CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
April 11th 2017

1. **STUDY TITLE**: Adherence to surveillance for second malignant neoplasms and cardiac dysfunction in the CCSS cohort

2. **WORKING GROUP AND INVESTIGATORS:**
Primary CCSS Working Group: Cancer Control
Secondary CCSS Working Groups: Chronic disease, Second neoplasms

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3. **BACKGROUND AND RATIONALE:**
The 5 year survival rate for childhood cancers continues to improve and now exceeds 84%.[1] As a result, there are more than 420,000 survivors of childhood cancer living in the United States, with the prevalence expected to reach 500,000 by 2020.[2] The chemotherapy, radiation and surgical treatments used to induce and maintain cancer remission are associated with a significant risk for treatment-related adverse health outcomes.[3] For example, the St. Jude Lifetime Cohort Study demonstrated that at age 45 years, 95.5% of survivors have at least one chronic health condition and 80.5% of survivors have a serious, disabling or life-threatening chronic health condition.[4] These survivors also have an increased risk of premature mortality with 18% of those surviving 5 years after therapy dying within the subsequent 25 years.[5] In response to this, there has been a concerted effort to lower therapeutic exposures when possible to minimize the risk of toxic effects. This has led to a decline in late mortality among 5-year survivors of childhood cancer.[6] For instance, the 15-year risk of death from any cause decreased

from 12.4% in the early 1970s to 6.0% in the 1990s.[6]

Two of the major contributors to the morbidity and premature mortality associated with childhood cancer therapy are the development of a subsequent malignant neoplasm (SMN) and the development of cardiac dysfunction. Survivors have a 10-fold increased risk of developing a SMN compared to the general population[7-8], a 15-fold increased risk of developing heart failure[5] and a 7-fold increased risk of premature cardiovascular death compared to control populations.[10] It has been demonstrated that surveillance programs for SMNs and cardiac dysfunction can reduce mortality from these conditions. Mathematical models have been used to show that in female survivors of adolescent Hodgkin lymphoma, one would need to screen 80 survivors to prevent 1 death from breast cancer.[12] Similarly computational models have shown that routine echocardiography every 10 years with subsequent medical intervention for positive results would reduce lifetime congestive heart failure risk in 15-year old 5-year childhood cancer survivors by 2.3%.[13]

Version 4.0 of the Childhood Oncology Group (COG) Long-Term Follow-Up Guidelines[14] published in 2013 advocates for periodic cancer surveillance in high-risk populations. The COG recommendations are summarized in Table 1.

Table 1: COG Recommended Cancer Screening Protocol for High-Risk Populations

Organ:	Population at Risk:	Suggested Screening:
Breast:	Females who received ≥20 Gy of chest radiation with potential impact to the breast	Yearly mammogram beginning 8 years after radiation or at age 25 (whichever occurs later)
GI:	Patients who received ≥ 30 Gy of radiation with potential to impact the colon/rectum	Colonoscopy every 5 years beginning 10 years after radiation or at age 35 (whichever occurs later)
Skin:	Patients who received any radiation	Yearly skin examination

In addition to risk-based screening, the COG guideline advises that all survivors comply with the American Cancer Society (ACS) guidelines for cancer screening in the general population. These guidelines are summarized in Table 2, below[14]

Table 2: ACS Recommended Cancer Screening Protocol for Standard Risk Populations	
Breast:	Annual mammogram starting at age 45 (can start at 40 if they wish to do so) until age 54 and then every 2 years and continuing as long as the woman is expected to live 10 more years or longer
Cervical:	Cervical pap smears starting at age 21 and then repeated every 3 years from aged 21-29, and every 5 years with an HPV test from age 30-65 with the potential to stop testing at age 65 if the patient meets specific criteria
GI:	Starting at age 50, colonoscopy every 10 years, double contrast barium enema every 5 years, flexible sigmoidoscopy every 5 years, CT colonography every 5 years or yearly fecal occult blood, fecal immunochemical or stool DNA testing

