EMPOWER-II: Promoting Breast Cancer Screening in Women Who Survived Childhood Cancer

DUKE CANCER INSTITUTE

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1.0. Background & Significance

Young women treated for childhood cancer with chest radiotherapy (RT) have a very high risk of breast cancer. By age 50, almost one in three women treated with chest radiotherapy (RT) for a childhood cancer will be diagnosed with breast cancer.[1] Risk is highest among Hodgkin lymphoma survivors, with a cumulative incidence of 35% by age 50. For perspective, the cumulative incidence of breast cancer, by age 50, among BRCA1 carriers is 31%; among women in the general U.S. population, it is < 5%.[1]

Survival and long-term outcomes following breast cancer among childhood cancer survivors is highly dependent upon stage of disease at diagnosis. In two systematic reviews,[2,3] we reported that the clinical characteristics of tumors (e.g., hormone status, location) in women treated with chest RT were similar to those among women with sporadic breast cancer. When detected at a node negative early stage, breast cancer in this high-risk population is highly curable. There are two very important therapeutic limitations in treating women for breast cancer following chest RT for a childhood cancer. First, using breast irradiation for local control of disease is rarely used due to the risk of radiation-induced tissue and fat necrosis in these women who have already been treated with high dose radiation to the breast. Second, for women with node-positive breast cancer, therapy for the childhood cancer limits the options for adjuvant therapy for secondary breast cancer.[2-4] Doxorubicin, an anthracycline, remains a mainstay in the treatment of advanced node-positive breast cancer.[5,6] However, if anthracyclines were used to cure the childhood cancer, they are relatively contraindicated in the treatment of breast cancer due to the substantially elevated risk of congestive heart failure. Of note, anthracyclines are commonly used in the treatment of childhood cancer. Reflecting the late stage at which most breast cancer is diagnosed in this population and the limitations in therapeutic options, the 10-year breast cancer-specific mortality is 19%; the 10-year all-cause mortality after a diagnosis of breast cancer is 32%.[1]

Thus, early detection in this high-risk population is imperative. As in women with a BRCA mutation or other genetic risk,[7-12] the combination of mammography and MRI for breast cancer surveillance among female childhood cancer survivors treated with chest RT is superior to either individual imaging modality.[2,3,13-15] Importantly, breast radiation from chest RT increases mammographic breast density.[2,3,14,16-18] Consequently, the sensitivity for detecting early invasive breast cancer is lower for mammography in this population. Thus, tumors detected by mammography are more likely to be larger and node-positive than those detected by MRI. However, mammography remains useful in surveillance as this imaging modality is better for detecting ductal carcinoma in situ, which often occurs in multiple quadrants in women treated with chest RT prior to age 30. For these reasons, breast cancer surveillance with annual mammography and breast MRI is recommended by the Children's Oncology Group (COG),[2,19] the American Cancer Society (ACS),[13,20] the International Guideline Harmonization Group,[3] and the National Comprehensive Cancer Network (NCCN),[21,22] starting at age 25 or 8 years after radiation, whichever occurs last. While ultrasound is an important diagnostic imaging modality, it is not recommended as a screening test in this high-risk population. The COG, the NCI-supported clinical trials group, is considered the authoritative body for making recommendations for second cancer surveillance for childhood cancer survivors.[23] This recommendation is considered the standard-of-care in North America.

Adherence to breast cancer surveillance is inadequate for this high-risk population. In a survey of female childhood cancer survivors living in North America, we found that only 55% of women who were treated with chest RT and were aged 25-50 years reported a mammogram in the previous two years; <3% reported a breast MRI.[24] Further, 47.3% of women under age 40 had never had a surveillance mammogram. Only 52.6% of women aged 40-50 were being regularly screened (2 mammograms within 4 years) – a proportion similar to two average-risk populations.[24] Of note, mammography was more common among the high-risk women who reported a physician recommendation than those who did not (ages 25-39 years, 76.0% vs 17.6%; ages 40-50 years, 87.3% vs 58.3%). Lack of awareness of risk was also a key barrier.[24-26] Most adult survivors of childhood cancer are disconnected from the cancer center and are followed by primary care providers (PCPs).

Established in 1994 the Childhood Cancer Survivor Study (CCSS) is the largest longitudinal cohort of childhood cancer survivors worldwide.[27] Currently, over 24,000 5+ year survivors diagnosed from 1970-1999 at

one of 31 institutions in North America are participating. Based on data from the Surveillance, Epidemiology and End Results (SEER), the CCSS cohort was found to be representative of the larger U.S. population of childhood cancer survivors.[28] Periodically we have evaluated the health care utilization patterns of the cohort and have reported that over 80%, regardless of risk level, are no longer followed at their treating institution while 88% have a PCP or another usual source of care.[29-32] Importantly, only a minority of CCSS participants have a Survivorship Care Plan (SCP).[29,30] While most PCPs are unaware of the risks following different therapies for childhood cancer, they are committed to caring for survivors. While the population of childhood cancer survivors continues to grow, estimated at 420,000 in the U.S. in 2013,[33] the average PCP only has a handful of survivors in a given practice, each with a different type of cancer treated with different therapies over different time periods.[34] PCPs report rarely receiving a SCP from the oncologist.[35,36] Thus, it should not be surprising that PCPs generally report being uncomfortable in managing long-term childhood cancer survivors because they are unfamiliar with the specific surveillance recommendations for second cancers.[34-38] Nevertheless, PCPs express a strong interest in caring for childhood cancer survivors.[35,36]

Individuals, including cancer survivors, have been found to differ in the extent to which they are inclined to change their habits and behaviors to conform to medical recommendations. The chronic illness care model emphasizes patient-oriented care, with patients integrated as active members of the care team.[39] Patient activation occurs when individuals believe they have an important role in their health and health care and have the necessary knowledge, skills, confidence, and commitment.[40] Positive changes in activation have been associated with positive change in a variety of self-management behaviors, either by initiating the behavior or maintaining an existing behavior at a relatively high level.[41,42] Because cancer survivors need ongoing care, and must play an important role in their long-term health care, (especially since PCPs may not be familiar with their health care risks), encouraging activation is both necessary and important. The 2003[43] and 2005[44] Institute of Medicine reports highlighted the suboptimal care of cancer survivors in the U.S., with the latter report being subtitled, 'Lost in Transition'. These seminal reports recognized the critical need for improving the health care of cancer survivors, particularly those at high risk for late effects and second cancers. A barrier in the transition process is the poor two-way communication (verbal, written, electronic) between cancer specialists and PCPs.[43,44] In order to deliver patient-centered care for individuals with complex medical needs in a medical home, using a shared care model, PCPs have called for better two-way communication and individualized and timely information,[45-48] particularly in the management of high-risk cancer survivors.[35-37,49,50] The goal of PCP activation is to: (1) increase provider knowledge about the importance of early detection of breast cancer for childhood cancer survivors, and specifically for their patient; and (2) motivate providers to educate and screen survivors. The combination of patient and PCP activation for breast cancer surveillance in this high-risk cohort may yield the best outcomes.

