Childhood Cancer Survivor Study
Analysis Concept Proposal

Study Title: Late Cardiovascular Disease Risk Prediction among Childhood Cancer Survivors and Scalable Clinical Informatics Tools for Electronic Health Record Integration

Working Groups: Chronic Disease, Epidemiology/Biostatistics

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Background and Rationale:

Cardiovascular disease (CVD) represents a leading cause of late morbidity and mortality among childhood cancer survivors.[1,2] Previous analyses from the Childhood Cancer Survivor Study (CCSS) clearly document the significant impact of cancer treatment on heart health in adulthood.[3-5] The development of validated risk calculators for heart failure, stroke, and myocardial infarction provides clinical decision support for individual risk prediction.[6-8] Nevertheless, an additional decade of longitudinal follow-up among CCSS participants provides an opportunity to refresh the risk calculators. Moreover, the concurrent advances in clinical informatics tools to leverage discrete data from the electronic health record (EHR) offer a lens to design tools to promote the scalability and impact of such risk calculators on clinical care. Indeed, even for well-established cardiovascular risk calculators validated in the general adult population, major barriers to implementation include time constraints to use and access the calculator.[9]

The use of web-based platforms for clinical decision support (CDS) is a helpful initial step to disseminate tools for widespread access for healthcare providers, yet the burden of data entry and external interface to the EHR impedes optimal integration into busy clinic workflows. Time constraints for manual data entry for survivorship care planning and treatment summary tools, such as Passport for Care (PFC) in the pediatric oncology space, highlight key barriers to guide innovation.[10] More than a decade after the Health Information Technology for Economic and Clinical Health (HITECH) Act, the initial promise of EHRs to streamline data access and improve patient care has been muddled with mixed responses among providers.[11,12] Novel

clinical informatics solutions to promote uptake of risk calculators (e.g. the CCSS late CVD risk calculator) could increase their impact. CDS involves providing the right clinical knowledge, targeted to the right user, and presented at the right time. CDS focuses on the end user (e.g. clinician) and incorporates metrics to maximize the impact of support tools.[13] The technology assessment model (TAM) offers a robust framework to evaluate potential EHR-based tools.[14] Specific metrics, such as provider time, system usability score, perceived usefulness, and perceived ease-of-use, offer tools to evaluate the implementation of a CDS tool for risk calculation.

Discrete data elements in the EHR to integrate such risk calculators enhance interoperability as survivors transition between health systems, particularly to adult care, as the cumulative incidence of CVD is expected to grow given the long latency between cardiotoxic exposures and late CVD. This interoperability is critical, as the observed proportion of survivors with suboptimal follow-up in the early survivorship is significant, and even among CCSS participants, increases to nearly two-thirds without a survivorship-focused visit in the previous two years.[15] EHR-based tools may also help engage primary care providers to identify survivors at risk for cardiotoxicity, as approximately half a million survivors live in the United States, underscoring the growing need for onco-primary care. Finally, leveraging key data elements in the EHR introduces the possibility of population health management to identify high-risk survivors, as well as survivors as low risk, to prioritize patient engagement, target cardioprotective lifestyle strategies, and support optimal transitions to adult survivorship-focused care.

This ACP will leverage and build upon the analyses associated with the R01-CA261750 (MPI: Howell, Mulrooney, Yasui, Bates, and team), which will develop (in CCSS) and independently validate (in SJLIFE) risk prediction models for heart failure, coronary artery disease, and heart valve disease, incorporating radiation therapy substructure doses, adjusting for demographics and chemotherapy exposures. To avoid potential overlap, this proposal will only develop prediction models for stroke and major adverse cardiac events (MACE) for the first aim. For the second and third aims, we will plan to implement each of the late CVD risk calculators as EHR-based tools for CDS.

Specific Aims:

Specific Aim 1: Given availability of follow-up 7 (FU7) outcomes, we will update the previous CVD prediction models (Chow et al, JCO 2014 and 2017) using the same methods based on proportional hazards models and a time-dependent receiver operating characteristic (ROC) curve approach to predict stroke and MACE following childhood cancer treatment as associated with baseline treatment and demographic factors (including age at diagnosis and gender) Final prediction models will continue to include data elements readily available in the EHR (demographics, chemotherapy exposures with cumulative doses) and different levels of granularity for radiation data (e.g., any chest field radiation, chest field radiation target dose, mean cardiac dose). We will consider both a 10-year risk estimate and risk by age 60 years old.

