

## Reducing Risk of Skin Cancer Among Childhood Cancer Survivors

### 1. Working Groups and Investigators Second Malignancy and Cancer Control

Investigators should include Greg Armstrong, Todd Gibson, Paul Nathan, Joe Nocera, Wendy Leisenring, Ann Mertens, and Kevin Oeffinger from CCSS; Alan Geller, Robyn Keske, Jessica Davine, Sebastien Haneuse, Abigail Waldman (HSPH) and Ashfaq Marghoob (MSKCC).

### 2. Background and Rationale:

**Elevated Skin Cancer Risk Among Survivors:** An estimated 20 years after receiving life-saving therapy, the 68% of childhood cancer survivors who were treated with radiation face the prospect of multiple and recurrent skin cancers that are far more common than in the general population. Skin cancers are the most common subsequent neoplasm faced by childhood cancer survivors. Survivors' cancers treated with radiation are more likely to recur, be aggressive, and difficult to treat. Among the Childhood Cancer Survivor Study (CCSS) cohort (mean age, 36), the rate of new skin cancers more than tripled between 2001 and 2010. The sites for skin cancers in this population vary—head and neck (43%), back (24%), and chest (22%); some skin cancers are more visible to the patient, while others are easier to discover by the physician or a family member. By a survivor's 35<sup>th</sup> birthday, 57% of those diagnosed with skin cancer have already had multiple occurrences. *Because of these extraordinarily high rates, in April 2012, the National Cancer Institute released a PDQ® (evidence-based data summary) strongly encouraging the use of the annual dermatological exam to screen for **early-onset skin cancer** in childhood cancer survivors.*

If physicians and patients were trained to routinely observe the skin for suspect moles and lesions, many cancer survivors' lesions could be detected at the pre-cancerous stage. However, less than half of Americans know the term "melanoma" and fewer still can identify a warning sign of skin cancer (38). Further, most primary care physicians, who are often on the front lines of dermatologic care, are untrained in the basic skin cancer examination. Indeed, only 30% of childhood cancer survivors have been screened for skin cancer.

**The Importance of Regular and Thorough Skin Examinations:** Since skin cancer and its precursors can be easily seen by the patient, their providers, and significant others, teaching skin self-examination and encouraging patients to alert their physicians to skin changes provides a key opportunity for prevention. In the general population, thorough skin self-examination (TSSE) reduced incidence and mortality due to melanoma by an estimated 60% in one major case-control study. Two recent studies provide the strongest evidence to date for the diagnosis of thinner, curable tumors with physician skin screening, with 32% increased odds of having a T1 ( $\leq 1$  mm) melanoma at diagnosis following physician screening, and a 40% reduction in melanoma mortality for screened compared with unscreened control populations from adjacent regions. The American Academy of Dermatology (AAD) has recommended that individuals practice skin self-examination to detect new and/or changing lesions. Patients are encouraged to perform skin self-examinations regularly (e.g., monthly) and are educated as to the signs of suspicious pigmented lesions using the ABCDE (**A**symmetry, **B**order, **C**olor, **D**iameter, **E**volution) algorithm. These recommendations are also appropriate for those who are at highest risk for skin cancer, such as childhood cancer survivors, as the patterns of skin cancers are the same as for the general population—they just occur at an earlier age and at a far more accelerated rate in survivors.

**Technology Can Facilitate Follow-Up on Abnormal Findings:** For many patients, lack of access to expert skilled examinations and long wait times to see a dermatologist hinders or delays diagnosis and precludes treatment of early-stage skin cancers. A national survey of dermatologists found mean wait times for patients with an urgent changing mole of 38 days (range: 20-73 days).

