiation dose						
None (0 Gy)						
1-399 cGy						
400-999 cGy						
1000-1999 cGy						
≥2000 cGy						
Average dose of testicular RT mean (SD						
GU/Prostate Surgery						
Yes						
no						
Radiation to the hypothalamus						
None						
1-2999 cGy						
≥3000 cGY						
Cyclophosphamide Equivalent Dose (mg/m^2)						

None						
1-3999						
4000-7999						
8000 -11999						
12,000-15999						
16,000-19,999						
>20,000						
Mean CED (SD)						
General Health (self-reported)						
Excellent						
Very good						
Good						
Fair or Poor						
Marital status						
Married or living as married						
Not married or living as married						
Educational Status						
Did not graduate HS						
Completed high school/GED						
Some College						
Insurance Status						
Yes						
No						

AIM 1 – Prevalence of Testosterone Replacement Therapy (TRT) in adult survivors of childhood cancer

Table 2 Characteristics of Survivors and Siblings with Testosterone Replacement Therapy (TRT)

	Survivors on TRT		Siblings on TRT	
	Total N	Freq. (%)	Total N	Freq. (%)
Race/Ethnicity				
White (non-Hispanic)				
Black (non-Hispanic)				
Hispanic				
Other				
Age at completion of MHQ				
20-29 years				
30-39 years				
40-49 years				
50+ years				
Mean age in years (SD)				
Average age at beginning testosterone Mean (SD)				
Type of Testosterone Therapy				
Injection				
Patch				
Pills				
Other				
Sexual Activity in lifetime				
Yes				
-with opposite gender				
-with same gender				
No				
Sexual Activity in the last year				
Yes				
No				
General Health				
Excellent				
Very good				
Good				
Fair or Poor				
Marital status				
Married or living as married				
Not married or living as married				
Meet CDC guideline for physical activity				
Yes				
No				
Educational Status				
Did not graduate HS				
Completed high school/GED				
Some College				
Insurance Status				
Yes				
No				
Depression				
Yes				

No							
Other major Psychiatric Illness Yes No							

AIM 2 – Determine the association of demographic and treatment factors with Testosterone Replacement Therapy (TRT) in adult survivors of childhood cancer

Table 3 –univariate and multivariate analysis for cancer treatment factors associated with TRT in adult survivors

Characteristics	Survivors on TRT					Multivariate Analysis		
	N (%)	OR	95% CI	p		OR	95% CI	p
Ethnicity								
White (Non-Hispanic) Black (Non-Hispanic) Hispanic Other		Ref				Ref		
Age at Completion of MHQ								
20-29 year 30-39 year 40-49 years 50+ years		ref				ref		
Cancer Diagnosis								
Leukemia CNS tumors Hodgkin"s Disease Non-Hodgkin's Lymphoma Kidney (Wilms) tumor Neuroblasoma Soft Tissue Sarcoma Bone Cancer		ref						
Age at Cancer Diagnosis								
0-4 years 5-9 years 10-14 years 15-21 years		ref				ref		
Testicular RT								
None 1-399 cGy 400-999 cGy 1000-1999 cGy ≥ 2000 cGy		ref				ref		
Cranial Radiation								
None 1-2999 cGy ≥3000 cGy		ref				ref		
Cyclophosphamide Equivalent Dosing (mg/m2)								
None 1-3999 4000-7999 8000-11,999 12,000-15,999 16,000-19,999		ref				ref		

≥20,000								
GU/Prostate surgery								
No yes	ref					ref		

AIM 3 – Quatify the Risk for each of the four male health late effect accoring to the level of CED exposure

Table 4 – Prevalence of each of the Male Health Outcomes in Adult Survivors of Childhood Cancer

	Infertility		TRT*		Erectile dysfunction		Sexual dysfunction	
Total N for each category	N=		N=		N=		N=	
	Yes N (%)	p	Yes N (%)	p	Yes N (%)	p	Yes N (%)	p
Race								
White								
Black								
Hispanic								
Other								
Age at MHQ								
20-29								
30-39								
40-49								
>50								
Age at Cancer Diagnosis								
0-4								
5-9								
10-14								
15-21								
Diagnoses								
Leukemia								
CNS tumors								
Hodgkin Lymphoma								
NHL								
Kidney tumor								
Neurobalstoma								
Soft Tissue Sarcoma								
Bone Cancer								
Cyclophosphamide Equivalent Dose (CED) mg/m2								
1-3999								
4000-5999								
6000-7999								
8000-15999								
16,000-19,000								
≥20,000								
Testicular RT cGy								
None								
1-400								

