Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: A Phase III, randomized, single blind, attention controlled, multi-center study of the effects of a rehabilitation intervention on participation restrictions of female breast cancer survivors

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For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Definition of participation. This study is focused on breast cancer survivors' ability to engage in life, fulfill social roles, and perform activities and daily routines. Disability scholars use various labels for this construct**.** We are using the language of the **World Health Organization**, where the word ***"participation"*** describes a *state of health and functioning in which a person can fully engage in roles and life situations*.[1]

Operationalization. The construct of participation is multidimensional.[2] The objective aspects of participation include whether and how often an activity is performed; the subjective aspects include the level of difficulty and satisfaction with activity engagement.[3] Most measures of participation focus on activities that fulfill social roles within particular environments, according to personal, societal, and cultural standards.[2] As such, measures of participation generally privilege the individual's perspective as he or she has the best vantage point from which to judge the degree to which he or she is fulfilling various roles within home and community settings.

Prevalence. A population-based study (in which the most common diagnosis for women was breast cancer) reported 31% of both recent and long-term cancer survivors reported restrictions in their ability to participate in roles and life activities. This proportion was significantly more than the 13% of age-matched controls without cancer reporting participation restrictions.[4] In a 2017 study of 245 breast cancer survivors, 90% reported at least some difficulty completing work activities, 87% reported difficulty doing strenuous activities, 78% reported difficulty doing moderate activities, and 74% reported difficulty completing household activities.[5]

Persistence. There is no compelling evidence to suggest that participation restrictions resolve naturally over time. While the studies cited above did not use a longitudinal design, the proportions of recent and long-term survivors reporting participation restrictions are remarkably similar.[4] Research indicates that even after underlying physical impairments have resolved, limitations in recreational activities,

sexual activities, work, and daily activities can persist two[6] to six[7] years after breast cancer treatment.

Causes and consequences. Multiple factors interact to restrict activity participation, and co-morbidities play a large role in generating disability for cancer survivors.[8, 9] Regardless of the etiology, participation restrictions affect both quantity and quality of life. Lower participation in valued activities predicts shorter overall survival in women treated for breast cancer.[10-12] In samples of women living with or recovering from breast cancer, self-reported disruption in daily activities is associated with greater depression[13] and is predictive of less positive mood over time.[14] As such, optimizing participation and promoting functional recovery are important aspects of cancer survivorship.[15, 16]

Scientific Premise

Gap. We lack evidence-based interventions that directly target participation in roles and life activities.[17] Self-management interventions and multidimensional survivorship programs improve symptom management, distress, and quality of life, yet they do not consistently or conclusively improve the outcomes of social functioning or role functioning that are most similar to participation.[18, 19] Rehabilitation interventions primarily address physical impairments. While important, impairment reduction alone may not improve activity participation. For example, a recent meta-analysis[20] found that exercise improves social and emotional well-being of breast cancer survivors, but does not have a significant effect on functional well-being (the aspect of quality of life that is most similar to the construct of participation[21]). Further, because not all underlying impairments can be remediated, adaptive approaches directly targeting activity participation are needed.

Premise. Cheville and colleagues found that the number of physical impairments explained only half of the variance in participation restrictions reported by women with advanced breast cancer.[22] Recent models of cancer rehabilitation acknowledge that participation in roles and activities is influenced not only by physical impairments, but also by other personal factors, environmental factors, and activity demands.[23] We assert that a structured intervention can increase breast cancer survivors' active coping and proficiency in manipulating the environment and adapting activities and that weekly application of those skills can lead to enhanced activity participation. Support for this assertion is presented below, where we describe our preliminary studies. Our approach is designed to catalyze functional recovery by encouraging women to take strategic, incremental actions to optimize activity engagement, without waiting for symptoms and side effects to fully resolve.

Changing the Field. This Behavioral Activation/Problem-solving (BA/PS) intervention could be utilized by rehabilitation therapists, nurses, and social workers in clinical or workplace environments. Occupational therapists, in particular, provide billable services with the ultimate goal of maximizing the ability to function at home and in the community.[24] The BA/PS intervention provides a standardized way to move beyond treating impairments and to directly optimize the ability to engage in activities related to valued roles.

Preliminary Studies Supporting the Scientific Premise

Overview. Our team has conducted pilot studies to establish the feasibility of our methods and demonstrate the intervention's acceptability and potential efficacy. We describe below how we addressed issues that allow us to feel confident that the proposed RCT will be successful.

