Communicating Health Information and Improving Coordination with Primary Care (CHIIP) Study: a CCSS Ancillary Study

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BACKGROUND/SIGNIFICANCE

There are nearly half a million survivors of childhood cancer estimated to be living in the United States.[1] Premature CV disease is a leading contributor to late morbidity and mortality in this population.[2-6] Cohort studies from North America and Europe, including the CCSS, have consistently shown that survivors have a 5+ fold increased risk of serious CV morbidity or mortality vs. the general population, corresponding to ~5% cumulative incidence by age 45 years.[2-10] Among survivors that have been exposed to cardiotoxic cancer treatments (i.e., anthracyclines and chest radiotherapy), this risk can be markedly greater (**Table 1**).[5,6] Demographic characteristics such as age at treatment and gender, and off-target and indirect effects of both radiotherapy and chemotherapy may also affect CV health.[5,6,11-13]

TABLE 1. *Cardiovascular (CV) risk group outcomes among the original CCSS cohort through age 50.*

Serious CV event	**Predicted low risk***		**Predicted high risk***	
	No. events / no. at risk	Cumulative incidence / relative risk (RR) vs. siblings	No. events / no. at risk	Cumulative incidence / relative risk (RR) vs. siblings
Ischemic heart disease	73 / 8801	2.3% / RR=2.3, p<0.001	89 / 764	19.9% / RR=17.8, p<0.001
Heart failure	18 / 5197	1.0% / RR=1.8, p=0.11	108 / 2059	12.4% / RR=41.5, p<0.001

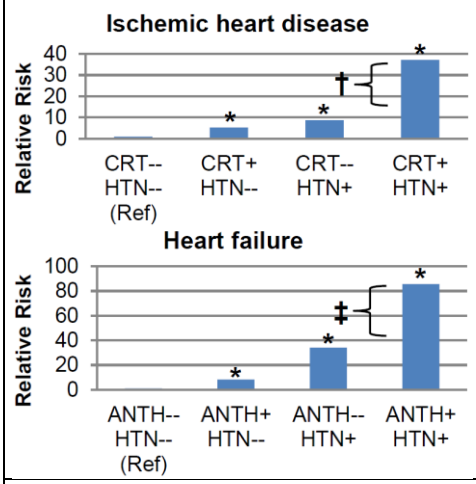
*Risk prediction for 5-yr survivors (n=13,060) through age 50, based on sex, diagnosis age, anthracycline and chest radiotherapy doses.[11,14] Area under the curve [AUC]/C-indices for these models ranged 0.70-0.76 (CCSS), and 0.66-0.82 (external validation cohorts).

Multiple studies in childhood and adult cancer survivors also have shown that even after considering treatment exposures, the presence of conventional CV risk factors such as hypertension, diabetes, and dyslipidemia are important, and may further increase the risk of serious CV disease *in more than additive fashion.*[6,15,16] Among CCSS participants, hypertension was associated with significantly increased relative excess risks due to interaction [RERI] for ischemic heart disease (after chest radiotherapy) and heart failure (after anthracyclines; **Figure 1**); RERI was also significantly increased for dyslipidemia and diabetes.[6] Furthermore, survivors predicted to be at high risk for ischemic heart disease and heart failure, on the basis of their cancer treatment exposures alone, also had higher self-reported rates of hypertension, dyslipidemia, and diabetes vs. survivors predicted to be at low risk (**Table 2**). Among childhood cancer survivors, the development of these conditions also tends to occur at younger ages compared with siblings or the general population.[17-20] Given the relatively young age of onset of these conditions that occur more typically in older adults, and the limited knowledge of cancer survivor-specific screening guidelines among general practitioners,[21,22] most high risk survivors likely do not

receive recommended CV screening studies.[23-25] *Thus, there is a compelling rationale to develop interventions for this high risk population designed to target these modifiable CV risk factors.*

A frequent limitation of many studies that have examined the relationship between hypertension, dyslipidemia, diabetes, and subsequent more serious outcomes in survivors of childhood cancer, including some of our own work, is reliance on self-report and/or the use of medications as surrogates for these risk factors, in lieu of physiologic or more objective clinical data. Where such data have been available, they often have been collected retrospectively, in a non-standardized fashion, or are only available in cross-sectional analyses with either relatively limited sample sizes, recruited from a single center, and/or a focus on a single cancer type, all of which limit generalizability.[4,18,19] However, these studies support the hypothesis that underdiagnosis of these CV risk factors is common among survivors.

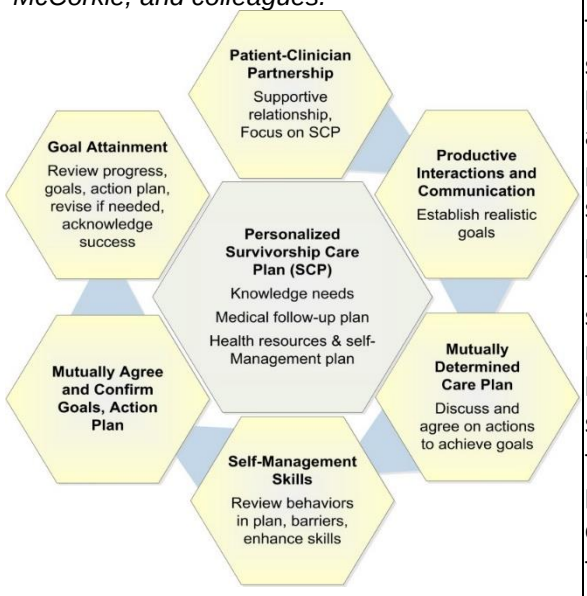
FIGURE 1. *Relative risk of serious CV outcomes in CCSS per treatment exposures & hypertension status.*[9]



ANTH[racycline]; CRT, chest radiotherapy; HTN, hypertension. Relative excess risk due to interaction (RERI) between treatment exposure & hypertension for these 2 outcomes: †RERI=24 (95% CI 12-40), ‡RERI=45 (95% CI 17-106). *RERI>0 indicates that interaction was more than additive.* *P<0.01 vs. referent.