Treatment with anthracyclines and radiation to a field that involves the heart places survivors at elevated risk for cardiac dysfunction. It is recommended that these survivors be screened with echocardiogram or comparable cardiac imaging every 1-5 years. The interval of screening depends on the prior treatment with radiation, the age at treatment and the cumulative dose of anthracyclines received (Table 3).[15] Pediatric studies of anthracycline cardiotoxicity typically describe risks based on the cumulative dose of doxorubicin. A table for conversion of anthracycline exposures to doxorubicin isotoxic equivalents is provided in the COG guideline (Table 4).[15] Despite a 2015 study evaluating anthracycline toxicity equivalency ratios that proposes alternative equivalencies for daunorubicin, the COG guidelines for equivalency will be used in this study because the goal of this study is to determine compliance with COG guidelines and because the 2015 paper came out after the end of the data collection period for this study.[16]

Table 3: Recommended Frequency of Echocardiogram or Comparable Cardiac Imaging			
Age at Treatment*:	**Radiation with Potential Impact to Heart:**	**Anthracycline Dose**:**	**Recommended Frequency:**
< 1 year old	Yes	Any	Every year
	No	< 200 mg/m^2	Every 2 years
		≥200 mg/m^2	Every year
1-4 years old	Yes	Any	Every year
	No	< 100 mg/m^2	Every 5 years
		≥ 100 to < 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
≥ 5 years	Yes	< 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
	No	< 200 mg/m^2	Every 5 years
		≥ 200 to <300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
Any age with decrease in serial function			Every year
*Age at time of first cardiotoxic therapy (anthracycline or radiation) **Based on doxorubicin isotoxic equivalent (See Table 4)			

Table 4: Conversion of Anthracycline Exposures to Doxorubicin Isotoxic Equivalents	
Anthracycline:	**Doxorubicin Isotoxic Equivalents:**
Doxorubicin	1
Daunorubicin	1
Epirubicin	0.67
Idarubicin	5
Mitoxantrone	4

The CCSS has previously reported on the cancer screening practices of survivors. Using the original CCSS cohort and the 2002-2003 follow-up questionnaire, the authors showed that:

1. Among average risk female survivors, 80.9% and 67.0% reported a PAP smear and mammogram respectively within the recommended period.[17]
2. Among high-risk survivors of both genders, only 46.2%, 11.5% and 26.6% reported a mammogram, colonoscopy, and complete skin exam respectively within the recommended period.[17]

3. Only 28% of survivors identified to be at high risk of developing heart failure reported having a screening echocardiogram in the recommended period.[18]

The factors that predict a survivor's adherence to recommended screening are complex. It has been shown that survivors who are black, older at interview or uninsured are less likely to receive risk-based care.[18] In a study of mammography in at-risk female survivors, the strongest predictor of adherence was having a physician recommend the test.[18] The investigators also found that having a primary care physician, heightened awareness of increased risk of breast cancer, increased general health concerns and a positive decisional balance regarding the pros vs. cons of mammography were associated with increased adherence with mammography.[18] In a study of compliance with colorectal cancer (CRC) screening, individuals who reported a physician visit related to their prior malignancy were 50% more likely to receive the suggested CRC surveillance. [19] The investigators also demonstrated that participants who discussed their risk of developing cancer with their physician, had > 10 physician visits in the past 2 years, were over 50 years old or were married were more likely to be adherent with CRC screening. [20] It is imperative to identify populations that are at risk for not receiving adequate long-term care as it has been demonstrated that we can effectively develop programs to target at-risk survivors and increase their compliance with recommended screening practices.[21]

Prior CCSS analyses of adherence to SMN and cardiac surveillance have been limited by the fact that:

1. The COG guidelines were only released in 2003 and so assessing "adherence" was difficult given that most survivors and their health care providers were likely unaware of the guidelines at the time of the 2002-2003 CCSS survey;
2. Survivor care plans were less widely used during that period than they are now. However, questions relating to use of a survivorship care plan were included in the FU5 survey allowing, for the first time, direct assessment of the impact on care plans on screening;
3. The analyses only included participants in the original CCSS cohort (diagnosed 1970-86) so that the behaviors of more recently treated survivors couldn't be assessed.