For the past 15 years, we have conducted a series of extramurally supported studies aimed at reducing the morbidity and premature mortality associated with breast cancer and other serious medical outcomes in this high-risk population of young women. To date, we have (1) characterized the magnitude of breast cancer risk,[1,51] and risk of other serious chronic conditions;[51-53] (2) identified factors that modify their breast cancer risk;[1,54-56] (3) led in the development and dissemination of national and international guidelines for breast cancer surveillance;[2,3,21,22] (4) documented the very low rates of surveillance among these women;[24,57] and (5) identified the barriers and facilitators to completing a mammogram and/or breast MRI.[24-26] These efforts led to the EMPOWER-I Study (R01-CA134722), which was a 2-arm, randomized controlled trial among women aged 25-50 to test the efficacy of targeted mailed materials followed by a telephone-delivered brief motivational interview, on mammogram (primary outcome) and breast MRI (secondary outcome) surveillance rates compared with an attention control. We hypothesized that women in the intervention group would have a 20% higher rate of surveillance mammography than women in the control group. At the 1-year follow-up, 39.8% of women in the intervention group completed a surveillance mammogram compared with 19.6% of those in the control group. The intervention group was 2-times more likely than the control group to have a surveillance mammogram (adjusted RR=2.0; 95% CI 1.6-3.4; p=0.013). However, overall uptake for breast MRI was low and there was not a significant difference between groups (intervention: 18.7%, control: 16.4%). Key barriers identified for not obtaining an MRI and / or mammogram were: 'doctor didn't order it', 'put it off', 'cost', and 'haven't had any problems'. Importantly, among the women in the intervention group who did not complete an

MRI, 86.7% reported that their PCP did not recommend this surveillance test. Following completion of the study, we partnered with Right Action for Women (RAW), a national philanthropic program that provides financial assistance for high-risk women who need a surveillance breast MRI. Based upon our efforts, RAW now provides assistance for an annual low cost breast MRI to all women in the U.S. who are in this risk group and whose income is below the 400% Federal Poverty Level.

In summary, women who were treated with chest RT for a childhood cancer are at increased risk of developing breast cancer at a young age. Early detection of breast cancer in this population is associated with improved survival and other long-term outcomes. Interventions provide the opportunity to reduce cancer-related morbidity and mortality. To accomplish this, survivors must be knowledgeable about cancer-related health risks, recommended health screening procedures, and other risk-reducing interventions. The proposed study will provide the opportunity to evaluate the impact of theoretically-based intervention aimed at increasing awareness of risk and breast cancer surveillance options and facilitating women in obtaining a breast MRI and mammogram. Knowledge derived from this research will inform future intervention studies not only among female, but also male survivors at risk for other late effects. Based upon our findings and with input from our Patient and PCP Advisory Boards, we propose the EMPOWER-II study, with a primary goal of increasing the rate of women completing the recommended combination of breast MRI and mammogram. Extending from the core component of the EMPOWER-I intervention (targeted mailed educational materials) we will evaluate the utility of patient activation with and without added PCP activation.

2.0 Objectives and Hypotheses

The objective of this study is to determine the impact of maximizing patient and PCP activation on breast cancer surveillance rates among women previously treated with chest RT for a childhood cancer. We hypothesize that maximizing patient activation with smartphone-based technology will significantly increase surveillance rates. With signed permission for medical record release, we anticipate that surveillance guidelines and recommendations sent from the CCSS directly to the PCP (PCP activation) will prompt discussions between providers and patients and result in further boosting the surveillance rates. Thus, we will determine the incremental increase in surveillance rates by adding PCP activation to patient activation. In addition, we will explore moderating and mediating patient- and provider-level factors that predict breast MRI and mammography completion and timing of the obtained surveillance; and estimate the replication costs of the interventions and costs resulting from the interventions.

As a supplement, we will also establish a breast imaging repository by obtaining all screening and diagnostic breast imaging completed by women enrolled in the EMPOWER-I (completed study) and EMPOWER-II Studies. We hypothesize that the proportion of females treated for a childhood cancer with chest radiotherapy will be more likely to have heterogeneously dense or extremely dense breast tissue than women without a history of cancer. We will then evaluate mammographic breast density, background parenchymal enhancement on breast MRI, and other potential radiomic biomarkers.

As current circumstances created by the COVID-19 endemic have hindered participants' ability to safely partake in screening practices, two additional objectives have been added to obtain additional information from participants available to us during this time. Participants will be contacted by phone and invited to participate in a voluntary survey containing brief qualitative questions regarding the ways in which COVID-19 may have impacted the participant's life and their ability to receive care during and after this time. Questions will also pertain to participant insurance coverage and the impact of coverage on screening behaviors. There are no hypotheses related to these inquiries, as the questions are simply exploratory in nature.

2.1 Objectives

Primary objective: To determine the effectiveness of: (1) a smartphone-based Patient Activation (PA) intervention and (2) PCP activation added to patient activation (PA+PCP), compared to control (C) participants receiving the EMPOWER-I intervention targeted mailed materials, on completing a breast MRI and mammogram.

2.1.1 To determine the effectiveness of PA+PCP compared to PA on breast cancer surveillance rates (breast MRI + mammogram).

2.1.2 To determine the effectiveness of the two interventions on rates of each individual surveillance test: breast MRI or mammography.

2.1.3 To explore moderating and mediating patient and PCP-level factors (from baseline and end-of-study surveys of participants and their PCPs) that predict breast MRI and mammography completion and timing of the obtained surveillance. The 12-month follow-up surveys have been postponed to approximately 18 months to acknowledge the COVID-19 impact on screening availability and feasibility for participants at this time. This change is reflected in all responses regarding the 12-month survey throughout this protocol.

2.1.4 To estimate (1) the replication costs of the interventions and (2) costs resulting from the interventions.

2.1.5a Annotate the repository with sociodemographics of the women, radiation dose/field, and measures of ovarian function, and imaging modality.

2.1.5b Utilize the Mazurowski method of deep learning-based segmentation for normalization of the breast MRIs.

2.1.6 Characterize mammographic breast density, by single-reader radiology review and by semi-manual, semi-automated computer software (Cumulus), in childhood cancer survivors using the breast imaging repository and compare to the mammographic breast density in a cohort of women without a history of cancer and undergoing routine breast mammography, matched 1:3 for age at study, calendar year of mammogram, race/ethnicity, and menopausal status.

2.1.7 Measure BPE on breast MRIs, by single-reader radiology review and by computer-based algorithm, in the repository and compare to a cohort of high-risk women without a prior cancer who are undergoing breast cancer screening with breast MRI; match 1:2 for age at study, calendar year of breast MRI, race/ethnicity, and menopausal status.

2.1.8 Gather exploratory information regarding participant's insurance coverage, cost burdens related to recommended screening practices, and how this burden influences screening engagement.

2.1.9 Explore how participant's past, present, and future screening behaviors may have been impacted by the COVID-19 pandemic, as well as how they have been engaging in telehealth and other alternative options during this time.

2.2 Hypotheses

We will test the following hypotheses:

For primary objective: Compared to C, women randomized to PA and PA+PCP will have significantly higher rates of breast cancer surveillance (breast MRI and mammogram) than women in the C group.

Given the primary focus of the trial on non-economic endpoints (and sample size requirements associated with these endpoints), we will not conduct formal hypothesis tests on the economic outcomes.

3.0 Participant Recruitment and Enrollment

We will enroll 320 women from the Childhood Cancer Survivor Study (CCSS), alternatively known as the Long-Term Follow-Up Study (LTFU) to participants. The CCSS is a multi-institutional, multi-disciplinary collaborative research resource established to systematically evaluate long-term outcomes among children

diagnosed with cancer who survived five or more years from diagnosis. Participants will be recruited in three waves (97/wave) by the CCSS Coordinating Center, which has extensive experience recruiting for our studies. We anticipate enrolling 97 participants in Year 1 and then the remaining 194 in Year 2. All eligible members of the CCSS cohort will be identified by the CCSS Statistical Center. We will randomly sample CCSS members from this eligibility list to contact regarding participation in this study.

An introductory letter of invitation will be sent via e-mail by the CCSS Coordinating Center. Included in this e-mail will be (1) an invitation to join the EMPOWER-II study; (2) instructions on how to download the Eureka platform and (3) a brief summary of study activities. A second letter will be sent to non-responders via regular mail. After 3 weeks, a telephone interviewer from the CCSS Coordinating Center will then call potentially eligible cohort members who fail to respond to 2 invitation letters and invite them to participate. After 3 weeks, a final invitation letter will be sent via regular mail. Once interested participants have downloaded the Eureka app, they will receive push notifications leading them to an FAQ sheet and eligibility checklist within the app. Eligible participants will then receive an electronic consent form via the app along with a HIPAA waiver, and a link to the privacy policy of Eureka. We will continue attempting to accrue subjects from the eligibility list until 320 members have been randomized in the study. With over 1,400 women in the CCSS potentially eligible for this study and the high participation rate in EMPOWER-I, we do not anticipate a problem in enrolling 320 participants. During the study enrollment, there will be an estimated 1,456 women who fulfill the eligibility criteria.