Also unanswered is the degree to which survivors known to have hypertension, dyslipidemia, or diabetes are adequately treated (undertreatment). We are unaware of studies that have attempted to examine CV risk factor undertreatment among childhood cancer survivors, and such studies are rare among survivors of adult cancers.[26-30] Our prior research showed that survivors with these CV risk factors, defined on the basis of medication use, were at significantly greater risk of more serious CV events (e.g., ischemic heart disease, heart failure) vs. other survivors.[6,16] Thus, we hypothesize that survivors may be significantly undertreated even when diagnosed. The drivers of undertreatment may be related to healthcare providers not intervening sufficiently and/or non-adherence to appropriate interventions among survivors themselves.[26,31,32]

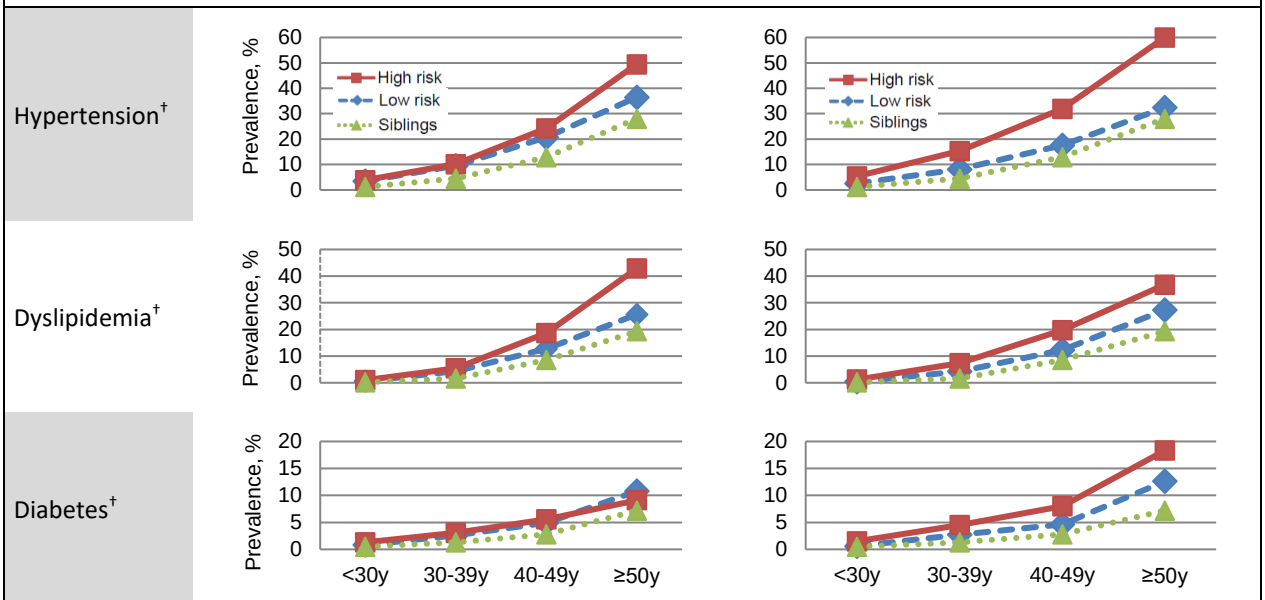
FIGURE 2. *Survivorship self-management model (adapted from Schulman-Green, McCorkle, and colleagues.*[46]



The study's intervention will feature an IOM-recommended survivorship care plan [SCP], which is designed to promote knowledge/awareness of personal health risks among survivors and to help disseminate that information to primary healthcare providers.[33] Prior research has shown that >80% of adult survivors of childhood cancer are followed by primary care providers,[24,25,34] and that while the majority of internists and family practitioners report caring for childhood cancer survivors, receipt of a SCP remains uncommon and the vast majority of surveyed providers do not report familiarity with long-term follow-up guidelines for childhood cancer survivors.[21,22] Our SCP intervention also will be enhanced by the use of recently developed and validated individual CV risk predictors our group has created specifically for childhood cancer survivors (**Tables 1, 2**). Although the SCP is by itself a tool to foster self-management, we will further supplement it with well-established, focused chronic disease self-

management strategies now being applied to improve coordination of cancer survivorship care (**Figure 2**).[35-38] Collection of directly measured data also offers an opportunity to further refine risk prediction in the future, beyond using self-report alone (**Table 2**).

TABLE 2. *Prevalence of selected CV risk factors by 10-year age groups, stratified by CV-risk status* among the original CCSS cohort (n=13,060) and a sibling comparison group (n=4,023).*



Prediction AUC (C-index)‡	**Ischemia**	**Heart failure**
with the above risk factors	0.76 (0.74)	0.76 (0.78)
without the 3 risk factors	0.74 (0.73)	0.75 (0.77)
Difference in model fit	p=0.01 (p=0.07)	p=0.04 (p=0.03)

*Low and high risk groups for ischemic heart disease and heart failure based on prediction models developed for 5-yr cancer survivors (see Table 1). †Defined as those who reported being diagnosed by a physician for the condition(s) and who took specific medications to treat that condition(s) for >1 month or for ≥30 days in a 1 year period during the previous 2 years. ‡Prediction AUC (C-indices) based on 10,521 survivors with CCSS questionnaire data, and incorporates presence of CV risk factor information (†) present at baseline risk assessment (age 26).

In summary, our proposal will systematically assess the magnitude of underdiagnosis and undertreatment, along with contributing survivor- and provider-specific barriers, among adult-aged CCSS participants predicted to be at high risk of future serious CV disease. Results from this proposal may significantly advance our understanding of CV disease risk among childhood cancer survivors of all ages, *given that many of the cancer treatments CCSS participants received remain in common use today.*[39,40] If successful, our IOM-based personalized intervention will increase the proportion of survivors and healthcare providers who are aware of current screening guidelines, who receive/deliver more appropriate CV treatment, and who adhere to these guidelines and treatments. The cumulative effect will be a mitigation of survivors' long-term CV risks.

To accomplish our aims, we will leverage the largest childhood cancer survivor cohort in the world, the Childhood Cancer Survivor Study (CCSS; n=24,466), to recruit a subset of adult-aged participants for direct, in-person (in-home) assessments. We will use new validated CCSS-derived prediction models for ischemic heart disease and heart failure based on original cancer treatment exposures to select high risk study participants, provide personalized risk information to participants and their primary healthcare providers, and aid providers' clinical decision-making.

AIM 1. Determine the prevalence of underdiagnosis and undertreatment of conventional CV risk factors (i.e., hypertension, dyslipidemia, and diabetes) among CCSS participants predicted to be at high risk (n=800) for future serious CV disease (i.e., ischemic heart disease, cardiomyopathy/heart failure) on the basis of their original cancer treatment exposures (e.g., chest radiotherapy, anthracycline doses).