Acceptability of randomization. In our first pilot study, 31 women undergoing chemotherapy for breast cancer were randomized to the intervention or usual care.[25] We learned that our participants would accept randomization and those assigned to usual care had adequate retention in the 3-month study (94%). Additionally, in our team's larger studies of similar interventions (two RCTs of a supportive care intervention each with >250 participants[26, 27] and an RCT of a home-based BA/PS intervention for 61 older adults with cancer[28]) we have successfully randomized participants and kept data collectors blind to group assignment.

Potential efficacy. After completing the first pilot RCT,[25] we enrolled 32 women who had completed breast cancer treatment and were experiencing participation restrictions (per the screening tool that will be used in this study) into two studies, each using a single arm study design.[29] One of the studies included a no-treatment run-in phase to assess the stability of functional limitations after cancer treatment. There was no change in quality of life during the 6-week no-treatment run-in phase. A longitudinal analysis showed a main effect of time for overall quality of life (as measured by the Functional Assessment of Cancer Therapy-Breast; FACT-B; $F(5, 43.1) = 5.1$, $p = 0.001$), including a significant improvement in functional well-being. Women reported an average increase of 10 points on the FACT quality of life measure immediately after the intervention. A change in 5 points has been found to signal clinically meaningful improvement on the FACT total score.[30, 31] There were also significant improvements in adaptive coping (as measured by the Brief COPE), namely active coping (F (3, 31.7) = 4.9, $p = 0.007$), planning (F (3, 36.0) = 4.1, $p = 0.01$), and reframing (F (3, 29.3) = 8.5, $p < 0.001$).[29]

Use of BA/PS to address various activities. A content analysis of session data from the first pilot study indicated that participants did not rely exclusively on one type of adaptive strategy, but brainstormed diverse strategies that changed *what* activities were done (32% of solutions), and *where* (10%), *when* (21%), with *whom* (16%), and *how* (21%) they were done.[32] The content analysis also revealed that women used the intervention to address 11 types of challenging activities (e.g., exercise, instrumental activities of daily living, work, socializing). In the subsequent two studies using the BA/PS structure, we similarly demonstrated that one parsimonious structure could address up to 13 different types of activities[28, 33] according to the participant priorities. When analyzing the types of goals set by participants in those two studies, we demonstrated that BA/PS targets both the ability to perform activities as well as satisfaction with performance.[33]

Feasibility of telephone delivery. We delivered the intervention by telephone in our three pilot studies involving women with breast cancer[25, 29] because of feedback from participants in our previous studies[26, 34, 35] who consistently appreciated that our interventions do not require them to return to or extend their stay at the cancer center. In our Alabama site, Dr. Bakitas has been able to recruit participants to similar studies of individually-tailored, telephone-delivered interventions and has found that having a local recruiter and interventionist (e.g., with a local accent) has allowed for successful recruitment and retention.

Summary. Our pilot studies used a structured, problem-solving and action planning approach to find ways to increase participation in valued daily activities. We have used participant feedback to create a standardized treatment manual that flexibly addresses the individual needs of cancer survivors. Definitive efficacy testing is warranted as the studies demonstrate the feasibility, acceptability, and potential efficacy of our approach.

Case Example of BA/PS to Illustrate the Significance and Scientific Premise

"Amy" was a 53-year old woman enrolled in our third pilot study. She had a mastectomy to treat her Stage II breast cancer followed by 18 weeks of chemotherapy and 8 weeks of radiation. She was seen by physical therapy to address her severe fatigue, peripheral neuropathy, and lymphedema in her right arm.

Amy reported three challenges with daily activities. First, she was working 24 hours a week, but felt exhausted and overwhelmed at work. Her long-term goal was to resume full-time work, but was currently calling in sick and coming in late and was "burning out the good will" of her employer. Second, she had lived in a large home since divorcing and now felt it was too much for her to take care of properly. She wanted to get back to regular cleaning and start to downsize her possessions. Third, because her physical challenges absorbed her coping resources, she was finding it difficult to reengage with her previous practice of meditation.

In the first BA/PS session, Amy's goal was to re-establish her daily meditation practice. She knew how to meditate, so the session focused on identifying an achievable goal and constructing an action plan that would be manageable, given the barriers of fatigue and time management she had identified. In the second session, she was happy to report that she had meditated six out of the seven days and had enjoyed the experience. In subsequent sessions, she updated her action plan to accommodate any new barriers to meditating.

