

**Reproductive Health Survivorship Care Plan
Trial Protocol**

**NCT02667626
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Design of a randomized controlled trial on the efficacy of a reproductive health survivorship care plan in young breast cancer survivors

Introduction

There are nearly 3.5 million breast cancer survivors in the United States, with 19% of new cases occurring in women age 45 and younger. Most young breast cancer survivors (YBCS) undergo chemotherapy and/or endocrine therapy, treatments that can impair ovarian function and result in significant reproductive health issues. These include hot flashes, infertility, sexual dysfunction, and limited contraception options, which negatively impact quality of life in survivorship. Evidence-based clinical strategies to manage these late effects have been identified, but have limited dissemination among YBCS and their healthcare providers (HCPs), resulting in unmet informational needs among YBCS on reproductive health [3].

Breast cancer survivors seek health information and advice from their HCPs and online. Information seeking in YBCS is associated with increased self-efficacy, satisfaction with treatment decisions, and improved quality of life [6,8]. Coupled to underinsurance, limited healthcare access and high mobility in YBCS, these information-seeking characteristics motivated us to develop a web-based intervention on reproductive health for YBCS and their HCPs.

In 2006, the Institute of Medicine recommended development of survivorship care plans (SCPs) to support the transition of care from cancer treatment to survivorship. SCPs aim to inform patients about the effects of cancer treatment, guide follow-up care, and improve care coordination. Internet accessible SCPs for breast cancer survivors have been developed, but contain limited reproductive health guidance. Randomized controlled trials on the efficacy of SCPs on patient-reported and health services outcomes have included YBCS, but none have focused on reproductive health.

The web-based Survivorship Care Plan in Reproductive Health (SCP-R) intervention was developed to address unmet informational and clinical management needs for hot flashes, fertility-related concerns, contraception, and sexual health in YBCS. Research findings, professional society guidelines and clinical expertise on these reproductive health issues were curated into screening and management strategies that will be delivered to YBCS and their HCPs via the SCP-R intervention. A web-based intervention and text message support were chosen to enhance intervention accessibility.

This report details the design, recruitment, and baseline characteristics of YBCS and HCP participants of the randomized controlled trial testing the efficacy of the SCP-R intervention on improving reproductive health in YBCS. We hypothesize that YBCS who receive the SCP-R intervention will be more likely to improve on at least one of four targeted reproductive health outcomes (hot flashes, fertility-related concerns, sexual health, and contraception) compared to waitlist controls.

Material and Methods

The SCP-R trial will test the efficacy of a 24-week, web-based educational intervention with text message support in improving reproductive health issues experienced by female YBCS.

Following online eligibility screening and consent, YBCS complete an enrollment questionnaire and undergo a 7-day run-in period for reporting daily hot flash frequency and severity via text messaging. Adherent participants are randomized in a 1:1 ratio to the intervention or waitlist control arm. Participants in the intervention arm receive access to the full web-based SCP-R intervention and reproductive health text message prompts, while participants in the waitlist control arm receive access to a list of curated web-based resources and study adherence text messages. All participants will be followed for 24 weeks, report daily hot flash frequency and severity via text messaging, and complete a 12-week and a final 24-week questionnaire.

To support YBCS-HCP interactions, one HCP is nominated by each YBCS participant to receive the same study materials as their patient. Following eligibility screening and consent online or by paper, HCP participants whose YBCS patients are randomized to the intervention arm will receive access the full web-based educational intervention; HCP participants whose YBCS patients are randomized to the waitlist control arm will receive access to the list of curated web-based resources. HCP participants will complete an enrollment and a 24-week questionnaire. The UC San Diego institutional review board approved all study procedures, and the trial was registered at clinicaltrials.gov (NCT02667626).

Intervention prototype development and refinement

In line with community-based participatory research [22], a stakeholder panel was formed to design and conduct the study. The panel was comprised of 2 YBCS advocates and 6 investigators with clinical and research expertise in reproductive health, primary care, breast oncology, health behavior and randomized trials. To develop the intervention, we conducted systematic reviews and searched professional medical society guidelines for evidence on managing hot flashes and sexual health, addressing contraception needs and predicting fertility potential [23–25]. Supplemented by clinical expertise and review of existing web-based resources from professional medical societies and cancer advocacy groups, these evidence- and guideline-based practices were summarized into the SCP-R prototype. SCP-R was designed to improve self-efficacy by providing both up-to-date evidence and actionable steps for symptom management. The multi-level intervention further promoted taking actionable steps by incorporating reinforcement from the YBCS' HCP.