- *Hypothesis: At the initial home-visit, ~60% (n~480) will have a blood pressure, lipid, and/or glucose value that meets clinical thresholds for intervention. Among those with abnormalities, 40% will have a known pre-existing CV risk factor diagnosis but are undertreated, and 80% will be newly diagnosed.*

AIM 2. Among survivors found to be underdiagnosed or undertreated (Aim 1), in a randomized controlled design, compare changes in blood pressure, lipid, and blood glucose values from baseline to 1-year between those receiving the intervention (providing clinical results and survivorship care plans [SCPs] to participants and their healthcare providers, supplemented by clinician-led remote counseling sessions with participants to review SCP contents and teach CV risk factor self-management strategies) vs. control (providing clinical results without SCP to participants and their healthcare providers; with delayed access to the intervention).

- *Hypothesis: At the 1-year follow-up home visit, survivors randomized to the intervention arm will have a lower probability of having an undertreated CV risk factor compared with survivors in the control arm.*

AIM 3. Determine barriers among (Aim 2) survivors (at baseline and 1-year: knowledge of past cancer treatment, self-efficacy, health-related attitudes, medication adherence) and their primary healthcare providers (at 1-year only: knowledge and self-efficacy towards childhood cancer survivorship care) that contribute to undertreatment of hypertension, dyslipidemia, and diabetes.

- *Hypothesis 1: At baseline, underdiagnosis and undertreatment will be associated with lower knowledge, self-efficacy, and medication adherence, as well as a "self-controlling" health attitude among survivors.*
- *Hypothesis 2: At 1-year follow-up, intervention-arm participants will report improved knowledge, self-efficacy, and medication adherence vs. controls; healthcare providers who received the SCP will report improved knowledge and self-efficacy towards CV risk and survivorship care vs. providers of controls.*

This research will improve management of the most prevalent non-cancer cause of morbidity in childhood cancer survivors by increasing our understanding of CV risk factor underdiagnosis and undertreatment. If successful, the intervention would be low cost and easily disseminated, with potential implications for and application to survivors of all cancers.

APPROACH

The study's first primary aim will be answered by recruiting a cross-sectional sample of predicted high CV risk patients. Those who meet eligibility criteria will then be randomized to a controlled intervention with delayed intervention controls to answer the study's second and third primary aims.

Aim 1 Endpoint: Prevalence of underdiagnosis and undertreatment of the following target CV conditions.

Underdiagnosis defined for each as:

- Hypertension: Joint National Committee (JNC7/8)[41,42] considers systolic 120-139 and diastolic pressures 80-89 mmHg to be suggestive of pre-hypertension; *lifestyle intervention* is recommended.[41,43] Hypertension is suspected if systolic ≥140 or diastolic ≥90 mmHg, and in addition to lifestyle modification, *pharmacologic treatment* is recommended for adults <60 years (treatment threshold ≥150 systolic if ≥60 years).[42] We will ascertain the prevalence of pre-hypertension and hypertension; both may be eligible for Aim 2. *However, with the introduction of the 2017 ACC/AHA hypertension guidelines, the classification system has shifted such that systolic ≥130 or diastolic ≥80 mmHg are now considered*

Stage 1+ hypertension (with treatment threshold reduced accordingly).[44] As such, with our 12/2017 protocol modification, we will adopt these slightly more stringent thresholds for eligibility and drop the prior "pre-hypertension" category.

- Dyslipidemia: American Heart Association and American Academy of Pediatrics recommend intervening *(lifestyle modification first; if unsuccessful, consider pharmacologic therapy)* among childhood cancer survivors for LDL ≥160 mg/dL or fasting triglyceride ≥150 mg/dL.[45] As fasting blood draws are not as commonly done in most primary care settings now for initial screening, for non-fasting (<10 hours) samples, a triglyceride ≥200 mg/dL is considered high. This study will use these cut-points to define dyslipidemia. These thresholds were largely in-line with those defined by a recent NIH-sponsored expert panel,[46] and largely similar to prior NCEP Adult Treatment Panel recommendations.[47]
- Diabetes: American Diabetes Association classifies fasting blood glucose 100-125 mg/dL or HbA1c 5.7-6.4% as suggestive of impaired glucose tolerance (pre-diabetes). Similar to dyslipidemia, as fasting blood draws are not as commonly done in most primary care settings now for initial screening, for non-fasting (<8 hours) samples, blood glucose 140-199 mg/dL will be classified as suggestive of pre-diabetes if HbA1c was <5.7%. *Lifestyle intervention* is recommended (metformin prevention considered for select high risk populations).[48] Diabetes requires fasting blood glucose ≥126 mg/dL or HbA1c ≥6.5%. If not-fasting, random blood glucose ≥200 mg/dL would be concerning for diabetes if HbA1c was <6.5%. In addition to lifestyle modifications, *metformin* is typically started with additional agents as indicated. We will ascertain the prevalence of pre-diabetes and diabetes; both may be eligible for Aim 2.

Undertreatment defined for each as:

- While any participant who was previously undiagnosed is also technically undertreated, we will reserve this definition to those who previously or currently reported to CCSS as being diagnosed with hypertension, dyslipidemia, or diabetes (either managed by lifestyle modifications or medication therapy), if their home-sampled value falls outside the recommended therapeutic range: blood pressure ≥130/80 mmHg, LDL ≥160 mg/dL, triglyceride ≥150 mg/dL (if fasting <10 hours: ≥200 mg/dL), or HbA1c ≥7.0% (different than the HbA1c diabetes diagnosis threshold[65]).

Aim 2 Endpoint: Probability of intervention subjects having an undertreated CV condition compared with the control group at 1-year follow-up.

Aim 3 Endpoint: Barriers among survivors and their primary healthcare providers that contribute to undertreatment of hypertension, dyslipidemia, and diabetes.

Inclusion Criteria

Aim 1:

1.1.1 CCSS participant who is age ≥18 years at time of initial consent.

1.1.2 High CV risk status based on CCSS risk prediction models for cardiomyopathy and ischemic heart disease.

1.1.3 Living in the U.S., within 50 miles of a designated exam service provider (e.g., EMSI) based on CCSS's available contact information at the time of approach.

1.1.4 Able to read, write, and speak English.

1.1.5 Ability to understand and the willingness to provide informed consent.

Aim 2, in addition to the satisfying the above criteria, participants must also meet the following criteria:

1.1.6 Abnormal CV condition identified on home visit. Defined as having at least one of the following:
- Average blood pressure ≥130/80 mmHg (≥130/80 if existing hypertension diagnosis)
- LDL ≥160 mg/dL
- Triglyceride ≥150 mg/dL (if ≥10 hours fast) or ≥200 mg/dL (if <10 hours fast)
- If not known to be diabetic: Glucose ≥100 mg/dL (if ≥8 hours fast) or ≥140 mg/dL (if <8 hours fast)
- HbA1c ≥5.7% (if not known to be diabetic), HbA1c ≥7% (if known diabetic).