In the second session, she set a goal to downsize some items in the attic. Using the BA/PS framework, she set an achievable goal and identified modifications that would help her make enough progress to feel successful, but not become exhausted. For example, she brainstormed bringing up a lawn chair to avoid sitting on the floor, setting the alarm on her phone to encourage rest periods, gathering packing supplies on the day before starting the project, and stretching her arm that morning to help her be limber. She also identified where in the attic she would start (i.e., objects that were not too heavy, not likely to stir up unhappy memories, etc.).

In the third session, Amy said she met her goals. However, she was distraught because she was meeting with her boss at the end of the week due to poor work attendance and performance. She used the BA/PS framework to explore the work challenges and brainstorm options for how to improve performance in targeted areas (e.g., organize her work files over the weekend and gather her work supplies and lunch the night before). As part of her action plan, she figured out how she would share this analysis and action plan with her boss.

In the fourth session, Amy said she shared her plan with her boss who was grateful that she had come to the meeting with a plan instead of simply an intention to do better. As a result of the meeting, she was not put on probation and she used her identified solutions to function better at work. Over the remaining sessions, she continued to set achievable goals for functioning better at work, organizing her home, and meditating. She said that planning out manageable steps to reach her long-term goals had been invaluable and had "saved her job.

2. Specific Aims and Objectives

Aim 1: To test the effect of BA/PS on *participation* in roles and activities of breast cancer survivors.

Hypothesis 1a (primary: participation satisfaction): Compared to attention control participants, BA/PS participants will report greater participation as measured by the Patient-reported Outcomes Measurement Information System (PROMIS) Satisfaction with Social Roles and Activities Short Form 8a.[36, 37]

Hypothesis 1b (secondary: participation ability and productivity): Compared to attention control participants, BA/PS participants will report higher activity performance as measured by the PROMIS Ability to Participate in Social Roles and Activities Short Form 8a[36, 37] and higher productivity as

measured by the Disability Days Section of the Medical Expenditure Panel Survey[38] and the Work Limitations Questionnaire-Short Form.[39]

Aim 2: To test the effect of BA/PS on *quality of life* of breast cancer survivors.
Hypothesis: Compared to attention control participants, BA/PS participants will report higher quality of life as measured by the Functional Assessment of Cancer Therapy- General (FACT-G).[21, 40, 41]

Exploratory Aim: To test the effect of BA/PS on the outcomes of *coping*, *goal adjustment*, and *distress*.
Hypothesis: Compared to attention control participants, BA/PS participants will report greater adaptive coping (Brief COPE[42]), greater goal adjustment (Goal Disengagement and Goal Reengagement Scale[43]), and less distress (Hospital Anxiety and Depression Scale[44, 45]).

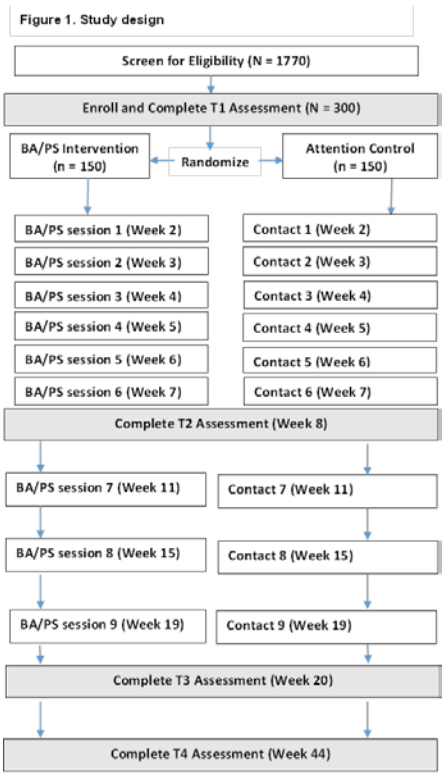
3. General Description of Study Design

Overview. This is a single Institutional Review Board (IRB) study where the Massachusetts General Hospital (MGH) IRB will provide oversight for all sites. The sites include a) MGH Institute of Health Professions (MGH IHP); b) Dartmouth-Hitchcock Medical Center (D-H) which includes the Norris Cotton Cancer Center and its affiliated oncology practices and c) University of Alabama at Birmingham (UAB).

