CCSS Concept Proposal

1. Study Title

Trends in Utility-based Health-related Quality of Life Among Childhood Cancer Survivors

2. Working Group and Investigators

This proposed research will be conducted within the Psychology (primary) and Chronic Disease (secondary) Working Groups.

Proposed investigators:

Jennifer Yeh	jennifer.yeh@childrens.harvard.edu
Lisa Diller	lisa_diller@dfci.harvard.edu
Kevin Krull	kevin.krull@stjude.org
Kevin Oeffinger	oeffingk@mskcc.org
Wendy Leisenring	wleisenr@fhcrc.org
Greg Armstrong	greg.armstrong@stjude.org
Rebecca Howell	rhowell@mdanderson.org
Melissa Hudson	melissa.hudson@stjude.org
Janel Hanmer	hanmerjz@upmc.edu
Zachary Ward	zward@hsph.harvard.edu

3. Background and rationale

Health utility is a summary measure of health-related quality of life, estimated using preference or desirability for living in a particular state of health compared to other states of health or death. Utility measures, expressed on a standardized scale ranging from 0, representing death, to 1.0, representing perfect health, enable comparisons of quality of life outcomes between patient groups (e.g. cancer patients vs. HIV patients) and with the US general population. In addition to their use in reflecting quality of life in cost-effectiveness studies (via quality-adjusted life expectancy calculations), utilities also provide informative estimates of quality of life as an outcome (1).

Using the SF-6D utility measure and the CCSS Original Cohort data, we previously found that survivors had statistically lower utility scores than the general population (0.769 vs. 0.809, p<0.001, two-sided) (2). In particular, young adult survivors (ages 18-29) reported scores comparable to general population estimates for 40-49 year-olds. Among survivors, SF-6D utility scores were largely determined by number and severity of chronic conditions. No statistical or clinically significant differences were identified between siblings from CCSS and the general population (0.793 vs. 0.809, p=0.05).

By using data collected in CCSS Follow-up Survey #5 for the combined cohort (Original and Expansion), this proposal aims to build upon the initial work described above and provide further insight into the impact of treatment-related toxicities on survivor and sibling quality of life, in particular with aging survivors and newer therapies.

4. Specific aims/objectives/research hypotheses

Aim 1. Describe health-related quality of life among the CCSS Cohort participants.

Hypothesis #1: Survivors will have lower SF-6D utility scores compared to the general population overall (across all treatment eras) and across all chronological age groups.

Hypothesis #2: Siblings of cancer survivors will demonstrate SF-6D utility scores similar to those of the general population across all chronological age groups.

Aim 2. Assess trends in health-related quality of life over diagnosis eras.

Hypothesis #1: Survivors treated in more recent diagnosis years will have higher (i.e. improved) SF-6D utility scores than those treated in earlier years, adjusting for current chronological age. (or time since diagnosis).

Hypothesis #2: SF-6D utility scores for siblings of cancer survivors will be similar across years of survey completion, adjusting for current chronological age (or time since diagnosis).

Aim 3. Compare changes in SF-6D utility scores among the CCSS Original Cohort participants between Follow-up 2 Survey and Follow-up 5 Survey

Hypothesis #1: Survivors will report greater changes in SF-6D utility scores compared to siblings.

Hypothesis #2: Siblings will report similar changes to those of the general population.

Analysis Framework

a. Study population

Original Cohort survivors and siblings who completed the SF-36 survey at Follow-up 2 or Follow-up 5.

Expansion Cohort survivors and siblings who completed the SF-36 survey at Follow-up 5.

MEPS participants who completed the SF-12 in 2003 and 2014.

We will focus on individuals 18 years and older as the SF-6D was developed to assess health utility scores in adults.

We will vary the study population for each aim to minimize risk of confounding. For example, in Aim 2, we will omit older individuals from the Original Cohort to ensure that the analysis will focus on Original and Expansion Cohort individuals of a similar chronological age range (or time since diagnosis range).

b. Outcome(s) of interest:

Our analysis will focus on Short Form-6D (SF-6D) utility weights as the outcome of interest. Both the CCSS and Medical Expenditures Panel Survey (MEPS) collected health status data in 2003 and 2014 that will allow for the calculation of the SF-6D (3, 4). Specifically, SF-36 data collected in the CCSS Follow-up Surveys 2 and 5 for cancer survivors and siblings, and SF-12 data collected in MEPS for general population individuals without a cancer history (i.e. the population comparator).