All participating survivors will be compensated $50 for each survey completed at baseline and at the end of the study ($100 total for each survivor). We will also compensate PCPs for their time in answering the short survey at baseline and at the end of the study. We will compensate at the same rate as the survivor participants: $50 per survey ($100 total for each PCP).

At Duke:

We will administer surveys (print at baseline and end-of-study) for the PCPs of the CCSS participants in order to collect information on PCP factors. Primary care providers will be given an information sheet with a written summary about the research including: (1) purpose of the research; (2) time involved; (3) assessment of minimal risk; (4) statement regarding benefit to participants; (5) contact for questions about the research; and (6) contact for questions about rights as a research participant. Their completion of the brief study surveys will serve as implied consent and they will not be separately consented for participation, as we believe this would serve as a barrier. The cover letter will be written as to indicate that the completion and return of study surveys implies consent to participate in EMPOWER-II.

Supplemental Imaging

There will be no additional recruitment/enrollment for the supplemental study. It involves collecting and analyzing data on women who enrolled in EMPOWER-I and EMPOWER-II Studies and completed a breast imaging study as part of clinical care. Imaging studies will only be obtained for women who participated in EMPOWER-I and EMPOWER-II and signed a HIPPA authorization and medical release form.

3.1 Inclusion Criteria

Eligible participants will include women who:

3.1.1 Participants in the Childhood Cancer Survivor Study (CCSS);
3.1.2 Were diagnosed with a childhood cancer prior to the age of 21 years;
3.1.3 Were treated with ≥ 10 Gy of chest RT (recent revision with a lower dose threshold);[1]
3.1.4 Do not have a history of breast cancer;
3.1.5 Have not had both a breast MRI *and* mammogram in the previous 24 months;
3.1.6 Do not have a contraindication to MRI (i.e., pacemaker);
3.1.7 Are 25 years of age or older at time of enrollment;

3.1.8 Have an interval from their chest RT to the time of enrollment of at least 8 years;
3.1.9 Have a smartphone;
3.1.10 Are English-speaking.

3.2 Randomization and Stratification

After completion of the baseline questionnaire, participants will be randomly assigned, in a ratio of 1:1:1, to one of the three groups (control, PA, PA+PCP). Randomization will be stratified by age at study enrollment (25-39, ≥40), by cancer diagnosis (Hodgkin lymphoma, other cancers), and by receipt of a previous breast imaging exam (either mammogram or breast MRI) in the previous 24 months (yes, no). Because we did not observe a difference in mammography or breast MRI surveillance between white, non-Hispanic and minority survivors in EMPOWER-I, we will not stratify by race/ethnicity. However, we will oversample from minorities in CCSS with the goal of having 18% of participants in the trial coming from minority populations. Further, since only a small percent of participants had a family history of breast cancer (<1%) or did not have a PCP (8%), we will not stratify by these two factors. However, we will have tailored push notifications / video vignettes for women without a PCP that are intended to help them find one. These three stratification factors were chosen because of the desire to maintain balance between the three arms with respect to age, cancer diagnosis, and recent single imaging study while simultaneously keeping the number of strata to a minimum and ensuring stratum size does not get too small.[58] We will use a permuted block randomization scheme with a block size of three and six. A computer-based random number generator will be used to generate the sequence of assignments in advance.

3.3 Consent Process

A letter of invitation will be sent to all participants by the CCSS Coordinating Center. Interested participants who have downloaded the Eureka app will receive an electronic consent form through the app. The Project PIs and research assistant, as well as the staff at the CCSS Coordinating Center, will be available to respond to questions or concerns of the survivor. Survivors will be informed that participation is voluntary and will not affect their continued participation in other aspects of the CCSS. The purpose of the study and potential risks and benefits will be explained during the informed consent process. All data gathered will be kept in a secured location and available only to members of the research study team. The key elements of the informed consent procedure which will be explained to participants are: (1) the research status of the study; (2) the potential risk and the provisions for it; (3) the lack of guarantee of benefit from participation; (4) the voluntary nature of the study; (5) the lack of consequence to medical care of the decision to consent or refuse to participate; and (6) the freedom to withdraw from the study or to refuse to answer specific questions or to participate in any aspect of the study at any time.

4.0 Design and Procedures

This is a phase III, 18-month, 3-arm randomized controlled trial. Extending from the core component of the EMPOWER-I intervention (targeted mailed educational materials) we will evaluate the utility of patient activation with and without added PCP activation. Data will be collected at baseline and approximately 18-months through patient and provider surveys and medical record review. The primary outcome will be a self-reported breast MRI and mammogram.

The baseline and end-of-study surveys will be self-administered through the Eureka app. Non-compliant participants will be given an option to complete the surveys online through a link sent via email and push notification. A follow-up push notification and email will be sent for non-responders. If the participants are unable to complete the app or online surveys after automated and email reminders, the CCSS Coordinating Center will administer the questionnaires over the phone. A print option via regular mail, followed by a phone call from the study team, will be sent as a final attempt to collect survey data. The questions pertaining to socio-demographics, general health status, health care access, and health and cancer screening practices are standard CCSS items. Considering potential technical issues as well as the effects of the COVID-19 pandemic, follow-up of end-of-study data may take a few months to allow patients to return completed surveys and qualitative interviews.

A final attempt to collect study outcomes (mammogram, breast MRI, breast ultrasound, medical records and pathology) from 63 participants who are more than 3 months past the approximated 18-month study window will be done via 2 regular mailings, an email notification (sent by the Duke team), and a follow-up phone call from the CCSS Coordinating Center who will administer the questionnaires over the phone. The mailed packet will include 2 options to complete the end-of-study survey: a) a full survey set or b) an abbreviated version of the survey focusing on the main study outcomes (i.e. were they able to get their breast cancer screening tests done and where). PCP factors will also be collected for this group. This attempt extends this group's participation by up to a year. These participants have already completed the baseline survey but have not responded to multiple automated and email reminders within the initial 18-month study period. This extended timeline will not be applicable to those who are currently active in the study.

To collect information on PCP factors, the Duke team will administer the baseline and end-of-study surveys (print via fax) for the PCPs of the CCSS participants. We will ask women in the baseline survey for the name and contact information for their PCP and will solicit this information via the Eureka app for those who don't have one at baseline.

After completion of the baseline measurement questionnaire, participants will be randomly assigned, in a ratio of 1:1:1, to one of the three groups: control, patient activation (PA), or patient activation + primary care provider activation (PA+PCP). An overview of the 3 groups is presented in ***Appendix I***. All participants will receive the mailed education materials used in EMPOWER-I.

Recurring notifications, sent through the Eureka App, will be added to remind participants of pending study activities. Also, a cost sharing survey and a Eureka App user experience survey will be added to the End of Study Questionnaire.

This study will use a 3-group comparative effectiveness design comparing:

- Targeted mailed educational materials (C) including a Survivorship Care Plan;
- C + patient activation (PA) consisting of (1) a HIPAA compliant smartphone app that will be used to administer surveys and provide electronic copies of breast cancer screening resources; and (2) tailored push notifications and app messages with links to video vignettes discussing the primary barriers to breast MRI and mammography identified by participants in EMPOWER-I;
- C + PA + PCP activation (PA+PCP) with physician materials about breast cancer risk in this population along with national and international guidelines for breast cancer surveillance.

Specific intervention components are explained in greater detail in ***Appendix II***. During the developmental stages for this study, our Patient and PCP Advisory Boards provided recommendations for the interventions and study materials. A summary of their feedback can be found in ***Appendix III***.