Teledermatology(TD) leverages the power of computers and Internet technology to enable clinicians to interact with patients over long distances in less time. Store and forward (SAF) technology allows digital images and medical information for a patient to be forwarded to a clinician, who may review the files at any time. Acquiring dermoscopic images of lesions using a special magnifying lens attached to a simple mobile phone camera allows dermoscopic details of lesions to be transmitted as well in real time. This technology allows teledermatologists and the primary care physician to facilitate rapid access to a dermatologic exam. One study found strong concordance between SAF TD utilizing mobile phone cameras and in-person exams. Another study found that TD using a dermoscopic lens can find small-diameter basal cell carcinoma (BCC), nearly all of which can be treated by dermatologists or primary care physicians by shave biopsy or use of the topical agent imiquimod, compared with the invasive surgical procedures required to treat larger lesions. As of 2009, there were 62 certified TD centers in the US; the Veterans Administration, which serves 8 million Americans, also has a rapidly growing TD referral system, as does Kaiser Permanente. Given the continued rapid expansion of technology and the emphasis on improving quality of care, the presence of teledermatology in the US will likely continue to grow.

**The Role of Patient Activation:** Because few survivors report having a physician skin exam, *a key issue is activating patients to conduct skin self-examinations, request physician exams, and obtain treatment when worrisome lesions are found.* Web-based education is promising and provides the opportunity for detailed learning, particularly for a cancer in which knowing what a suspect lesion looks like is key. However, providing a website is rarely enough to spur behavior change and web-based interventions generally have low levels of use.. The widespread availability of cell phone technology and teledermatology now make it possible to test different ways to use these technologies to improve skin cancer early detection and treatment for high-risk populations. The use of text messaging is particularly appropriate because of low cost, popularity among young adults, vast geographic coverage, and immediacy of the message. The duration of text messaging interventions have ranged from 1.5 to 12 months, with delivery frequency ranging from daily to monthly. In 2011, more than 87% of the general US population owned a cellular telephone (with higher rates in those younger than age 50), and approximately 193 billion text messages were sent every month; 85% of the 30-49 age group regularly used text messages, with use rates growing. In light of studies showing the low use of stand-alone websites, appropriate leveraging of repeated but varying text messages may serve to activate patients, accelerate use of web-based resources, and increase the feasibility of public health interventions on a population-wide scale.

To date, there have been two published dermatology-related interventions utilizing mobile phones. One randomized controlled trial found that text messaging as a reminder tool significantly improved adherence to sunscreen application, and had high rates of user satisfaction. A second study found significant improvements in treatment adherence for atopic dermatitis self-care behaviors, following a text-messaging intervention; user satisfaction was high. Studies in other target areas suggest the feasibility and utility of text message interventions.

*The contribution of the proposed work is the development of a scalable intervention to address the most prevalent type of cancer among childhood cancer survivors—skin cancer.* Melanoma and other skin cancers are the only visible cancers, but few can identify its telltale warning signs(38). In the past decade, the epidemic of skin cancer among survivors has become apparent, while traditional methods to reach this high-risk population have fallen short as evidenced by their low rates of screening and extraordinarily high rates of disease. Successful incorporation of patient and physician activation coupled with use of teledermatology to speed diagnosis has significant potential to improve skin cancer detection and reduce their skin cancer risk. This study will teach lifelong early detection activation skills to survivors as they continue to develop new skin cancers, and has great relevance to the emerging network of skin cancer advocacy groups and disease-specific organizations (see letter of support from National Council) serving the hundreds of thousands of childhood cancer survivors, transplant recipients, and first-degree relatives of melanoma patients, all at sharply higher risk of skin cancer.

### 3. Specific Aims/objectives

There are currently more than 325,000 Americans who are long-term survivors of childhood and adolescent cancer. While these groups have greatly benefited from recent medical advances, primarily increasing overall survival rates, treatment advances have come at a cost. It is now clear that childhood radiation therapy has caused survivors to be at extremely high risk for non-melanoma skin cancer (NMSC) and increased risk of melanoma. The rate of new skin cancers among childhood cancer survivors more than tripled between 2001 and 2011; these survivors are diagnosed at an average age of 33, some 30 years earlier than in the non-radiation exposed population. Despite their elevated risk, only 30% of survivors report being examined for skin cancer even though 90% have seen their primary care physician or oncologist in the prior year.

