Title: Randomized Trial of Cardiomyopathy Screening in At-Risk Adult Survivors of Pediatric Malignancies

Working Groups: Cancer Control, Chronic Disease, Epidemiology/Biostatistics

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Background

While the anthracyclines (e.g., doxorubicin, daunorubicin) have contributed significantly to childhood cancer survival, they confer an excess risk of asymptomatic left ventricular dysfunction, cardiomyopathy, congestive heart failure, and death. Anthracycline cardiotoxicity results in loss of cardiac myocytes, thus impeding myocardial development. Unfortunately, these myocardial effects can be progressive and harmful, yet asymptomatic. Cardiotoxicity has been reported at all dose levels, but the risk increases with higher cumulative dose, younger age at first exposure, time after exposure, and female sex. As many as 5% of at-risk survivors will develop congestive heart failure within 15 years after treatment. These effects remain asymptomatic in as many as 57% of survivors until exacerbated by physiologic stressors such as infection or pregnancy. Irradiation of CV structures (mantle, mediastinal, whole-lung, and total body irradiation) has been associated with various adverse CV outcomes, including cardiomyopathy, constrictive pericarditis, and accelerated atherosclerosis, predisposing to early-onset coronary artery disease, myocardial infarction, and stroke. Like anthracycline sequelae, these effects may be acute or delayed and are frequently subclinical. Risk factors include higher doses, fractionated doses > 2.0 Gy/day, irradiation of a larger heart volume, younger age at exposure, preexisting cardiac disease, and concomitant cardiotoxic chemotherapy. The late manifestations of CV irradiation also include myocardial fibrosis, valvular disease, autonomic dysfunction, and conduction abnormalities.

Collectively, the frequency and severity of adverse CV outcomes reported in childhood cancer survivors suggest that specific diagnostic and treatment groups may benefit from screening and early intervention to remediate conditions that can adversely impact CV health. These concerns have motivated the development of CV screening recommendations by the Children's Oncology Group (COG) and other survivorship advocacy groups. All currently available guidelines recommend evaluation of left ventricular systolic function by echocardiography or comparable imaging (e.g., multiple uptake gated acquisition scan). The frequency of CV screening recommended by COG is based on age at cancer diagnosis and the cumulative dose of cardiotoxic therapies. Annual screening is recommended for survivors at the highest risk of CV dysfunction, including those treated with high cumulative doses of anthracycline for age or with both anthracyclines and cardiac radiation. Biannual screening is recommended for who received intermediate cumulative doses of anthracycline for age. For survivors considered at low risk of CV dysfunction, such as those treated with low cumulative anthracycline doses for age, screening every 5 years is recommended. Full details are available at www.survivorshipguidelines.org.

Specific Aims

We propose a randomized clinical trial to promote cardiomyopathy screening: **E**valuation of **C**ardiovascular **H**ealth **O**utcomes among **S**urvivors (**ECHOS**). Relying on the unique resources of the Childhood Cancer Survivor Study (CCSS), we will recruit adult survivors of childhood cancer (treated with anthracycline chemotherapy and/or chest radiation) *who have not had CV screening during the past five years.* They will be randomized to one of two intervention arms: 1) A mailed individualized cancer treatment summary informing survivors about their exposure-based risks, recommended lifestyle changes, and recommended long-term follow-up (standard care). 2) Standard care plus a phone counseling intervention by an advanced practice nurse (APN) that incorporates motivational supportive techniques targeting individual behavioral constructs likely to influence CV screening participation.

Our primary aim (Aim 1) is to assess the efficacy of the intervention in increasing the rate of CV screening. The secondary aims (Aims 2 & 3) will identify changes in survivor behavioral characteristics in response to the intervention, their mediating effects on the primary outcome, and the cost-effectiveness of the intervention.