Specific Aim 2: Leverage discrete demographic and treatment exposure data in the EHR to create an EHR-based version of the updated CCSS CVD prediction models as a tool to enhance clinical decision support and population health management.

Hypothesis: a) Data elements included in the final updated prediction models will be readily available in a discrete format within the EHR and will be feasible to implement as an EHR tool.

b) Compared with the web-based platform, the EHR tool will reduce provider time, yield a greater system usability score (based on the technology acceptance model), and will be highly acceptable for implementation among providers (target n=15).

Specific Aim 3: Implement the EHR-based late CVD risk prediction tool at another CCSS institution to evaluate its interoperability and scalability.

Hypothesis: The EHR-based late CVD risk prediction tool will be feasible and scalable at another CCSS institution with similar usability and acceptability (target n=30 providers to survey).

Analysis Framework:

Study Population: The entire CCSS cohort that completed the baseline questionnaire and has available medical record abstraction form (MRAF) data. We will also use sibling data to provide a general population reference as survivors' CVD risk groupings are compared against siblings to determine low, moderate, and high risk status.

Outcomes of Interest:

1) CVD outcomes (Grade 3-5) as defined by CCSS' adapted definitions of the Common Terminology Criteria for Adverse Events
   - Stroke
   - MACE, defined as cardiomyopathy (CTCAE grade 3–5 left ventricular systolic dysfunction), myocardial infarction (CTCAE grade 3–5 coronary artery disease), stroke (CTCAE grade 2–5 cerebrovascular accident), and other cardiovascular-related mortality (other CTCAE grade 5 cardiac events)
2) EHR-based Tool Implementation Metrics
   - Primary Outcome: Provider Time
     - This will be measured based on the total time (in seconds) that the provider spends to generate the risk score using the EHR-based tool vs the web-based platform.
   - Secondary Outcomes:
     - Systems Usability Score (Appendix A)
       - This will be assessed based on the well-established System Usability Score Survey, which includes a reference standard for comparison and is widely used in the CDS literature with suitability for small sample sizes (n<15).[19,20]
     - Technology Acceptance Model (TAM; Appendix B)[21,22]
       - Perceived Usefulness
       - Perceived Ease-of-Use

Explanatory Variables:

1) Age at cancer diagnosis
   - 0 to 5-years-old

- 6 to 10-years-old
- 11 to 14-years-old
- 15 to 20-years-old

2) Sex of cancer survivor
3) Cancer treatment exposures
    - Cumulative doxorubicin equivalent dose
    - Platinum agents
    - Cranial radiation therapy (none, 1-19 Gy, >= 20 Gy)
    - Mean Chest and heart radiation therapy doses
    - Alkylators
4) Provider characteristics (for aims 2 and 3)
    - Years in Practice
    - Age
    - Sex/Gender
    - Provider Type (Pediatric Oncologist, Advanced Practice Provider, Pediatric Cardiologist, General Pediatrician, Registered Nurse, Other)
    - Primary Team (Liquid Tumor, Solid Tumor, Brain Tumor, Other)
    - Familiarity with survivorship care (5-point Likert Scale)

Variable	Categories	Baseline Questionnaire
Age at Diagnosis	0 to 5-years-old	
	6 to 10-years-old	
	11 to 14-years-old	
	15 to 20-years-old	
Sex	Male	A.2
	Female	
Cumulative Doxorubicin Equivalent Dose	None	Medical Record Abstract Form
	1-99mg/m2	
	100-249mg/m2	
	≥250mg/m2	
	Unknown	
Chest Radiotherapy Dose*	None	Medical Record Abstract Form
	<5 Gy	
	5-14 Gy	
	15-34 Gy	
	≥35 Gy	
Mean Cardiac Radiation Dose*	None	Medical Record Abstract Form
	<5 Gy	
	5-14 Gy	
	15-34 Gy	
	≥35 Gy	
Platinum Agents	Yes/No	Medical Record Abstract Form
Stroke	Grade 3 to 5	Refer to chronic disease matrix