1.1.7 Be free of any known (self-reported) ischemic heart disease or cardiomyopathy.

1.1.8 Have access to a telephone or computer to receive a phone or web video counseling/intervention session at baseline and at 4 months.

Exclusion Criteria, applicable to all participants

1.1.9 Individuals with known cardiomyopathy or ischemic heart disease based on prior CCSS surveys are excluded. While not likely to be common, participants who *newly* report in our study's baseline survey that they have cardiomyopathy or ischemic heart disease can have a home visit completed but will then be done with the study regardless of their home visit results.

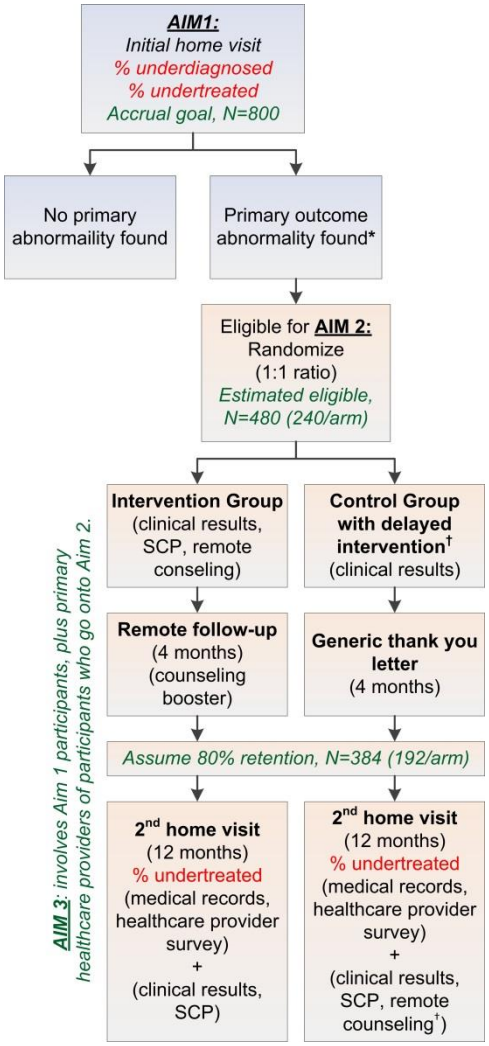
1.1.10 Not currently known to be pregnant; individuals known to be pregnant and otherwise eligible for the study can be enrolled once no longer known to be pregnant. Participants who report being pregnant AFTER randomization can remain in the study.

1.1.11 Individuals receiving active cancer treatment. Participants who report starting active cancer treatment AFTER randomization can remain in the study.

Estimated Accrual

The proposal would seek to enroll up to 800 participants to answer Primary Aim 1. If 60% of those participants are found to have an abnormal CV condition, up to 480 would then be eligible to participate in the randomized controlled trial as part of Primary Aims 2 and 3 (n=240 in each study arm).

Treatment Plan Overview



* ≥1 of the following: blood pressure ≥130/80 mmHg (≥130/80 if existing hypertension diagnosis); LDL ≥160 mg/dL; triglyceride ≥150 mg/dL (fasting) or ≥200 mg/dL (non-fasting); if not known to be diabetic, glucose ≥100 mg/dL (fasting) or ≥140 mg/dL (non-fasting) or HbA1c ≥5.7% (if not previously diabetic), HbA1c ≥7% (if known diabetic). †Controls can receive the intervention *after* the 2nd home visit & survey completion.

Assignment of Study Group

Among those who meet eligibility criteria for primary aim 1 but not primary aim 2, participation will end after the 1st home visit. Similarly, if we adopt a tiered consent process, those who could be eligible for aim 2 but who do not provide consent to the randomized intervention portion of the study, their participation will end after the 1st home visit.

Among participants who meet eligibility for primary aim 2, there this will be a computer randomization on a 1:1 basis to intervention: control assignment, with the control group eligible to receive the intervention on a delayed basis (following the 2nd home visit). The study's goal will be to review in-person collected test results in real-time (within 1-2 days of being received at St. Jude) and determine eligibility with randomization assignment the same day. Given the intervention, it cannot be blinded to either participant or study clinician. Staff who perform the home visits and the study biostatisticians will be blinded to the study group assignment.

Intervention Group

The intervention is a personalized clinician-led SCP-focused self-management counseling session that is generalizable to a real clinical setting. A printed SCP with personalized health history, recommendations, and clinically meaningful results from the initial home visit (i.e., average blood pressure, lipid profile, diabetes screening, BMI) will first be mailed to survivors on the intervention arm. We will then schedule participants for a remote counseling session via telephone or HIPAA-compliant web video if the participant prefers. The 1st session with a study clinician will ideally be ≤30 minutes to review the SCP and make mutually agreed upon goals and an action plan. We will ask scripted questions designed to address understanding of the SCP, elicit intentions to act on the SCP information, and elicit potential barriers and their solutions related to any planned actions. After the session, the personalized action plan will be mailed to the participant.

Approximately 4-months after the initial counseling session, participants will schedule a 2nd session by telephone, or HIPAA-compliant web video if the participant prefers, with the study clinician to follow-up on the action plan, address any barriers to the plan and mutually agree on a revised plan if needed (ideally ≤15 min). The clinician will also rate the survivor's completion of the action plan from 0 (none of the plan completed and no apparent intention to complete the plan) to 10 (action plan complete).

For the both the baseline and 4-month follow-up sessions, the duration of the sessions will be recorded to determine the feasibility of delivering the intervention within the time allotted (≤30 and ≤15 minutes, respectively). The sessions also will be audiotaped for process evaluation of content and fidelity of the clinician adherence to the intervention manual.

Delayed Intervention Control

Survivors in the control arm will receive a copy of clinically meaningful baseline home visit results, with a general recommendation to seek medical follow-up in instances where any of those values are abnormal since we consider it unethical to withhold such information. A copy also will be sent to their designated healthcare provider. *As such, the control group's health may be improved simply by study participation.* At 4-months, participants will receive a generic thank you letter by mail for participating. This will include a reminder of the 2nd home visit, and to enhance control group retention, control participants will be told that they can receive the study intervention (minus the 4-month booster session) after completing the 2nd home visit and any associated surveys. This will include reviewing an SCP and self-management strategies with the study clinician, but we will avoid using those exact terms to minimize control group contamination.