Aim 1: To test the hypothesis that at 1 year after the intervention, a significantly greater proportion of the APN phone counseling group will have undergone cardiovascular screening, as compared to the standard care group. CV screening will be defined, based on established CV screening recommendations, as completion of an imaging evaluation of left ventricular systolic function (i.e., echocardiogram, multiple uptake gated acquisition scan, or cardiac magnetic resonance imaging).

Aim 2. To measure changes induced by the intervention in survivors' knowledge, motivation, fear, beliefs, affect, readiness for medical follow-up, and self-efficacy and these changes' potential mediating effects on CV screening participation.

Aim 3. To estimate the cost-effectiveness of ECHOS intervention in terms of the cost of left ventricular systolic function imaging per additional survivor.

Methods

This CCSS ancillary study was funded through an NIH grant. The intervention trial has now been completed and we are poised to begin publishing the study findings. The methods below reflect the successful completion of accrual and follow-up, as well as the methods for analyzing the primary outcome.

This Institutional Review Board-approved study comprised a randomized, two-arm trial in which the primary outcome was completion of cardiomyopathy screening within one year following intervention (Figure 1). Participants were recruited from the CCSS, a 26-institution retrospective cohort study currently following more than 12,000 long-term survivors of childhood cancer diagnosed between 1970 and 1986. Since enrollment in 1994-1998, participants have been surveyed periodically to track important health outcomes, health care utilization patterns, and health behaviors and practices. The CCSS cohort methodology and study design have been previously described in detail. Survivors were eligible to participate in ECHOS if they: 1) age ≥25 years, 2) had received anthracyclines and/or chest-directed radiation involving cardiac structures, 3) had received no cardiomyopathy screening during the

past 5 years, 4) were not actively participating in a long-term follow-up program that provided risk-based health screening, and 5) had a history of providing direct (non-surrogate) responses to CCSS surveys. Additionally, for logistics reasons, survivors living abroad from North America and those without telephone access were excluded from participation.

Following receipt of informed consent, participants were assigned to study arms by using a computerized, randomly permuted block method; they were stratified by age (<30 years vs. ≥30 years), sex, and cancer diagnosis (hematological malignancy vs. solid tumor). Following a baseline assessment, members of the standard care group were mailed a personalized SCP outlining their specific cancer treatments and health risks and providing tailored recommendations for cardiomyopathy screening from the COG Guidelines, version 3.0 (www.survivorshipguidelines.org). The packet also included a laminated card summarizing treatment exposures, future health risks, and recommendations for follow-up that could be given to the primary care provider. Following baseline assessment, survivors in the APN intervention arm were mailed the same personalized SCP and laminated card as described for participants in the standard care arm. These survivors also received two telephone counseling sessions from an APN, 1 and 3 weeks after receiving the individualized SCP. After each call, the survivor was sent a follow-up letter summarizing the conversation. The counseling sessions were tailored to address individual barriers to completion of cardiomyopathy screening. Factors addressed in tailoring of APN counseling to overcome barriers to screening included health knowledge deficits (e.g., cancer treatment history, cardiomyopathy risk associated with cancer treatment, health screening tests recommended for cardiomyopathy, benefits of early detection of cardiomyopathy), health perceptions (e.g., risk of cardiomyopathy to future health, importance of cardiomyopathy screening based on cancer treatment, fear/anxiety related to undergoing cardiomyopathy screening, fear/anxiety about what screening tests will show), and health care access (e.g., insurance access, insurance coverage of screening, identification of primary care practitioner, communication with primary care practitioner and insurance company, identification of screening facilities).

One year after completion of the intervention (i.e., receipt of the personalized SCP for the standard care group and 1 year after the last APN telephone call for the intervention group), a follow-up questionnaire was distributed to assess self-reported adherence to cardiomyopathy screening and reasons for non-adherence. Medical records were requested to validate screening participation and results.

