CCSS Concept Proposal

1. Study Title

Projections in trends in life expectancy and quality-adjusted life expectancy among childhood cancer survivors

2. Working Group and Investigators

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

Proposed investigators:

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

3. Background and rationale

Childhood cancer survivors are at elevated risk for chronic conditions and premature death. Based on excess mortality estimates from the original CCSS cohort (1970-1986), five-year childhood cancer survivors are projected to live on average 10 years less than individuals without a cancer history (1). Late-mortality among survivors treated more recently has been shown to have decreased (2), yet how these lower risks translate to gains in life expectancy is unknown. Further, despite the evolution of treatment designed to reduce toxicities, self-reported health status among survivors has not improved (3). Overall survivor health-related quality of life has also been shown to be largely influenced by the presence or absence of chronic conditions (4). These findings underscore the need to understand the overall impact of treatment-related morbidity on long-term survivor health and late mortality and assess whether there have been improvements in survivor length and quality of life over the past three decades of treatment.

Mathematical models are effective tools for simulating the clinical course of disease, synthesizing data from multiple sources and projecting the impact of health risks and interventions for a population (5). Employing a simulation modeling approach, we first propose to project the conditional life expectancy (LE) for survivors using absolute excess risks for specific causes of mortality (e.g. late recurrence, secondary malignancies, cardiac events,

pulmonary conditions, external causes and other causes). Second, we will estimate the morbidity and mortality associated with treatment-related late effects using quality-adjusted expectancy (QALE) as the outcome measure. A quality-adjusted life year (QALY) is based on the assumption that health is a function of length of life and quality of life, and combines the value of these two attributes into a single number (6). To calculate QALY and QALE, preference weights, or utilities, are used to characterize a given health state relative to perfect health and death, on a 0 to 1 scale. These weights can be derived from SF-36 survey responses (7, 8). To calculate QALE, utility weights are multiplied by the time spent in each health state and summed up over an individual's lifetime.

Leveraging data from both the Original and Expanded Cohorts, we aim to project trends in both life expectancy and QALE for survivors diagnosed between 1970 and 1999.

4. Specific aims/objectives/research hypotheses

Aim 1. To estimate the cumulative effect of original cancer and treatment-related mortality risks on survivor life expectancy (LE) by treatment era.

Hypothesis: Survivors treated more recently will have greater projected life expectancy than those treated in earlier treatment eras.

Aim 2. To assess the cumulative effect of late-effects on quality-adjusted life expectancy (QALE) by treatment era.

Hypothesis: Survivor QALE will vary by treatment era.

5. Analysis Framework

a. Outcome(s) of interest:

Our analysis will focus on two main outcomes of interest:

1. Life Expectancy (Aim 1)
2. QALE (Aim 2)

Methods for each aim/outcome are described below.

Aim 1. To estimate the cumulative effect of disease- and treatment-related mortality risks on survivor life expectancy by treatment era.

Using methods previously described (1), we will develop a simulation model of the lifelong excess mortality risks to project the conditional life expectancy for a cohort of childhood cancer survivors.

Model overview. At the start of the model simulation, a cohort of five-year childhood cancer survivors will enter the model. Each month, survivors will face a risk of dying from one of the following mutually exclusive categories: recurrence or progression of primary cancer, subsequent neoplasms, cardiac causes, pulmonary causes, external causes and all other causes. Survivors will be followed throughout their lifetimes.

Model parameterization. Mortality risk from recurrence by age (or years since diagnosis) will be based on CCSS data. All other mortality risks by age (or years since diagnosis) will consist of two components: 1) absolute excess risk (AER) mortality (estimated from CCSS data) and 2) baseline risk (based on US lifetables) (9). For the mortality risk estimations, to ensure consistency, we will use ICD-9 and ICD-10 codes as described in the Armstrong et al. 2015

late mortality study (2). See Table 1 for an example of AER estimates from CCSS data that will be requested.

Given the limited follow-up period of the CCSS, we will extrapolate AER risk estimates beyond the data available based on epidemiologic data and/or Working Group expert opinion. We will conduct extensive sensitivity analysis to assess how these assumptions influence results. We will also conduct probabilistic sensitivity analysis in which all parameters are simultaneously varied based on underlying distributions to more fully account for uncertainty.

Depending on the AER mortality estimates incorporated into the model, the model can be used to simulate and project outcomes for various cohorts of survivors. For example, by using AERs for the Overall CCSS cohort, we can project outcomes for the Overall CCSS cohort. By using AERs estimated for cohorts by diagnosis year (i.e., 1970-79, 1980-89, 1990-99), we can project outcomes for these specific cohorts and provide insights on trends in outcomes by treatment era.