MACE	Cardiomyopathy (CTCAE grade 3–5 left ventricular systolic dysfunction), myocardial infarction (CTCAE grade 3–5 coronary artery disease), stroke (CTCAE grade 2–5 cerebrovascular accident), and other cardiovascular-related mortality (other CTCAE grade 5 cardiac events)	Refer to chronic disease matrix

*We will consider radiation as both continuous and categorical in different models, choosing the

Statistical Analysis:

Specific Aim 1: *Given the availability of FU7 outcomes, we will update the previous CVD prediction models (i.e., Chow et al, JCO 2014 and 2017) using the same methods based on proportional hazards models and a time-dependent receiver operating characteristic (ROC) curve approach to predict individual risk for stroke and MACE following childhood cancer treatment as associated with baseline treatment and demographic factors (including age at diagnosis and gender). Final prediction models will continue to include data elements readily available in the EHR (demographics, chemotherapy exposures with cumulative doses) and different levels of granularity for radiation data (e.g., any chest field radiation, chest field radiation target dose, mean cardiac dose). We will work closely with Yutaka Yasui, Rebecca Howell, and Daniel Mulrooney to ensure that updated prediction models are consistent with similar work being developed in their separate R01 using CCSS and SJLIFE data.*

- Cox proportional hazards models will be used to generate hazard functions for overall CV morbidity, mortality, and individual CV outcomes of interest (stroke and MACE) associated with baseline treatment and demographic variables of interest.
  - For any baseline covariate found to be associated with CV disease, we will *a priori* explore first-order interactions with gender and age at cancer diagnosis.
  - Death will be classified as a competing risk in this analysis.
  - Relapse or original disease and secondary malignancy will NOT be considered competing risks but will be adjusted in the model as covariates.
  - In contrast to some CV prediction analyses performed in adult patients, the time scale used will be 5 years since cancer diagnosis (i.e. entry into the CCSS cohort), adjusted for age at time of diagnosis.
  - In order to examine changes in hazard over time, the hazard function for overall CV morbidity, mortality, and individual CV outcomes will be plotted over time.
  - As a subanalysis, we will also include cardiometabolic risk factors (Type 2 diabetes, hypertension, and hyperlipidemia), similar to other CCSS analyses, at ages 20 and 25 (to reflect the transition from pediatric to adult survivorship), as these are readily available in the EHR and could further refine at risk populations in transition to adult survivorship-focused care.

- Separate ROC curves incorporating those covariates identified as being significantly associated with each respective CV outcome will be used to estimate the corresponding area under the curves (AUCs) (Figure 1).
    - As AUCs associated with covariates may vary over time, we will first calculate and compare global AUCs (up to ages 50 to 60 if possible)
    - The most parsimonious combination of covariates associated with greater AUC will be selected for each outcome of interest. *A priori,* we will be most interested in knowing which covariates are associated with the largest global AUC.
- For these selected covariates, a risk score will then be devised by assigning integer points based on the beta-coefficients from their respective proportional hazards model(s) (Table 1).
    - Points are then summed to compute an overall risk score with the corresponding risk of CV outcomes associated with each score. ROC curves with corresponding AUCs will also be generated for risk score sums and compared with the prior ROC/AUCs to ensure that no significant loss in discriminatory power has occurred (Figure 1).

Assuming no significant loss in discriminatory power, the summed risk scores will then be categorized into 3 clinically relevant risk categories: low, average, and high (if the actual range of CV risk appears narrower, then low vs. high-risk categories will be used instead). The true-positive and true-negative rates will then be calculated for each risk category (Table 2).

Specific Aim 2: *Leverage discrete demographic and treatment exposure data in the EHR to create an EHR-based version of the updated CCSS CVD prediction models as a tool to enhance clinical decision support and population health management.*

Summary statistics for the TAM metrics (i.e., Provider Time, System Usability Score, etc.) will be calculated. Normality will be tested for the participants' overall scores, and non-normal data will be described using medians and IQRs, while normal data will be described using means and 95% confidence intervals. Median scores by providers for the EHR-based tool and the web-based platform will be compared using non-parametric analysis via Wilcoxon Rank Sum Tests (or, if the same users are asked about attitudes toward EHR-based vs web-based tools, then McNemar's Test will be used), and means will be compared using paired T-tests. This will be analyzed for Provider Time, System Usability Score, and Acceptability as measured by TAM (Table 3).