4. **SPECIFIC AIMS / OBJECTIVES / RESEARCH HYPOTHESES**:

The specific aims and objectives of this proposal are to:

(I) High-risk Patients

a. Adherence: To determine the proportion of childhood cancer survivors who are deemed as high-risk (see table 1 for definition of high risk) based on COG guidelines for the development of a SMN (breast, colorectal or skin) or cardiac dysfunction that are adherent to the recommended surveillance guidelines for SMNs and cardiac dysfunction according to the COG guidelines.

b. Predictors of adherence: To determine the demographic, disease, treatment, socio-economic and follow-up care factors (e.g. location and provider of follow-up care, possession of a survivor care plan) associated with adherence to recommended surveillance guidelines for SMN and cardiac dysfunction.

(II) Standard Risk Patients

a. Adherence: To determine the proportion of childhood cancer survivors at standard risk for the development of a SMN (cervix, colorectal or breast) that are adherent to the ACS screening guidelines recommended for the general population.

b. Predictors of adherence: To determine the demographic, disease, treatment, socio-economic and follow-up care factors in standard risk patients associated with adherence to the recommended screening guidelines for SMN

(III) To evaluate whether high risk survivors who were compliant with applicable standard risk screening guidelines (ACS) are more likely to adhere to each of the high-risk surveillance guidelines (cardiac, GI, breast and dermatologic), compared to those who don't adhere to the standard risk guidelines.

The hypotheses of this proposed study are:

(I) Adherence to all COG recommended surveillance protocols will have increased from the 2002-2003 analyses and is possibly attributable to broader dissemination of the COG guidelines and the greater availability of survivorship care plans

(II) Patient-related factors that will predict increased adherence to recommended screening tests (both COG guidelines for high-risk patients and ACS guidelines for standard risk patients) will include: higher level of education, greater household income, being employed, having health insurance, more frequent physician visits, possession of a cancer survivorship care plan, increased anxiety/fear regarding past diagnosis, being married, not living alone, having children and having healthy habits (not smoking, low alcohol consumption, appropriate levels of physical activity)

(III) Healthcare provider-related factors that will predict increased compliance with recommended screening tests (both COG guidelines for high-risk patients and ACS guidelines for standard risk patients) will include: type of provider (cancer specialist), location of interaction (cancer survivor clinic), and availability of a survivor care plan.

(IV) Patients who adhere to recommended standard-risk surveillance guidelines will be more likely to adhere to the high-risk screening guidelines

5. **ANALYSIS FRAMEWORK**:

Subject Population:

The study sample will consist of all survivors and siblings who responded to the F/U #5 questionnaire. Survivors who have developed one of the target cancers as a SMN (skin, colon,

breast or cervical) will be excluded from the analysis of adherence to that specific guideline. Similarly, survivors who have developed grade 3 or 4 cardiac toxicity will be excluded from analysis of echocardiogram adherence. For analysis of adherence to population screening guidelines, adherence rates will be compared to siblings and to aggregate data available from the National Health Interview Survey (NHIS) at http://www.cd.gov/nchs/SHS/tables.html

Survivors will be defined as high-risk of developing a specific malignancy if they meet the following criteria:

A. Skin Cancer:
    a. Received any radiation
B. Colon Cancer:
    a. Received ≥ 30 Gy of radiation to the abdomen, pelvis, spinal, or TBI, which had the potential to impact the colon/rectum
C. Breast Cancer:
    a. Received ≥20 Gy of chest radiation with potential impact to the breast

Survivors will be defined as high-risk of developing cardiac dysfunction if they meet either/both the following criteria:

A. Anthracycline exposure:
    a. Received any anthracycline agent
B. Radiation exposure:
    a. Any radiation exposure to a field that includes the heart