Seven focus groups with 37 YBCS were conducted to refine the content and presentation of the SCP-R [26]. For the intervention arm, we initially planned to provide each participant with only the SCP-R sections relevant to her specific reproductive issue(s). Based on focus group feedback, we changed the intervention design to allow participants in the intervention arm to access to all SCP-R sections.

The final SCP-R intervention included four sections for each of the four planned reproductive health issue (hot flashes, fertility-related concerns, vaginal symptoms and contraception) and an additional fifth issue on genetic cancer risk. For each issue, the four sections included: 1) a 1- to 2-page SCP framed in a question and answer format; 2) a detailed summary of the systematic review results with hyperlinks to primary research articles; 3) a summary of clinical guidelines with hyperlinks; 4) a list of curated web-based resources. This content was programmed into the study website. The intervention arm will be able to access all 4 sections for all 5 issues (Appendix A); the waitlist control arm will only be able to access the list of curated web-based resources for all 5 issues.

Website and text messaging platforms

We collaborated with an experienced web architect to develop a HIPAA-compliant website that enabled online participant registration, consent, completion of questionnaires, automated randomization and access to group-specific intervention material, integration with MOSIO, a text messaging software, and pairing of YBCSs with their nominated HCPs. The web portal is programmed to send study gift cards and weekly reminders on incomplete tasks to YBCS and HCP participants.

The text messaging platform is programmed to push daily text messages to all YBCS participants to ascertain hot flash frequency and severity. Natural language processing is embedded to minimize variation in how participants provide hot flash responses. In addition, biweekly text messages with reproductive health prompts will be sent to YBCS participants in the intervention arm, while biweekly study adherence text messages will be sent to YBCS participants in the waitlist control arm. The text messaging platform supports opt out by participants and two-way text messaging capabilities between participants and study staff.

This web- and text message-based design supports streamlined YBCS screening, consent, follow-up, and data collection, enables geographically diverse recruitment and utilizes fewer resources compared to a traditional in-person RCTs. Daily hot flash text messages will provide near real-time data collection to minimize recall bias.

YBCS eligibility, recruitment, consent and enrollment

YBCS are eligible if they report experiencing at least one of the four targeted reproductive health issues: hot flashes (≥ 4 per day with ≥ 1 at least moderate in severity), moderate to high pregnancy and/or fertility concerns (fertility or pregnancy subscale score >3 on the Reproductive Concerns After Cancer Scale), not using contraception or using a less effective method (barrier or fertility awareness methods, withdrawal, or spermicides), or vaginal atrophy symptoms (≥ 1 symptom of vaginal dryness, irritation, soreness or dyspareunia over the past 4 weeks reported as at least moderate in severity). Additional eligibility criteria include: ages 18-50 at study enrollment, diagnosed with stage 0-III breast cancer between ages 18-45, completed primary cancer treatment including surgery, chemotherapy and radiation, are not pregnant at enrollment, are able to read English and access the Internet, and are able to complete daily text message hot flash diaries.

YBCS are recruited from the following sources: (1) cancer advocacy organizations including the Young Survival Coalition, Susan G. Komen San Diego and Army of Women-a program by the Dr. Susan Love Research Foundation, (2) referrals from health care providers and patient advocates, (3) Research Match, (4) previous observational studies conducted by the investigators. Interested YBCS are directed to the study web portal to create a secure personal account, followed by online access to study description, screening for eligibility and consent.

Consented participants complete the enrollment questionnaire and undergo a 7-day daily hot flash text message run-in period. Participants receive two daily text messages prompting them to report the number of hot flashes and severity of each hot flash (mild, moderate, severe, or very severe) in the previous 24 hours. Participants with at least 70% adherence over 7 days are then randomized.

YBCS randomization

Computerized, blocked randomization with equal allocation to intervention and waitlist control arms was undertaken. Randomization is stratified by the four a priori reproductive health issues in order to

maintain balance between the intervention and waitlist control groups with regard to these factors. Fifteen unique strata were created based on possible combinations of experiencing one or more of the four late effects.