Analysis of Aim 1

T-tests and Chi-square tests will be used to compare categorical and continuous characteristics in the 2 groups at baseline. The proportions of survivors completing cardiomyopathy screening within one year of intervention will be compared between the groups using relative risks based on a generalized linear model with a log link and Poisson working model with robust standard errors. The model will be adjusted for gender, age and COG-recommended screening frequency group. All analyses will be based on intent to treat. For analysis purposes, participants will be categorized by Children's Oncology Group (COG) cardiomyopathy risk group as high, intermediate, or low risk for whom the frequency of cardiomyopathy screening is recommended every year, 2 years, and 5 years, respectively.

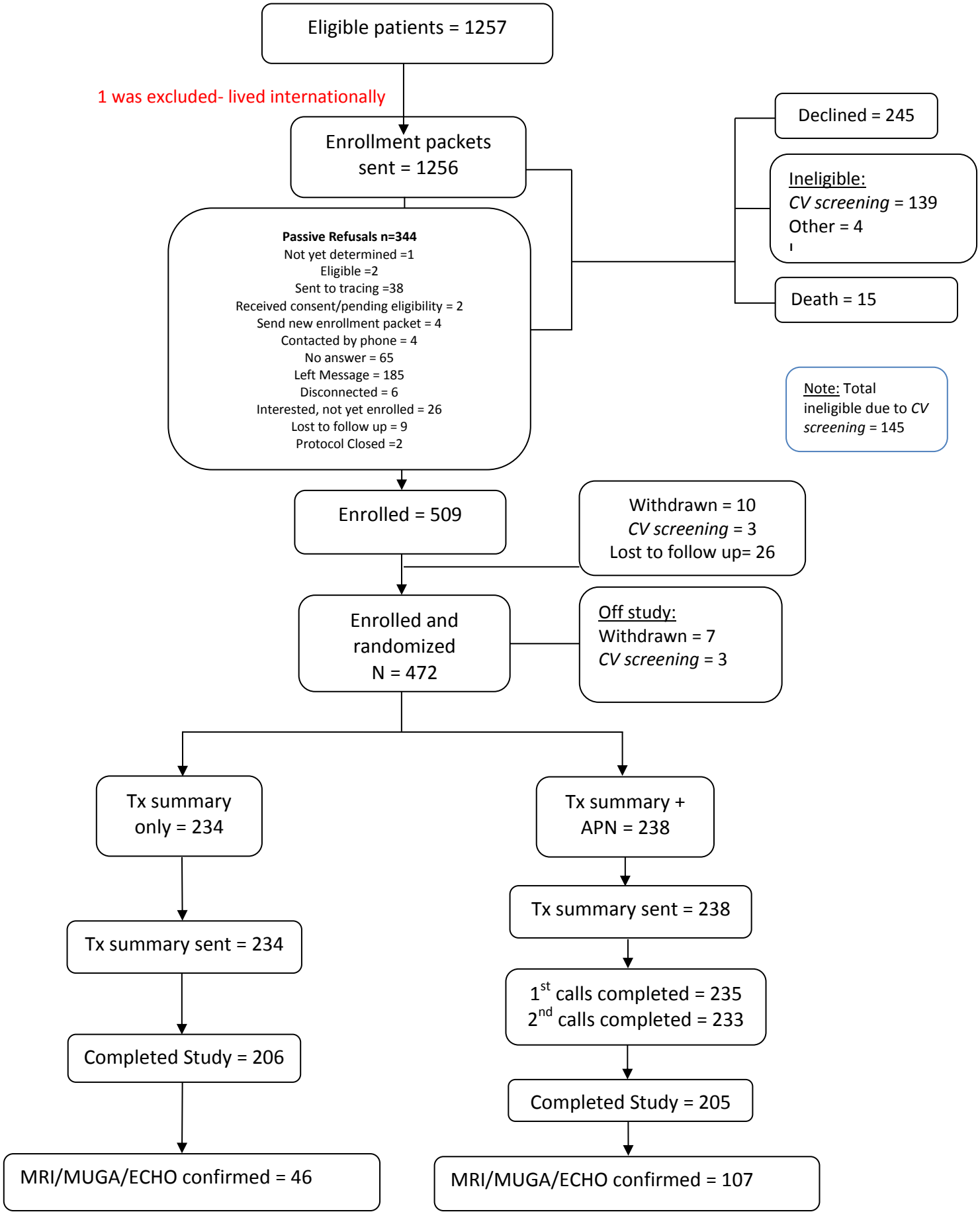
Analysis of Aims 2 & 3

Specific Aim 2: We will model variables as outcome variables independently using repeated measures ANCOVA. We have at least 95% power to detect a 0.3 SD effect size for each outcome. Using the MIXED procedure in SAS, the two intervention groups' baseline dependent measurements and stratification

variables will be between-subject factors, and time will be a within-subject factor. Because the questionnaire data are measured on a discrete scale, we will explore transformations to the outcomes that result in more normally distributed data, so that the underlying theoretical assumptions of our model are met. One such monotonic transformation involves converting the scales to proportions of the total scale and applying the logit transformation. The impact of demographic and other independent variables (e.g., health status) will be assessed by including them as covariates in this model.
We will also explore the potential mediating effects of the cognitive appraisal variables (knowledge, intent to have CV screening, perceived severity/susceptibility, perceived barriers to CV-screening, readiness for medical follow-up), the motivation variables (self-efficacy, intrinsic motivation, CV-self-regulation), the affect variables (fear arousal, BSI Depression, Brief Perceived Stress Scale), and the survivor-provider interaction variables (PACIC, Health Care Climate, decisional control) on CV-screening adherence. We will use structural equation modeling, which incorporates the steps necessary for testing mediation