Specific Aim 3: *Implement the EHR-based late CVD risk prediction tool at another CCSS institution to evaluate its interoperability and scalability.*

This will be implemented at Texas Children's Hospital and Children's Healthcare of Atlanta, which both use the same EHR platform (Epic). Following the same procedures described for Aim 2, summary statistics for the TAM metrics will be calculated at the second site to assess scalability. We will compare scores between sites and, if similar, will combine the values to further strengthen the analysis and generalizability of the results. If they are different, this will provide an opportunity to discuss next steps for generalizability and scalability of such tools.

Proposed Tables and Figures:

Table 1: Multivariate hazard function coefficients (coeff) for covariates associated with each CV outcome of interest and corresponding risk score (if assigned).

	Overall CV morbidity			CV mortality			Stroke			MACE		
Covariate	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score

TABLE 2: XX year cumulative incidence of CV outcomes, true-positive rates, and true-negative rates associated with each risk score category.

Outcome	Low risk			Average risk			High risk		
	Cum. incid	True-positive rate	True-negative rate	Cum. incid	True-positive rate	True-negative rate	Cum. incid	True-positive rate	True-negative rate
Overall morbidity									
Mortality									
Stroke									
MACE									

Table 3. Metrics for Implementation of CCSS CVD Risk Calculator.

	EHR-based Tool	Web-based Platform	P-Value
Provider Time (in seconds)			
Usability Score			
Perceived Usefulness			
Perceived Ease-of-Use			

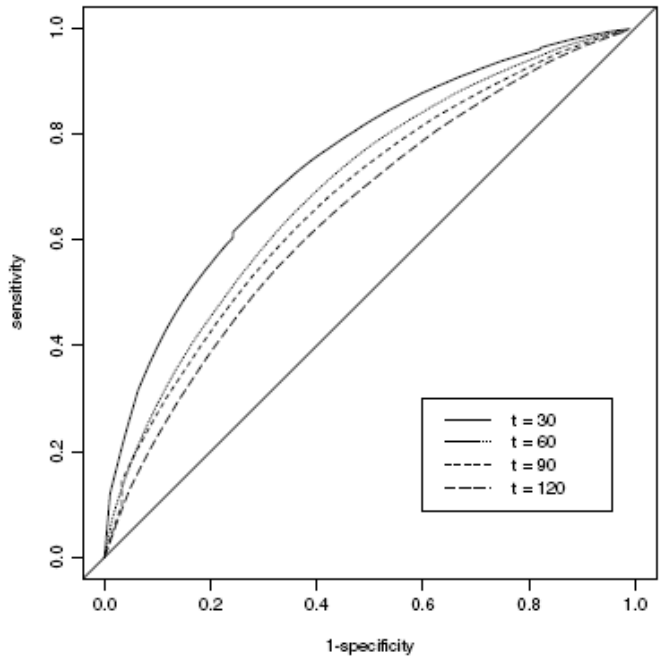

Figure 1: ROC curves for different time intervals associated with the most parsimonious model.