MEPS data

MEPS is a nationally representative survey of the US noninstitutionalized civilian population ages 18 and older (5). The sampling frame of the Household Component of the Medical Expenditure Panel Survey (MEPS-HC) is drawn from respondents to the National Health Interview Survey. The MEPS-HC collects data from a nationally representative sample of households through an overlapping panel design. The two years of data for each panel are collected in five rounds of interviews. This provides continuous and current estimates of health care expenditures and outcomes at both the person and household level for two panels for each calendar year. The Self-Administered Questionnaire given to all adults aged 18 years or older in MEPS includes the SF-12v2. While MEPS includes only 1 year of follow-up on any given person, we will use cross-sectional data as a proxy for estimating longitudinal changes for the general population.

SF-6D scoring algorithm

The SF-6D scoring algorithm uses 7 of the questions from the SF-12 or 11 questions from the SF-36. These questions were used to construct health scenarios that were evaluated using the standard gamble technique in a representative sample of the UK population. Regression analysis was then used to model the preferences assigned to each health state. With the resulting scoring algorithm, a utility-based score can be assigned to each health state ranging from 0 (representing death) and 1 (representing full health). This scoring algorithm was constructed to be consistent across SF-12v1, SF-12v2, SF-36v1, and SF-36v2.

Planned analysis

We will estimate mean SF-6D utility scores for the entire CCSS survivor and sibling samples at FU2 (original cohort) and FU5 (full cohort) and within sex- and age-specific groups. For the comparator, we will estimate SF-6D scores using MEPS data. Among the survivors, we will estimate mean scores within each original cancer diagnosis group, by treatment exposure and by psychosocial factors. As our previous analysis found that SF-6D scores were influenced by the number and severity of chronic conditions (based on the Common Terminology Criteria for Adverse Events (CTCAE version 4.03) (6), we will also estimate mean survivor SF-6D score within subgroups defined by number of chronic conditions (any grade, grades 3-4 only), as well as maximum severity of conditions (see Table 2 as an example).

We will compare mean values (using Walsh's 2-sided t-test) to assess differences, trends and changes in health utility across groups. We will then use multivariable linear regression based on a stepwise selection approach to assess the influence of original cancer, diagnosis era, treatment exposures, psychosocial factors and chronic condition(s) characteristics on survivor SF-6D utility scores. These analyses will focus on examining the association between these factors and utility scores. We will plan to examine cancer diagnosis in separate models those with treatment exposure variables due to collinearity between diagnosis and treatment. Because the large sample size of the CCSS and MEPS can influence statistical significance, we will identify differences in utility scores that are both statistically significant ($p \leq 0.05$, two-sided) and clinically meaningful to patients (7). We will define a Minimally Important Difference (MID) as a 0.03 point difference in SF-6D score (8, 9). To yield nationally representative estimates, the MEPS results will incorporate sampling and post-stratification weights (10). All statistical analyses will be performed in SAS 9.3 (SAS Institute, Cary, NC).

As MEPS includes only 1 year of follow-up on any given person, we will use cross-sectional data as a proxy for estimating longitudinal changes in the general population. For example, for comparisons with the CCSS Original Cohort data collected in 2003 and 2014, we will estimate the change in SF-6D utility score from 20-30-year-old females in 2003 to 30-40-year-old females in 2014 using MEPS data. When presenting these results, we will explicitly acknowledge the limitations associated with this approach.

c. Explanatory variables

Patient characteristics

- Sex
- Race/ethnicity
- Diagnosis age
- Attained age

Treatment era

- 1970-79
- 1980-89
- 1990-99

Chronic conditions at FU2 and FU5 (across all organ systems)

- Number of conditions (grades 1-4, grades 3-4 only)
- Maximum grade among all conditions
- Note: we will also explore whether SF-6D scores vary by organ system (i.e., subsequent neoplasms, hearing, vision, speech, endocrine, respiratory, cardiac, gastrointestinal, renal, musculoskeletal, neurologic, hematologic, and infection diseases)

Psychosocial factors

- Insurance
- Marriage
- Education
- Employment
- Household income

D. Table and figure examples

Tables 1-4 below are examples of how model outcomes will be presented in the manuscript.

Table 1. SF-6D utility scores for CCSS survivors, CCSS siblings and MEPS general population: overall and by age-stratum.

	Survivors Mean (95% CI)	Siblings Mean (95% CI)	MEPS* Mean (95% CI)	Survivors vs. MEPS		Siblings vs. MEPS	
				P-value	Met MID* criteria?	P-value	Met MID* criteria?
Both sexes							
Overall							
18 to 29 years							
30 to 39 years							
40 to 49 years							
50 to 59 years							
Females							
Overall							
18 to 29 years							
30 to 39 years							
40 to 49 years							
50 to 59 years							

Males							
Overall							
18 to 29 years							
30 to 39 years							
40 to 49 years							
50 to 59 years							

*Defined as a 0.03 point difference in SF-6D score compared to MEPS.