- The principal investigator, Dr. Lyons, is Professor of occupational therapy at MGH IHP. Dr. Lyons will oversee all aspects of the study (e.g., train and supervise team of coordinators and interventionists, monitor participant recruitment, data collection, and data analysis, and lead the writing and publication of results). Dr. Lyons will not recruit participants from MGH and will not deliver the intervention.
- The D-H research team will recruit and enroll participants, will collect all of the outcome data, and will deliver the intervention to participants. Data collection activities will be conducted from MGH IHP once enrollment has been completed in 2022.
- The UAB research team will recruit and enroll participants and will deliver the intervention to participants. The UAB-based statistician and data analyst will lead the data analysis.

Research question. This RCT was designed to answer the question "Is BA/PS efficacious in enhancing activity participation and quality of life of breast cancer survivors?" The primary aims are to assess the efficacy of BA/PS over time (Aims 1 and 2). We will also explore other potential effects of BA/PS on adaptive coping, goal adjustment, and distress (Exploratory Aim).

Design Overview. The study team will recruit 300 women over the age of 18 reporting participation restrictions after completing curative treatment for Stage 1-3 breast cancer within the past year. Half of the participants will be randomized to the 4-month BA/PS intervention which consists of 6 weekly telephone calls followed by 3 monthly telephone calls. BA/PS is designed to teach problem-solving and action planning to promote functional recovery. The other half of participants will be assigned to an attention control condition providing education about survivorship topics. This control condition will allow us to account for the effect of time and history, and the non-specific effects of attention.



Assessments. Assessments will be administered via telephone by a D-H research assistant blind to group assignment. Participants will complete outcome assessments upon enrollment (T1) and at 8 weeks (T2), 20 weeks (T3) and 44 weeks (T4) later. The T2 assessment captures the short-term outcomes of the most intensive part of the intervention (i.e., after six weekly sessions). The T3 assessment will capture the short-term outcomes at the end of the full intervention. The T4 assessment explores the sustained effect of BA/PS (six months after BA/PS ends). Our decision to include the T4 assessment was influenced by a systematic review that indicated it often takes six months to see maximum effects of interventions targeting participation in adults with physical disabilities.[46] The study aim is to test whether the BA/PS intervention affects the "slope" of functional recovery over time. With the longitudinal data, we will also be able to explore the pace of improvement and whether the two groups differ at these clinically relevant time points.

4. Subject Selection

Inclusion Criteria with justification

1. Age of 18 years or older.
2. Experiencing reduced participation (i.e., a score of $\geq$ 10 on the modified Work and Social Adjustment Scale[47]).
3. Females diagnosed with Stage 1-3 breast cancer and within one year of completion of locoregional treatment and/or chemotherapy with curative intent and absence of disease recurrence.

Biological variables of age and gender. In our pilot studies, the intervention has been flexible enough to be used with various challenges that occur across the age range.[25, 29] This proposal's focus upon female breast cancer survivors reflects our pilot research population and allows us to focus recruitment resources with a smaller, closely aligned number of providers. We have decided to focus on females with breast cancer because of the very low prevalence rate of breast cancer in males. Because the D-H and UAB sites see a mean of 3.8 males each year with breast cancer, we will not enroll enough males to allow us to draw sound conclusions that are generalizable to a male population.

Medical co-morbidities. We considered the advantages and disadvantages of excluding women who have medical co-morbidities that affect their daily activities. Cancer survivors report an average of five

co-morbidities[48] that interact with cancer treatment and affect activities. The most prevalent co-morbidities are hypertension, eye or ear problems, and arthritis.[48] Excluding people with such co-morbidities is conceptually appealing in that it would allow a focus on only "cancer-related disability." However, in practice it is difficult to determine whether disability is caused by cancer, a comorbidity, or an interaction of the two. Further, comprehensive cancer rehabilitation must address both pre-existing and treatment-related conditions.[49] Because we ultimately want to develop a generalizable intervention that has broad applicability for cancer survivors experiencing disability (i.e., strong external validity), it is necessary to develop and test interventions that can address any type of participation restriction, regardless of its source. Therefore, we will not exclude potential participants solely because of medical co-morbidities.

Time since treatment. We are targeting survivors who are within one year of completing curative therapy because we are interested in supporting the middle phase of survivorship (i.e., the transition from active treatment toward extended survival).[50] We recognize that interest in and readiness for the intervention can come at different times for survivors. In our pilot studies, semi-structured interviews revealed that some women would have preferred to begin the intervention immediately after treatment ended (i.e., when they were experiencing the most difficulty re-establishing routines). Other women felt the need for intervention after 6 months had gone by (i.e., when they had a sense of their residual participation restrictions). While a one-year window of time may add heterogeneity, we think it will enhance the generalizability of the findings if BA/PS can address varying needs over time.