HCP eligibility, recruitment, consent, enrollment and procedures

At enrollment, each YBCS participant nominates a HCP with whom they wish to discuss reproductive health issues. Study staff contact nominated HCPs by email, phone and/or fax for study recruitment. After five contacts, non-responsive HCPs are mailed the study consent, enrollment questionnaire and their patient's SCP materials. Interested HCPs are directed to the study web portal to create a secure personal account, followed by online access to study description, screening for eligibility and consent. Consented HCP participants complete the enrollment questionnaire and are provided with access to their patient's intervention materials, i.e. full SCP-R or only curated web-based resource lists. HCPs will complete a 24-week questionnaire and may opt to complete all study procedures (consent, questionnaires) and access intervention materials in a paper format.

Blinding

Study staff and YBCS and HCP participants are blinded to treatment allocation. Automated computer allocation of participants into intervention or waitlist control arm within the study portal allow for study staff to be blinded to assignment. YBCS and HCP participants are informed about participant randomization in the trial but are not notified of assignment until they complete their final study tasks. YBCS and HCP participants assigned to the waitlist control arm will be able to access the full SCP-R materials following completion of their final study tasks. Although 3 HCPs were nominated by more than one YBCS participant, each HCP only had participants in the same study arm.

YBCS outcome measures

Hot flash frequency and severity over the prior 24 hours will be measured in each questionnaire and via daily via text messages using the following questions: "How many hot flashes have you had in the past 24 hours?" and "How many of your hot flashes in the past 24 hours would you categorize as mild, moderate, severe and/or very severe?" The hot flash score is calculated as the weighted sum of the number of hot flashes in each severity category multiplied by a severity-exclusive weight (1-mild, 2-moderate, 3-severe, 4-very severe). For the primary analysis, a decrease of 50% in the hot flash score will be defined as an improvement in hot flashes for the primary composite outcome. Secondary hot flash outcomes will include quality of life measured by the 29-item Menopause-specific Quality of Life (MENQOL) scale, confidence to talk with a HCP about hot flash management, plans to implement and implementation of a suggested tip from the intervention materials.

Fertility-related concerns will be measured with the Reproductive Concerns After Cancer Scale (RCAC), specifically fertility potential and pregnancy subscales. The RCAC is an 18-item multidimensional scale composed of 6 subscales (fertility potential, pregnancy, child's health, disclosure to partner of fertility status, personal health, acceptance of infertility) measuring reproductive health concerns of young adult female cancer survivors. The two subscales were chosen, because the SCP-R content addressed these constructs. Each subscale consists of 3 questions with response options ranging from 1 "Strongly disagree" to 3 "Neither agree nor

disagree” to 5 “Strongly agree”. Scores for the fertility and pregnancy subscales will be calculated by averaging responses (range 1-5), scores > 3 indicating concern. For the primary analysis, scores ≤ 3 in follow up will be considered an improvement in fertility-related concerns for the primary composite outcome. Secondary fertility-related outcomes will include the overall RCAC score, referral, consultation and treatment with a fertility specialist, pregnancy planning, and confidence to talk with a HCP about fertility-related concerns and plans to implement and implementation of suggestions from the fertility SCP.

Contraception outcomes will be analyzed in participants at risk of unintended pregnancy, defined as having a uterus and at least one ovary, sexually active in the 24 months prior to or during the study, ≤ 45 years old. For the primary analysis, use of highly effective birth control methods (intrauterine devices, female sterilization, male partner sterilization, combined hormonal contraception, progestin implants or injections) during follow up will be considered an improvement for the primary composite outcome. Secondary contraceptive outcomes will include confidence to talk with a HCP about contraception, plans to implement and implementation of suggestions from the contraception SCP.

Sexual health will be measured the Vaginal Atrophy Symptoms Score, a 4-item scale on vaginal dryness, soreness, irritation and dyspareunia experienced in the prior 4 weeks [29]. Each item has a 4-point Likert scale response (0-none, 1-mild, 2-moderate, 3-severe). The scale will be summarized by averaging responses, with higher scores indicating a greater level of vaginal atrophy. For the primary analysis, a decrease of 50% in the score will be defined as an improvement in vaginal symptoms for the primary composite outcome. Secondary outcomes included sexual desire, arousal, orgasm and pain via the 19-item Female Sexual Function Inventory (FSFI), confidence to talk with a HCP about vaginal symptoms and sexual health management, plans to implement and implementation of a suggested tip from the intervention materials.