Model outcomes. Model outcomes will include lifetime cause-specific mortality, conditional life expectancy (defined as the projected number of years a survivor is expected to live, based on year of birth, age upon surviving cancer for 5 years, and sex), cause-specific attributable proportion of overall mortality risk, and conditional ten-year mortality probabilities. Loss in life expectancy will be calculated as the difference in life expectancy between a cohort of survivors and a cohort of general population individuals without a cancer history (which face zero risk of disease- or treatment-related mortality risks). Subgroups of interest will include treatment era (e.g., 1970-74, 1975-79, 1980-84, 1985-89, 1990-94, 1995-99), which will be further stratified by broad treatment groups (e.g., surgery only, chemotherapy + no radiation, radiation + no chemotherapy, chemotherapy + radiation). As data allow, we may further stratify treatment groups by radiation type (e.g., any cranial radiation and all other radiation), radiation dose (<20 Gy, ≥20 Gy chest radiation), and/or particular chemotherapies (e.g., anthracycline) to provide more clinically meaningful risk subgroups.

These analyses will provide estimates on projected trends in survivor life expectancy by treatment era and broad treatment groups. Additional subgroups of interest will cancer type and other characteristics, such as age at original cancer diagnosis.

Aim 2. To assess the cumulative effect of late-effects on quality-adjusted life expectancy by treatment era.

Building on the model of excess mortality risks associated with late-effects to estimate the cumulative impact on survivor life expectancy described above, we will develop an individual-level Monte Carlo microsimulation model of the natural history of late-effects that will allow for greater flexibility in capturing multiple dimensions of heterogeneity (e.g., risk of developing individual or multiple late-effects), better reflect variability and uncertainty, and allow the risk of future events to depend on prior events, such as treatment for original cancer. We will use this model to estimate QALE for the overall CCSS cohort, as well as by treatment era (e.g., 1970-74, 1975-79, 1980-84, 1985-89, 1990-94, 1995-99) and broad treatment subgroups (e.g., surgery only, chemotherapy + no radiation, radiation + no chemotherapy, chemotherapy + radiation). Similar to Aim 1 above, we will further separate these groups by radiation type, radiation dose and/or chemotherapies, as well as underlying cancer diagnosis groups, as data allow.

Model overview. In a microsimulation model, individuals transition among health states one at a time and the detailed information for each individual is continuously tracked, allowing the natural history, prognosis, and course of disease to be conditional on that individual's risk

factor profile and history of treatment. Specifically, events are simulated for a sequence of individuals using random numbers based on event probabilities (e.g., the probability of developing congestive heart failure), thus producing individual "case histories." Characteristics (e.g., age, sex) of each person are randomly drawn from distributions derived from data. The model tracks individuals from entry into the model until death. By examining the clinical course of a disease, represented by the particular pathway an individual took through the health states prior to dying, the model can generate a survival time for that individual. By running large numbers of simulated cases (e.g., 1,000,000), a distribution of survival values can be obtained. Therefore, the model will have the ability to reflect patient variability in disease natural history and long-term outcomes.

At the start of the simulation, representative cohorts of 5-year childhood cancer survivors will enter the model. Movement through the health states will occur in monthly increments. Individuals will be allowed to develop multiple health conditions. Once individuals develop a chronic condition, they will also face condition-specific mortality risks. Each month, individuals will face mortality risks for late recurrence, excess late-effects mortality (e.g. external causes, other causes) and background mortality.

Model parameterization. To parameterize the model, we will leverage the wealth of CCSS data to 1) estimate risk factor profiles and 2) derive health state utility weights for select Common Terminology Criteria for Adverse Events (CTCAE 4.0) health conditions (grade 3- 5) (10, 11) (Figure 1). Conditions will include (but are not limited to) secondary cancers, congestive heart failure, stroke, heart attack, renal failure, gonadal failure and lung fibrosis.

Risk profiles. We will estimate risk profiles for the select health conditions using CCSS data for the overall cohort and broad treatment exposure groups. Risk profiles, defined as the yearly risk of developing a specific health condition by attained age or years since diagnosis, will be based on CTCAE data.

Our model will be based on several simplifying assumptions: (a) late-effects risks are largely determined by treatment exposures associated with original cancer treatment; (b) CTCAE grade 3-5 conditions account for the majority of long-term toxicity; (c) survivors are at risk for developing multiple late-effects and face competing mortality risks; (d) risk for some health conditions, such as CHF, is comprised of two additive components (late-effects-related absolute excess risk and age-related risks as observed in the general population). Additionally, the model will simulate the risk of multiple chronic conditions under the assumption of independence.