Specific Aim 3: If the APN intervention arm is found to be more effective than standard care, the relevant effectiveness measure for this comparison is the difference in the proportion of at risk cancer survivors who participate in screening at follow up in the intervention study arm as compared to the standard care arm. The costs are those of delivering the APN counseling component above and beyond those of the development of the standard care intervention. Cost estimation will be based on: 1) identifying all cost-based activities (APN training, call attempts, time spent counseling, call summary mailings, intervention manuals, and leaving messages when call attempts are not successful); 2) estimating the average number of times each activity is performed over the intervention period per survivor in the target population, and 3) estimating the unit costs of each activity.

A summary of study recruitment is provided in the CONSORT diagram below:


Eligible patients = 1257
1 was excluded- lived internationally
Enrollment packets sent = 1256
Declined = 245
Ineligible:
CV screening = 139
Other = 4
Death = 15
Passive Refusals n=344
Not yet determined =1
Eligible =2
Sent to tracing =38
Received consent/pending eligibility = 2
Send new enrollment packet = 4
Contacted by phone = 4
No answer = 65
Left Message = 185
Disconnected = 6
Interested, not yet enrolled = 26
Lost to follow up = 9
Protocol Closed =2
Note: Total ineligible due to CV screening = 145
Enrolled = 509
Withdrawn = 10
CV screening = 3
Lost to follow up= 26
Enrolled and randomized N = 472
Off study:
Withdrawn = 7
CV screening = 3
Tx summary only = 234
Tx summary + APN = 238
Tx summary sent = 234
Tx summary sent = 238
Completed Study = 206
1st calls completed = 235
2nd calls completed = 233
Completed Study = 205
MRI/MUGA/ECHO confirmed = 46
MRI/MUGA/ECHO confirmed = 107

Baseline characteristics of at-risk adult survivors of childhood cancer assigned to APN Intervention (n=238) vs. control (n=234) group