Early detection is crucial to reduce the morbidity caused by NMSCs and the morbidity and mortality incurred due to melanoma. The extraordinarily *high rates of skin cancer, multiple recurrences, and new primary tumors in this young population point to the strong need to increase rates of skin self-examination and physician skin cancer examinations*. Both patient and provider action are needed to detect and treat early skin cancers and to find new solutions to ensure expedited follow-up care and treatment, especially among those who live where they have little access to dermatologists.

To reduce skin cancers among this young and dispersed patient population, several key issues need to be addressed: (1) how to provide them with the skills needed to conduct effective skin self-examinations; (2) how to prompt action from their physicians when worrisome moles and lesions are found; and (3) how to ensure rapid access to dermatologic exams, which in some parts of the US can take weeks or months to schedule. The widespread availability of cell phone technology and teledermatology (remote expert assessment of a photographed lesion or mole) make it possible to test different ways to use these innovative technologies to improve skin cancer early detection and treatment. The proposed comparative effectiveness study will compare the impact of patient activation and education: a) alone; b) in combination with physician education; and c) in combination with physician education and rapid access to dermatologic screening through teledermatology.

Our **specific aims** are to:

**Specific Aim 1:** Determine the impact of a Patient Activation and Education intervention (PAE) with and without physician activation (PAE + MD) and teledermatology (PAE + MD + TD) on skin cancer early detection practices measured at 12 and 18 months:

*Hypothesis 1.1:* Compared to PAE, participants randomized to the addition of physician education (PAE + MD) or physician education with teledermatology (PAE + MD + TD) will report higher rates of: (1) thorough skin self-exams and (2) full-body skin cancer exams;

*Hypothesis 1.2:* Compared to those receiving physician education (PAE + MD), those randomized to the addition of teledermatology (PAE + MD + TD) will report higher rates of: (1) thorough skin self-exams, and (2) full-body skin cancer exams.

**Specific Aim 2:** Determine the impact of the intervention on time to diagnosis

*Hypothesis 1.1:* Compared to PAE, participants in PAE + MD and PAE + MD + TD will have a shorter time interval between discovery of a lesion and date of diagnosis;

*Hypothesis 1.2:* Compared to PAE + MD, participants in PAE+MD+TD will have a shorter interval between discovery of a lesion and date of diagnosis.

**Specific Aim 3:** Estimate the cost and cost-effectiveness of the intervention as a secondary outcome

Results from this intervention will have important implications for childhood cancer survivors and other high-risk populations, including organ transplant recipients (> 225,000 recipients) and first-degree

relatives of melanoma patients (>2 million Americans), all of whom share strong deficits in skin self-examinations and receipt of physician examinations for skin cancer.

**Specific Aim 4:** Determine the sun protection and tanning bed practices of childhood cancer survivors

#### 4. Analysis Framework

**Study Overview:** The *objective* of this study is to determine the impact of a 12-month patient activation and education intervention on early recognition of skin cancer practices among childhood cancer survivors formerly treated with radiation. All participants will receive text messages encouraging them to examine their skin and request physician examinations while concurrently driving them to a study website that provides education related to the associated skills, and reinforces and expands the text messages. We hypothesize that the addition of physician activation and teledermatology arms will further boost participant's likelihood of performing skin self-examinations and receiving physician examinations of the skin (Aim 1). We anticipate that positive findings from the teledermatologist sent directly to participants' physicians will prompt discussions between physicians and patients and result in timely referrals and expedited treatment (Aim 2). We will also evaluate the cost of the intervention and its cost-effectiveness by estimating the costs of delivering the interventions and the impact of the intervention on subsequent health care utilization and direct medical costs during the 18-month study period (Aim 3). Data will be collected through three surveys (baseline, 12- and 18 months), and through medical record review, including pathology report review. This will be the first randomized study to measure the maintenance of early detection of newly-learned skin cancer practices for a period as long as 18 months.

#### Conceptual Model

The proposed study will be guided by the Patient Activation Model), which posits that activated patients are better prepared to participate in self-management activities. Patient activation is increasingly seen as central to achieving improvements in the quality of care, better health outcomes and less costly health care service utilization. Activation involves four stages: (1) believing that taking an active role as a patient is important, (2) having the confidence and knowledge necessary to take action, (3) actually taking action to maintain and improve one's health, and (4) staying the course even under stress. The significance of patient activation has been recognized in current health care reform efforts, including by the Center for Medicare and Medicaid Innovation.