COVID-19 Response

Study outcomes may be affected by the loss of jobs and/or health insurance of study participants due to the COVID-19 pandemic. In light of this, the study period for participants who consented or who received a study invitation prior to the COVID recruitment hold will be extended to 18 months. These participants will receive their end-of-study survey through the Eureka app once they complete their screening tests (mammogram and/or breast MRI) or at approximately 18 months, whichever is sooner. An email from the Principal Investigator will be sent to current participants informing them of this change.

Supplemental Imaging at Duke

To establish the breast imaging repository, each radiology center will be contacted to obtain CDs of all screening and diagnostic breast imaging exams (standard clinical process for receiving outside radiologic imaging exams) of women enrolled in EMPOWER- I and EMPOWER-II. The data (demographics, cancer type, date of diagnosis, age at diagnosis, treatment information) from the CCSS and EMPOWER Studies will be used to annotate the repository. The quality of all imaging studies added to the repository will be evaluated. A deep-learning segmentation method will be applied to optimize comparability between imaging studies.

To characterize mammographic breast density, a clinical and a semi-automated reading will be done. Cumulus, a validated semi-manual, semi-automated, standard computer-assisted thresholding software program, will also be used to estimate the total area and dense area of the breast from which % mammographic density is calculated (dense area/total area x 100). Findings will be compared to a non-cancer population of women who have screening mammograms at Duke. The EMPOWER survivors will be matched 1:3 to the non-cancer population, matched for age at study(within 2 years), calendar year of mammogram, race/ethnicity (white, non-Hispanic; African American, non-Hispanic; Hispanic; Asian; other), and menopausal status (pre-menopausal, post-menopausal).

A BPE (minimal, mild, moderate, marked), will be assigned to each MRI reviewed. BPE will also be measured by a fully automated computer algorithm developed by Duke Radiology collaborators. Findings will be compared to a non-cancer high-risk population of women who have screening breast MRIs at Duke (current repository with 900+ MRIs). The EMPOWER survivors will be matched 1:2 to the non-cancer population, matched for age at study, calendar year of mammogram, race/ethnicity, and menopausal status.

The Breast Cancer Surveillance Consortium's publicly available data on breast density will be used to confirm our findings in cases where the quality of images may be inadequate or when there is an inadequate number of non-cancer controls for the matching.

5.0 Data Collection:

The data collection planned for this study will be obtained from the Eureka app, mail, and telephone-based self-report questionnaires and medical record report (breast MRI and/or mammogram reports).

Supplemental Imaging

Duke's source of research material will be a limited data set placed in a breast imaging repository. The data will have encrypted identifiers and will be used specifically for research purposes.

The Duke EMPOWER Breast Imaging Repository will create a custom data collection and management system which collects information on patient demographics, medical history, breast imaging results, and pathology outcomes.

5.1 Primary and Secondary Outcomes:

The following items were developed in 'Mammography and High-Risk Survivors of Pediatric Cancer' (R21 CA106972; PI: Oeffinger)[24-26] and refined for EMPOWER-I (R01CA134722).

- *Breast MRI practices:* Items that characterize breast MRI practices, including a differentiation between screening and diagnostic breast MRI and barriers to having an MRI.
- *Mammogram practices:* Items that characterize mammogram practices, including a differentiation between screening and diagnostic mammography and barriers to having a mammogram.
- *Ascertainment of the primary and secondary breast cancer surveillance outcomes:* The primary outcome will be a self-reported breast MRI and mammogram. If a survivor reports that she has had a breast MRI and/or a mammogram, she will be asked the contact information for the imaging center. We will then contact the imaging center, provide the signed medical record release form (from enrollment), and request a faxed copy of the imaging report(s).
- *Descriptive data on physician visits, abnormal imaging studies, biopsies and cancers:* In the end-of-study survey, participants will be asked to describe all medical visits during the study period, including routine non-procedure breast-related visits. Women who have had a mammogram and a breast MRI or ultrasound will be asked if they had an abnormal imaging study and the follow-up procedures for this imaging study. As per CCSS standards, if a woman reports a breast cancer, we will seek copies of the pathology and operative reports and provide this information to the CCSS Pathology Center.

5.2 Mediating and Moderating Variables:

Items designated with an asterisk were developed in the 'Mammography and High-Risk Survivors of Pediatric Cancer'[24-26] and refined for the EMPOWER-I Study. In EMPOWER-II, we will also include measures of patient activation and self-efficacy.

- *Patient Activation Measure (PAM):* measures patient activation 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.[59]
- *Knowledge of breast cancer surveillance recommendations:* determines the level of knowledge regarding the recommendations for breast cancer surveillance and the benefits and other considerations of screening.
- *Barrier scales:* elicits a rank order of the most relevant and important barriers of breast MRI and those associated with mammogram, for those women who did not obtain the recommended screening.
- *Pros and Cons of Breast MRI and Mammography:* Rakowski and colleagues operationalized the concept of barriers and facilitators in the Pros and Cons of and Mammography instrument.[60,61] In EMPOWER-I, with the assistance of Rakowski, we developed and tested the utility of the Pros and Cons of Breast MRI instrument.
- *Family history of breast cancer*
- *Attitudes towards breast cancer screening / Risk perception and health beliefs:* will assess both general preventive health beliefs and breast cancer specific health beliefs, including breast cancer risk perception.
- *Intention for engaging in breast surveillance and Communication with PCP about breast cancer surveillance:* will assess whether women scheduled a visit with their PCP, their intention for surveillance, if they discussed breast cancer screening with their PCP, and the outcome of this discussion.
- *Affect:* will be measured using the adapted and shortened version of the Positive Affect Negative Affect Scale (PANAS). We will focus on emotions related to managing health.[62]
- *Future breast screening intentions:* future plans for breast MRI and mammogram will be included, "When do you plan to have a breast MRI / mammogram in the future?" with the following options: within the next 6 months, in 6 months to 1 year, in 1-2 years, in 3-4 years, in 5 or more years, when my doctor recommends, when I have a symptom, not planning to have one, don't know.
- *Self-Efficacy:* measures confidence in discussing breast surveillance with the PCP and obtaining the recommended screening using items developed by Champion and colleagues.[63]

5.3 PCP Variables:

We will administer a baseline and end-of-study survey of the PCPs of women in EMPOWER-II. For this survey, we have modified a survey that we assisted Dr. Tara Henderson in developing as part of her career development award (K07CA134935; PI: Henderson; Co-Mentor: Oeffinger).[35,36] Items within the survey include:

- *Demographics:* age, gender, years in practice, practice setting
- *Past experience and comfort level:* number of adult survivors of childhood cancer seen in last five years (categorical), frequency of receiving an SCP (categorical), comfort level with caring for survivors of three cancer types (Likert scale), and familiarity with available guidelines (Likert scale).
- *Knowledge:* Using a hypothetical vignette of a 29-year old female patient treated for Hodgkin lymphoma with chemotherapy and chest RT we will ask questions about screening for thyroid dysfunction, breast cancer, and cardiac dysfunction.

5.4 Economic Measurements:

In the proposed study, we will capture information regarding the replication costs of the intervention and health services resulting from the intervention. For the replication costs, the dollar amount will be determined per participant, for the materials, postage, PopSockets, and notifications/app messaging/mobile data use will

be determined per participant. To determine the health services resulting from the intervention, we will survey participants at the end-of-study measurement regarding their use of specific health care services (routine or acute medical visit unrelated to breast cancer screening, non-procedure breast-related medical visit). We will collect a copy of all breast imaging studies from the imaging facility. In addition, women reporting a breast biopsy or breast surgery will be asked to provide the contact information of the physician/medical facility so that we can obtain a copy of all breast surgical procedures. This strategy has been successfully employed in other CCSS studies, including EMPOWER-I.

5.5 Insurance Coverage and COVID-19 Impact Phone Survey:

After completion of the end of study survey, participants in the PA and PA+PCP groups will be contacted by phone to invite them to participate in a voluntary brief phone survey that will cover topics related to participant insurance coverage, COVID-19, and how these issues may have impacted their engagement in the EMPOWER intervention. All participation will be voluntary and participants will not receive additional compensation if they choose to participate in this additional study component.

6.0 Statistical Analyses

The primary analysis involves comparing the proportion of women with a self-reported breast MRI and mammogram in each intervention arm to C. In EMPOWER-I, we used self-report of the imaging studies. We also sought to obtain medical record (fax) confirmation of the self-reported imaging studies. We were successful in obtaining the proper reports for 85.7% of the participants. However, for the remaining 14.3%, we were unable to confirm the study due to lack of information provided by the participant regarding the imaging facility, the imaging facility being unable to locate records and the facility sending only partial information, despite multiple attempts to collect the data. Importantly, the findings were not substantively different when we repeated the analysis including only women with a fax-confirmed imaging study. Stratifying on the randomization strata, differences in these proportions will be estimated with stratum-adjusted proportions calculated using the weighted average of the stratum-specific differences and accounting for the sampling scheme. The Cochran-Mantel-Haenszel test[64] will be used to test for differences between (1) PA and C, and (2) PA+PCP and C in an intent-to-treat analysis where women who do not complete the end-of-study assessment will be counted as not having had a breast MRI and mammogram. We will also perform a secondary analysis of women with a fax-confirmed imaging study. Based on EMPOWER 1 results, we do not expect results to differ based on race/ethnicity, but will verify this result here. The analytic methods for the secondary objectives will be the same as for the primary objective, using the Cochran-Manetel-Haenszel test to examine differences between the interventions (PA, PA+PCP) on breast cancer surveillance rates (breast MRI + mammogram) and on rates of each individual surveillance test.

To explore moderating factors that may be associated with obtaining a breast MRI and a mammogram, we will use mixed effects models. The mixed model is $\mathbf{Y}_i = \mu(\mathbf{X}_i, \alpha, \mathbf{Z}_i, \mathbf{b}_i) + \mathbf{e}_i$ where for participant *i*, $\mathbf{Y}_i$ is the response vector capturing whether the participant had a breast MRI and mammogram, $\mathbf{X}_i$ is a fixed effects design matrix that includes indicators for treatment group, randomization strata, assessment time (baseline and end-of-study), potential confounders, and moderator variables, $\mathbf{Z}_i$ is a design matrix for the random effects that would allow random subject deviations from the population average response, $\boldsymbol{\alpha}$ contains the fixed effects regression coefficients, $\mathbf{b}_i$ contains the random effects coefficients, $\mathbf{e}_i$ is the vector of error terms, and $\mathbf{b}_i$ and $\mathbf{e}_i$ are normally distributed with means of zero. We will test whether variables significantly moderate having a breast MRI or mammogram by testing whether the regression coefficients associated with these variables are significantly different from zero. Further, by including interaction terms between potential moderating variables and the treatment group indicator, we will test whether the effectiveness of the intervention differs by the moderating factors.

To explore mediating factors, we will follow MacKinnon and colleagues' recommendations and examine potential factors in a post-hoc manner and make necessary adjustments.[65] For example, we will fit path analysis models using the statistical packages LISREL or EQS, inspect the path coefficients, and choose the appropriate statistical tests of mediating effects according to MacKinnon et al. We may also consider testing model equivalence to examine whether the mediating path model is equivalent across the control and intervention groups. While several different tests have been used to test mediating factors, MacKinnon and colleagues recommend using tests developed from the product of coefficients methods, where the parameters are estimated using regression, and the standard error of their product is obtained by the delta method. This test can be readily implemented using software made available by MacKinnon et al.[65] All analyses will be adjusted for the stratification factors used at randomization.

Costs for each component of the intervention will be collected to determine the cost per person. This will include the dollar costs of the materials, personnel time for creating the cancer treatment summaries, PopSockets, mailings, and notifications/app messaging/mobile data costs. From this data, we will estimate a dollar cost and time cost per person. This will not include the costs for developing the materials, as our goal is to determine the dissemination cost per person. Upon completion of the study, we will have developed several "deliverables" that can be disseminated for use by other investigators. These will include the cancer treatment summary template, harms and benefits of cancer surveillance information, and patient and physician education handouts. These materials will be made publicly available on the CCSS website: http://www.stjude.org/ccss.

We will identify utilization of screening and diagnostic imaging (breast MRI, mammography, and ultrasound), diagnostic procedures (fine needle aspiration, core needle biopsy and excisional biopsy), breast surgery, and non-procedure breast-related physician visits. Each service will be multiplied by a unit cost amount in order to estimate total costs. We will use Medicare's 2008 Direct Practice Expense and Resource Based Relative Value Scale (RBRVS) to estimate average unit costs for physician and laboratory services. Although most study participants will not be Medicare beneficiaries, Medicare's reimbursement methodology was developed to reflect true resource costs.[66] 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 costing methodology has been employed in economic analyses related to screening mammography.[67,68] In sensitivity analysis, we will evaluate a range of unit cost estimates, both lower and higher than the average Medicare reimbursement level. Patient time and travel costs will be estimated from the literature.[67]

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 patient screened and the cost per additional breast cancer case detected as a result of the intervention. Because these health outcomes do not capture events that follow breast cancer diagnosis, our cost estimates will not include the costs of events that follow diagnosis (e.g., costs of breast cancer treatment). As previously mentioned, we will not conduct formal hypothesis tests on the economic outcomes given the primary focus of the trial on non-economic endpoints (and sample size requirements associated with these endpoints). Resource utilization and cost data are typically skewed, and therefore the sample size of the trial will likely be insufficient to detect significant differences in costs between study arms.[69] 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.[70,71] This analytic approach is appropriate in economic studies that "piggyback" randomized trials.[72]

Supplemental Imaging

We will tabulate the BI-RADS breast density assessment and look at the distribution of the categorical assessment by clinical review by age at the time of the mammogram (<40, 40+ years), menopausal status at the time of the mammogram (pre-menopausal, post-menopausal), age at childhood cancer diagnosis (<10, 10-20), and time from childhood cancer diagnosis (<15, 15-24, 25+ years).

The clinical review categories will be dichotomized to BI-RADS 1 and 2 (fatty replaced, scattered areas of fibroglandular tissue) vs BI-RADS 3 and 4 (heterogeneously dense, extremely dense). Our primary outcome

will be the comparison of the proportion of childhood cancer survivors with BI-RADS 3 and 4 to that o fthe matched controls. The two populations will be compared using the Mantel-Haenszel test statistic.

Demographic variables will be compared between the survivor and non-cancer controls using a t-test, Wilcoxon rank-sum, and Fisher's exact test as appropriate. A chi-square test will be used to test for differences in the proportion of BPE measurements between the survivor and non-cancer control groups with the BPE recorded as an ordinal variable. The BPE will also be dichotomized into nominal variables using threshold BPE values (i.e., minimal vs valid, moderate, or marked). Receiver operating characteristic curves will be used to determine the optimal BPE threshold to maximize both sensitivity and specificity for distinguishing the survivors from the non-cancer controls. A logistic regression will be used to calculate OR and 95% confidence intervals.

We will also use the fully automated algorithm to compare the eight BPE continuous measures between the two populations. For the comparisons, we will construct adjusted linear regression models. We will be underpowered for the comparisons but will be able to generate the necessary preliminary data in order to design future studies and comparisons.

6.1 Missing Data

Every effort will be made to minimize missing data and participant drop-out, both among the women and their PCPs. The primary analysis is an intent-to-treat analysis and will include all women who are randomized to the study regardless of whether they complete the end-of-study assessment (participants who drop out will be counted as failures in this analysis). Secondary analyses will include exploratory comparisons restricted to women who complete the end-of-study assessment. If potential moderating and mediating factors are missing, we will use multiple imputation.[73] We will explore missing patterns among the PCPs and may consider using multiple imputation if it is warranted.

6.2 Sample Size and Power

The primary aim involves two pair-wise comparisons of equal importance. For each comparison, we fix the probability of a Type I error at 0.025 in order to maintain the overall probability of a Type I error at 0.05. We powered the study to detect a difference of 20% for each pair-wise comparison assuming equal randomization to each of the three arms and that the proportion of women in the control group who will have a mammogram and an MRI will be approximately 10% based on our previous work. Table 1 shows the power we expect to have using two-sided Mantel-Haenszel tests and indicates that we should have sufficient power to detect a clinically meaningful difference even if the proportion of women in the control arm with the primary endpoint is somewhat higher than we expect. The power calculation of the Cochran-Mantel-Haenszel tests assumes a common risk ratio among the strata, that all strata generate the same proportion for the control arm and intervention arm.

Table 1. Power to detect a difference between an intervention and control arm

Proportion with mammogram and MRI in the control arm	Proportion with mammogram and MRI in an intervention arm	Difference	Power among all participants
10%	28%	18%	83%
10%	30%	20%	90%
15%	35%	20%	80%

Supplemental Imaging

To inform our power calculations, we used densiy measures reported on the outside radiology reports for women in EMPOWER-I and then used three different proportions of BI-RADS ¾ density: 0.60, 0.65, 0.70. We then used the age-appropriate breast density proportions reported by the Breast Cancer Surveillance Consortium (http://tools.bcsc-scc.org/dataexplorer/) as shown in Table 2. We will use a 1:3 matched non-cancer population for comparison.

Table 2. Power to detect a difference between the two populations.

	EMPOWER (N=102)	Breast Cancer Surveillance Consortium (N=1,072,517)	Delta	POWER
Scenario I	0.60	0.54	0.06	0.21
Scenario II	0.65	0.54	0.11	0.57
Scenario III	0.70	0.54	0.16	0.89

As noted above, we will use a 1:3 matched non-cancer population for comparison. Of note, the sample above is based on our estimates of mammograms we will obtain during the proposed funding period. As noted, after the funding period, we will continue to collect breast imaging studies among women in EMPOWER-II, thus increasing the potential power of the analysis.

Using Cumulus, the measured percent mammographic density is a continuous number and will be summarized using descriptive statistics such as the mean, median, and range. Summaries may be presented by age at exam, menopausal status, age at childhood cancer diagnosis, and time from cancer diagnosis. Analyses will proceed as described for BI-RADS density using models adjusted for the matching factors (age at study, calendar year of study, race/ethnicity, menopausal status).

7.0 Data Storage and Confidentiality

All information will be labeled with unique study identification numbers and stored in password-protected computerized databases. Study files will be kept in locked cabinets and access restricted to study staff. No data will be sent over the internet unless it is encrypted. Only key personnel will have access to the information in the database on an as-needed basis. Key personnel may not alter the data in the database or directly view all of it without specific cause and approval of the PIs. All email with subject-identifiable information will be encrypted. Findings will be presented in aggregate form only, with no references made to the individual participant's data. Confidentiality of each participant's data will be protected with utmost care with all questionnaire data identified solely by a code number. A list matching participant's names and code numbers will be maintained on a separate sheet of paper kept in locked storage at the CCSS Coordinating Center.

At Duke

All staff members will be informed prior to employment and at regular intervals as to the necessity for keeping all data confidential. All written study material will be stored in locked file cabinets. Any identifying data will be kept on the Duke Cancer Institute server and each staff member's PC will be password protected. The names, geographic designation, and contact information for participants and their primary care providers will be sent to Duke staff via data reports through the Eureka platform and stored in the Duke server.

Supplemental Imaging

Data will be entered into the Duke EMPOWER database. The images will be stored in Digital Imaging and Communications in Medicine (DICOM) format, transmitted to a Picture Archiving and Communications System (PACS) reading station for review and retrieval, and permanently and securely archived in the Computational Environment for Radiological Research which is housed on a secure institutional server.

8.0 Data and Safety Monitoring

This protocol presents no greater than minimal risk to the subjects and adverse events are not anticipated. The entire Data and Safety Monitoring Plan for the study can be found in ***Appendix IV***. All study staff at Duke University, Memorial Sloan Kettering Cancer Center, and St. Jude Children's Research Hospital will be thoroughly trained in the methods for identifying when an unanticipated problem or adverse event occurs and how to complete forms to report the event. All unanticipated problems and adverse events will be reported to the Principle Investigators, Drs. Oeffinger and Ford, who will report them to the IRB as soon as possible and within the following time frames: 1) report any death and potentially life-threatening events within 3 days of

notification of the event, 2) report any serious/unexpected adverse events associated with the study within 3 working days, 3) all other adverse events will be reported within 15 calendar days, 4) discuss any event that does not meet the above requirements with the study team and report yearly to the Duke IRB. This data will be reported to the DSMB for independent assessment.

Appendix I: Overview of Study Arms and Mediating/Moderating Variables

Content and Mediating / Moderating Variables Addressed for each group

Group	Intervention	Content	Mediating / Moderating Variables Addressed
Control **(C)**	Mailed targeted print materials	• Survivorship Care Plan: individual cancer treatment summary, screening recommendations, and risk-reducing interventions to maintain health after treatment for childhood cancer • One-page description of the potential benefits and other considerations of breast cancer screening for women with a similar cancer history • A PopSocket with the EMPOWER logo. This is a convenient reminder method to keep participants engaged. • How to find a PCP • List of low cost options for mammography / breast MRI • A template of a letter that can be used, if needed, to obtain approval for coverage of a breast MRI from an insurance company	• Knowledge / awareness • Risk perception • Barriers reduction
C + Patient Activation **(PA)**	Smartphone-based	• *Push notifications and app messages are tailored in content and timing*. See ***Appendix II*** for details. • Culturally tailored video vignettes (90 seconds each) will supplement several of the push notifications and app messages and include the following: i) How to find a PCP (applicable only for women without a PCP) ii) How and why to talk to your provider about breast cancer screening with breast MRI / mammography iii) Cost of breast MRI (finding low cost options and insurance letter templates for the PCP) iv) Focus on importance of screening and ways to make it a priority v) Why screening is important even in the absence of symptoms or breast problems • CCSS app will include an electronic version of the mailed targeted print materials.	• Patient Activation: - Knowledge / awareness - Self-efficacy to talk to PCP about breast cancer screening - Active role in early detection - Taking action • Risk perception • Barriers reduction • *Affect* • *Health beliefs*
C+PA+PCP Activation	Faxed materials from Duke to	• Cover letter with patient's name, history of chest RT, and recommendation for breast MRI and mammography (with source information) and contact information	• Knowledge of risk and surveillance recommendations

(PA+PCP)	PCP office manager	• Executive summary – breast cancer in childhood cancer survivors treated with chest RT and current breast cancer surveillance recommendations • FAQ (one-page) discussing common questions, e.g., "why both a breast MRI and mammogram are recommended", "my patient has dense breast tissue", "what about radiation exposure from mammograms", and "cost of imaging" • Template of letter for insurance company for pre-authorization (if needed) of a breast MRI with the key words for insurance carriers and the ICD10 codes	• Barriers reduction with language for insurance company coverage and ICD10 codes • Self-efficacy to answer patient questions about surveillance

Appendix II: Intervention Components

Control (C) Group:

The control group will only receive the print materials. We will use the core component of the EMPOWER-I intervention. Targeted print materials will be sent to women in all three groups (C, PA, PA+PCP) by 2-day express mail and by email and will include the items listed in ***Appendix I***. A Survivorship Care Plan will be included in all the targeted print materials. Based upon input from our Patient Advisory Board, we have changed the laminated card to a PopSocket and added an information sheet to find a PCP (if the participant does not have one). In addition, the information on low cost mammograms and breast MRI will include a link to the MRI Assistance Program (http://www.rightactionforwomen.org/assistance/) and the information on low cost mammography that was used in EMPOWER-I. All women enrolled in EMPOWER-II who meet the financial criteria for assistance (income below 400% National Poverty Level) will be eligible for assistance. For purposes of the non-profit status of RAW, women need to submit either the previous year's tax return or, if applicable, a copy of a Medicaid letter. Once these steps are completed, the participant's PCP can then order a breast MRI that is scheduled by DiagnosticWorks at one of their sites across the U.S. This step is not necessary in Canada, where a PCP can order a breast MRI for this high-risk population and have it covered by insurance.

Patient Activation (PA) Group:

Building upon the core intervention components used in EMPOWER-I (i.e., print educational materials), we will evaluate the utility of patient activation through use of automated, highly tailored and interactive push notifications, supplemented by linked 90-second video vignettes and mapped to the behaviors being encouraged, and a survivorship-specific smartphone app (Eureka app). The push notifications are built to work in concert with the Eureka app and do not require the app to be open to receive push notifications. Opening the push notifications will trigger study-related activities within the Eureka app. We will use the Eureka mHealth Research Platform for sending push notifications, brief surveys for updating information, video vignettes, and study activity reminders. The mHealth Research Platform Resource is a mobilized cohort and infrastructure to carry out clinical research studies using mobile and digital technology developed by the University of California, San Francisco (UCSF). The goal of the Resource is to provide an infrastructure for efficient data collection, storage, and sharing that can be configured to support internet- or mobile phone app-based research studies. Eureka supports data collection for consenting participants on behalf of IRB-approved research studies, stores that data on secure cloud-based servers, and provides access to that data to platform users (including

participants and study teams) with a granular password protected user permissions system. The Eureka Privacy Policy and Data Security Measures agreement document has been uploaded into the eIRB. This is the IRB-approved policy all participants will have to agree to as part of the app registration process.

Our goal is to develop an inexpensive set of automated tailored notifications, video vignettes, and materials that do not rely on personnel time and thus can more easily be disseminated. The overarching goal of this approach is to activate the participant to make an appointment with her PCP and to discuss, request, and obtain breast cancer screening. We have also incorporated a reminder strategy in the push notifications and app messages.

The push notifications, app messages, and video vignettes are based upon an algorithm that is highly tailored in content (e.g., history of prior screening, specific barriers, etc.) and timing (e.g., will be informed by the timing of decision-making mapped to the behaviors being encouraged) and will ask specific questions (e.g., do you have a PCP, have you had a breast MRI and/or mammogram in the last 12 months, have you ever had a breast imaging study, do you have an appointment with PCP and when). The information sent via the Eureka app will be tailored to participants' answers. The number of push notifications and app messages that a participant receives will be variable, will occur at least monthly until screening is completed (based upon their responses), and will include:

EMPOWER-II IN-APP & SMS TEXT MESSAGES
POST-RANDOMIZATION: INTERVENTION & CONTROL
Text message: Welcome to the EMPOWER study! You will be receiving information on resources for breast cancer screening in the mail soon. Thank you for your participation!
IN-APP TEXT: Self-management Survey Please answer the following questions about your health.
IN-APP TEXT: Mammogram Survey Please answer the following questions about getting a mammogram.
INTERVENTION
IN-APP TEXT: The information that we sent you in the mail about breast cancer screening may also be accessed electronically through this link (link to LTFU website).Please click the link below and watch this brief Welcome video -Video 1
IN-APP TEXT: Click the link below: -Video 2
IN-APP TEXT: Please fill out a brief survey. -> Takes the user to: **SURVEY ACTIVITY** Have you had BOTH an MRI and mammogram since receiving your EMPOWER packet or in the last 12 months? -YES -> survey activity: screening -NO ->PCP question and monthly MRI/mammogram reminders (parallel tracks sent 2 weeks between each other)
IN-APP TEXT: We are happy that you have completed BOTH your breast MRI and mammogram. We have 5 questions for you. Please update your information in the next survey: **SURVEY ACTIVITY** **When did you get your mammogram?**

-MM/YEAR
Where did you get your mammogram?
-Facility name
-Facility address

When did you get your breast MRI?
-MM/YEAR
Where did you get your breast MRI?
-Click if the same location as your mammogram -> (checkbox/radio button option to select if same as mammogram facility)
-Facility name
-Facility address

Who ordered your test/s?
-Primary care doctor (family physician, general internist, gynecologist, general practitioner)
-Oncologist (including a nurse practitioner or physician assistant)
-Other, please specify:_____

(If Oncologist or Other than a Primary care doctor: branched based on previous response)
Do you also have a Primary care doctor in addition to your previous answer?
-NO- Thank you for updating your information
-YES- Please provide us the following information about your Primary care doctor:
Name
Address

IN-APP TEXT:
(Cost)
Cost shouldn't keep you from getting a breast MRI and mammogram. Please complete the following brief survey.

Survey Activity
Have you had BOTH an MRI and mammogram since receiving your EMPOWER packet or in the last 12 months?
-YES -> survey activity: screening
-NO ->completed activity and shows the below screen:

EMPOWER yourself and learn about your options for low cost screening. Click the link for breast MRI financial assistance (www.rightactionforwomen.org/assistance/) and watch the video through the link below:
-link to Video 5

IN-APP TEXT:
(Priority)
We understand that you are busy, but having BOTH a mammogram and breast MRI are better than either one individually. Please complete the following brief survey.

Survey Activity:
Have you had BOTH an MRI and mammogram since receiving your EMPOWER packet or in the last 12 months?
-YES -> survey activity: screening
-NO ->completed activity and shows the below screen:

Here is a brief video on how to make screening a priority:
-link to Video 6

IN-APP TEXT:
(Absence of symptoms)
EMPOWER yourself to get screening even before you have symptoms or breast problems. Please complete the following brief survey.

Survey Activity:
Have you had BOTH an MRI and mammogram since receiving your EMPOWER packet or in the last 12 months?
-YES -> survey activity: screening
-NO ->completed activity and shows the below screen:

Please watch this brief video explaining the importance of having a breast MRI and mammogram:
-link to Video 7

IN-APP TEXT: Do you have a primary care doctor?
-NO -> monthly How to find a PCP reminder + video
-YES -> triggers Survey activity: PCP

IN-APP TEXT:
Label: Having a primary care doctor is important for your health. We understand that finding one may be difficult.

Question: Do you have a primary care doctor?
-YES -> triggers Survey activity: PCP
-NO -> monthly How to find a PCP reminder + video (see below):

Please click the link to find some helpful resources on “How to find a primary care doctor”.
-link to Video 3

SURVEY ACTIVITY

Please provide us your updated primary care doctor’s information:
Name
Address

IN-APP TEXT: Talk to your primary care doctor about the importance of getting a breast MRI and mammogram.

If you have made an appointment with your primary care doctor, please select “Yes”, otherwise choose “No”
Yes ->
-triggers Appointment picker
-completing Appointment picker triggers:
(Survey (label))Here’s how to talk to your doctor about breast cancer screening:
-link to Video 4

Text message: Please check in with the EMPOWER study! Please complete your survey activity and watch the brief video after the survey.

Text message: Please watch this brief video about breast cancer screening.
-link to pending video (3,4,5,6, or 7)

Text message: Your primary care doctor’s appointment is coming up soon. Don’t forget to talk about breast cancer screening. Please don’t forget to take your SURVIVORSHIP CARE PLAN to your doctor. Here’s how and why to talk to your doctor about breast cancer screening.
-link to Video 4

Text message: This is a reminder that you will be receiving your End of Study EMPOWER Survey soon. Please complete the survey when you get it. Thank you for participating in the EMPOWER study!

IN-APP TEXT: End of Study Survey
Please answer the following questions about your health.

CONTROL
IN-APP TEXT: The information we sent you in the mail about breast cancer screening may also be accessed electronically through the link below: -link to LTFU website
Text message: Click here to stay up to date with LTFU news -link to LTFU newsletter and resource page
Text message: This is a reminder that you will be receiving your End of Study EMPOWER Survey in about another 6 months from now. Please complete the survey upon receipt. Thank you for your continued participation in the EMPOWER study!
Text message: This is a reminder that you will be receiving your End of Study EMPOWER Survey in 2 weeks. Please complete the survey when you get it. Thank you for participating in the EMPOWER study!
IN-APP TEXT: End of Study Survey Please answer the following questions about your health.

PCP Activation (PA+PCP) Group:

In developing the PCP activation intervention, we reviewed the literature on medical knowledge transfer methods, transforming primary care, and dealing with busy primary care practices. Importantly, the typical PCP will have only a handful of adult survivors of childhood cancer in their practice, each with a different cancer, treated with different therapies over different eras. Thus, the challenge is to get the right information to the right person at the right time. When the participant in the PA+PCP group responds to an above automated app message indicating that she has scheduled an appointment and has provided a name and office address and fax number for the PCP, the following information will be sent to the PCP's office manager by the research team at Duke via fax:

- Template cover letter with the patient's name, notation of previous history of chest RT, and recommendation for breast MRI and mammography and contact information for the CCSS;

- Executive summary – breast cancer in childhood cancer survivors treated with chest RT and current breast cancer surveillance recommendations (with links to citations for those who want additional information);

- FAQ (one-page) discussing common questions, such as "why both a breast MRI and a mammogram are recommended", "my patient has dense breast tissue", "what about radiation exposure from mammograms", and "cost of imaging";

- Template of letter for insurance company if needed for pre-authorization of a breast MRI with the key words for insurance carriers and the appropriate ICD-10 codes.

Appendix III: Recommendations from our Patient and PCP Advisory Boards

During the development stage for EMPOWER-II, we held conference calls with our diverse **Patient Advisory Board** that consists of six childhood cancer survivors, four of whom participated in the EMPOWER-I study. Their invaluable feedback included:

- Enthusiasm about the use of text messages - would be 'less likely to be lost in the shuffle of papers'
- Include a text reminder 1-2 weeks prior to the visit with the PCP to remind them to talk about breast cancer screening with their primary care provider
- Importance of the involvement of their PCP, including the ability to share their SCP with him/her, 'so they take us seriously and know that screening is important and needed'
- Highlight the need for obtaining both a breast MRI and mammogram
- Tailor the message to reflect the diversity of the participants
- Make sure to include a video vignette about 'how to talk to your doctor' about screening

In the pre-study phase, prior to study enrollment, we will finalize our push notifications, app messages, and video vignettes, with the assistance of our Patient Advisory Board.

In preparing this protocol, we held conference calls with our **PCP Advisory Board** that consists of six physicians – two general internists, two family physicians, and two obstetrician-gynecologists. We selected physicians of women who participated in EMPOWER-I as well as community-based and academic physicians who attended the American Society of Clinical Oncology, the American Academy of Family Physicians, and the

American College of Physicians co-sponsored “Cancer Survivorship Symposium: Advancing Care and Research, A Primary Care and Oncology Collaboration” in January 2016. Recommendations included:

- Mail the information to the office practice manager and ask him/her to ‘flag this information’ and bring it to the attention of the PCP. This will help avoid ‘getting lost in the pile’.
- Remember the 7 second rule – get to the ‘ask’ in the first 7 seconds of reading.
- Remind PCPs how their patient will benefit from the communication.
- Include a pre-addressed fax page with three questions for the PCP: (1) Is this information new to you; (2) Will you discuss breast cancer screening with your patient; and (3) If the patient desires, will you order a breast MRI?

We will finalize our PCP materials with the assistance of our PCP Advisory Board prior to study enrollment.

Appendix IV: Data and Safety Monitoring Plan

To ensure the safety and data integrity of the project, we plan to request that the NIH funding institution appoint a **Data and Safety Monitoring Board (DSMB)**. Duke Cancer Institute / Duke University does not have a standing external DSMB and thus, in accordance with NCI guidelines, we will work with our program officer to develop a DSMB to monitor this phase III study (https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf).

We will be prepared to suggest potential members of the DSMB who would be fully independent of Duke University, Memorial Sloan Kettering Cancer Center, and St. Jude Children's Research Hospital and who would possess relevant expertise in cancer survivorship, cancer screening, behavioral interventions, and clinical trials statistical analysis. However, we expect that final decisions on membership will be made by the NCI. We anticipate that members will be appointed during the study set-up phase. This will enable the DSMB to review the Manual of Operating Procedures - which the investigative team will have developed, including the research protocol, informed consent documents, and safety and quality control monitoring plan - before initiation of the study, and for the DSMB to develop an explicit set of expectations and guidelines based on NIH requirements and considerations which will be followed for all the monitored period.

The DSMB will be responsible for assuring that subjects are not exposed to unnecessary or unreasonable risks and that the investigators conduct the clinical trial according to the highest scientific and ethical standards. Ongoing responsibilities of the DSMB will include:

- Reviewing routine reports prepared by the PIs on study activities, with emphasis on data integrity and patient safety issues, including: reports on adverse events to the NIH Project Officer, recommendations to the Project Officer concerning continuation or termination of the trial, protection of the confidentiality of the trial data and the results of monitoring, ensuring adequate protection of human subjects and addressing ethical concerns based on Federal Guidelines;
- Reviewing Serious Adverse Events (SAEs) - SAE reports will be sent to the DSMB within 48 hours; the DSMB will then propose an action plan to be sent to the PIs and the funding institution;
- Evaluating the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit ratio, and other factors that can affect study outcome;
- Considering the impact of factors external to the study when new information, such as scientific or therapeutic developments, become available and may affect the safety of participants, their willingness to participate in the study, or the conduct of the trial;
- Reviewing study performance, making recommendations and assisting in the resolution of problems reported by the PIs;
- Protecting the safety and privacy of study participants;
- Reporting on the safety and scientific progress of the trial;
- Making recommendations to the funding institution concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Ensuring data integrity;
- Ensuring confidentiality of the trial data and the results of monitoring;
- Assisting the funding institution by commenting on any problems with study conduct, enrollment, sample size, statistics, and/or data collection; and
- Reviewing and evaluating requests for protocol modifications after the trial begins and advise the funding institution as to whether the study should continue as approved or undergo a protocol modification.

We anticipate very few adverse events for this study. In EMPOWER-I, we had no adverse events. Events that are not expected given the nature of the research procedures and the subject population being studied, and that suggest that the research places subjects or others at greater risk of harm or discomfort related to the research than was previously know or recognized, will be reported to the Duke IRB as an unanticipated problem. Harm to a subject need not occur for an event to be an unanticipated problem. All study staff at Duke University, Memorial Sloan Kettering Cancer Center, and St. Jude Children's Research Hospital will be

thoroughly trained in the methods for identifying when an unanticipated problem or adverse event occurs and how to complete forms to report the event. All unanticipated problems and adverse events will be reported to the MPIs, Drs. Oeffinger and Ford, who will report them to the IRB as soon as possible and within the following time frames: 1) report any death and potentially life-threatening events within 3 days of notification of the event, 2) report any serious/unexpected adverse events associated with the study within 3 working days, 3) all other adverse events will be reported within 15 calendar days, 4) discuss any event that does not meet the above requirements with the study team and report yearly to the Duke IRB. These data will be reported to the DSMB for independent assessment.

Given the minimal risk nature of the interventions, the modest size of the study sample (N=320), and the fact that the project does not use an investigational medication or device, we expect that members of the DSMB will be able to participate in meetings via teleconference. After the first meeting, we anticipate that the DSMB will meet approximately biannually at set intervals until recruitment is complete. Additional meetings may be necessary, depending on problems encountered or any special circumstances. The DSMB will be provided with a report that will contain safety data summaries for each data collection center, patient demographics and compliance data, recruitment, visit schedules, missed visits, outcomes and Medical Event Forms and any other adverse events. The DSMB will be able to request specific information and analyses from the PI for monitoring purposes at any time during the study. A final meeting will be held shortly after completion of the study.

9.0 References

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