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Optimization of a technology-supported physical activity intervention for breast cancer survivors: *Fit2Thrive* study protocol

Siobhan M. Phillips¹, Linda M. Collins², Frank J. Penedo³, Kerry S. Courneya⁴, Whitney Welch¹, Alison Cottrell¹, Gillian R. Lloyd¹, Kara Gavin¹, David Cella², Ronald T. Ackermann⁵, Juned Siddique¹, and Bonnie Spring¹

¹Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 N. Lake Shore Drive, Chicago, IL, USA

²The Methodology Center and Department of Human Development & Family Studies, The Pennsylvania State University, 435 Health and Human Development Building, University Park, PA, USA

³Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University, 633 N. Saint Clair Street, Chicago, Illinois 60611, Chicago, IL, USA

⁴Faculty of Physical Education and Recreation, University of Alberta, 1-113 University Hall, Van Vliet Complex, Alberta, Canada

⁵Department of Medicine, Feinberg School of Medicine, Northwestern University, 750 N. Lake Shore Drive, Chicago, IL, USA

Abstract

Fit2Thrive is a theory-guided physical activity promotion trial using the Multiphase Optimization Strategy (MOST) to test efficacy for improving physical activity of five technology-supported physical activity promotion intervention components among breast cancer survivors. This trial will recruit 256 inactive breast cancer survivors nationwide. All participants will receive the core intervention which includes a Fitbit and standard self-monitoring *Fit2Thrive* smartphone application which will be downloaded to their personal phone. Women will be randomized to one of 32 conditions in a factorial design involving five factors with two levels: support calls (No vs. Yes), app type (standard vs. deluxe), text messaging (No vs. Yes), online gym (No vs. Yes) and Fitbit Buddy (No vs. Yes). The proposed trial examines the effects of the components on physical activity at 12 and 24 weeks. Results will support the selection of a final package of intervention components that has been optimized to maximize physical activity and is subject to an upper limit of cost. The optimized intervention will be tested in a future trial. *Fit2Thrive* is the first trial to use the MOST framework to develop and test a physical activity promotion intervention in breast

Corresponding Author: Siobhan M. Phillips, 680 N Lake Shore Drive, Suite 1400, Chicago, IL 60611, smphillips@northwestern.edu, 312-503-4235.

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cancer survivors and will lead to an improved understanding of how to effectively change survivors' physical activity. These findings could result in more scalable, effective physical activity interventions for breast cancer survivors, and, ultimately, improve health and disease outcomes.

Keywords

physical activity; breast cancer survivors; Multiphase Optimization Strategy; technology

INTRODUCTION

Approximately 3 million breast cancer survivors live in the U.S. and this number is expected to increase to 4 million over the next decade [1]. Breast cancer survivors are at an elevated risk of chronic conditions and compromised quality of life (QOL; [2, 3]). Increased physical activity is associated with reduced treatment-related side effects (e.g. fatigue, depression), cancer recurrence and mortality, and improved QOL and survival [4–7]. However, up to 70% do not meet moderate to vigorous physical activity (MVPA; [8–11]) recommendations. Although many factors [12–18] contribute to low MVPA, the lack of accessible, effective MVPA programs is a major barrier [19]. Therefore, it is important to develop theoretically-sound, remotely-delivered, low cost MVPA interventions to increase scalability [18–22].

Previous research indicates social cognitive [23] constructs including self-efficacy, outcome expectations, social support and goal-setting may be useful targets for MVPA interventions among breast cancer survivors [15, 24, 25]. However, interventions targeting these constructs typically use bundled packages consisting of multiple components (i.e. daily logs, support calls, feedback) delivered simultaneously. This makes it impossible to disentangle which intervention components, at what levels, and in what combination(s) do, or do not, impact targeted constructs and maximize MVPA. Information about the effects of discrete components is needed to optimize intervention configuration so MVPA is increased and burden and cost kept reasonable to assure scalability [20, 26]. Using traditional study designs (i.e. randomized clinical trials) to test each component individually is inefficient in terms of time and expense. More efficient research methods must be used to compare the effects of multiple individual intervention components simultaneously.

The purpose of the present study is to apply the multiphase optimization strategy (MOST; [27, 28]) to test a set of technology-supported MVPA intervention components for breast cancer survivors targeted at social cognitive constructs known to impact MVPA and designed with dissemination and implementation in mind. MOST is an innovative multi-phase framework inspired by ideas from engineering that uses highly efficient experiments to evaluate intervention components' individual and combined effects. The present study will use MOST to examine the effect of five MVPA intervention components. The results will provide the basis for developing an optimized intervention that is both efficacious and scalable. In this case, efficacious and scalable is defined as the largest expected increase in average daily MVPA minutes that can be obtained for an implementation cost of no more than \$550 per participant. MVPA is not covered by insurance for cancer survivors. We chose

\$550.00 as the upper limit on cost because this is the approximate average of the per person amount Medicare covers for cardiac rehabilitation (~\$683.00) [29] and the diabetes prevention programs (up to \$450)[30], similar lifestyle programs in other chronic disease populations. While MOST has been used in behavioral interventions to target obesity [31, 32] and substance abuse [33], the proposed study represents the first systematic effort to use MOST to design a MVPA intervention for breast cancer survivors with high scalability potential because it uses technology (smartphones) participants already own and requires no on-site visits.

STUDY AIMS

The *Fit2Thrive* trial was designed to pursue the following objectives. The first objective is to identify which components, or component levels, meaningfully contribute to improvement in average daily minutes of MVPA. The second objective is to apply the results obtained from objective 1 to build an intervention made up of only components that have a detectable effect on MVPA. If this set of components exceeds the upper limit on cost (\$550), we will identify the combination of components and component levels corresponding to the largest increase in MVPA that can be obtained for up to \$550.00 per person. Finally, we will explore potential mediators and moderators of component main effects and interactions.

METHODS

Rationale for Selection of Set of Candidate Components

Five intervention components that are candidates for inclusion in the optimized intervention, each with two possible levels, were chosen for examination in this full factorial trial. Thus, participants will be assigned to one of 32 conditions ($2^5=32$). All participants will receive the “core” intervention. The components were chosen in collaboration with breast cancer survivors and are based on our conceptual model in Figure 1. This model was developed based on our prior work indicating social cognitive theory constructs may be useful intervention targets [15] and our on-line needs assessment with almost 300 survivors and interviews with 28 survivors [34]. All components are designed to be completely remotely-delivered (i.e. require no in-person contact). Although each of the five components may have an impact on multiple social cognitive theory constructs, each is designed to target one primary social cognitive construct. Each component is hypothesized to enhance intervention adherence via one primary social cognitive theory mediator, thereby leading to increased physical activity participation.

The five components to be tested include:

1. **Telephone Support Calls.** Telephone coaching and support calls have been associated with increased physical activity among cancer survivors [35]. However, the isolated effects of telephone support calls in the context of a technology-supported intervention have never been tested in breast cancer survivors. Hence, we are examining the effects of bi-weekly telephone support calls versus no support calls in the current trial. We expect that the support calls will bolster the effects of the intervention.

2. **App Type.** All participants will have access to a standard self-monitoring app. Such apps have been shown to be effective for increasing physical activity in the general population [36]. Half of participants will receive a standard version of the app, and half will receive a deluxe version of the app which will have additional modules including a newsfeed where study staff will post content specifically tailored to survivors and designed to enhance behavior change (e.g. benefits of physical activity for survivors, stories of other survivors who have successfully changed their behavior), a planning tool and a goal-setting challenge tool which have been shown to be associated with increased physical activity participation [15] and adherence [37]. We hypothesize these additional modules will result in increased physical activity compared to the standard self-monitoring app.
3. **Text Messages.** Text messages show promise as a cost effective method to prompt physical activity in the general population [38, 39]. Few published studies have examined text messages, alone, or in combination with other components in physical activity interventions with cancer survivors. We will test their effects in the current trial. Half of the participants will receive regular text messages and half will not.
4. **On-line Gym.** DVD-delivered interventions show promise for increasing physical activity and improving health outcomes in older adults [40, 41]. We hypothesize that providing survivors with access to online exercise videos and a weekly schedule for using the videos will increase their physical activity in comparison to not having access to this resource. Half will be provided access to the online exercise videos and half will not.
5. **Fitbit Buddy.** Higher levels of social support have been associated with increased physical activity participation among cancer survivors [15, 42]. Thus, half of participants in the current trial will join with a buddy of their choice (friend, co-worker or family member). As part of this component, the chosen buddy will receive a Fitbit. We hypothesize that the extra support from a buddy will result in greater adherence to the intervention and greater increases in MVPA.

In addition to testing the five components, above, all participants will receive a core intervention to build essential competencies needed to increase physical activity safely. The core will consist of a standard self-monitoring smartphone app, educational materials, Fitbit and exercise prescription for gradually and safely progressing through the program.

Component Cost Estimation

Table 1 displays the estimated cost of delivering the lowest and highest levels of the intervention. All conditions will receive the core intervention, which includes a website, *Fit2Thrive* smartphone application and Fitbit. The costs of the core includes maintenance and troubleshooting of the website and smartphone application estimated at 20% of a programmer's time with a salary and fringe benefits of \$75,000. We estimate the cost per participant to be $(\$75,000 * .20 \text{ effort}) / 150 \text{ participants/year} = \$100.00/\text{person}$. A \$150 per

person fee is also included to access the study's web infrastructure and server. The average retail price for the Fitbit is \$100.00 per person, and it costs another \$3.87 to mail alongside general and component-specific instructions. We anticipate a research assistant will spend 30 minutes, on average, to provide technical assistance to each study participant. With the salary and fringe benefits of a research assistant assumed at \$38,000/year or \$18.27/h. The costs would be \$9.14/person. Therefore, the core costs \$363.01 per participant. The additional costs associated with delivery of each of the intervention components are detailed below:

1. Telephone Support Calls: Each telephone support call was estimated to take approximately 30 minutes including call preparation, the call and conclusion notes. With the salary and fringe benefits of a lifestyle coach assumed at \$38,000/year or \$18.27/h. The costs would be \$54.81/person for 6 calls ($18.27 \times 6 = \$54.81/\text{person}$).
2. App Type: The costs of developing and maintaining the deluxe app components of the smartphone application are estimated at ~7.5% of a programmer's time with a salary and fringe benefits of \$75,000 (\$37.50/person). In addition, the staff costs of maintaining and updating the Challenges, Goal-setting tool and Newsfeed content is estimated at \$20/person. The total cost of this component is \$57.50 per person.
3. Fitbit Buddy: The Fitbit and its accessories have a retail cost of \$100.00 per person. Mailing the Fitbit to the buddy costs \$3.87. The additional staff time required to recruit, enroll and create and maintain the buddy content is estimated at 2 hours of a lifestyle coach's time or \$36.54 per person. Thus the total cost for this component is \$140.41 per participant.
4. Online Gym: The digital download costs \$15.00 per person. The additional staff time required to create and maintain the YouTube channel is estimated at \$25.00 per person. The total cost of the online gym components is \$40.00 per person.
5. Text Messages: All text messages will be sent through the *Fit2Thrive* smartphone application. Thus, participants will not be charged per text message or need to have a text messaging service plan. The costs of developing and maintaining the text message component of the smartphone application are estimated at ~5% of a programmer's time with a salary and fringe benefits of \$75,000 (\$25.00/person). In addition, the staff costs of maintaining and updating the text message database and algorithms is estimated at \$20/person. The total cost of this component is \$45.00 per person.

Study Design

The effects of the five individual intervention components will be examined by means of a complete factorial experiment with $2^5=32$ experimental conditions (see Table 2). Although similar components have been included in bundled physical activity interventions previously found to be successful, none of these prior studies were designed to estimate the impact of any individual component. We chose a factorial experimental design because it has two characteristics essential to the success of MOST: a) it separates component effects allowing for the estimation of the main effects of each candidate component and the interactions

between components [43] and b) it is more economical compared to alternative designs (such as conducting five individual experiments) because substantially fewer subjects are required to achieve the same power [43–45].

Table 2 displays the experimental conditions for this study. It is important to understand that this factorial design should not be considered a 32-arm randomized control trial (RCT). All of the estimated main effects and interactions will be based on all experimental conditions. For example, the main effect of telephone support calls would be estimated by comparing the mean of experimental conditions 1–16 with the mean of conditions 17–32, and the main effect of App Type would be estimated by comparing the mean of experimental conditions 1–8 and 17–24 with 9–16 and 25–32. Thus, all 256 participants will be included in all effect estimates.

Participants will complete data collection at baseline, post-intervention (12 weeks) and at 24 week follow-up. An overview of participant flow through the study is provided in Figure 2.

Recruitment and Screening

Eligibility—In an effort to increase the ecological validity of the study, there are very few exclusion criteria for this trial. The minimal criteria for entry into the study are: a) being female; b) 18 years of age, c) having been diagnosed with Stage I–III breast cancer within the last 5 years; d) completed last primary cancer treatment (adjuvant chemotherapy, radiation therapy or surgery) at least 3 months prior to enrollment; e) capable of participation in a physical activity program without exacerbating any pre-existing condition(s) and f) self-report participating in less than 60 minutes per week of MVPA. Participants must also be able to read, write and speak English, own a smartphone, have access to a computer with internet and be willing to receive telephone support calls and find a buddy to participate with them if assigned to those conditions. There will be no restrictions on geographic location as the study will be delivered completely remotely (i.e. require no in-person visits). Finally, all participants will be required to pass the Physical Activity Readiness Questionnaire (PAR-Q; [46]) or obtain written approval from their physician to participate in the trial.

Recruitment Procedures—Women will primarily be recruited through an e-blast sent to members of the Army of Women®, an online initiative that connects breast cancer researchers with women who are willing to participate in research. The database currently consists of 375,000 women and men. Of these, ~30% self-report a breast cancer history. If we are not able to sufficiently meet our recruitment goals using the Army of Women®, additional resources including local clinics, on-line forums, social media sites (i.e. Facebook, the Sisters Network and Nueva Vida) and fliers at community organizations and events will be used. Prior to participation in the program, all participants will be required to read and sign a university Institutional Review Board approved informed consent.

Online Screening—All interested women will complete an online screening that assesses study entry criteria. Within 1–2 business days, all eligible candidates will be emailed a copy of the informed consent and a study overview document to review. Within 5 business days of

completing the online screener, eligible candidates will be contacted by staff for a Recruitment Call to go over the study in greater detail and further screen for eligibility.

Recruitment Call—This call will last approximately 10 to 15 minutes. Study staff will review study details and confirm candidates' eligibility and their intent to participate in the study. Interested and eligible participants will be emailed the online version of the informed consent and instructed to sign and submit it online if interested in participating. Individuals who require physician consent will also be sent an email with a form to give permission for the study team to contact their physician. Once this form is complete, the study team will acquire physician consent.

Randomization

After completing baseline assessments and receiving physician consent if needed, eligible participants will be randomly assigned to one of the 32 intervention conditions using computer-generated randomly permuted blocks. To prevent bias, allocation will be concealed in the following ways: 1) all 32 conditions will be assigned a code to correspond to the condition and the key for this coding scheme will be kept separate from the randomization allocation; 2) the individual conducting the randomization is blinded to participant details until allocation has been completed and 3) a concealed allocation sequence in RedCap will be used which will be inaccessible to the anyone other than the individual conducting the randomization. Women will be blinded to the fact they are being randomized and not know they may be getting a subset of intervention components. They will first be notified of their intervention component assignment via mail when they receive their study packet. The nature of the intervention precludes blinding of staff and complete blinding of participants. However, the statistician will be blinded.

Study Packet

All participants will be mailed a study packet which will include the following: Fitbit, study overview, basic safety information, instructions for downloading and using the Fit2Thrive app, study calendar and component specific instructions. Participants will be scheduled for an orientation call within 2 to 10 business days after the study packet has been mailed.

Orientation Call

This call will last approximately 15–25 minutes. Study staff will reiterate the expectations for the overall intervention, describe each intervention component to which they are assigned, answer any questions, and troubleshoot any technical issues they may be having.

Intervention

Core Intervention—To build essential competencies needed to increase physical activity safely, the core intervention will be delivered to all participants. The core will include the following:

- *Fit Lessons*: This will provide participants with information and knowledge about the benefits of physical activity for breast cancer survivors, safe rate of progression through an exercise program and strategies for effectively changing

and maintaining physical activity behavior (i.e. social support, goal-setting), and special safety considerations for breast cancer survivors. Fit Lessons will be available as a standalone site and embedded within the app.

- *Standard smartphone app:* Features of this app include the functionalities of monitoring and tracking physical activity (i.e. steps, minutes, miles) and viewing progress towards weekly physical activity goals, via charts and graphs (See Figure 2).
- *Fitbit:* Participants will be provided with the Fitbit Zip, belt clip, wristband and two extra coin cell batteries. They will be instructed to wear the device on the provided belt clip or wristband during all waking hours of every study day to assist in monitoring and tracking physical activity. The Fitbit communicates wirelessly with the *Fit2Thrive* app enabling Fitbit data to be integrated into the app. Should the device be lost or broken or additional extra batteries needed during the intervention, participants will be instructed to contact the study team immediately and new materials will be mailed.
- *Exercise Prescription:* Participants will be provided with an exercise prescription to gradually increase their physical activity to meet the public health recommendations of 150 minutes per week of moderate to vigorous aerobic physical activity. A hard copy of this prescription will be included in the study packet and in the Fit Lessons section of the app. In addition, the weekly goal will be displayed on the homepage.

While the core interventions builds essential competencies needed to increase physical activity safely, data indicate a Fitbit, alone, is likely not sufficient to produce significant sustained changes in physical activity behavior [47]. We don't anticipate the addition of the basic app will significantly improve the efficacy of the Fitbit. Thus, we will be testing several other components.

Intervention Components

1. Telephone Support Calls. Participants assigned to the "Yes" level of this component will receive a call from study staff to discuss progress, provide motivation and encouragement, discuss physical activity and cancer survivorship and troubleshoot any issues they may have. These calls will focus on helping survivors build self-efficacy by targeting 3 of the 4 sources of efficacy information proposed by Bandura: a) providing social persuasion; b) giving strategies for achieving mastery experiences and c) teaching the skills necessary to properly interpret psychological and physiological responses related to MVPA. All study staff leading these calls will have a bachelor's degree and receive extensive training in physical activity, cancer survivorship and behavior change. These calls will occur bi-weekly (6 total) during the initial 12 week intervention period. All calls will be scripted and recorded for quality control. Those assigned to the "No" level will not receive any calls.(Figure 3)

2. App Type: Participants will either receive the standard or deluxe app. The deluxe app will include all of the features of the standard app plus the additional app modules listed below (see Figure 4).
 - a. *Weekly Goal-Setting Tool*: Allows participants to schedule activities for specific days of the week and schedule reminders for these activities.
 - b. *Challenges*: Provides weekly challenges (i.e. 5,000 steps/day challenge; 5 min MVPA/day) in which participants can enroll. Progress is automatically tracked and progressively harder challenges are “unlocked” as participants complete less intense challenges.
 - c. *Newsfeed*: Space where study staff will post content specific to breast cancer survivors including a weekly Fit Study (lay summaries of physical activity research related to breast cancer and behavior change) and Fit Survivor Spotlight (stories about breast cancer survivors who are active).
3. Fitbit Buddy: Participants assigned to the “Yes” level of this component will select a “buddy” from their personal life (friend, co-worker, child, spouse, sibling, etc.) to help support them. Participants will provide the study team with their buddy’s email address. The buddy will be sent a recruitment email which will include a link to screening. Buddy eligibility criteria include the following: at least 18 years of age, have access to a computer with the internet, own a smartphone, pass the PAR-Q or receive physician consent and be willing to a) receive emails from the study team, b) wear a Fitbit Zip and transmit Fitbit data to the study team and c) friend participant in the Fitbit app and d) provide support and encouragement to the participant. If a buddy is not eligible or indicates they are not interested in participating, the participant will be asked to choose a different buddy. All buddies that are eligible and interested in participating will sign an informed consent. After consent is signed, buddies will complete a brief demographic questionnaire and be mailed a Fitbit. They will also have the option to participate in the same online questionnaire assessment as participants at baseline, 12 weeks and 24 weeks. All buddies that complete at least 2 out of the 3 assessments will be permitted to keep their Fitbit. The Fitbit is not mailed until physician consent is received, if needed, and/or questionnaires are complete for buddies agreeing to participate in that portion of the study. Data from the buddy will be stored for future analyses.

Both the participant and “buddy” will receive training materials on how to make the most out of the Fitbit buddy relationship which will include how to use the social features within the Fitbit app, how to seek support (participant) and how to provide support (buddy) as well as some basic educational information on physical activity and cancer survivorship (buddy). Additionally, both the *Fit2Thrive* participant and her buddy will receive automated bi-weekly emails (6 total) from study staff during the initial 12 week intervention period with links to a website that is only accessible to participants in this condition and their buddies that contains specific ideas on how to enhance their relationship and facilitate

increased social support. Those in the “No” level of this component will not receive any of these materials.

4. On-line Gym: Participants assigned to the “Yes” level of this component will receive access to a digital download for a commercially available walking DVD and suggestions for weekly workouts from the same instructor’s YouTube channel which will be embedded into a study website that is only be accessible to individuals assigned to this intervention component. Weekly schedules with links to all of the videos will be sent for the initial 12 weeks via an automated email. These videos will be vetted by the research team for safety and appropriateness for breast cancer survivors prior to posting and will incorporate modifications to accommodate a variety of health and fitness levels. Those in the “No” level will not receive any exercise videos.
5. Text messages: Participants assigned to the “Yes” level of this component will receive regular messages (between 1 to 5 messages per day) that are motivational, target social cognitive theory constructs and provide feedback on intervention progress (see Table 3 for examples). These messages were developed with breast cancer survivors to ensure they addressed issues relevant to them. Messages will be automatically sent to all individuals in this condition. Survivors in the “No” level of this condition, will only receive messages reminding them to track activity when they have not entered or tracked it on a given day. They will not receive any motivational messages.

All intervention components are independent from one another (i.e. components are never discussed or incorporated together in any way). To reduce the risk of contamination, every participant’s condition assignment is checked a minimum of 3 times by independent staff members and delivery of each component is automated to the extent possible to minimize human error. Staff are extensively trained in study procedures. Our database contains algorithms that automatically populate lists of participants assigned to each of the 5 components and then each component is automated to the extent possible. The text messages and app type are automated and an algorithm ensures they are only sent/accessible to participants in the appropriate condition. The Online Gym emails and Buddy conditions each have a separate study specific RedCap database which contains participants assigned to each condition. Emails are automated from these database to be delivered only to those in the appropriate condition. The only component that is not automated is telephone support calls. To prevent contamination and minimize the chance someone not assigned to telephone support calls is called, a separate support call database is maintained that only includes individuals assigned to this condition.

Follow-up

During the 12 week follow-up period, participants will have access to all the intervention materials. However, all staff contact as part of the components will cease.

Data Collection

All participants who consent to participate will be mailed a baseline data collection packet via the U.S. Postal Service. This will include: an accelerometer, instructions for wearing the accelerometer, an accelerometer log to record wear time, and a self-addressed stamped envelope to mail the monitor back to investigators. Participants will be instructed to wear the monitor for seven consecutive day on the non-dominant hip during all waking hours except when bathing or swimming (see further details, below). Demographic and disease characteristics, social cognitive constructs, and behavior will be assessed online using RedCap.

All participants who consent to participate will be mailed via the U.S. Postal Service a baseline data collection packet. This will include: the ActiGraph accelerometer, instructions for wearing the ActiGraph, an accelerometer log to record wear time, and a self-addressed stamped envelope to mail the accelerometer back to investigators. Participants will be instructed to wear the accelerometer for seven consecutive day on the non-dominant hip during all waking hours except when bathing or swimming (see further details, below). Demographic and disease characteristics, social cognitive constructs, and behavior will be assessed online using RedCap.

A personalized link to a battery of questionnaires will be e-mailed to all participants. Participants will complete the questionnaires online at home and all data will be stored in RedCap.

Participants will be regularly reminded via phone or email to complete assessments until the ActiGraph monitor is returned. If the questionnaires are not completed prior to the monitor being returned, they will be contacted to complete the questionnaires up to three more times after the monitor is returned. Participants will not be randomized until all data are complete. The same procedures will be followed at post-intervention (12 weeks) and at 24 week follow-up.

All Fitbit data and data on app usage will be stored in a database developed specifically for this study that is on a secure, password protected server only accessible to study investigators.

Technical Support

All participants will be sent an email one week before the intervention launches and on the day the intervention launches with the ability to schedule a technical support call with a study team member if they are having issues with any component of the intervention. Any participant who has not downloaded the app or synced the Fitbit will be emailed and called to determine if they need technical assistance starting 5 to 7 days before they are scheduled to start. In addition, they will be encouraged to contact study staff via phone or email as soon as possible if a technical issue arises. All participants will be instructed to inform the study team , immediately, if they lose their Fitbit or it malfunctions and they will be sent a new device. An inventory will be maintained of all equipment to track usage. Finally, any participant that does not have any data from the app for 7 consecutive days throughout the entire 24 week period, will be contacted by study staff to remind them to wear the Fitbit

and/or enter activity data and check-in and make sure they are not experiencing any technical difficulties.

Safety Monitoring

All participants will be instructed to report any injuries to study staff within 24 hours of the event occurring. In addition, they will be emailed a personalized link to a non-spontaneous adverse event questionnaire to be completed at weeks 8, 16 and 24. Any participant who does not complete this form will be contacted via phone by study staff who are blinded to the participants study condition and will conduct the non-spontaneous adverse event questionnaire over the phone.

Privacy and Confidentiality

Participants will use a QR code specific to them to login to the app. To protect their privacy, no personal information will be stored or associated with their app account. All Fitbit and app data will be collected using the University server cluster which has limited physical access, is firewalled and regularly monitored for security issues. All phone encrypted data transmissions use a secured SSL protocol with a unique token per each participant. All data are backed up regularly and any personal health information and HIPAA data are stored on separate data clusters with unique keys and limited firewalled access. Participants will be informed of all potential privacy and confidentiality risks and practices in place to ensure protection in the informed consent.

OUTCOME MEASURES

The primary outcome of this study is average daily minutes of MVPA as measured by accelerometry. Additionally, all social cognitive theory constructs will be examined and explored as potential mediators of effects. Finally, we will explore potential moderators of effects including age, race/ethnicity, comorbidities, disease characteristics and intervention component fidelity.

Primary Outcome: Physical Activity

Physical activity will be measured using both self-report and an objective measure. The Godin Leisure Time Exercise Questionnaire[48] will be used to assess self-reported physical activity at each measurement period. Additionally, physical activity will be assessed objectively by accelerometry at baseline, 12 weeks and 24 weeks an ActiGraph accelerometer (Model GT3X-BT; Actigraph, LLC, Pensacola, FL). The Actigraph is a valid and reliable measures of physical activity [49, 50] has been widely used in oncology research [51, 52]. Participants will be instructed to wear the activity monitor during all waking hours (excluding time spent bathing or swimming) on the non-dominant hip for 7 consecutive days The accelerometer will be set to collect activity data in one-minute intervals (i.e., epochs). Once returned, accelerometry data will be immediately downloaded and checked for several criteria. Specifically, participants must have at least 5 days of valid measurement with ten hours of valid wear time [53]. If these criteria are not met, participants will be asked to re-wear the monitor. The average number of minutes of daily total activity and time spent in sedentary, light, moderate, and vigorous activity will be

calculated using established cut points [53]. Moderate and vigorous activity will be summed to obtain the total volume of MVPA.

The Fitbit is used to collect activity data throughout the intervention. This means participants wear both the Fitbit and ActiGraph during 12 week and 24 week assessments. Data from the Fitbit will not be used as the primary physical activity outcome. Instead, Fitbit data will be used to monitor adherence as detailed below.

Feasibility and Acceptability

Feasibility of each component will be measured during the intervention, immediately post-intervention (12 weeks) and immediately after the 12 week follow-up period. Measures include: a) participant retention (# of participants who drop out/# of participants randomized in each component); b) intervention adherence (% of weeks adhered to exercise prescription during intervention period as determined by the Fitbit and manually entered activity minutes); c) intervention maintenance (% of weeks adhered to exercise prescription during follow-up period as determined by the Fitbit and manually entered activity minutes); d) objective (where possible) and self-reported usage of intervention components and e) safety as measured by the number and severity of adverse events reported spontaneously and during the non-spontaneous assessments. Acceptability will be measured via a process evaluation immediately post-intervention and at the end of the follow-up period. This evaluation will assess the following: perceived effectiveness of intervention components; plans to continue physical activity and component use; elements of intervention components liked/disliked; satisfaction with program delivery, assessments and staff. Items will be rated on a scale from 1 (worst) to 5 (best).

Fidelity

Fidelity to each component will also be measured as detailed in Table 4.

Demographic and Disease Characteristics—Participants will self-report on demographic characteristics and health status including age, race/ethnicity, marital status, education, income and comorbid conditions. They will also self-report disease and treatment characteristics including date of diagnosis and last treatment, disease stage, hormone receptor status, and treatment received.

Social Cognitive Theory Constructs—All social cognitive theory constructs will be assessed including self-efficacy, goal-setting, outcome expectations, and barrier/facilitators. Measures to be used are displayed in Table 5.

Patient Reported Outcomes—The PROMIS Physical Function Short Form 20a [59] will be used to assess participants' physical function. The scale has two subscales: limitations and interference. For the 6 limitations items, participants will rate the level of difficulty they have had executing discrete activities over the past 7 days on a scale from 1 (unable to do) to 5 (without any difficulty). For the 4 limitations items, patients will rate the degree to which their health limits them in specific activities on a scale from 1 (cannot do) to 5 (not at all). Higher scores reflect better physical function. The reliability of this measure

ranges from $\alpha=0.90$ to $\alpha=0.95$ [60]. The PROMIS Fatigue Short Form 8a [59] will be used to assess participants' frequency of fatigue symptoms ranging from 1 (not at all) to 5 (very much) and fatigue interference ranging from 1 (never) to 5 (always) over the past 7 days. Higher scores reflect higher levels of fatigue. The reliability of this measure ranges from $\alpha=0.90$ to $\alpha=0.95$ [60]. The PROMIS Depression Short Form 8a [59] will be used to ascertain the frequency of a variety of depressive symptoms over the past 7 days on a 5 point scale from 1 (never) to 5 (always). Higher scores reflect higher depressive symptoms. The reliability of this measures ranges from $\alpha=0.90$ to $\alpha=0.95$ [60].

Data Analytic Plan

Power—Power for the study is based on the MVPA change at 12 and 24 weeks. Based on our prior work [61], we assumed an intraclass correlation (ICC) of 0.633, a standard deviation of 17.82 min/day of MVPA and an attrition rate of up to 15% at the 24 week time point. . Based on these assumptions, and an initial sample of 256 subjects, we will have 80% power to detect a main effect as small as 6 minutes per day under a two-tailed hypothesis test. .

Aim 1: Determine Effects of Each Component on Physical Activity—We will employ an intention-to-treat (ITT) approach by including all participants recruited into the study regardless of compliance. To examine the effects of each intervention component on average daily minutes of accelerometer-measured MVPA at weeks 12 and 24, we will use intention-to-treat linear mixed model analyses to test the significance of the main effects and interactions. We will also test 2-way interactions between intervention components. Because we will use effect $(-1,1)$ coding rather than dummy $(0,1)$ coding, and because all factors in this experiment have two levels, the power for tests to detect main effects and interaction effects are identical for effects of identical size. We will also include two-way and higher order interactions between all components (e.g., Factor 1 by Factor 2 by time interaction).

Aim 2: Component Selection—As discussed above, because we are interested in intervention scalability, our optimization criterion is the combination of components and component levels corresponding to the largest increase in MVPA that can be obtained for up to \$550.00 per person. To choose these components, we will, first, identify the significant main effects and interactions of the components on MVPA. We will use the traditional $p=0.05$ for significance. Based on these results, ineffective components will be eliminated. Components that are empirically demonstrated to be efficacious for increasing MVPA will be considered candidates for inclusion in the optimized intervention. All combinations of these components will be considered. Combinations that exceed the \$550.00 threshold will be eliminated and the reaming combinations will be evaluated. The combination of components with the largest effect will be retained. The least effective component or components will be eliminated until the combined cost of all components is below this threshold.

Finally, there is the possibility that none of the components will be considered effective. If this is the case, we will further explore why this is the case by examining the feasibility and acceptability measures and interviewing participants and will proceed with conducting a

pilot test of new or revised components and then another optimization experiment using these new or revised components.

Exploratory Aim: Identify potential mediators and moderators of the efficacy of each intervention component

Potential Mediators: A separate model will be estimated for each potential social cognitive theory construct mediator and each intervention component. We will use the approach for estimating mediation in multilevel models [62], where mediation is assessed by fitting two models using linear mixed modeling. Model 1 estimates the component effects on physical activity with the mediator included as a time-dependent covariate. Model 2 estimates the component effects on the mediator, itself, over time. If B_Y =coefficient for mediator from Model 1, and B_M =coefficient for component from Model 2, $B_Y \times B_M$ = mediation effect (i.e. effect of mediating variable on component). Dividing the mediation effect by the component effect estimated in Aim 1 yields the percent mediated (i.e. proportion of component effect mediated by the mediator). Standard errors and 95% confidence intervals for the mediation effect and percent mediated estimates will be calculated using bootstrapping [63].

Potential Moderators: To improve our understanding of whether subgroups of survivors differentially respond to individual intervention components, we will explore effect modification by age, BMI, menopausal status at diagnosis, chemotherapy, and time since diagnosis (i.e. overweight/obese v. normal; chemotherapy v. no chemotherapy).

We will also explore whether the feasibility and acceptability of and fidelity to each component moderates effects. An intervention component will be considered feasible if: (a) participants assigned to this conditions monitor their physical activity on >80% of the study days and (b) participants use the component on 75% of intervention weeks. An intervention will be considered acceptable if 75% of participants provide an average rating on all measures of 4. These data will be used to provide information on why specific components are, or are not, effective and insight into how they may be improved in future studies.

Finally, we will undertake exploratory analyses on the effect of the intervention components on patient reported outcomes.

DISCUSSION

Advances in early detection and treatment have resulted in a large, and growing, population of breast cancer survivors, a trend expected to continue over the next decade [1]. Breast cancer survivors have special health needs. Physical activity interventions represent one behavioral modality with the potential to attenuate the negative side effects of treatment and improve health and disease outcomes. However, the majority of breast cancer survivors do not meet the public health and cancer-specific recommendations for physical activity. Most physical activity interventions for breast cancer survivors involve at least some on-site component and are intensive, professionally delivered multicomponent programs that do not incorporate web or mobile technology posing threats to adherence and generalizability.

The *Fit2Thrive* study is designed to determine the effects of 5 different technology-supported physical activity promotion intervention components on physical activity. The core intervention and components to be tested were designed in conjunction with breast cancer survivors to ensure they address and are relevant to survivors' and provide content specific to breast cancer survivors' needs. The rationale for the choice of the five components being tested is rooted in social cognitive theory [64] constructs with the potential to reduce attrition and improve adherence, and in turn, improve outcomes. This intervention was also designed considering dissemination and implementation from the start. We have engaged survivors in the intervention development, are recruiting nationwide and deliver the intervention completely remotely via an app that participants download to their personal smartphone.

The *Fit2Thrive* study has several potential limitations. Our sample may not be representative of all breast cancer survivors in the U.S. due to the recruitment strategies employed and the technology requirements. Participants in this trial are likely to be more technologically savvy and motivated to change their physical activity behavior than the general breast cancer survivor population. Another limitation is that only intervention costs are being considered. We are not considering additional costs to participants should they choose to make other discretionary purchases relevant to exercising (e.g., shoes, clothing, weights, exercise equipment, gym memberships). Additionally, there could be other components we are not testing in our MOST optimization trial which could be more effective for increasing MVPA in breast cancer survivors and fall under our upper limit for cost. However, we are only able to test a finite number of components given budgetary and resource constraints which are limitations of all studies. In addition, because of the large number of experimental conditions in this optimization trial, there may be a greater potential risk for protocol deviations. We have automated components to the extent possible and taken extensive precautions to reduce this risk via extensive staff training and supervision, manualizing study procedures and implementing rigorous quality control procedures. Finally, while a strength of MOST methodology is that it allows us to test the main effects of each component and moves beyond a traditional treatment package approach, further studies will be needed to delineate what works best for whom.

Fit2Thrive represents the first systematic effort to use MOST methodology to optimize the design of a theoretically-guided, technology supported physical activity intervention for breast cancer survivors. Our approach, if successful, will allow us to assemble the most effective intervention package that has the potential to be distributed in a variety of real world settings. The next steps in our research agenda will be to either: (a) pilot test our optimized intervention packages in a randomized control trial before proceeding to a fully powered trial or (b) use information from our exploratory analyses and collect additional follow-up data from participants regarding why particular components were not successful and how we should modify components before proceeding with an additional optimization study to test different components. We plan to include more diverse populations and settings in these next steps to further increase the scalability of the *Fit2Thrive* intervention. Ultimately, this work will significantly contribute to the understanding of how to effectively increase and maintain physical activity to improve health and disease outcomes in breast cancer survivors.

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Figure 1.
Fit2Thrive Conceptual Model

Figure 2.
Participant Flow Through Study

Figure 3.
Fit2Thrive Standard App

Figure 4.
Fit2Thrive Deluxe App

Table 1

Lowest and Highest Cost Level/Person of the Fit2Thrive Intervention

Intervention Component Levels	Lowest Level Cost/Person	Highest Level Cost/Person
Core intervention	\$363.01	\$363.01
Support Calls	\$0.00	\$54.81
App Type	\$0.00	\$57.50
Fitbit Buddy	\$0.00	\$140.41
Online Gym	\$0.00	\$40.00
Text Messages	\$0.00	\$45.00
Total	Minimum Cost: \$363.01	Maximum Cost: \$700.73

Table 2

Experimental Conditions

Exp Condition	Core Intervention	Telephone Support Calls	App Type	Fitbit Buddy	Online Gym	Text Messages
1	Yes	No	Standard	No	No	No
2	Yes	No	Standard	No	No	Yes
3	Yes	No	Standard	No	Yes	No
4	Yes	No	Standard	No	Yes	Yes
5	Yes	No	Standard	Yes	No	No
6	Yes	No	Standard	Yes	No	Yes
7	Yes	No	Standard	Yes	Yes	No
8	Yes	No	Standard	Yes	Yes	Yes
9	Yes	No	Deluxe	No	No	No
10	Yes	No	Deluxe	No	No	Yes
11	Yes	No	Deluxe	No	Yes	No
12	Yes	No	Deluxe	No	Yes	Yes
13	Yes	No	Deluxe	Yes	No	No
14	Yes	No	Deluxe	Yes	No	Yes
15	Yes	No	Deluxe	Yes	Yes	No
16	Yes	No	Deluxe	Yes	Yes	Yes
17	Yes	Yes	Standard	No	No	No
18	Yes	Yes	Standard	No	No	Yes
19	Yes	Yes	Standard	No	Yes	No
20	Yes	Yes	Standard	No	Yes	Yes
21	Yes	Yes	Standard	Yes	No	No
22	Yes	Yes	Standard	Yes	No	Yes
23	Yes	Yes	Standard	Yes	Yes	No
24	Yes	Yes	Standard	Yes	Yes	Yes
25	Yes	Yes	Deluxe	No	No	No
26	Yes	Yes	Deluxe	No	No	Yes
27	Yes	Yes	Deluxe	No	Yes	No

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Exp Condition	Core Intervention	Telephone Support Calls	App Type	Fitbit Buddy	Online Gym	Text Messages
28	Yes	Yes	Deluxe	No	Yes	Yes
29	Yes	Yes	Deluxe	Yes	No	No
30	Yes	Yes	Deluxe	Yes	No	Yes
31	Yes	Yes	Deluxe	Yes	Yes	No
32	Yes	Yes	Deluxe	Yes	Yes	Yes

Table 3

Example Text Messages

Type of Message	Example Messages
Real-time Progress	Way to hit 45 minutes of physical activity this week. You're halfway toward your goal!
	Finish week 12 strong by meeting your weekly goal. You're already 75% of the way there!
	Way to accomplish your goal this week! Keep it up!
Weekly Feedback	Awesome job meeting your goal! Continue the streak this week and meet your goal again!
	You did not do any exercise last week. Make sure you do some activity this week to get back on track!
	Good job on achieving 80% of your goal last week. This week, aim for 100%!
Self-efficacy	Acknowledge your progress and celebrate the changes you've made as part of Fit2Thrive so far-big or small! Look at all you're capable of!
	Becoming regularly active is a gradual process. Give yourself credit for what you've done so far! Keep moving and you will achieve all you set out to do!
Outcome Expectations	Exercise has been shown to decrease stress levels. Even just 10–15 minutes can have a relaxing effect!
	Low on energy today? Exercise can be re-energizing for your mind and body. Try going for a 10-minute walk and see how you feel!
Overcoming Barriers	Exercise can be fun! Be sure to explore new types of activities to find workouts you will enjoy and stick with.
	Think of a healthy reward for each week you meet your goal. This can help keep you feeling good and your motivation high!
Goal-setting	Be specific with when, where and how you will get moving to increase your chances of success!
	Write down your activity goals and post them as a reminder to get moving!
Social Support	Know someone who likes to exercise too? Having a workout buddy can give you support and inspiration!
	Finding a local walking group can be a great way to get your exercise in and meet new people. Give it a try!
Lifestyle Physical Activity	Cleaning your house can be a productive way to fit some activity in. Put in some extra effort and see if you can break a sweat!
	Lunch time is a great time to go for a walk and break up your day! You'll start the second half of your day more refreshed!
Fit Fact	Did you know, the average human walks about 5 times around the earth on the equator in a lifetime? Get moving and make it 6!
	Did you know, it takes about 23 seconds for your blood to circulate through your entire body? Stay active and keep that blood pumping!

Table 4

Measures of Fidelity to Intervention Components

Component	Measure
Core Intervention	Average number of days open the app and wear the Fitbit
Support Calls	Total percentage of support calls attended
App Type	Average number of times the Deluxe app content is accessed (Newsfeed) or used (goal-setting tool and challenges)
Text Messages	Average number of messages read
Online Gym	Average number of self-reported times used per week
Fitbit Buddy	Average number of self-reported times interacted each week

Table 5

Social Cognitive Theory Measures

SCT	Measure	Description	Reliability Value (α)
Construct Self-efficacy	Exercise Self-Efficacy Scale [54]	Assesses beliefs in ability to be physically active over the next 12 weeks, generally, and despite common barriers, respectively	0.90
	Barriers Self-Efficacy Scale [54]	Assesses beliefs in ability to be physically active over the next 12 weeks despite common barriers	0.86
Outcome Expectations	Multidimensional Outcome Expectations for Exercise Scale [55]	Assesses social, self-evaluative, and physical outcome expectations for physical activity	0.82 (physical) 0.81 (social) 0.84 (self-evaluative)
Goal-setting	Exercise Goal Setting Scale [56]	Assesses physical activity-related goal-setting, self-monitoring and problem solving.	0.89
Facilitators/ Barriers	Social Support for Exercise Scale [57],	Measure physical activity support received from friends, family and other survivors	0.84 for each subscale
	Physical Activity Enjoyment Scale [58]	Measures enjoyment and satisfaction with current physical activity program	0.93 to 0.96
	PROMIS Physical Function Short Form 20a [59]	Measures participants' limitations and interference over the past 7 days.	0.90 to 0.95 [60]
	PROMIS Fatigue Short Form 8a	Measures participants' frequency of fatigue symptoms and interference over the past 7 days.	0.90 to 0.95 [60]