Since 2004, there have been a number of cross-sectional studies that have found patient activation to be related to healthy behaviors (e.g. physical activity, frequency of eating fruits and vegetables), appropriate use of the health care system (e.g. having a regular source of care, not delaying care), consumer behaviors (e.g. researching physician qualifications, preparing a list of questions for a doctor visit), and chronic care self-management (e.g. eye examinations for people with diabetes, keeping diary of blood pressure readings) (. Other evidence suggests that primary care providers likely play an important role in increasing patient activation. For example, one study found that patients who report that their provider helped them in very concrete and specific ways (e.g. helped them to learn to monitor their condition, set goals, and/or set up an exercise program), were more activated than patients who did not have this experience. Patient- centered medical homes are measuring patients' activation levels, and using it as a "vital sign" to help tailor patient care plans. A checklist brought by the participant to their routine visit can encourage the physician to examine the skin, make a referral if necessary, motivate patients to conduct skin self-examinations, record the high-risk status of their patient, and make early detection practices routine in subsequent visits. Because of these benefits, we will integrate a checklist as part of the intervention.

Although the Patient Activation Model is an essential component of the conceptual model, other mediating variables shown to be important in the early detection of skin cancer are also key component parts of the conceptual model. These include **risk perception** because of one's prior cancer status, **self-**

**efficacy** to perform a skin self-examination and to ask a physician for a skin exam, **barriers** (e.g. not knowing what type of moles or lesions to look for), and **awareness** of basic warning signs of melanoma and basal cell carcinomas.

**Research Design**

**Design Overview:** The proposed randomized controlled trial uses a three-group comparative effectiveness design comparing:

*Patient activation and education (PAE)*, including text messaging (12 messages over a 6 month period) and web-based tutorials for a 12-month duration (a website and smartphone app);

*PAE plus physician activation (PAE + MD)*: adding physician activation/educational materials about: (1) survivors’ increased skin cancer risk; (2) the benefits of and the skills needed to conduct full-body skin exams; and (3) the importance of recommending routine SSE to patients;

*PAE physician activation, plus teledermatology (PAE +MD +TD)*: adding participant receipt of a dermoscopic lens to take photographs of suspect moles and lesions reviewed by the teledermatologist; report sent to participants’ physician, with recommendations and action steps needed to obtain expedited care for his/her patient. Participants and physicians will take part in the study for 12 months after enrollment (see Figure).

**Primary study outcomes**, measured at 12- and 18-months (maintenance of practices) are the following:

1. At least one thorough skin self-examination in the two months prior to both the 12- and 18-mo. survey;
2. At least one physician skin examination prior to 18-mo. survey (patient-reported; physician-confirmed);
3. A shorter time interval between the first finding of a suspect lesion after randomization and the date of diagnosis(patient-reported; physician-confirmed).