Interaction with Primary Healthcare Providers

All participants, at time of consent, will be asked to list their current and past (within the last 2 years) primary healthcare provider(s). Current designated providers will receive a copy of all materials sent to study participants. Thus, healthcare providers of participants randomized to the intervention arm will be mailed a print copy of the SCP with home visit results and the survivors' personalized action plan. We will directly send the SCP to providers because studies have shown that reliance on survivors alone to disseminate a copy of their SCP to their provider is problematic.[49,50] An analysis of existing CCSS data showed that receipt of a print media intervention and fostering increased survivor-physician dialogue was associated with increasing adherence to screening.[25] Providers can contact the research team with any questions regarding the SCP and action plan contents.

- Following the 1st home visit, healthcare providers designated by participants randomized to the control arm will be mailed a print copy of the home visit results only.

- Following the 2nd home visit, healthcare providers of participants on both study arms will be surveyed with regards to their self-efficacy (including self-reported knowledge) towards providing care for childhood cancer survivors. The survey will be accompanied by a cover letter, copies of clinical results (both groups), a SCP (intervention group only), and the patient's signed HIPAA authorization and Medical Record Release (if available), requesting records from the past 3 years. If the budget permits, the study will provide an upfront honorarium to providers (not exceeding $20). Non-responding providers will receive a 2nd survey packet (inclusive of clinical results, SCP if applicable, and the signed HIPAA authorization and Medical Record Release if available) approximately a month later with an alternative cover letter. No honorarium will accompany the 2nd packet. This will be faxed to the provider's office if a fax number is available, and/or mailed. We will repeat this process two more times if no response is received after another month.

For participants (either intervention or delayed control arm) with clinically actionable results but who have no current healthcare provider, the study team has access to resources to aid participants in finding providers in their area who have expertise in treating survivors of childhood cancer. This will be clearly explained on their results letter and by phone or web-video.

Duration of Therapy and Follow-Up

All study participants will be followed through their 2nd home visit, approximately 1-year after their 1st home visit unless they withdraw consent from the study prior. All participants following the 2nd home visit will receive a copy of their clinically relevant results embedded in a SCP. As mentioned above, those on the control arm can then have the option of having a 30 minute counseling session to review those results and the SCP with the study clinician.

Study Procedures

An overview of study procedures can be found in **Table 3**.

TABLE 3. *Summary of required observations.*

	Initial home visit	**Baseline counseling session**	**4-month booster**	**2nd home visit**
Intervention group	Questionnaires* Anthropometrics Blood draw	Goals/Action Plan Call duration Call fidelity	Rating of Action Plan completion	Questionnaires* Anthropometrics Blood draw
Control group	Same as intervention group	-	-	Same as intervention group
Primary healthcare provider(s)	-	-	-	Provider survey Clinical records
Time window to complete	<2 mo of enrollment (max: <6 mo)	<2mo of home visit (max: <3 mo)	3-5 mo from baseline	11-15 mo from 1st home visit (no max))

*Participants will be asked to complete the questionnaires prior to the scheduling of their home visits.

Baseline Questionnaire

This will include items on: 1) past medical history, 2) current health and medication adherence, 3) lifestyle habits, and 4) attitudes towards healthcare and current mood (**Table 4**).

TABLE 4. *Components of baseline questionnaire, exclusive of questions on past medical history and lifestyle habits.*	
***Health-related self-efficacy**[51]	10-item (4-point Likert scale) survey (will be reduced to 5-items) that measures perceived ability to set-goals, cope and recover from setbacks. Results have been found to be a strong predictor of subsequent health behavior change.[96]
***PROMIS anxiety & depression**[52,53]	These domains (adult 4-item survey; all 5-point Likert scale) are of secondary interest. Prior research via a longer instrument (Profile of Mood States) did not show SCPs associated with mood changes or anxiety.[50,85]
***Multidimensional Health Locus of Control [MHLC]**[54]	18-item survey (6-point Likert scale) will classify participants with regards to their attitudes towards healthcare screening into "worried", "collaborative" and "self-controlling" typologies, which have been associated with differential likelihoods of obtaining recommended screening in retrospective CCSS analyses.[78]
***Medication Adherence Scale (MMAS-4)**[55]	Well-established 4-item (0=high, 1-2=medium, 3-4=low adherence) instrument initially used to study hypertension, but since validated for other diseases.[100] Will be administered separately for blood pressure, lipid, and diabetes medications. Secondary analyses will examine adherence by medication burden.

First Home Visit

This will include:

- Signature on HIPAA authorization and Medical Record Release form (optional).
- Standing height: in centimeters, to the nearest 0.1 cm.
- Weight: in kilograms, to the nearest 0.1 kg.
- Blood pressure at rest: 3 times; each at least 3 minutes apart.
- Waist circumference: in centimeters, to the nearest 0.1 cm; just above the uppermost lateral border of the right ilium [hip bone]; at the end of a normal expiration.
- Blood draw (no fasting required): lipid profile, blood glucose, hemoglobin A1c, insulin, and samples for ancillary biological studies (**Table 5**).

TABLE 5. *Overview of blood samples, draw order, vial type, volume.*		
Draw order / Analyte	**Vial type**	**Volume**
1) Lipid profile, glucose, insulin level*	Heparin plasma separator tube (green top)	3.0 mL
2) Hemoglobin A1c*	EDTA tube (lavender top)	1.0 mL
3) Protein & DNA-based assays	EDTA tube (lavender top)	7.5 mL
4) General chemistries	Serum separator tube (red/gray top)	7.5 mL
5) Proteomics, metabolomics	EDTA separator tube (pearl)	7.5 mL
6) RNA for gene expression	PAXgene tube	2.5 mL
*These also will be drawn at the 2nd home visit; remaining tubes would NOT be drawn at the 2nd home visit unless they could not be successfully drawn at the first visit. 2nd home visit only: blood spot offered for failed venous draws.		

With our 7/2020 protocol modification, in response to the unexpected closure of the study's original exam service provider (EMSI), replacement service providers may include those that do not provide home-based services but rather fixed laboratory / service centers that the participant travels to in order to obtain the specified research blood draw. In these instances, only tubes 1-2 (**Table 5**) will be drawn and processed on-site (i.e., tubes 3-6 will not be drawn).

Baseline Counseling Session (Intervention Group)

A printed SCP with personalized health history, recommendations, and clinically meaningful results from the home visit (i.e., average blood pressure, lipid profile, diabetes screening, BMI) will first be sent to survivors on the intervention arm. We will then schedule participants for a remote counseling session by

phone or web video, per participant choice). This will be scheduled as soon as possible following the initial home visit with a goal of having this being completed within 2 months of the home visit. Sessions completed outside of the 2-month window will be flagged (but remain eligible for analysis). The following outcomes will be measured at this time point:

- Creation of a personalized goals and action plan.
- Counseling session completion rates, with goal of obtaining ≥85% completion within 2 months of the initial home visit.
- Call duration, with goal of achieving ≥85% being ≤30 minutes in duration.
- Study clinician fidelity to the intervention. Fidelity will be scored using standard methods across 8 levels with the 8th a global rating. Trainers will review audiotapes of sessions, with fidelity ratings and feedback to the clinician until the mean of 4 consecutive global ratings are ≥3.5 (scale: 0 [poor] to 5 [very good]). Once certified, trainers will review audio recordings and complete fidelity ratings for 15% of sessions, more if fidelity dips below a global rating of 3 (satisfactory) for 3 of 10 sessions.