		Control Group		Intervention Group		
		N	%	N	%	P-value
Gender	Female	122	52.1	130	54.6	
	Male	112	47.9	108	45.4	
Race	White non-Hispanic	208	88.9	210	88.2	
	Black	3	1.3	3	1.3	
	Other	21	9.0	25	10.5	
	Unknown	2	0.9	0	0.0	
Education	High school or less	25	10.7	21	8.8	
	Post HS training/some college	65	27.8	70	29.4	
	College graduate	92	39.3	90	37.8	
	Post graduate level	52	22.2	57	23.9	
Household income	<$60,000	90	38.5	85	35.7	
	$60,000 +	138	59.0	144	60.5	
	Unknown	6	2.6	9	3.8	
Diagnosis	Bone cancer	39	16.7	44	18.5	
	CNS	1	0.4	0	0.0	
	HD	43	18.4	37	15.5	
	Kidney (Wilms)	27	11.5	11	4.6	
	Leukemia	77	32.9	81	34.0	
	NHL	20	8.5	28	11.8	
	Neuroblastoma	11	4.7	10	4.2	
	Soft tissue sarcoma	16	6.8	27	11.3	
Age at cancer diagnosis	0-4	65	27.8	60	25.2	
	5-9	47	20.1	52	21.8	
	10-14	57	24.4	63	26.5	
	15-20	65	27.8	63	26.5	
Years since diagnosis	28 years or less	104	44.4	96	40.3	
	more than 28 years	130	55.6	142	59.7	
Health status	Excellent	40	17.1	31	13.0	
	Very good	108	46.2	102	42.9	
	Good	71	30.3	86	36.1	

		Control Group		Intervention Group		
		N	%	N	%	P-value
	Fair	12	5.1	16	6.7	
	Poor	3	1.3	1	0.4	
	Unknown	0	0.0	2	0.8	
Chemotherapy	Yes	211	90.2	220	92.4	
	No	23	9.8	18	7.6	
Radiation	Yes	157	67.1	166	69.7	
	No	76	32.5	72	30.3	
	Unknown	1	0.4	0	0.0	
Both chemotherapy and radiation	Yes	134	57.3	148	62.2	
	No	99	42.3	90	37.8	
	Unknown	1	0.4	0	0.0	
Chest radiation	Yes	65	27.8	63	26.5	
	No	163	69.7	173	72.7	
	Unknown	6	2.6	2	0.8	
Brain radiation	Yes	48	20.5	65	27.3	
	No	180	76.9	171	71.8	
	Unknown	6	2.6	2	0.8	
Alkylating agent	Yes	164	70.1	178	74.8	
	No	70	29.9	60	25.2	
Anthracycline	Yes	189	80.8	200	84.0	
	No	45	19.2	38	16.0	
Surgery	Yes	189	80.8	193	81.1	
	No	44	18.8	45	18.9	
	Unknown	1	0.4	0	0.0	
Amputation (MRAF)	Yes	19	8.1	22	9.2	
	No	214	91.5	216	90.8	
	Unknown	1	0.4	0	0.0	
Completed CV screening	Yes	206	88.0	205	86.1	
	No	28	12.0	33	13.9	

Comparisons of reasons for no screening between arms among those without confirmed cardiomyopathy screening

		Treatment summary + APN (n=85)		Treatment summary only (n=141)		
		N	%	N	%	P-value
Did not think important/didn't understand why needed	no	74	87.1	109	77.3	
	yes	11	12.9	32	22.7	
Too busy/did not have time	no	57	67.1	107	75.9	
	yes	28	32.9	34	24.1	
Could not afford test/no insurance	no	65	76.5	120	85.1	
	yes	20	23.5	21	14.9	
Concerns about insurance coverage or payment	no	60	70.6	123	87.2	
	yes	25	29.4	18	12.8	
MD didn't recommend/order	no	78	91.8	113	80.1	
	yes	7	8.2	28	19.9	
Forgot/haven't done it/don't think about it	no	81	95.3	124	87.9	
	yes	4	4.7	17	12.1	
Other	no	83	97.6	136	96.5	
	yes	2	2.4	5	3.5	
Not having medical f-u, don't like medical procedures	no	84	98.8	138	97.9	
	yes	1	1.2	3	2.1	
Had previous testing	no	83	97.6	139	98.6	
	yes	2	2.4	2	1.4	
Plan to have screening in future	no	84	98.8	138	97.9	
	yes	1	1.2	3	2.1	.