**Outcomes and measures**

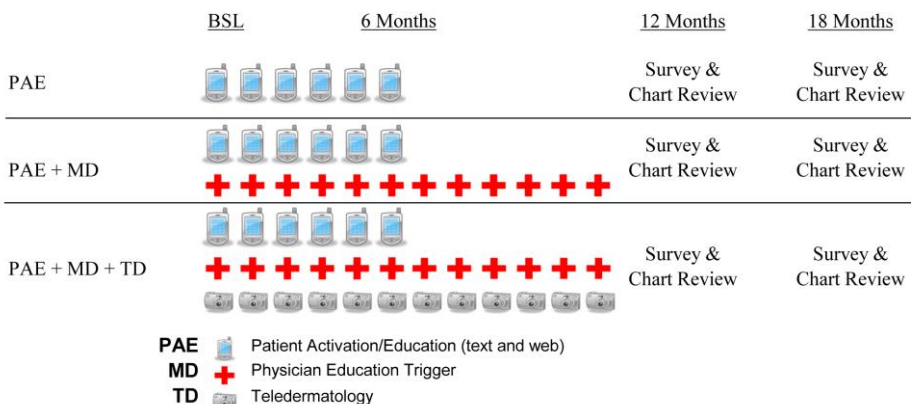
**Primary outcomes**

*Thorough Skin Self-Examination (TSSE)*: Self-report of TSSE has been validated (20, 97), and as an outcome will be defined as performing at least one TSSE during the 2 months prior to the 12- and 18-month follow-up assessments. At each assessment, participants will be asked how often in the prior two months they had carefully examined each of eight areas of the body (‘the front of you from the waist up’, ‘the front of your thighs and legs’, ‘the bottom of your feet’, ‘your calves’, ‘the backs of your thighs’, ‘your buttocks lower parts of your back’, ‘your upper back’, ‘and your scalp’ (20, 97). Those who respond ‘once’ or more times to each of these 8 questions will be considered to have performed TSSE.

*MD Skin Exam*: Completion of an MD skin exam will be assessed at baseline and 18 months by participant report and chart review. Report of an exam will be based on response to the validated question modified for time period: ‘During the past 18 months, has a doctor deliberately checked all or nearly all of your whole body for the early signs of skin cancer’ (98, 99). We will ask about the extent of

the examination (Did it include the lower back? The scalp?) and whether the participant was completely undressed for any part of the examination. Patients will be asked if exams were performed by a dermatologist, oncologist, primary care physician, or other and whether the examination took place during a routinely scheduled visit or was prompted by the participant’s incidental finding of a new

lesion. We will corroborate the participant’s self-report via chart review. We will employ a standard form



asking the physician or office manager to note whether there is a record of a skin exam and/or recommendation to perform a skin self-exam as well as the disposition of a follow-up visit should the primary physician have made such a referral. For confirming other medical information, CCSS participants are routinely asked to provide the names and addresses of their primary care physicians and/or oncologists, and CCSS studies have been successful in obtaining 70% of pathology reports requested. Physician offices will be incentivized a total of \$25.00 for review of the participant's medical record related to the skin exam to be completed after their final survey is completed. RA effort will be dedicated to retrieving charts and pathology reports.

Mediating Variables: We will also examine the impact of the intervention on key mediating variables hypothesized to be related to behavior change and test for interaction between these variables and PAM.

*Patient Activation Measure (PAM):* Patient activation has been found to be predictive of health status, health care utilization, health behaviors, and disease-specific self-management tasks (63). The 13-item PAM has been developed to measure patient activation as a major component of self-management potential, and includes: believing one has an active role to play, having the confidence and knowledge to take action, taking action, and staying the course under stress. Treatment and care management for patients can therefore be tailored to the individual's level of patient activation. All of the measures on the 13-item PAM fall within a 0.5-1.5 acceptable range as the 22-item scale and was considered to be reliable and valid (100).

*Risk perception:* We will utilize Rodrique's measure of perceived risk related to skin cancer (Cronbach alpha =0.74) (101).

*Self-efficacy* regarding completion of a thorough skin self-examination and getting a skin exam by a physician will be assessed on 5-point Likert scales, using items developed by Geller and Emmons in their study of self-exam among siblings of melanoma patients(29, 102) and others(103).

*Barrier Scales:* We will use measures of barriers developed in our randomized trial of melanoma siblings(29). The barriers assessed are specific to TSSE and physician skin exams.

*Predictor Variables-Demographics and Skin Cancer Risk Factors:* Key demographic and health care variables include age, sex, education, race, ethnicity, study site, work status, marital status. Standard skin cancer risk factors will also be assessed, including skin phototype.

*Skin Cancer Knowledge:* Knowledge will be tested with multiple-choice questions on shape, color, location, warning signs, and risk factors for melanoma, basal cell, and squamous cell carcinoma.

*Attitudes towards TSSE* (bodily or social unease and positive personal gain) are predictive of TSSE, and will be assessed using items developed from our melanoma sibling study(29).