It is possible that some randomized participants will fail to schedule a session despite multiple contact attempts. *We will cease scheduling attempts if no session has been scheduled by 3 months after the initial home visit.* These participants will not be eligible for the 4 month booster session (discussed below). However, we will still attempt to re-assess their health status at the 1-year time point with a 2nd questionnaire and home visit. *If a participant has to cancel and reschedule, the rescheduled date can fall outside the 3 month deadline and we will attempt to do the booster session within the target time range still.*

Baseline Return of Results (Control Group)

Survivors in the control arm will receive a copy of clinically meaningful baseline home visit results, with a general recommendation to seek medical follow-up in instances where any of those values are abnormal since we consider it unethical to withhold such information (see **Table 6**). A copy also will be sent to their designated healthcare provider. These will be issued within one month of the home visit.

Handling of Critical Results

Staff will be asked to ship out blood samples within 24 hours (could be slightly longer on weekends) of collection, and data forms will be faxed, both to the CCSS data coordination center at St. Jude. Once received, labs will be processed in real-time (i.e., not batched) by the CLIA-certified lab at St. Jude. Copies of data forms and any examiner shipping manifest will be forwarded to the study team at FHCRC. In the event that a critical test result is found (see **Table 6**), the PI or his designee, will attempt to notify the participant more quickly by phone to seek medical follow-up (rather than waiting for a letter to be generated and mailed to the participant). This process is similar to and adapted from that used by the CDC-sponsored NHANES for their in-person mobile assessments.

TABLE 6. *Classification of test results.*				
	Goal	**Borderline**	**Abnormal**	**Critical**
Systolic blood pressure (mmHg)*	<120	120-129 systolic	130-179	≥180
Diastolic blood pressure (mmHg)	<80		80-119	≥120
LDL cholesterol (mg/dL)	<130	130-159	≥160	-
Triglyceride (mg/dL), if fasted ≥10 hrs	<150	-	150-749	≥750
Triglyceride (mg/dL), if not fasting	<200	-	200-749	≥750
Glucose (mg/dL), if fasted ≥8 hrs	<100	100-125	126-299	≥300[†] or ≤50[‡]
Glucose (mg/dL), if not fasting	<140	140-199	200-299	≥300[†] or ≤50[‡]
Hemoglobin A1c (%)	<5.7	5.7-6.4	≥6.5	-

*We will drop the highest of 3 systolic measurements, and average the remaining 2 for systolic & diastolic values. [†]If not previously known to have a diagnosis of diabetes. [‡]If known diabetic only, as this would be concerning for therapy-related hypoglycemia.

Four-month Booster Session

Among the intervention group, the study will attempt to schedule the participant for a brief 15-minute check-in by phone or web-video 4-months (±1 month) after the initial counseling session. For intervention subjects who have such booster sessions outside the 3-5 month window, their data will be flagged but would still remain eligible for analysis. The following outcomes will be captured at this time point:

- Study clinician rating of participants' action plan completion, ranging from 0 (none of the plan completed and no apparent intention to complete the plan) to 10 (action plan complete).
- Similar to the baseline session, we will cease trying to schedule this booster session if no session has been scheduled by 5 months after the initial counseling session. We will still attempt to re-assess their health status at the 1-year time point with a 2nd questionnaire and home visit. *If a participant has to cancel and reschedule, the rescheduled date can fall outside the 5 month deadline.*

Among the control group, participants will receive a generic thank you letter by mail for participating. No outcomes will be measured in this group at this time point.

Second Questionnaire and Home Visit

The 2nd questionnaire and home visit should take place approximately 1-year after the initial questionnaire and home visit. The study will send participants an abridged version of the baseline questionnaire (by mail, with phone/email follow-up as necessary) with a reminder that a 2nd home visit is also due soon. After the participants complete the follow-up questionnaire, the study will work with the exam service provider to contact the participant to arrange for the 2nd home visit. The study will attempt to have all 2nd home visits occur within 3 months of the 1-year anniversary, and visits that occur outside that 3-month window will be flagged (but remain eligible for analysis). The following outcomes will be measured at this time point:

- Same physical measurements as before: standing height, weight, blood pressure at rest (3 times), and waist circumference.
- Blood draw (no fasting required): lipid profile, blood glucose, hemoglobin A1c, and insulin (**Table 5**; other assays will not be drawn unless they could not be drawn at the first home visit).
- Handling of any critical results will be conducted similarly as per the baseline home visit. In contrast to venous samples, DBS-based measurements of the lipid profile, glucose, insulin, and hemoglobin A1c will not be released back to participants or their providers. This is because such measurements are not performed in a CLIA-certified setting and are currently designed for epidemiologic research

only (and not for clinical care), and also will be batched (in contrast to venous samples which are processed in near real-time).

Primary healthcare provider measurements

Following the 2nd home visit, accompanying the mailing of a copy of participant materials (intervention group: clinical results and SCP; control group: clinical results only), all designated providers will be asked to answer questions adapted from the NCI/ACS SPARCCS.[56]

We will also request outpatient clinical records (clinician notes, medication lists, laboratory results) spanning the study period (and up to 2 years prior to the 1st home visit) from all participants' primary healthcare providers. We will abstract records for: 1) documentation of the participant's prior cancer history and CV risk status in relation to past cancer exposures; 2) any reference to a SCP or long-term follow-up guideline; 3) any CV screening planned or undertaken [coded separately]; 4) presence of any of the three target CV risk factors as a diagnosis/problem; and 5) interventions to address any CV risk factor [coding lifestyle or drug prescription separately]. Medications will be reviewed to examine whether, among those undertreated at the 1st home visit, there is subsequent treatment intensification (e.g., going from lifestyle prescription alone to adding medication; from lower to higher drug doses; from single to multiple drugs; **Table 7**), and whether treatment intensity differs across study arms after the intervention.