Outcomes of Interest:

A. Cardiac screening (FU 2015- C1a, C1b)
B. GI screening (FU 2015- C1e, C1f)
C. Dermatologic screening (FU 2015- C1i)
D. Breast screening (FU 2015- C1j, C1k, C1l)
E. Cervical screening (FU 2015- C1m)

Exploratory Variables:

A. Sociodemographic Variables:

-Age (BL, FU 2015 & birth date)
-Gender (BL)
-Race/ ethnicity (BL)
-Highest grade or level of schooling (FU 2015- A4)
-Current employment status (FU 2015- A5)
-Household income (FU 2015- A7)
-Insurance coverage (FU 2015- A10)
-Marital status (FU 2015- M2)

B. Disease / Treatment Variables:

-Cancer diagnosis
-Age at diagnosis
-Chemotherapy vs. surgery vs. radiation vs. BMT vs. combination
-Doxorubicin-equivalent dose
-If "yes" to radiation →
  -Did they receive mantle or chest radiation
  -Did they receive abdominal, pelvic, and/or spinal (thoracic, lumbar, sacral) radiation

C. Health Status:

-Perceived general health (FU 2015- O1)
-Mental Health via the Brief Symptom Index (FU 2015 L1-18 & P1)
-Functional impairment (FU 2015 N25, 26)
-Activity limitations (FU 2015 N29)
-Pain (FU 2015- L20)
-Anxiety / fears as a result of previous cancer (FU 2015- L19)

D. Treatment Summary or Copies of Medical Record:

-Has cancer survivorship care plan (FU 2015- B7)
-Primary care doctor has a copy of survivorship care plan or records (FU 2015- B8)

E. Medical Care:

-Seen by a doctor in the last 2 years (FU 2015- B2)
-Last routine check up with tests for problems from cancer (FU 2015- B4)
  -Last visit with a cancer specialist (FU 2015- B4c)
  -Last visit to a special clinic for cancer survivors (FU 2015- B4d)
-Hospitalizations (FU 2015- U1)

F. Other:

-Family history of cancer (FU 2015- W4)

Data Analysis Plan:

Aim 1: We will assess each outcome separately:

High-risk surveillance:

- Adherence to COG-recommended breast-cancer surveillance (mammography or MRI) in female survivors at elevated risk for breast cancer

- Adherence to COG-recommended colorectal-cancer surveillance (colonoscopy) in survivors at elevated risk for colorectal cancer
- Adherence to COG-recommended skin-cancer surveillance (complete skin exam) in survivors at elevated risk for skin cancer
- Adherence to COG-recommended echocardiography in survivors at elevated risk for cardiomyopathy

Standard-risk screening:

- Adherence to ACS-recommended cervical cancer screening (PAP smear) in all females
- Adherence to ACS-recommended breast cancer screening (mammography) in all females not at elevated risk for breast cancer, and who have reached age 45 years
- Adherence to ACS-recommended colorectal cancer screening in all survivors not at elevated risk for colorectal cancer, and who have reached age 50 years. CCSS captures data on colonoscopy, flexible sigmoidoscopy and fecal occult blood, but not on double contrast enema or CT colonography.

We will determine the proportion of at-risk survivors who are adherent to the high-risk COG guidelines, and the proportion of survivors and siblings who are adherent to the standard-risk ACS guidelines. For the ACS guidelines, we will also obtain population data for guideline adherence from the NHIS at https://www.cdc.gov/nchs/nhis/SHS/tables.htm.

We will also compare the adherence proportions to those observed in the 2003 survey. Results will be reported as risk ratios with 95% confidence intervals. For each screening test, we classified survivors as (i) completing the test within the recommended period; (ii) completing the test, but not within the recommended period; or (iii) never having completed the test (Table 7). Only those survivors who completed the test within the recommended period will be considered to be "adherent" to the guidelines as of the relevant survey (2003 or FU5). We will also use the age at initiation of screening to calculate a cumulative prevalence.