*Detection Awareness:* Patients will be asked a number of questions regarding their awareness of TSSE and physician examination. These will include but not be limited to: how lesions were detected and who was the very first person who first believed that something was wrong with the spot? Possible responses will include yourself, your partner, other relative, a friend, or a doctor. Self-report of how many moles (0-5, 6-10, 11-20, 21-40,>40) will also be ascertained.

**Power calculations**

We will draw a stratified random sample of subjects (stratified by gender and across all 27 CCSS sites). Sample size considerations are based on an equal allocation of subjects to intervention arms. Our first main outcome analysis focuses on increases in both physician screening and skin self-examination; the prevalence of screening and expected effect sizes are derived from rates of physician screening in the CCSS population (13, 14) as well the melanoma sibling randomized control trial conducted by Geller and Emmons (29). Assuming that baseline physician screening rates are 30% across all randomization groups, a 10-15% increase in physician screening rates would be considered clinically significant improvement. Similar increases for self-screening were found in the melanoma sibling trial (29). With this consideration, using a main effects model, we would be able to obtain 80% power with a 0.05 significance level having a final sample of 200 subjects in each of the three groups completing the study at 18 months. Based on the assumption of a 25% attrition rate by month 18, we propose recruiting 801 subjects who will be evenly divided across the three intervention groups to achieve the final complete sample of 600 at 18 months. We will thus be able to detect an improvement in screening rates of 14% between *any two* of the three intervention groups using a two-sided Chi-square test with continuity correction and a significance level of 0.05. Power will increase/decrease as the screening rate improvements change (see Table 2).

**Table 2 Sample size for improvement in physician and self-screening**

Detectable difference	Sample size	Power
14%	200	80%
16%	150	80%
15%	150	75%
13%	200	75%

**Table 3 Sample size for mean wait time**

Detectable difference	Standard Deviation	Sample size (per arm)	Power
2.3 days	5	75	80%
2.6 days	5	60	80%
5 days	10	60	78%

**Our second primary outcome relates to time to diagnosis**, a continuous outcome variable. We used the following assumptions: mean wait time (time between call for appointment and actual appointment) of 38.2 days (95% CI = (35.4,41.0))(23). Based on the proportion of individuals with atypical moles and changing moles (104, 105), we assume that for each of the study groups there will be an estimated 60-75 subjects per 267 in each group who will seek care from their primary physician or dermatologist in the 18 month period. A clinically significant improvement in wait time would be between 14-21 days to facilitate earlier treatment if needed. Based on these values, assuming a range of potential standard deviations (5-25) we would have 80% power to detect a significant difference of at least 12.8 days with a significance level of 0.05 (see Table 3 for ranges).

7.7 days	15	60	80%
12.8 days	25	60	80%

**Data Analysis**

**Specific Aim 1 Analysis: Impact on TSSE and Physician Skin Exams:** We will conduct a complete assessment of descriptives. We will assess distributions, reporting means and standard deviations for continuous variables and frequencies for categorical variables for each of the outcomes and a priori determined mediating variables described above. Our main analysis will employ longitudinal models for the two dichotomous outcomes -- skin self-examination (yes/no) and physician exam (yes/no). Dichotomous analyses will be conducted using a logistic link function with an unstructured covariance matrix and random subject effect. Bivariate prediction models will be used to guide the creation of a multivariable model with variables whose bivariate significance is less than or equal to .10 being considered for the multivariable model. A main effects model will be evaluated using a mediational analysis (see C10.4) before finalizing on a parsimonious model. We will control for stratification variables (site and gender) in each model. All analyses will use Proc GLIMMIX in SAS or similar programming in R.

**Specific Aim 2 Analysis: Impact on Time to Diagnosis:** The objective of this aim is to assess the time interval between the participant’s first notice of a suspect mole or lesion and the date in which a definitive diagnosis is made (the date found in the chart review for the primary physician or referring physician’s date of diagnosis). This is a continuous outcome variable and thus we will employ mixed effects models using a random intercept, controlling for clinic site, with an unstructured covariance matrix, assuming a normal distribution. Similar to the analysis described above, we will begin with bivariate models to determine potential variables to include in a multivariable prediction model. We will also create a parsimonious main effects model that will be evaluated for mediational effects before determining a final model. We will control for stratification variables (site and gender) in each model. These procedures will be conducted in Proc Mixed in SAS or a similar program in R.