Risk factor profiles for each health condition will be estimated using the cumulative incidence function (12, 13) or subdistributional hazard models (14) to account for other health conditions and death as competing risks. As risk profiles will be based on self-reported data, we will also consider the robustness and quality of the data for each health condition and incorporate conservative assumptions as needed to avoid overestimating risks. We also recognize that the CCSS surveys ask about the first occurrence of each event and therefore does not provide information on secondary, subsequent or recurrent events. We will acknowledge this limitation in the presentation of our results. We also recognize that as survivors age, lifestyle factors (i.e. tobacco use) and other comorbidities (i.e. hypertension) may be important risk modifiers for specific chronic conditions. We will note this in our limitations and as data allow, explore this in sensitivity analyses.

For conditions that are common general population risks (i.e. secondary breast cancer, congestive heart failure, stroke), we will compare observed CCSS rates with general population estimates to determine the absolute excess risk in survivors. Examples of data

sources for general population risks include Framingham Heart Study (15) and Surveillance, Epidemiology, and End Results (SEER) program (16). For these conditions, baseline general population risks will also be incorporated into the model using these data sources.

Utility weights. Reflecting the decrement in quality of life associated with a specific health condition, we will use SF-6D utility weights based on SF-36 data (7, 8). This will include updating previous estimates for the Original Cohort (4) using data collected in Follow-up Survey #5 for both the Original and Expansion Cohorts.

For each health state, we will derive SF-6D weights. For individuals who develop 2 or more conditions, we will assign utility weights using established methods (e.g., minimum, multiplicative, additive) (17). Alternatively, as our previous analysis found that older attained age, female sex, and number of chronic conditions were associated with statistically significant SF-6D score decrements (4), we may use a multivariable model to inform utility weights for survivors in the microsimulation model. We will also consider using distress as a predictor of SF-6D decrements (18).

Competing mortality risks. To reflect competing mortality risks from late-recurrence, external causes and other causes (19), we will incorporate AER estimates from Aim 1. Condition-specific mortality risks will be based on CCSS data (as available) and general population estimates from published studies and databases (as needed). Background mortality risks will be based on US Life Tables (9).

Model outcomes. The microsimulation model will then be used to generate estimates of disease burden that will allow us to characterize the impact of morbidity and mortality associated with the health conditions on survivor long-term health. The main model outcome will be QALE. Loss in QALE will be calculated as the difference in QALE between a cohort of survivors and a cohort of individuals without a cancer history (which face zero risk of disease- or treatment-related morbidity or mortality risks and sex- and age-specific utility weights for the U.S. general population (20)). To characterize the heterogeneity in disease burden among the broad treatment subgroups, we will estimate the following: (a) proportion of the burden attributed to mortality; (b) proportion due to morbidity; and (c) proportion attributable to specific late-effects (i.e., secondary breast cancer, CHF, etc.). To reflect the impact of uncertainty surrounding risk factor profile estimates from the CCSS and general population, we will conduct probabilistic sensitivity analyses, in which all parameters will be simultaneously varied based on distributions, to generate uncertainty intervals for all modeled outcomes.

These analyses will provide insight on how QALE loss has improved by treatment era and broad treatment groups.

b. Study population

Original and Expansion Cohort participants

c. Exploratory variables

Aim 1

For Aim 1, we will focus primarily on how projected LE varies by 1) treatment era and 2) broad treatment groups:

Attained age or years since diagnosis

Patient characteristics

- Sex
- Race/ethnicity

Treatment era

- 1970-74
- 1975-79
- 1980-84
- 1985-89
- 1990-94
- 1995-99

Broad treatment groups

- Surgery only
- Chemotherapy, no radiation
- Radiation, no chemotherapy
- Chemotherapy and radiation

As noted above, we will further stratify broad treatment groups as data allow, balancing the need for more clinically relevant subgroups with the importance of having adequate number of cause-specific deaths for stable subgroup-specific estimates. Radiation and chemotherapy variables may include:

Chemotherapy

- Chemotherapy treatment (including alkylator, anthracycline, bleomycin, cisplatin, or methotrexate)
- Cumulative anthracycline dose (doxorubicin equivalent): none, <250 mg/m^2, ≥250 mg/m^2)
- Cyclophosphamide equivalent dose alkylating agent (0, >0-<4000, 4000-<8000, ≥8000 mg/m^2)

Radiation

- Radiation therapy (including cranial irradiation, chest irradiation, abdominal or pelvic irradiation, TBI)
- Cranial radiation dose
- Chest radiation dose (none, 0.1<10Gy, 10-19 Gy, ≥20 Gy)
- Abdominal/pelvic radiation dose
- TBI dose

Additional subgroup analyses may include characteristics of the original cancer diagnosis:

Original cancer diagnosis

- Cancer type
- Diagnosis age

Aim 2

For Aim 2, we will focus on the variables listed above (including the radiation and chemotherapy variables) as predictors in the cumulative incidence function or subdistributional hazard models for the select health conditions. Because our underlying assumption is that late

effects are largely determined by treatment exposures, we will most likely not include original cancer treatment as a predictor, but will explore this in initial analyses.