Table 2. SF-6D utility scores for CCSS survivors by number and severity of chronic conditions*

Characteristic	Number	SF-6D mean (95% CI)	Compared to no conditions	
			P-value	Met MID* criteria?
No conditions				
Number of conditions, grades 1-4				
1 condition				
2 conditions				
≥3 conditions				
Number of conditions, grades 3-4 only				
1 condition				
2 conditions				
≥3 conditions				
Maximum severity of condition(s)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

*Defined as a 0.03 point difference in SF-6D score compared to survivors with no conditions.

Table 3. SF-6D utility scores for CCSS survivors, CCSS siblings and MEPS general population: overall and by diagnosis era.

	Survivors Mean (95% CI)	Siblings Mean (95% CI)	MEPS* Mean (95% CI)	Survivors vs. MEPS		Siblings vs. MEPS	
				P-value	Met MID* criteria?	P-value	Met MID* criteria?
Both sexes							
Overall							
1970-79							
1980-89							
1990-99							
Females							
Overall							
1970-79							
1980-89							
1990-99							

Males							
Overall							
1970-79							
1980-89							
1990-99							

*Defined as a 0.03 point difference in SF-6D score compared to MEPS.

Table 4. CCSS Original Cohort: Change in SF-6D utility scores between Follow-up Survey 2 and Follow-up Survey 5

	Absolute change in SF-6D utility score		Survivors vs. Siblings		Siblings vs. MEPS	
	Survivors	Siblings	P-value	Met MID* criteria?	P-value	Met MID* criteria?
Both sexes						
Overall						
By age at FU Survey 2						
18-29 years						
30-39 years						
40-49 years						
Males						
Overall						
By age at FU Survey 2						
18-29 years						
30-39 years						
40-49 years						
Females						
Overall						
By age at FU Survey 2						
18-29 years						
30-39 years						
40-49 years						

*Defined as a 0.03 point difference in SF-6D score compared to MEPS.

We would like to request individual-level data from the CCSS Statistical Center. Using these data, we will then conduct the analyses to derive SF-6D utility weights.

1. SF-36 survey responses from FU2 (original cohort) and FU5 (full cohort)
2. Original cancer diagnosis
3. Age at original cancer diagnosis
4. Age at FU2 (original cohort)
5. Age at FU5 (full cohort)
6. Age at last completed survey
7. Interval between cancer diagnosis and last completed survey
8. Attained age
9. Sex
10. Race/ethnicity (non-Hispanic White, Other)
11. Insurance status
12. Marriage status
13. Education level

14. Employment status
15. Household income
16. Treatment (surgery only; chemotherapy, no radiation; radiation, no chemotherapy; chemotherapy and radiation; unknown)
17. Surgery (none, any, nephrectomy, splenectomy)
18. Chemotherapy with alkylator, anthracycline, bleomycin, cisplatin, methotrexate (yes/no)
19. Chemotherapy (cumulative anthracycline dose (doxorubicin equivalent))
20. Radiation (yes/no)
21. Chest radiation (yes/no; if yes, total dose)
22. Cyclophosphamide equivalent dose alkylating agent (0, >0-<4000, 4000-<8000, ≥8000 mg/m^2)
23. CTCAEs (grades 1-5) for each organ system by subcategory (yes/no; if yes, age at first diagnosis for each organ system; organ systems include subsequent neoplasms, hearing, vision, speech, endocrine, respiratory, cardiac, gastrointestinal, renal, musculoskeletal, neurologic, hematologic, and infection diseases)

5. Special consideration

For the analysis, we will request individual-level CCSS data.

Please note: data requested will overlap with data for Concept Proposal #14-3 (Estimating the burden of disease associated with late-effects among childhood cancer survivors).

References

1. Gold MR, Siegel JE, Russel LB, Weinstein MC, editors. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

2. Yeh JM, Hanmer J, Ward ZJ, Leisenring WM, Armstrong GT, Hudson MM, et al. Chronic Conditions and Utility-Based Health-Related Quality of Life in Adult Childhood Cancer Survivors. J Natl Cancer Inst. 2016;108(9).

3. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92.

4. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Medical care. 2004;42(9):851-9.

5. Medical Expenditures Panel Survery (MEPS) [Internet]. [cited January 14, 2014]. Available from: http://www.ahrq.gov/research/data/meps/index.html.

6. Cancer Therapy Evaluation Program. Common termiology criteria for adverse events (CTCAE), version 4.03. Bethesda, MD: National Cancer Institute. Available from: http://ctep.cancer.gov.

7. McGlothlin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. JAMA. 2014;312(13):1342-3.

8. Feeny D, Spritzer K, Hays RD, Liu H, Ganiats TG, Kaplan RM, et al. Agreement about identifying patients who change over time: cautionary results in cataract and heart failure patients. Med Decis Making. 2012;32(2):273-86.

9. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes. 2003;1:4.

10. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care. 1996;34(3):220-33.