**Specific Aim 3 Cost and Cost-effectiveness:** To estimate the costs of delivering the intervention, or the costs to replicate the intervention elsewhere, the following information will be collected from study records and personnel reports (Table 4). Commercially available items, such as teledermatology lenses, will be valued at their average retail price rather than the subsidized rate provided specifically for this study. Dermatologist and other personnel time will be valued at prevailing national average wage rates, and alternative values will be explored in sensitivity analysis.

**Table 4 Items included in intervention cost assessment**

Intervention	Item	
PAE	Automated text messages (12 per participant)	To estimate the economic impact of the intervention, we will survey participants at the 12-month and 18-month assessments regarding their use of specific health care services. At each assessment, participants will be asked about visits with primary care providers and dermatologists, receipt of diagnostic procedures including biopsies and imaging, and treatment for any newly-diagnosed skin conditions. This participant-reported information will be verified and supplemented by data collected in chart reviews, including pathology reports. Each service will be multiplied by a unit cost
	Website hosting and maintenance	
PAE+MD	Physician mailings (personnel time, postage)	
	Bookmark of suspect moles	
	Exam instruction sheet	
PAE+MD+TD	Dermatologist time assisting, providing referrals	
	Teledermatology lens (1 per participant)	
	Photo upload (data transmission costs)	
	Dermatologist time reviewing photos	



amount in order to estimate total costs. We will use Medicare's Direct Practice Expense and Resource Based Relative Value Scale (RBRVS) to estimate average unit costs for physician and laboratory services. Although most study subjects will not be Medicare beneficiaries, Medicare's reimbursement methodology was developed to reflect true resource costs (106). For this reason, Medicare reimbursement may be used as a proxy for unit cost, even when the population of interest is not limited to Medicare beneficiaries. This methodology has been employed in economic analyses of other cancer screening interventions.(107, 108) In sensitivity analysis we will evaluate a range of unit cost estimates.

Our assessment of the downstream costs of the intervention, as well as the cost of the intervention itself, will allow us to perform a limited cost-effectiveness analysis. Specifically, we will estimate the cost per additional full-body skin cancer exam completed and the cost per additional skin cancer case detected, comparing the three intervention arms. Given the primary focus of the trial on non-economic endpoints and the associated sample size requirements, we will not conduct formal hypothesis tests on the economic outcomes. The economic impact of the intervention will be evaluated using standard incremental cost-effectiveness analysis methods, and sensitivity analysis will be used to assess the impact of assumptions and uncertainty on results and conclusions.(109, 110) Although estimation of lifetime costs and outcomes associated with the study interventions are beyond the scope of this proposal, results of the cost analyses will serve as preliminary data for future grants that explore the long-term cost-effectiveness of increasing skin cancer screening among childhood cancer survivors.

**Mediational analyses:** Based on the work of Baron and Kenney (111), mediational analyses will be conducted to determine if the prediction models within study arms vary based on mediating and/or moderating variables. We will compare these predictors across study arms to determine comparability and/or uniqueness to the specific interventions (e.g. we may see age or employment level being a predictor of increased web use in all three intervention arms and we may see educational attainment being a predictor of increased teledermatology use without being predictive of web use or physician communication). We will also conduct an analysis of level of engagement with the intervention based on the process tracking information. We will determine if this is predictive of our outcomes of interest.

**Missing Data:** Missing data are common occurrences in intervention studies. Some participants may refuse to participate and/or become lost to follow up, where others will skip some specific items on any one of the collection surveys. Whenever possible we will try to compare the characteristics of non-participants and/or lost to follow up with those in the study population to ensure that the study population is representative of the general population of interest. However even for those who agree to participate, missing values occur in some important covariates or even in outcomes. To the extent possible, we will use multiple imputation methods available in standard statistical packages such as SAS version 9.3 to account for missing data and provide an appropriate estimate of standard errors and confidence intervals in the presence of this added uncertainty.