TABLE 7. *Examples of CV medications & dose categories (mg)*

Medication (class)	**Low**	**Medium**	**High**
Hypertension			
Lisinopril (ACE-inhibitor)	≤10	11-30	>30
Amlodipine (calcium channel blocker)	≤2.5	2.6-9.9	≥10
High cholesterol			
Simvastatin (HMG CoA reductase inhibitor)	<20	20-39	≥40
Diabetes			
Glipizide (sulfonylurea)	<10	10-19	≥20
Insulin		Any dose	

Materials returned to participants and primary healthcare providers

Information the study will send (by mail) back to study participants and their designated current primary healthcare provider are summarized in **Table 8**.

TABLE 8. *Information the study will mail back to study participants and their current primary healthcare providers.*

	After the initial home visit / baseline counseling session	**After the 4-month booster**	**After the 2nd home visit**
Intervention group (participant & provider)	Clinical results Survivorship care plan Action Plan	Updated Action Plan	Clinical results Survivorship care plan
Control group (participant & provider)	Clinical results	-	Clinical results Survivorship care plan*

*Mailing of the care plan would not occur until AFTER the control group's designated healthcare providers are surveyed.

Off-Study Criteria

This would occur if:

- A participant withdrew consent for any further data submission, or
- The participant was unable to complete the initial home visit procedures (e.g., unsuccessful blood draw), or
- Once a participant has completed all study assessments.

STATISTICAL CONSIDERATIONS

Aim 1 Analytic Plan

Hypothesis: Approximately 60% of participants will have an abnormal CV risk-factor finding that meets clinical intervention thresholds, and among those with abnormalities, 40% will be undertreated and 80% newly diagnosed.

Primary analyses: We will calculate the prevalence of hypertension, dyslipidemia, and diabetes by self-report and by physiologic measurement. We will then calculate the proportions (with exact 95% confidence intervals) of participants who may be underdiagnosed as well as the proportions undertreated (like **Figure 3**). We will calculate the prevalence of directly measured pre-diabetes separately. **Secondary analyses:** We will examine whether rates differ by: sex; current age; time since cancer diagnosis; obese (BMI ≥30 kg/m^2) vs. not; health insurance vs. not; recent history of being seen in a dedicated long-term follow-up clinic for survivors vs. not; and lifestyle factors (smoking, low fruit/vegetable intake, low physical activity).

Sample size considerations: Based on prevalence estimates from CCSS surveys and our pilot (**Table 2, Figure 3**), we expect ~60% of high CV risk participants (n~480) to have an abnormal CV risk factor measurement; prevalence of individual risk factors ranging 20-40% (less when stratified by underdiagnosis/undertreatment status). With an overall sample n=800, we expect reasonable precision for our primary prevalence estimates (**Table 9**). Power to detect differences <10% in secondary analyses may be more limited.

TABLE 9. *Estimated power for Aim 1 analyses.*

Prevalence±95% CI	Minimum detectable proportions*	
N=800	N=320:480	N=200:200
5% ± 1.5%	5% vs. 1/11%	5% vs. 0/14%
20% ± 2.8%	20% vs. 12/29%	20% vs. 10/33%
50% ± 3.5%	50% vs. 40/60%	50% vs. 36/64%

*2-sample Fisher's exact test, 80% power, α=0.05.

Potential pitfalls / solutions: Our EMSI pilot achieved 60% enrollment. Funding from this proposal will enhance recruitment rates by providing an upfront (rather than conditional) participation incentive, which has been associated with higher rates of study participation.[57,58] We will closely examine the demographic characteristics, past cancer treatment exposures, and self-reported burden of CV and other chronic conditions of survivors who are approached vs. not approached, and who ultimately participate vs. not. If differences are found, we will apply inverse probability weighting as a way to assess the sensitivity of our estimates.

Aim 2 Analytic Plan

Hypothesis: survivors randomized to the intervention will have a lower probability of having an undertreated CV risk factor compared with the control group at 1-year follow-up.

Primary analyses: We will describe baseline characteristics (including mean/median values of our target CV parameters) and proportions of underdiagnosis and undertreatment of our 3 CV risk factors. Our primary analysis will focus on the difference in the probability of having a CV risk factor undertreated after the 2nd home visit across the 2 study arms. As in Aim 1, undertreatment of hypertension,

dyslipidemia, and diabetes at the 2nd home visit will be defined as blood pressure ≥130/80 mmHg, LDL ≥160 or triglyceride ≥150 mg/dL (if fasting <10 hours: ≥200 mg/dL), or HbA1c ≥7%, respectively. Survivors with pre-diabetes at baseline will be undertreated at the 2nd home visit if fasting glucose ≥100 mg/dL (non-fasting ≥140 mg/dL) *or* HbA1c≥5.7%. As some survivors may contribute up to 3 outcomes (persistent hypertension, dyslipidemia, and diabetes/pre-diabetes), we will use generalized estimating equations (GEE), accounting for intra-individual correlation of the 3 outcomes, to estimate the overall intervention effect as a single parameter (3-element vector). If multiple survivors share the same primary healthcare provider (unlikely), we will apply random effects models in lieu of GEE given multiple cluster types. Analyses will be conducted per intent-to-treat, and include all survivors with available end points.

Secondary analyses: In case survivors who were newly diagnosed (i.e., underdiagnosed) following their 1st home visit differ in their response to the intervention vs. those previously diagnosed but undertreated, we will examine estimates stratified by diagnosis status at the 1st home visit. For similar reasons, we also will examine estimates if pre-diabetes are excluded. In our primary model, we also will explore whether differences vary by sex, current age, time since cancer diagnosis, obese (BMI ≥30 kg/m^2) vs. not, health insurance vs. not, and recent history of being seen in a dedicated long-term follow-up clinic for survivors vs. not. We also will explore, among intervention participants, whether action plan scores from the 4-month session are associated with differential undertreatment rates (as a single parameter). Finally, we plan to also compare across the study arms, the measured CV risk factor values from the 2nd home visit separately: 1) average systolic pressure, 2) average diastolic pressure, 3) LDL, 4) triglyceride, 5) blood glucose, and 6) HbA1c. For this subanalysis we will use linear models, adjusting for the value at the 1st home visit as a covariate.