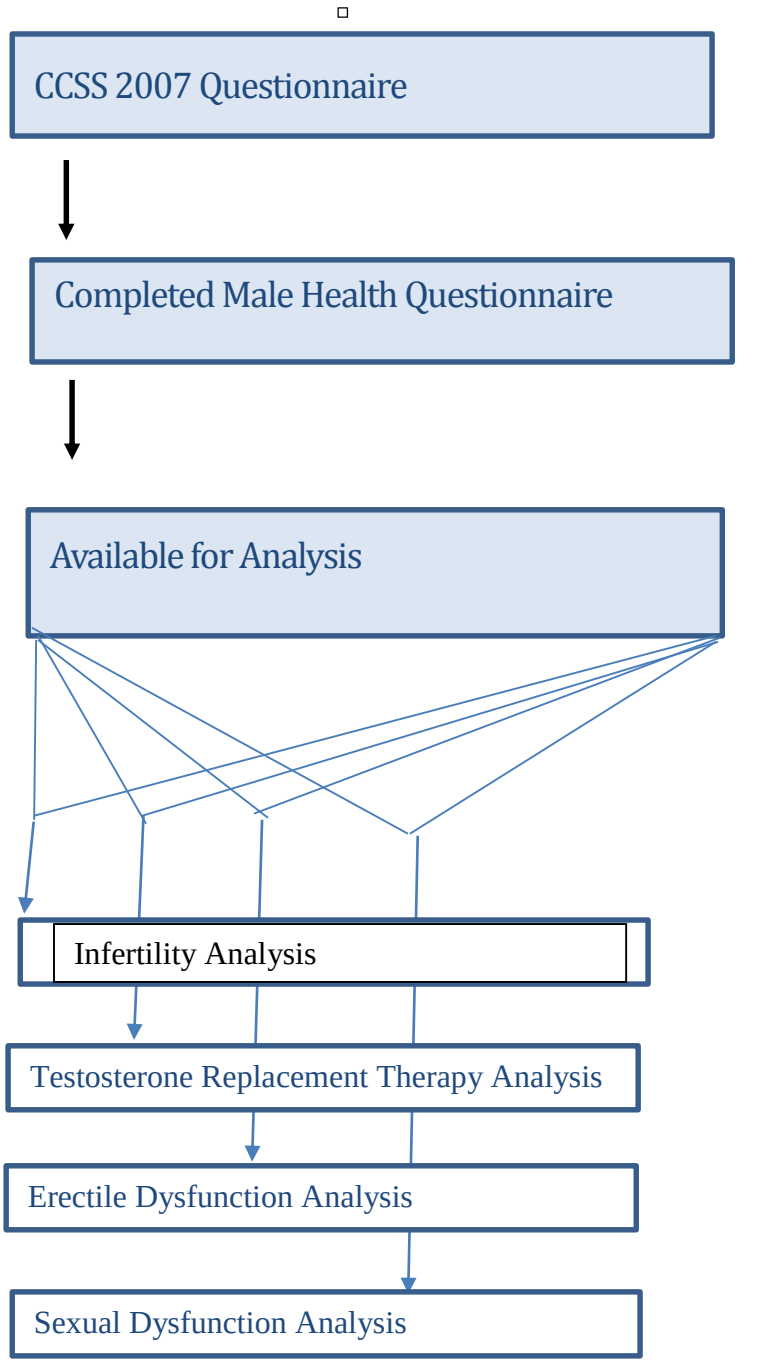
400-999								
999-2000								
>2000								
Cranial RT cGy								
None								
1-2999								
>3000								
Surgery on GU								
Yes								
No								
Prostate disease/surgery								
Yes								
No								
Surgery on Spinal cord								
Yes								
no								
Bleomycin								
Yes								
No								
General Health								
Excellent								
Very good								
Good								
Fair/Poor								

* **Testosterone Replacement Therapy (TRT)**

Table 6- multivariate analysis of Treatment and Basic Demographic Variables and Male Health Outcomes: Infertility, Testosterone Replacement Therapy (TRT), Sexual Dysfunction and Erectile Dysfunction