For each hypothesis below, for each screening outcome, among the at-risk population, the relevant risk factors will be evaluated using separate multiple variable generalized linear regression models with either a logit or log-link function, as appropriate, to directly estimate relative risks, adjusting for current age, gender (where appropriate) and race/ethnicity.

Hypothesis 2: The impact of potential predictors of compliance with each of the recommended screening guidelines (higher level of education, greater household income, being employed, having health insurance, more frequent physician visits, possession of a cancer survivorship care plan, increased anxiety/fear regarding past diagnosis, being married, not living alone, having children and having healthy habits-not smoking, low alcohol consumption, appropriate levels of physical activity, will be examined in multivariable regression models as described above.

Hypothesis 3: The impact of potential healthcare provider related predictors of compliance with each of the recommended screening guidelines, type of provider (cancer specialist), location of

interaction (cancer survivor clinic), and availability of a cancer care plan, will be examined in multivariable regression models as described above.

Hypothesis 4: We will assess the relationship between adherence to standard risk screening and high risk surveillance by fitting similar multivariable models to those described above, but with key risk factor of interest being completion of all relevant ACS standard risk screening. A separate model for each COG recommended screen will be fit among the subjects considered at high risk for the associated outcome. Covariates will be included in these models if they modify the association between ACS screening completion and the outcome (as a confounder). Care will be taken in selecting adjustment factors to avoid inclusion of variables that have a potential causal relationships with both ACS and COG screening completion (such as insurance availability), although we will explore the possibility of stratification and/or interactive effects.

Examples of Tables & Figures:

Table 5: Demographic, Disease & Health Status Data				
	Survivors (n=)		**Siblings (n=)**	
Characteristic:	**N**	**%**	**N**	**%**
Race/Ethnicity:				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Other				
Age Group:				
< 18 years				
18-24 years				
25-35 years				
35+ years				
Gender:				
Male				
Female				
Education:				
< High School				
High School Graduate				
College Graduate				
Unknown				
Employment:				
Employed or caring for home				
Looking for work or unable to work				
Student				
Household income				
<$20 000				
$20 – 59,000				

$60 – 99,999				
$100,000+				
Unknown				
Insurance Coverage:				
Canadian				
American Public				
American Private				
American None				
Marital Status:				
Married				
Single				
Divorced or separated				
Unknown				
Currently Have Children:				
Yes				
No				
Cancer Diagnosis:				
Leukemia				
ALL				
AML				
Other				
CNS tumor				
Medulloblastoma/PTEN				
Astrocytoma				
Other				
Lymphoma				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
Bone				
Osteosarcoma				
Ewing Sarcoma				
Other				
Wilms tumor				
Neuroblastoma				
Unknown				
Age at Diagnosis:				
0-4 years				
5-9 years				
19-14 years				
15-19 years				
Health Status- Perceived General Health:				
Excellent/good/very good				
Fair/poor				

Health Status- Mental Health:				
Normal				
Abnormal[+]				
Health Status- Pain As a Result of Previous Cancer:				
Yes				
No				
Health Status- Anxiety As a Result of Previous Cancer:				
Yes				
No				
Help with Personal Care:				
Yes				
No				
Help with Routine Needs:				
Yes				
No				
Chronic Disease Status:				
Grade 0, 1, 2				
Grade 3, 4				
Survivor has Survivorship Care Plan:				
Yes				
No				
Primary Care Doctor has Survivorship Care Plan or Records:				
Yes				
No				
Number of Physician Visits in the Past 2 Years:				
None				
1-4				
5-10				
11-20				
More than 20				
Most Recent Routine Check-Up Related to Past Cancer:				
Less than a 1 year ago				
1-2 years ago				
2-5 years ago				
More than 5 years ago				
Never				
Last Visit with a Cancer Specialist:				
Less than a 1 year ago				
1-2 years ago				