The estimated cumulative incidence function or subdistribution hazard models will then serve as inputs for the simulation model. The simulation model will focus on projecting QALE for subgroups based on treatment era and broad treatment groups. As noted above, broad treatment groups may be further stratified by additional treatment variables to reflect more clinically relevant subgroups.

For both aims, because the goal is to characterize the loss in life expectancy or QALE among childhood cancer survivors, our aim will be to portray the uncertainty in these estimates via probabilistic sensitivity analyses (not determine statistical significance between subgroups).

D. Table and figure examples

For Aim 1, we will request absolute excess risks (and 95% CI) by 5-year intervals since diagnosis (or attained age) for the following mortality causes (2) (see Table 1):

1. Late recurrence
2. Subsequent neoplasms
3. Cardiac causes
4. Pulmonary causes
5. External causes
6. Other causes

Table 1. Example of absolute excess risk (AER) estimates for Aim 1.

Overall cohort*	Absolute excess risk (AER), (95% CI)					
	Recurrence	Subsequent neoplasm	Cardiac causes	Pulmonary causes	External Causes	Other causes
Years since diagnosis						
5-9 years						
10-14 years						
15-19 years						
20-24 years						
25-29 years						
30-34 years						
≥35 years						

*Subgroups will include treatment era, broad treatment groups, and possibly age at original cancer diagnosis and original cancer diagnosis.

For Aim 2, because these data will serve as model inputs into a microsimulation model, we will request individual-level data, which we will then incorporate into the model with input and review by the collaborators listed in the Working Group. CCSS variables requested for each CCSS individual will include the following:

1. Original cancer diagnosis
2. Age at original cancer diagnosis
3. Age at baseline
4. Age at last completed survey
5. Interval between cancer diagnosis and last completed survey
6. Attained age

7. Sex
8. Race/ethnicity (non-Hispanic White, Other)
9. Treatment (surgery only; chemotherapy, no radiation; radiation, no chemotherapy; chemotherapy and radiation; unknown)
10. Surgery (none, any, nephrectomy, splenectomy)
11. Chemotherapy with alkylator, anthracycline, bleomycin, cisplatin, methotrexate (yes/no)
12. Chemotherapy (cumulative anthracycline dose (doxorubicin equivalent))
13. Radiation (yes/no)
14. Chest radiation (yes/no; if yes, total dose)
15. Cyclophosphamide equivalent dose alkylating agent (0, >0-<4000, 4000-<8000, ≥8000 mg/m^2)
16. 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)
17. Subsequent malignant neoplasms (histology, site, laterality of breast site (if available), age at SMN, chronic condition grade description, chronic condition grade (number), and for those that are grade 5 (death), cause of death (for those that died of SMN-death) and age at death)
18. Late-mortality (yes/no; if yes, date of death, cause (late-recurrence or ICD-9 or ICD-10 code)
19. SF-36 survey responses

Table 2 below is an example of how model outcomes will be presented in the manuscript.

Table 2. Example of model outcomes on Life Expectancy and QALE

Cohort	Life expectancy, years	QALE	QALEs		
			Loss in QALE*	Proportion attributable to morbidity	Proportion avertable via mortality
General population					
CCSS overall cohort					
By sex					
Men					
Women					
By cancer diagnosis					
ALL					
AML					
Other leukemia					
Central nervous system tumor					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Wilms tumor					
Neuroblastoma					
Osteosarcoma					
Ewing sarcoma					
By treatment era					
1970-79					
1980-89					
1990-99					
By broad treatment group					
Surgery only					
Chemotherapy, no radiation					
Radiation, no chemotherapy					
Chemotherapy and radiation					

*Compared to the U.S. general population

Special consideration

For the analysis on LE, we will request absolute excess mortality risk estimates from the CCSS Statistical Center. We will incorporate these risk estimates into a simulation model to project LE.

For the analysis on QALE, we will request individual-level CCSS data. We will then use this data to develop a simulation model capable of projecting QALE with input and review by the collaborators listed in the Working Group. Upon completion of the primary analysis by J Yeh, W. Leisenring will provide statistical support and review.

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).

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