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Project Requirements and Description

Requirements to submit AOI (all answers must be "yes" to proceed)

A comprehensive review of previously published data has been completed	Yes
The specific aims are clear and focused	Yes
The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator.	Yes
The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months	Yes

Project Title

Clustering of Core Health Outcomes and Determinants of Long-Term Social Functioning and Quality of Life Among Childhood Cancer Survivors: A Latent Class Analysis of the CCSS

Planned research population (eligibility criteria)

For Aim 1 and Aim 2, survivors and siblings aged ≥ 18 enrolled in the CCSS, excluding those who died, were lost to follow-up, developed COs before or within 5 years of diagnosis, or lacked outcome assessment. For Aim 3, only participants with available social functioning, physical, or mental summary scores are included. For Aim 4, only survivors who received treatment are included.

Proposed specific aims

Advances in treatment have raised childhood cancer survival to over 85% in developed countries; however, long-term morbidity remains substantial. Between 60-90% of survivors develop at least one chronic condition, and up to 80% experience severe or life-threatening complications. By age 50, survivors have three times more chronic conditions compared to their siblings, averaging 11 non-fatal and 3 severe outcomes by 35 years post-diagnosis. The International Childhood Cancer Outcome Project recently identified 20 core survivorship outcomes (COs); however, these outcomes have not been systematically enumerated in real-world cohorts due to inconsistent definitions and assessments. Although SJLIFE provides rigorous clinical

data, no study has examined the clustering of COs in relation to treatment and potentially modifiable behaviors. Despite reductions in treatment intensity, many survivors continue to experience systemic dysfunction affecting social functioning and QoL. Using the NCSI framework to capture treatment-related risk gradients, this proposal will characterize the prevalence and clustering of 20 COs among survivors and siblings, assess longitudinal associations with social functioning and QoL, and identify clinical and behavioral determinants, including modifiable lifestyle factors of survivorship burden. I hypothesize that survivors will have higher COs risk, four to five distinct clusters, poorer social functioning and QoL, and greater treatment intensity and unhealthy behaviors—particularly physical inactivity—will predict high-burden clusters.

Aim 1. Evaluate the prevalence of 20 standardized COs among survivors compared with their siblings. Estimate the prevalence of each CO and calculate adjusted odds ratios (ORs) comparing survivors to siblings, controlling for demographic and socioeconomic characteristics.

Aim 2. Create the physical and psychological clusters of survivorship and sibling COs
Multi-group Latent Class Analysis (LCA) will be employed to identify clusters of co-occurring COs among survivors and siblings, with invariant tests to assess comparability across groups.

Aim 3. Examine longitudinal changes in social functioning and QoL across survivorship clusters.
Using posterior probabilities from the latent class analysis (Aim 2), probability-weighted mixed-effects models will assess how social functioning, QoL, and metabolic equivalents change over time across clusters of survivors (reference = siblings), adjusting for age, lifestyle factors, and baseline outcomes.
Aim 4. Identify predictors and attributable lifestyle risks for survivorship clusters.
Identify treatment-, diagnosis-, and lifestyle-related predictors of survivorship clusters using weighted multinomial regression models among survivors and estimate the cluster burden attributable to smoking, drinking, poor diet, and physical inactivity through population-attributable fraction (PAF) analysis.

Will the project require non-CCSS funding to complete? No

If yes, what would be the anticipated source(s) and timeline(s) for securing funding?

Does this project require contact of CCSS study subjects for:

Additional self-reported information	No
Biological samples	No
Medical record data	No

If yes to any of the above, please briefly describe.

What CCSS Working Group(s) would likely be involved? (Select all that apply)

	Primary	Secondary
Second Malignancy		
Chronic Disease		✓
Psychology/Neuropsychology		✓
Genetics		
Cancer Control		
Epidemiology/Biostatistics	✓	

Outcomes or Correlative Factors

	Primary	Secondary	Correlative Factors
Late Mortality		✓	
Second Malignancy		✓	

Health Behaviors

	Primary	Secondary	Correlative Factors
Tobacco			✓
Alcohol			✓
Physical Activity			✓
Medical Screening			
Other			

If other, please specify

Psychosocial

	Primary	Secondary	Correlative Factors
Insurance			✓
Marriage			✓
Education			✓

	Primary	Secondary	Correlative Factors
Employment			✓
Other			

If other, please specify

Medical Conditions

	Primary	Secondary	Correlative Factors
Hearing/Vision/Speech		✓	
Hormonal Systems		✓	
Heart and Vascular		✓	
Respiratory		✓	
Digestive		✓	
Surgical Procedures			
Brain and Nervous System		✓	
Other			

If other, please specify

cGVHD, musculoskeletal conditions, subsequent neoplasm, temperature dysfunction

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Medications

Describe medications

Psychologic/Quality of Life

	Primary	Secondary	Correlative Factors
BSI-18			
SF-36	✓		
CCSS-NCQ			
PTS			
PTG			
Other			

If other, please specify

Other

	Primary	Secondary	Correlative Factors
Pregnancy and Offspring			
Family History			
Chronic Conditions (CTCAE v3)	✓		
Health Status			

Demographic

	Primary	Secondary	Correlative Factors
Age	✓		
Race	✓		
Sex	✓		
Other			

If other, please specify

Cancer Treatment

	Correlative Factors
Chemotherapy	✓
Radiation Therapy	✓
Surgery	✓

Anticipated Sources of Statistical Support

CCSS Statistical Center	Yes
Local Institutional Statistician	No

If local, please provide the name(s) and contact information of the statistician(s) to be involved.

Will this project utilize CCSS biologic samples?

No

If yes, which of the following?

If other, please explain

Other General Comments

Agree

I agree to share this information with St. Jude

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