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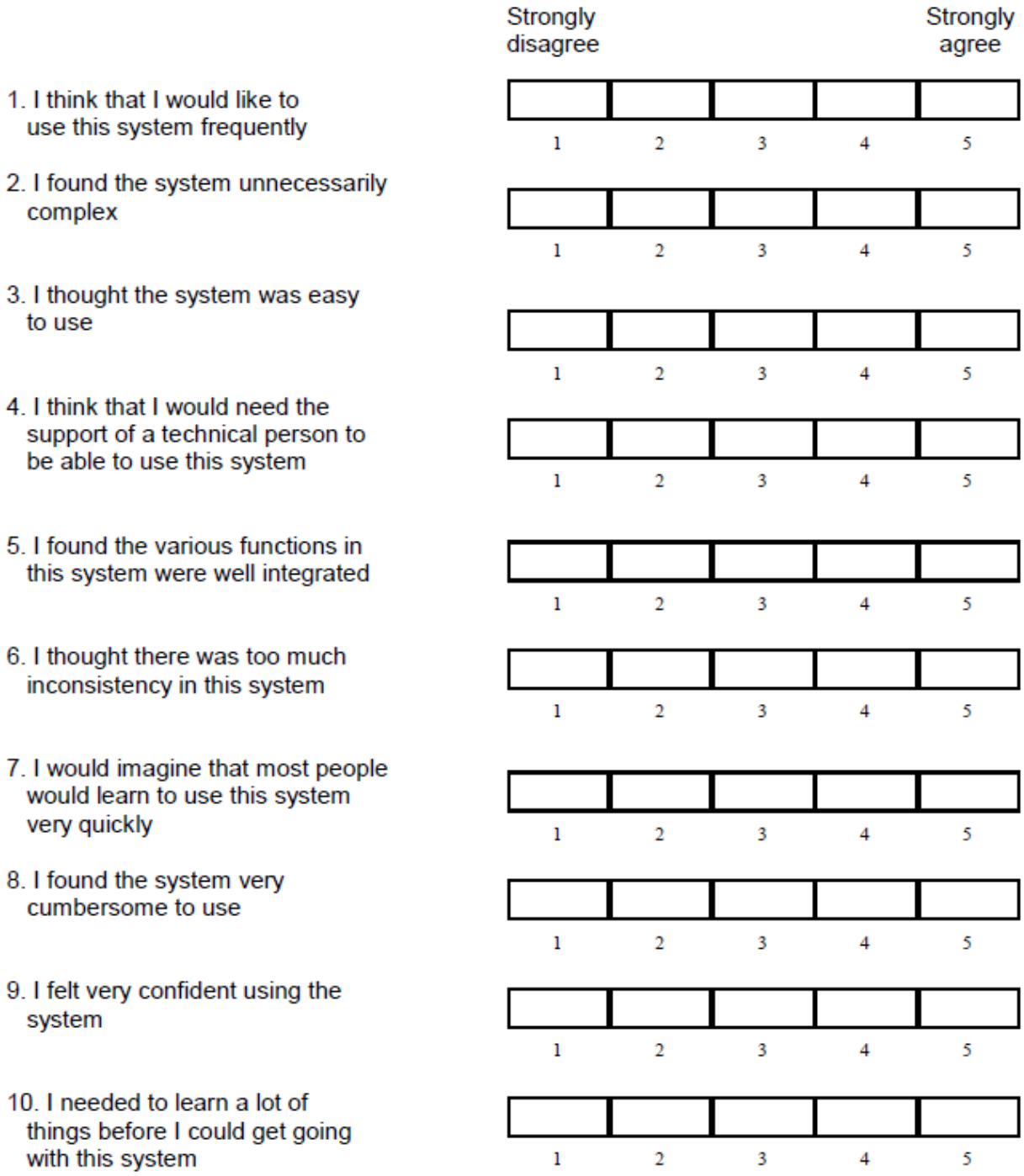
Appendix A. Systems Usability Score Survey



Appendix B. Technology Acceptance Model

Technology Acceptance Model

Perceived Usefulness (PU)	**Likely** *Extremely*	*Quite*	*Slightly*	*Neither*	*Slightly*	*Quite*	**Unlikely** *Extremely*
1. Using [this product] in my job would enable me to accomplish tasks more quickly.							
2. Using [this product] would improve my job performance.							
3. Using [this product] in my job would increase my productivity.							
4. Using [this product] would enhance my effectiveness on the job.							
5. Using [this product] would make it easier to do my job.							
6. I would find [this product] useful in my job.							

Perceived Ease-of-Use (PEU)	**Likely** *Extremely*	*Quite*	*Slightly*	*Neither*	*Slightly*	*Quite*	**Unlikely** *Extremely*
7. Learning to operate [this product] would be easy for me.							
8. I would find it easy to get [this product] to do what I want it to do.							
9. My interaction with [this product] would be clear and understandable.							
10. I would find [this product] would be clear and understandable.							
11. It would be easy for me to become skillful at using [this product].							
12. I would find [this product] easy to use.							