2-5 years ago				
More than 5 years ago				
Never				
Last Visit to a Special Clinic for Cancer Survivors:				
Less than a 1 year ago				
1-2 years ago				
2-5 years ago				
More than 5 years ago				
Never				
Admitted to Hospital in the Past 12 Months:				
Yes				
No				
Family History of Cancer:				
Yes				
No				

+Abnormal was defined as a sex-specific T-score of 63 or higher on the Global Severity Index or depression, anxiety or somatization subscales

Table 6: Risk Group				
	Survivors (n=)		**Siblings (n=)**	
Characteristic:	**N**	**%**	**N**	**%**
Breast Cancer Risk Group:				
COG High Risk*				
ACS Standard Risk**				
Not at Risk				
Colon Cancer Risk Group:				
COG High Risk***				
ACS Standard Risk****				
Not at Risk				
Skin Cancer Risk Group:				
COG High Risk*+				
Not at Risk				
Cervical Cancer Risk Group				
ACS Standard Risk*++				
Not at Risk				
Cardiac Dysfunction Risk Group:				
None*+++				
1 year **++				
2 year **++				
5 year**++				

*Female that received >20 Gy of chest radiation with potential impact to the breast

**Females over 45 years of age
***Received > 30 Gy of radiation with potential to impact the colon/rectum
****Over 50 years of age
*[+]Received any radiation
*[++]Females aged 21 to 65
*[+++]Did not receive > 30 Gy of chest radiation or have any exposure to anthracycline chemotherapeutic agents
**[++]See Table 3

Table 7: 2015 Cohort Adherence to Suggested Surveillance Interventions

Table 7a: Screening for GI Malignancy				
	High risk survivors*	**Standard risk survivors****	**Siblings****	**General Population****
Had test within recommended period				
Had test, but not within recommended period				
Never had test				
Don't know				

*Males or females that received > 30 Gy of radiation with potential to impact the colon/rectum as per COG guidelines
** Over 50 years of age as per ACS guidelines

Table 7b: Screening Mammography				
	High risk survivors*	**Standard risk survivors****	**Siblings****	**General Population****
Had test within recommended period				
Had test, but not within recommended period				
Never had test				
Don't know				

*Female that received >20 Gy of chest radiation with potential impact to the breast as per COG guidelines
**Females over 45 years of age as per ACS guidelines

Table 7c: Screening PAP Test				
	High risk survivors	**Standard risk survivors****	**Siblings****	**General Population****

Had test within recommended period				
Had test, but not within recommended period				
Never had test				
Don't know				

**Females aged 21 to 65 as per ACS guidelines

Table 7d: Screening Dermatologic Exam				
	High risk survivors*	**Standard risk survivors**	**Siblings**	**General Population**
Had test within recommended period				
Had test, but not within recommended period				
Never had test				
Don't know				

*Received any radiation as per COG guidelines

Table 7e: Screening Echocardiogram				
	High risk survivors*	**Standard risk survivors**	**Siblings**	**General Population**
Had test within recommended period				
Had test, but not within recommended period				
Never had test				
Don't know				

*Received > 30 Gy of chest radiation or had any exposure to anthracycline chemotherapeutics as per COG guidelines

Table 8: Predictors of adherence to mammography, colonoscopy, skin exam & echocardiogram guidelines in survivors at high risk of developing breast cancer, colorectal cancer, skin cancer or cardiac dysfunction.

	Mammography:				**Colonoscopy:**				**Skin Exam:**				**Echocardiogram:**			
	Univariate		**Multivariate**		**Univariate**		**Multivariate**		**Univariate**		**Multivariate**		**Univariate**		**Multivariate**	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI

Table 9: Predictors of adherence to mammography, colonoscopy, skin exam, pap test & echocardiogram guidelines in survivors at standard risk of developing breast cancer, colorectal cancer, skin cancer, cervical cancer or cardiac dysfunction.

	Mammography:				**Colonoscopy:**				**Skin Exam:**				**Pap Test:**				**Echocardiogram:**			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI

6. **SPECIAL CONSIDERATIONS**:
No special considerations exist for this proposal.

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