	Infertility					Testosterone Replacement Therapy					Sexual Dysfunction					Erectile Dysfunction			
	N=					N=					N=					N=			
	n, (%)	RR	95% CI	p		n, (%)	RR	95% CI	p		n, (%)	RR	95% CI	p		n, (%)	RR	95% CI	p
Age at diagnosis 0-4 5-9 10-14 15-21																			
Etnicity White NH BlackNH Hispanic other																			
Age at MHQ 20-29 30-39 40-49 50-59 >60																			
Cranial RTcGy None 1-2999 ≥3000																			
Testicular dose cGy None 1-399 400-1000 1000-1999 >2000																			
CED mg/m2 None 1-3999 4000-7999 8000-11999 1200-15999 16000-19,000 ≥20,000																			
Bleomycin Yes																			

No																			
Carboplatinum Yes No																			
Cisplatinum Yes No																			
Surgery on the GU tract Yes No																			
Surgery on the spine Yes No																			


CCSS 2007 Questionnaire
Completed Male Health Questionnaire
Available for Analysis
Infertility Analysis
Testosterone Replacement Therapy Analysis
Erectile Dysfunction Analysis
Sexual Dysfunction Analysis

References

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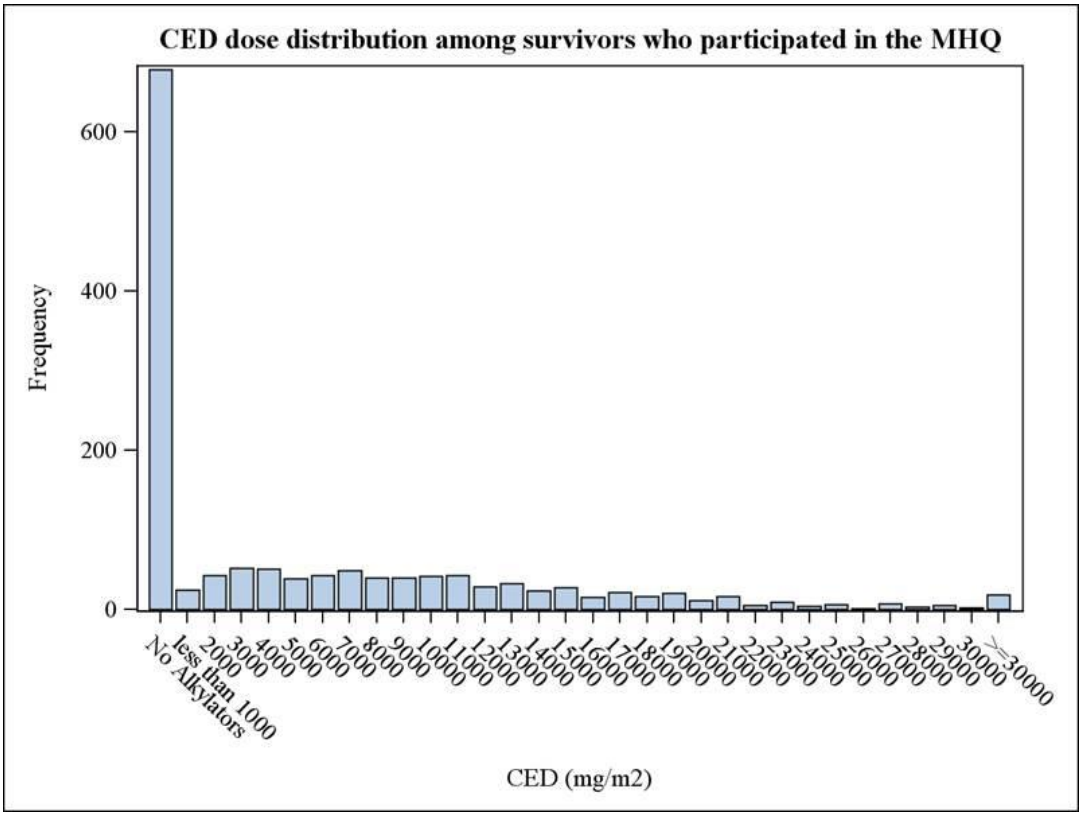
Appendix

1. 

2. And since that big spike at zero is a little distracting when thinking about potential breakpoints, here's the same graph showing just the people who got some alkylators: