EMPOWER Study: Promoting Breast Cancer Screening in Women Who Survived Childhood Cancer

Working Groups: Cancer Control, Second malignancy

Principal investigator: Kevin Oeffinger, MD

The following figure lists the members of the research team, consultants, and CCSS investigators.

Research Team

Memorial Sloan-Kettering Cancer Center

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Advisory Committee

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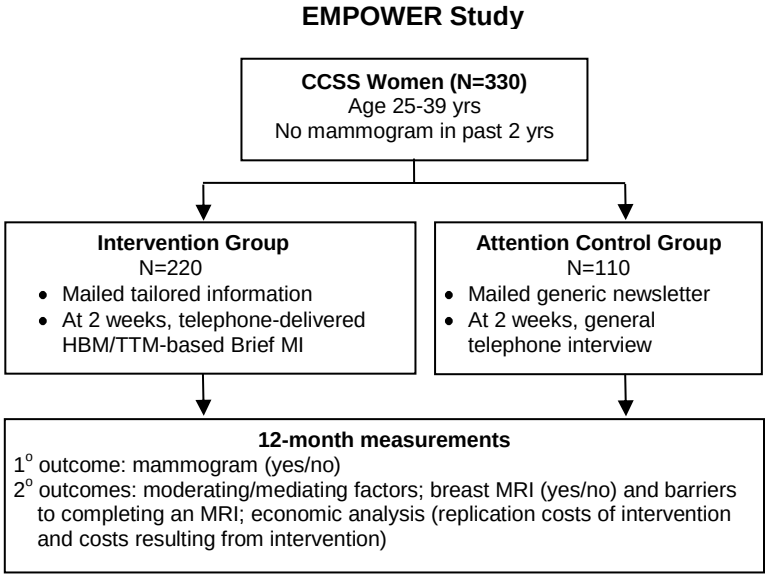
Background: This is a currently funded study that was approved as an ancillary study (R01 CA13472). As per discussions with Greg Armstrong, the following concept proposal consists of the grant application Aims page and the statistical analysis. As this grant has been in process for several years and has already completed enrollement. References or other information is available upon request.

A. SPECIFIC AIMS

Women treated with chest radiation for a childhood cancer have a significantly elevated risk of breast cancer at a young age, similar to that of women with a *BRCA* gene mutation. Because early detection of breast cancer is strongly associated with survival and therapeutic options (radiotherapy, chemotherapy) are limited among these women with previous chest radiation, breast cancer surveillance with annual mammography and adjunct breast MRI is recommended, starting at age 25. Most women treated with chest radiation are unaware of their risk and are not followed at a cancer center. Most primary care clinicians delivering care for this population are not aware of the significantly increased incidence of breast cancer at a young age following chest radiation. Thus, it is not surprising that most of women in this high risk population are not having screening mammograms and are not engaged in a regular pattern of annual surveillance.

Preliminary data suggest that a tailored education intervention consisting of a one-page summary of the previous cancer and cancer therapy with an adjoining recommendation for annual mammography may lead to increased rates of surveillance. Further, our data suggest that inclusion of a targeted and behaviorally-based method to address the pros and cons of mammography, screening self-efficacy and other related individual factors will further enhance the intervention, lead to increases in surveillance, and facilitate a maintenance pattern of screening. This is especially relevant for those women who require more intensive and personalized intervention (e.g., precontemplators, those with psychological barriers, etc.). This latter approach can optimally

be delivered by telephone through a Brief Motivational Interview (Brief MI) founded upon the Transtheoretical Model (TTM) and the Health Belief Model (HBM).



In an effort to increase the rate of breast cancer screening among this high risk population and to reduce the breast cancer associated morbidity and mortality faced by long-term survivors of childhood cancer, the proposed study brings together a research team with the necessary expertise and experience in both survivorship research and telephone delivered motivational interviewing with the unique resource of the 26-institution Childhood Cancer Survivor Study (CCSS). This cohort study includes the largest assembled group of women at risk for breast cancer following chest radiation. In the proposed intervention trial, among women who are 25 to 39 years of age and who have not had a mammogram (or similar screening imaging study) in the preceding two years, we will test the efficacy of an intervention aimed at increasing the likelihood of completing the recommended surveillance. We propose to call this trial the EMPOWER Study: **E**ncouraging **M**ammography/MRI and **P**reventive **O**pportunities for **W**omen **E**xposed to **R**adiation.

Primary aim Determine the efficacy of an intervention, consisting of mailed tailored print materials followed by a telephone-delivered Brief MI, on mammogram screening rates compared with an attention control.

Hypothesis Women in the intervention group will have a 20% higher rate of screening mammography than women in the attention control group.

Secondary aims
1. Explore moderating and mediating factors that predict mammogram completion and timing of the obtained surveillance.
2. Determine the percent of women who have an adjunct breast MRI and explore barriers to completing this imaging test (e.g., insurance/cost, physician authorization).
3. Estimate (1) the replication costs of the intervention and (2) costs resulting from the intervention.

Based upon the results of this study, a follow-up dissemination project will be developed both to train the CCSS coordinating center to provide the components of the intervention to the entire cohort of high risk women and to reach women with this risk who are not participants in the cohort.

D12. Sample Size and Power

We plan to enroll 110 women in the control arm and 220 women in the intervention arm for a total of 330 subjects. In the VISION study we had an attrition rate of 8%. For the proposed EMPOWER study, we estimate a 10% attrition rate, and thus anticipate that 300 women will complete the study measurements (100 in the control arm and 200 in the intervention arm). Based on data from the Mammogram Practices Study, we anticipate that the proportion of women in the control arm who will have a screening mammogram within the 12-month study period will be 10-15%. The table below shows the power that we will have to detect several differences in proportions between the two groups using a two-sided 0.05 level test. From this table we estimate that we will have greater than 90% power to detect a difference of 20% between the two groups.

Proportion with a mammogram in the control arm	Proportion with a mammogram in the intervention arm	Difference in proportions	Power
10%	20%	10%	52%
10%	25%	15%	86%
10%	30%	20%	98%
10%	35%	25%	99%
15%	25%	10%	44%

15%	30%	15%	78%
15%	35%	20%	95%
15%	40%	25%	99%

D13. Statistical Analysis

Analytic Plan

Data Editing/ Cleaning and Outlier Detection: Procedures outlined by Tabachnick & Fidell and Stevens will be used to detect potential univariate, bivariate, and multivariate outliers for all continuous variables, including statistical tests for this purpose.[134-136]

Assumptions Testing: The assumptions of the univariate and multivariate procedures will be tested using the most powerful and up-to-date procedures available.[135, 137, 138] For continuous variables, homogeneity of variance will be tested using the Brown-Forsythe Procedure if the distributions are mesokurtic or leptokurtic and the O'Brien Procedure for the distributions that are platykurtic.[139] For continuous variables that will be used as covariates in a logistic regression, the assumption of linearity in the logit will be tested using the procedures suggested by Hosmer and Lemeshow.[140] Any violations of assumptions will result in the consideration of transformations or alternative methods of analysis.

Non-participation: To assess the generalizability of our results, we will assess non-participant bias with two approaches. Socio-demographic characteristics and previous cancer therapy will be compared between participants and non-participants to determine if a particular subgroup of women is underrepresented in the study. This data is available through the CCSS cohort dataset, including previous screening mammography history. Second, women who decide not to participate will be invited to participate in a very brief interview intended to understand reasons for non-participation and intention of future mammography.

Attrition: Despite our efforts to encourage all participants to remain in the study, it is likely that some will drop out of the study at different points in time. We anticipate that any data missing due to attrition would be missing at random. We will employ several techniques for dealing with attrition, including 'estimating' missing data—viz. via filling in for missing values using results from the last iteration in an EM-algorithm application—complete data analysis, and intention to treat analysis. As an alternative to filling in missing values which can lead to spuriously lower standard errors (SE), we will also use multiple imputation. This method is chosen because it can handle categorical as well as continuous variables. Analysis based on imputed data will be compared to analysis for completers only. The difference between these two analyses can provide some indication of the bias introduced by attrition. Another method for handling attrition in surveillance studies is to assume that those who drop out of the study never obtained mammography. Conducting the analysis this way is referred to as an intention to treat analysis.

Primary Aim: Determine the efficacy of the intervention on mammography surveillance rates compared with a standard control.

The primary outcome is obtaining a screening mammogram (yes/no). Only medical record-confirmed mammograms will be considered to be a completed surveillance. Participants with a self-reported mammogram without a medical record-confirmed mammogram will be classified as 'no' for the primary outcome. For the primary analysis, participants who do not complete the 12-month trial will be classified as not having completed the screening mammogram. Descriptive statistics and graphical methods will initially be used to compare mammography screening rates between the two groups. To assess the efficacy of the intervention, mammography will be dichotomized into a yes/no outcome, Y_i=1 if the i^{th} subject had a mammogram and Y_i=0 if not. We will use a weighted average of the stratum-specific differences in the proportion of women undergoing a screening mammogram between the two arms to estimate the intervention effect taking into account the stratification factors used at randomization. Simple averages of the dichotomous outcome, Y_i, taken separately in each of the four strata yield stratum-specific maximum likelihood estimates of the proportions of women undergoing a screening mammogram for the j^{th} strata in the intervention arm, $\hat{p}_{2j}$, and the control arm, $\hat{p}_{1j}$. The estimate of the intervention effect will be calculated as $\sum_{j=1}^{4} w_j(\hat{p}_{2j} - \hat{p}_{1j})$ where the w_j are the widely-used Cochran-Mantel-Haenszel weights.[141] This weighted difference in proportions will be reported together with the appropriate 95% confidence interval (using a weighted average of the stratum-specific variance estimates). The proportions of screening mammograms in the two arms will be formally compared using the Mantel-Haenszel test statistic.[142]

Descriptive analyses will assess initial equivalency between the control and intervention groups at baseline and then again at 12 months follow-up. If significant differences are found (e.g., in socio-demographics) multivariate models will include covariates to adjust for these differences. In secondary analysis of the primary outcome, we will determine the efficacy of the intervention among the subpopulation of women who completed the 12-month measurements (excluding women who were lost-to-follow-up, withdrew from the study, or did not complete the 12-month measurements). We will also determine if there are significant differences in the findings when self-reported mammograms (or other imaging studies) are used instead of medical record-confirmed mammograms. While we do not expect the intervention effect to differ by age or race, exploratory subgroup analyses will estimate and descriptively compare the intervention effect among participants of different races and ages.

Secondary Aim 1: Explore moderating and mediating factors that predict mammogram completion and timing of the obtained surveillance.

Initially to assess factors that predict mammogram screening, bivariate associations of independent variables with the outcome of whether or not a participant had a surveillance mammogram, Y_i, will be described by cross-tabulation. Significance of the bivariate association will be assessed as follows: for categorical independent variables, the Mantel-Haenszel test will be used; and for continuous independent variables, logistic regression adjusted for the stratification factors will be used. Mixed effects models will be used to further explore moderating and mediating factors potentially predictive of a completing a mammogram. The mixed model is $\mathbf{Y}_i = \mu(\mathbf{X}_i, \alpha, \mathbf{Z}_i, \mathbf{b}_i) + \mathbf{e}_i$ where for subject i, $\mathbf{Y}_i$ is the response vector, $\mathbf{X}_i$ is a fixed effects design matrix that includes indicators for treatment group, assessment time (baseline and 12-months) and potential confounders or moderator variables, $\mathbf{Z}_i$ is a design matrix for the random effects that would allow random subject deviations from the population average response, α 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. By appropriate specification of the function μ($\mathbf{X}_i$,α, $\mathbf{Z}_i$, $\mathbf{b}_i$) this model can be applied to linear, binary, and categorical outcomes.

Moderating factors: By including interaction terms in the above model, we will assess potential moderating factors such as age, race/ethnicity, *health insurance*, and other sociodemographic variables. As specified in Baron and Kenny, moderating effects can be adequately address through interactions between the intervention and the above mentioned covariates.[143] An interaction with the treatment group indicator suggests differential effectiveness, and moderator variables with statistically significant interactions will remain in the model. Interactions will be estimated using cross-product terms between the intervention indicator and the mediating variable.

Mediating factors: Based on results from our Mammogram Practices Study and breast cancer screening intervention trials among women in the general population or familial risk, we are *a priori* interested in the mediating effect of five variable domains: knowledge of screening guidelines, breast cancer health beliefs, decisional balance of the pros and cons of mammography, self-efficacy, and psychological factors. The measurement of each of these domains is described in more detail in Section D8. For each of these domains, a global or subscale score will be used as appropriate. For example, from the BSI-18, a global score of psychological symptoms and a subscale score for each group of symptoms can be estimated. In contrast, the MHLC has three independent scales (internal control, chance, powerful others).

Tests of mediating effects are more challenging than tests of moderating effects, in part because of a lack of consensus in the most appropriate statistical procedures for such analyses. Recently, in a simulation study, MacKinnon and colleagues[144] found that the methods proposed by Clogg et al.[145] and Freedman & Schatzkin[146] entail the best statistical performance under specific conditions. Generally, we will follow MacKinnon et al.'s recommendations to examine these specific conditions in a post-hoc manner and make necessary adjustments. For example, we will fit path analysis models using the statistical packages LISREL[147] or EQS[148] and inspect the path coefficients and choose the appropriate statistical tests of mediating effects according to MacKinnon et al.[144] We may also consider testing model equivalence to examine whether or not the mediating path model is equivalent across the standard control group and the active intervention group. While several different tests have been recommended for testing 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 and associates at:

http://www.public.asu.edu/~davidpm/ripl/mediate.htm#whatis. All analyses will be adjusted for the stratification factors used at randomization.

Secondary Aim 2: Determine the percent of women who have an adjunct breast MRI and explore barriers to completing this imaging test (e.g., insurance/cost, physician authorization).
Adjunct breast MRI will be dichotomized into a yes/no outcome, M_i=1 if the i^{th} subject had a mammogram and M_i=0 if not. As described in the analysis for the primary aim, proportions of women undergoing an MRI will calculated using a weighted average across randomization strata and presented for each arm together with the difference between arms and appropriate 95% confidence intervals. To explore possible barriers to completing a breast MRI, the same analysis methods described above for the first secondary aim will be used. Bivariate associations between variables representing the barriers and the outcome will be described and tested. Logistic regression will be used to explore the joint association of multiple barriers with the probability of having an adjunct breast MRI.

Secondary Aim 3: Economic Analysis

Secondary Aim 3a: Estimate the replication costs of the EMPOWER intervention.
As described in Section 10, 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, mailing costs, telephone costs, and personnel time costs for creating the cancer treatment summaries and administering the telephone interviews. 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, CATI-scripts for stage-based brief motivational interviewing, and patient education handouts. At the end of the study, these materials will be made publicly available on the CCSS website: http://www.stjude.org/ccss.

Secondary Aim 3b: Estimate costs resulting from the intervention (New Section in Resubmission)
As noted in the 12-month measurements and section D10, we will identify utilization of screening and diagnostic imaging (mammography, ultrasound and MRI), 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.[149] 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.[150, 151] 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.[150]

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). 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. 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.[152] 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.[153, 154] This analytic approach is appropriate in economic studies that "piggyback" randomized trials.[155]

Ideally, cost-effectiveness analyses of health and medical interventions take a lifetime perspective and report outcomes in a universal metric such as quality-adjusted life years (QALYs).[153, 154] However, such an analysis of this particular intervention would require extensive simulation modeling and is therefore beyond the scope of

this proposal. The costs and outcomes estimated in this analysis will serve as preliminary data for future grants that more fully explore the long-term cost-effectiveness of increasing screening mammography participation in female childhood cancer survivors.

Exploratory Aim Regarding Receiving a Mailed Cancer Treatment Summary: The goal of this exploratory aim will be to better understand the emotional and psychological response to receiving a cancer treatment summary and the process by which women decide whether or not to obtain a mammogram. From the qualitative assessment (semi-scripted interview), we will collect information regarding the emotional responses related to receiving the cancer treatment summary and the cancer screening recommendations. As standard CCSS protocol, the telephone interviews will be audio-taped. The responses to the semi-scripted questions transcribed and imported into a software managing program (e.g., NVivo). An editing organizing style of analysis[156] will be used and emerging concepts and themes identified. Dr. Henderson, with the assistance of Oeffinger and Diller, will oversee this exploratory aim. This information will be used to inform future studies in this area, including study of the informed decision process.