Sample size considerations: Assuming 60% of Aim 1 participants (n=800) meet Aim 2 eligibility with a subsequent conservative 20% drop-out rate, ~380 survivors (190/arm) would have complete data. The study would be 80% powered (α=0.05) to detect RRs ≤0.88 (i.e., ≥12% reduction in the intervention vs. control group) if the prevalence of having an undertreated CV risk factor among controls after the 2nd home visit was 90% (10% reduction from baseline). If controls had an unlikely 50% reduction, we can still detect RRs ≤0.71. Analyses stratified by initial underdiagnosis or undertreatment status (~75-150/arm) will be able to detect RRs ≤0.79 to ≤0.86, respectively. Systematic reviews have reported RRs 0.6-0.8 for strategies similar our proposed interventions in the general population.[59,60] For continuous outcomes (secondary analyses), we will be powered to detect change equaling ~30% of 1 standard deviation, which equates to 5 mmHg systolic blood pressure, 3 mmHg diastolic pressure, 10 mg/dL LDL, 30 mg/dL triglyceride, 10 mg/dL glucose, and 0.3% HbA1c. Differences within these ranges have been reported by others for interventions conducted in the general population.[61-63]

Potential pitfalls / solutions: We will closely monitor rates of abnormalities identified in Aim 1, as that influences the number of survivors eligible for Aim 2. As discussed earlier, we will oversample survivors known to have rarer target conditions (e.g., diabetes) such that the power to detect differences in Aim 2 is enhanced. Separately, given the nature of the intervention, participants and the study clinician cannot be blinded. However, exam staff will be blinded to randomization status.

Aim 3 Analytic Plan

Hypotheses: 1) at baseline, underdiagnosis & undertreatment are associated with lower knowledge, self-efficacy, and medication adherence (if applicable), as well as a "self-controlling" health attitude among survivors; 2) at 1-year follow-up, compared with the control arm, the intervention arm will be associated with improved knowledge, self-efficacy, and adherence rates among survivors, and improved knowledge and self-efficacy

among healthcare providers.

Baseline survivor-specific factors: Using data from all Aim 1 participants, determine whether those underdiagnosed and undertreated at the time of the 1st home visit have lower knowledge (i.e., less accurate recall of prior anthracycline or chest radiotherapy exposures [chi-square test]) and lower health-related self-efficacy [t-test or Wilcoxon rank-sum] compared with those not affected. Similarly, among those who report medications for the CV risk factors of interest, determine whether those undertreated have lower medication adherence (i.e., lower mean MMAS-4 scores [t-test or Wilcoxon rank-sum]) vs. those not undertreated. Finally, determine if different health-related behavioral attitudes ("worried", "collaborative" and "self-controlling")[64] are associated with differential rates of underdiagnosis and undertreatment [chi-square test]. *A priori,* we hypothesize that the proportion undertreated will be greatest among "self-controlling" survivors vs. "collaborative" and "worried" (least undertreated) survivors. In subanalyses, we will analyze underdiagnosed participants (i.e., newly diagnosed per 1st home visit) separately from those undertreated (i.e., existing diagnosis but not meeting standard therapeutic goals) relative to the referent group (those without any abnormal CV risk factor). We also will use a combined logistic regression model to determine if knowledge, medication adherence, and health-related behavioral attitudes remain associated with underdiagnosis and undertreatment (combined and separately) after multivariate adjustment. Exploratory covariates are similar as before, and include sex, current age, insurance status, healthcare utilization, self-perceived CV risk, and family history of CV disease.

Post-intervention analysis: Among Aim 2 participants (and their designated healthcare provider), we will examine the differences between intervention and control groups following the 2nd home visit with respect to 1) survivor knowledge [chi-square test], 2) survivor self-efficacy [t-test or Wilcoxon rank-sum], 3) survivor-reported medication adherence [t-test or Wilcoxon rank-sum], and 4) provider-reported knowledge and self-efficacy [chi-square tests] related to the care of childhood cancer survivors. All analyses will be intent-to-treat and include all survivors and providers with available end points. Subanalyses can stratify these outcomes by initial underdiagnosis vs. undertreatment status. *We also will analyze practice changes over the 1-year intervention period using clinical records.* This includes comparing [chi-square test] whether documentation rates differ across study arms of: 1) any CV-related screening, 2) CV-related interventions [both lifestyle and drug prescriptions], and 3) treatment intensity (**Table 7** earlier). If any survivors share the same healthcare provider, we will apply bootstrap methods to account for the effects of clustering. In secondary analyses, we will determine, via logistic regression adjusting for randomization status, whether providers of survivors who remain undertreated have lower self-reported knowledge and self-efficacy related to the care of childhood cancer survivors vs. providers of survivors no longer undertreated.

Sample size: For covariates assessed at baseline in Aim 3, we will be able to detect differences ≥5%, RRs ≤0.8 / ≥1.2, and ≥20% of 1 standard deviation (**Table 10**). Among randomized participants (240/arm) and subanalyses (e.g., analyzing undertreatment, underdiagnosis separately: ~75-150/arm), detectable differences will be less.

Potential pitfalls / solutions: Self-reported medication adherence is not as accurate as data from pharmacy databases.[100] However, use of these databases is unlikely to be feasible even in large integrated health systems given the relative rarity of childhood cancer survivors. Given upfront randomization, any reporting biases should be similar across study arms. Should our study uncover a suggestive association with adherence, this would provide data to support the use of more expensive medication monitoring devices in a follow-up study.[100] We also anticipate some missing healthcare

provider responses. It is possible that providers on the intervention arm who receive the SCP could be more motivated to respond (all providers will get clinically relevant results from home visits). We will closely monitor response rates for providers across the study arms, and will compare the characteristics of responding vs. non-responding providers using American Medical Association databases (physicians only) and publically available information from state licensing boards and the internet (physicians and other providers).[28,102] In sensitivity analyses, we can examine the differences across study arms after adjustment for characteristics that appear to differ between responding and non-responding primary healthcare providers.

TABLE 10. *Minimum detectable differences (80% power; α=0.05) per chi-square (proportions, relative risks) or t-test (% standard deviation). * ~60% (480 of 800) with abnormal CV finding.*

Covariate frequency	**Baseline***	**Post-intervention & subanalyses**		
	N=320:480	**240:240**	**150:150**	**75:75**
10% (e.g., primary care provider self-efficacy towards childhood cancer survivorship care[27,28])	5%/17% RR 0.5/1.7	3%/20% RR 0.3/2.0	2%/22% RR 0.2/2.2	- /28% RR -/2.8
25% (e.g., MHLC self-controlling or worried typologies[64]; survivor anthracycline self-knowledge[65])	17%/34% RR 0.7/1.4	15%/37% RR 0.6/1.5	12%/40% RR 0.5/1.6	8%/47% RR 0.3/1.9
60% (e.g., MHLC collaborating typology[64]; survivor radiotherapy self-knowledge[65]; high medication adherence[29,30,62,66,67])	50%/70% RR 0.8/1.2	47%/72% RR 0.8/1.2	44%/75% RR 0.7/1.3	37%/81% RR 0.6/1.3
% standard deviation (e.g., MMAS-4,[55] survivor self-efficacy[51])	20%	26%	33%	46%

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