HCP measures

HCP preparedness and confidence in talking to their patients about each of the four reproductive health issues will be measured. Each preparedness item had a 4-point Likert scale response (very unprepared, unprepared, prepared, and very prepared). Each confidence item had a 7-point Likert scale response (not at all confident, slightly confident, somewhat confident, moderately confident, quite confident, very confident, and extremely confident). Demographic, medical specialty, and experience and volume of breast cancer patients, and satisfaction with SCP materials will also be measured.

YBCS participant adherence and retention

We will deploy several approaches to motivate YBCS participants to complete the study. Participants will receive up to \$100 in Amazon gift cards for completing each of 3 questionnaires and daily hot flash text messages. Weekly, automated reminder emails to complete study tasks will be sent via the web platform. Telephone call and/or text message reminders will be undertaken for overdue tasks for up to 5 contacts. On hot flash text messages, daily reports will be generated to monitor responses and identify those who had not responded in ≥ 3 consecutive days for study staff contact.

HCP participant adherence and retention

HCP participants will receive up to \$40 in Amazon gift cards for completing each of 2 questionnaires. Weekly, automated email reminders to complete study tasks and view their patient's SCP will be sent via the website platform. HCPs who opted to participate via paper materials will be contacted by telephone calls to their medical practice to confirm receipt and encourage completion overdue tasks for up to 5 contacts. If a final questionnaire is not received within two months of mailing, questionnaires will be resent.

Statistical Analysis

The primary analysis will be intent-to-treat. The primary composite outcome will be an improvement in at least one reproductive health issue over the 24 week study, defined as: $\geq 50\%$ improvement in enrollment hot flash score, $\geq 50\%$ improvement in enrollment vaginal atrophy symptom score, use of highly effective contraceptive methods (sterilization, long-acting reversible contraception, injectables, pills, patch or vaginal ring), and fertility and pregnancy concern subscale scores <3 . Logistic regression models will be used to test for differences by intervention versus control arm; odds ratios with 95% confidence intervals for intervention effect will be reported.

To quantify intervention effects on each of the four reproductive health issues, we will also undertake secondary analyses to compare changes in each issue separately. As participant responses will be measured at enrollment, 12 and 24 weeks, we will compare each health issue outcome between the intervention and waitlist control groups using linear mixed effect models for the continuous outcomes (hot flash score, vaginal atrophy symptom score, fertility concerns score) and GEE models for binary outcomes (use of effective contraceptive method). Best linear unbiased predictors from the mixed models will also be used to impute missing outcomes for the primary composite outcome. Similar analysis will be conducted for secondary outcomes, which include additional YBCS-reported symptoms and actions, as well as healthcare provider preparedness and confidence.

Sample size

YBCS participants will be randomized into two arms: intervention and waitlist control. We will measure outcomes at enrollment, 12 weeks, and 24 weeks. Leveraging published data on hot flashes [31], we based sample-size calculations on detecting meaningful changes in hot flash frequency and score. With a sample size of 50/arm, there will be 80% power to detect a 0.57 effect-size between groups on hot flash score changes from baseline to 24 weeks based on a 2-sided t-test with $\alpha=0.05$. This effect-size translates to a group difference of 1.2 hot flashes or 3 units in the hot flash score, if we assume the standard deviation of the change was 2 hot flashes or 5 score units per patient per day. Incorporating all the repeated measurements on each participant should ensure sufficient power to detect an even smaller effect size. In particular, assuming 2 post-randomization measures with autocorrelation 0.5, there is 80% power to detect a 0.44 effect size with 50 samples in each arm and 2-sided significance level 0.05.

Considering the composite primary outcome of improvement in at least 1 reproductive health issue, we have 80% power to detect a 27% group difference, e.g., 25% in the control arm and 52% in the treatment improve on at least one outcome. Given that some participants may have the same healthcare provider, we account for a clustering effect as follows: we assume as a worst-case scenario that on average 3 participants shared a provider, and that intraclass correlations (ICC) of the study outcomes due to a shared physician is 0.1. This results in a design

effect of 1.2, requiring us to inflate the sample-size by 20%. We further anticipate 20% sample size loss due to the run-in period prior to randomization, and an additional 20% drop-out rate. Hence, we aim to enroll 196 participants and randomize 157 to ensure sufficient power.