Exclusion Criteria with justification

1. Non-English speaking.
2. Non-correctable hearing loss.
3. Moderate-severe cognitive impairment indicated by a score < 3 on a 6-item cognitive screener.[51]
4. History of severe mental illness (i.e., schizophrenia, bipolar disorder), current major depressive disorder, active suicidal ideation, or active substance misuse documented within the medical record or by self-report.

Rationale. While the intervention is amenable to translation to other languages and modification for use with a hearing-impaired population, these adaptations are beyond the scope of the current proposal. Similarly, the highly structured program has been able to accommodate subtle cognitive difficulties[52] that are often reported after cancer treatment, but we need to exclude survivors with gross cognitive deficits that would impede safe and independent application of the action plan. Also, the needs of women with schizophrenia, bipolar disorder, major depressive disorder, suicidal ideation, and substance misuse disorders are greater than can be adequately provided by our telephone-delivered intervention. People who are excluded according to these criteria will be referred to clinic-based rehabilitation or behavioral services.

Strategies to minimize bias in sampling. Our eligibility criteria are clearly defined so that the sample is not biased by relying upon a clinician's determination of a given patient's "appropriateness" or need for the study. Our use of the telephone for study and intervention procedures, along with our flexible staffing (i.e., staff available during early evening hours), allows us to reduce barriers to participation that may be experienced by working women or mothers with small children.

Procedures to identify potential participants. Our research team has established a successful mechanism in which we collaborate with clinicians to identify eligible patients each week. We apply for a Health Insurance Portability and Accountability Act (HIPAA) waiver to allow research staff to screen clinic schedules and/or use the i2b2 portal to identify potential study participants. The project coordinator consults with the clinicians to confirm eligibility based upon clinical characteristics. Clinicians deliver the brochure describing the study to patients. Our project coordinator is available in the clinic or by telephone to further explain the study to patients, screen for eligibility, and initiate informed consent procedures. If a patient is unable to be approached in clinic, we have an IRB-approved letter template describing the study and asking patients to contact us if they are interested or await a courtesy phone call from our team to see if they would like to hear more about the study. The letter is signed by the treating clinician(s), accompanied by a study recruitment brochure, and mailed out by the study team.

In order to maximize recruitment, we will bring our recruitment brochures to events that may include breast cancer survivors such as wellness fairs, support groups, and cancer survivorship events. Screening and consenting after these events will follow the established procedures and scripting that have been approved by the Committee for the Protection of Human Subjects (CPHS) at Dartmouth College. We also run a Facebook advertising campaign, posting IRB-approved information about the study on Facebook with a link so that interested people can provide their email or phone number so that we can tell them more about the study and screen for eligibility. If necessary, we will post advertisements on print and other social media platforms (e.g., local newspapers, Instagram, Twitter), cancer center platforms (e.g., waiting room screens, websites), and online support group or advocacy platforms (e.g., Army of Women). Any inquiries resulting from our registration in ClinicalTrials.gov will be fielded by the D-H project coordinators, using our telephone procedures to screen and initiate informed consent procedures as appropriate.

5. Subject Enrollment

In our previous studies, we have found that many people like to take the study materials home and take some time to decide whether or not to enroll. This study will be recruiting survivors, people who have completed treatment and may not be returning to the cancer center frequently. Additionally, we are recruiting participants via Facebook, where we need to conduct all screening and consenting via telephone. In these situations, we use telephone consent procedures that have been approved by the Dartmouth Committee for the Protection of Human Subjects previously. It should be noted that our telephone procedures mirror our in-person procedures. We train our study staff to give the person ample opportunity to feel comfortable, express concerns, and ask you any questions he or she might have and to pause more often and ask if they have questions to make up for the absence of non-verbal signals that help assess the degree to which a person is paying attention and understanding. We also train study staff that they can only proceed with the informed consent discussion only when the person has a copy of the consent form in front of them so that they can follow along.

The project coordinators use a study brochure to describe the study and if the person is interested in learning more they use a template to screen participants according to the eligibility criteria. If the person is eligible, the project coordinators proceed with informed consent, explaining each section of the consent form (which has either been given to them in paper form if in the clinic or sent via Docusign at D-H or Adobe esign at UAB if enrolling remotely or from self-referral). Participants who decide to enroll either sign the paper copy of the consent form (signing two copies, as does the project coordinator; one copy is given to the participant and one copy is retained by the project coordinator) or use the Docusign/Adobe esign link to electronically sign and return the informed consent document; once co-signed by the project coordinator, a copy is sent to the participant. No study activities are initiated until

the signed consent form is in the hands of the project coordinator. At that time, the baseline assessment is scheduled.

6. STUDY PROCEDURES

Data Collection

A clinical research coordinator blind to group assignment will administer standardized telephone interviews, scheduled at the participants' convenience. On the rare occasion that a woman is unable to complete the surveys by telephone, the coordinator will send a link to a secure electronic Redcap survey or mail a hard copy of the surveys with a postage paid envelope in order to do everything we can to minimize missing data. Data is directly entered into the Redcap software system. Recap is programmed with quality controls that facilitate rigorous data collection, such as not allowing interviewers to skip questions.

Data Collection Schedule

Measures and Data Collection Schedule

Aim	Construct	Instrument	# of Items	T1 Week 0	T2 Week 8	T3 Week 20	T4 Week 44
	Characteristics	Demographics and Clinical Characteristics	9	X			
Aim 1	Participation & Productivity	PROMIS® (Satisfaction and Ability to Participate in Social Roles and Activities) Disability Days and WLQ-SF Individual activity targets	16 25+2 3-9	X	X	X	X
Aim 2	Quality of Life	FACT-G	28	X	X	X	X
Exploratory Aim	Adaptive Coping	Brief COPE subscales	6	X	X	X	X
Exploratory Aim	Goal Adjustment	GDGRS	10	X	X	X	X
Exploratory Aim	Distress	Hospital Anxiety and Depression Scale (HADS)	14	X	X	X	X
	Perceived benefit	Perceived Benefit Questions	5		X		

The coordinators will administer the outcome assessment battery by telephone upon enrollment (T1), after completion of the most intensive portion of the intervention (T2), after completion of the full intervention (T3) and six months after completion of the intervention (T4). Coordinators begin to call participants up to three weeks before the survey target date to schedule the survey; they will continue to call participants until either the survey is completed or four weeks passes beyond the target date. If participants are unable or unwilling to complete the outcome assessments by telephone, we will offer them the opportunity to complete the measures on paper (mailed with a hard copy and postage paid return envelope) or electronically (a link to a Redcap survey will be sent by email).

Measures

Eligibility Assessment

Participation restrictions and gross cognitive impairments: *The Work and Social Adjustment Scale (WSAS)*. The WSAS is a five-item scale of participation restrictions related to work, home management (e.g., cleaning, shopping, childcare), leisure, and relationship activities.[47, 53] Items are rated from 0-8 (0 = not at all impaired, 8 = very severely impaired). Test-retest reliability is acceptable at $r = 0.73$. As in the preliminary studies, we will use a WSAS cutoff score of ≥ 10 as a way to identify people with at least a moderate level of participation restrictions.

Sociodemographic and Clinical Characteristics to Describe the Sample

Enrolled participants will report their age, race, ethnicity, employment status, education level, marital status, insurance status, number of dependent children living at home, and household income. We will ask three questions related to COVID-19 status from the PhenX toolkit (https://www.phenxtoolkit.org/covid19/) related to whether a participant has been diagnosed with COVID-19, whether a family member was diagnosed with COVID-19, and the degree to which their work is impacted by COVID-19. We will use data from the medical record to describe stage, treatment and co-morbidities or self-report if the participant is recruited outside of D-H or UAB.[54]

Participation

Participation satisfaction (primary outcome): Participation is a construct with two dimensions: satisfaction and ability. Disability scholars have argued that the subjective assessment of satisfaction with daily routines and activities is a defining feature of participation.[55] As such, we will use the PROMIS S*atisfaction with Social Roles and Activities Short Form 8a*[36, 37] as our primary outcome. Initial validation studies used exploratory and confirmatory factor analysis and two-parameter item response theory modeling to explore differential item functioning and to increase the precision of the PROMIS participation items.[36, 37] The resulting 8-item subscales (i.e., satisfaction and ability) address routine, work, leisure, family, and social activities. The scales were used in a recent large study of cancer survivors.[45]

Participation ability (secondary outcome): We will use the second 8-item PROMIS scale entitled *Ability to Participate in Social Roles and Activities Short Form 8a*[36, 37] to measure the ability aspect of participation. The scale was developed in conjunction with the satisfaction scale, as described above. We added an item to solicit participant perceptions of the degree to which their challenges are related to cancer or its treatment so that we can determine if the source of the restrictions moderates the effect of the intervention.

Productivity (secondary outcome): We will use relevant questions from the Disability Days section of the *Medical Expenditure Panel Survey (MEPS)* [38, 56] to capture days missed from work and lost household productivity. Missed days of work have been defined as half or more of a day missed from work due to a physical illness, or injury, or mental or emotional problem (including those missed because of hospitalizations). MEPS questions can be used to measure missed days of school if survivors are enrolled in school or training. For all participants, including those who are not employed or are on leave, we will assess lost household productivity by measuring days spent in bed, defined in MEPS as half days or more spent in bed because of physical illness or injury, or mental or emotional problems. We will also use the *Work Limitations Questionnaire-Short Form (WLQ-SF)[39]* to assess productivity. The WLQ has 25 items, and 4 subscales that assess limitations in 4 job dimensions (time, physical, mental/interpersonal/output). The subscale scores represent the percentage of time in the previous 2 weeks that participants may be limited in performing in the specific dimension. An overall WLQ Productivity Loss Score is the weighted sum of the 4 subscale scores and indicates the percentage decrement in productivity. The WLQ demonstrated high validity and reliability[39, 57] and has been used in cancer survivor populations.[58-60] While developed to assess productivity at paid work, it has been used with homemakers as well.[61]

Individual Activity Targets (secondary outcome): During the first session of the intervention and control conditions, the occupational therapist elicits the participant's individual recovery goals. The participant rates each activity with Likert scales for three characteristics: frequency of current performance (very often, often, once in a while, almost never, never), importance of the activity (1-10), and satisfaction with the activity (1-10). These ratings were used in a similar study by our team and provided a simple and pragmatic tool for assessing individualized outcomes.[62]

Quality of Life

Quality of Life: The *Functional Assessment of Cancer Therapy- (FACT-G)* is a 28-item self-report measure of health-related quality of life specifically designed for breast cancer patients.[40, 41] The items of the tool assess perceived well-being in physical, social, emotional, and functional domains. Subscale scores are derived in each domain as well as a total score. [41]

Exploratory Outcomes

Coping: *Brief COPE*.[42] Our pilot research has suggested that BA/PS increases participants' use of active coping, planning and positive reframing.[29] These coping styles are measured by three subscales of the Brief COPE. The Brief COPE has been shown to have excellent psychometric properties among cancer patients including evidence of construct, convergent and concurrent criterion validity.[63] To minimize respondent burden, we will not administer the 28-item Brief COPE, but will instead utilize the three subscales of interest.

Goal adjustment: *Goal Disengagement and Goal Reengagement Scale (GDGRS)*.[43] The GDGRS is a 10-item scale that measures two aspects of goal adjustment. Four items measure dispositional goal disengagement (i.e. the general inclination to relinquish untenable goals). Six items measure dispositional goal reengagement (i.e., commit to new goals). The internal consistency of the scales is generally high.[64] We will use the GDGRS to explore the potential efficacy of BA/PS on goal adjustment.

Distress. *Hospital Anxiety and Depression Scale (HADS)*is a 14-item self-report measure of depressive and anxiety symptoms specifically designed for medical patients.[44] [45]The HADS contains only the cognitive symptoms of depression and anxiety, thus eliminating the somatic symptoms that are poor indicators of psychiatric distress in the medically ill. Items are rated on a four-point scale from 0 (not at all) to 3 (very often) and yield subscale scores for both depression and anxiety. Higher scores indicate more severe symptoms. Because breast cancer survivors can experience significant distress regarding their ability to perform social roles and life activities, we will use this scale to explore the potential efficacy of BA/PS on this outcome.

Perceived benefit. We have developed six questions modeled after those uses in a recent rehabilitation RCT.[65] The questions will help us to describe the credibility and utility of the intervention versus control conditions. Using a three-point scale (not at all, some, a great deal), participants will rate the degree to which the program helped them gain confidence, reduce distress, adjust habits and routines, set goals, and exercise. These reflect the areas that participants in the pilot studies reported were affected by the intervention. It should also function as a manipulation check in that the intervention is hypothesized to work by setting goals and the control condition does not include goal setting as active component. At minimum, the intervention participants should report higher levels of benefit on the goal setting item.

Subject Stipends or Payments

Participants will be paid $25 for completion of each of the Time 1, Time 2, and Time 3 assessments and will be paid $30 upon completion of the Time 4 assessment (total = $105 per participant). Participants who wish to accept the payments are required to complete a W9 form that will be submitted to Massachusetts General Brighamby the project coordinator along with the payment request. The W9 form will be completed on paper if the participant is recruited within clinic or will be completed via Docusign software if recruited outside of the clinic (e.g., social media). Docusign is HIPAA compliant and has been approved for use in this project by Dartmouth-Hitchcock.

Method for Assigning Subjects to Treatment Groups

Scheme. Participants will be randomly assigned to group (1:1) using a computer-generated program overseen by Dr Azuero. The randomization scheme will be stratified by site (D-H and UAB), time since treatment completion (i.e., <6 months and >6 months), and receipt of chemotherapy (yes versus no) and will be blocked within strata (block lengths of 2 and 4 varied randomly).

Process and blinding. The PI or project managers will manage the randomization process, looking up the id number in an established excel file and assigning the local interventionist to communicate assignment to the participant and initiate treatment activities. The project coordinators will remain blind to group assignment and participants will be instructed not to discuss their assignment with the project coordinator collecting the outcome assessments.

When and How to Withdraw Subjects

Participants will be withdrawn from the study at their request (e.g., lack of interest in or perceived need for intervention, lack of time for study assessments).

Data Collection and Follow-up for Withdrawn Subjects

Our team continues to attempt to contact participants for each session and study assessment unless and until they ask us to stop/express the desire to withdraw. Each study contact is an extension of informed consent where participants are told what is occurring, what happens next, and that their participation is voluntary. When we are unable to reach participants by telephone for at least 30 days we send a letter conveying our attempts to reach them and ask them to contact us to continue with study activities or withdraw, as they prefer.

Treatment Regimen

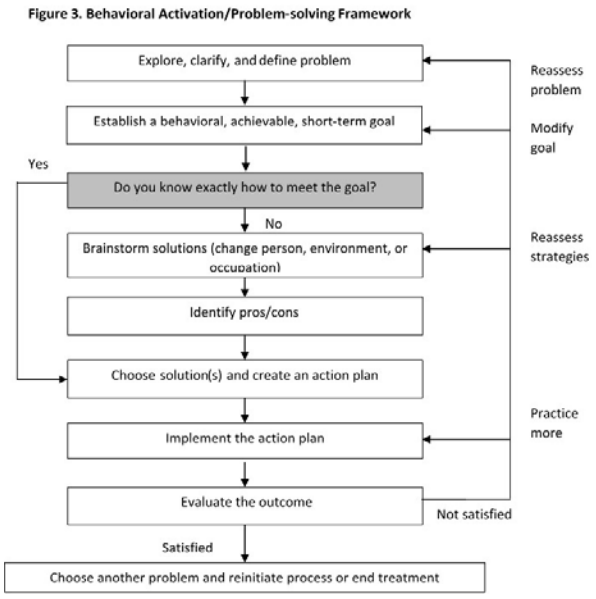
Theoretical Background of BA/PS

Our approach to improving activity participation reflects self-regulation models that emphasize alignment between goals and circumstances.[66-69] Recognition of a discrepancy between one's goals and circumstances leads to either adaptive or maladaptive coping. Adaptive coping can be viewed as efforts to change the activity, environment, or self. These efforts manifest themselves in active coping (i.e., taking action instead of waiting for problems to disappear), planning (strategically deciding what actions to take), and positive reframing (adjusting expectations and interpretations of events).[29] Goal adjustment is another self-regulation strategy with two components.[70] The first component, goal disengagement, prevents the negative emotional consequences of pursuing a futile goal. The second component, goal reengagement, directs renewed energy towards attainable goals. BA/PS is designed to promote adaptive coping and goal adjustment through a process of strategic goal-setting, problem-solving, and action planning centered on increasing the ease and enjoyment of activity participation and life roles, which leads to lower distress, improved productivity, and higher quality of life.

The BA/PS Intervention (Experimental condition)

Framework (Figure 3). BA/PS teaches survivors to a) systematically examine the reasons an activity is challenging, b) set achievable short-term goals that have the potential to improve participation, c) brainstorm solutions including activity adaptations and environmental modifications, d) construct and implement a detailed action plan, and e) evaluate the results and level of goal attainment. The structured process gives participants repeated practice in goal reengagement that leads them progressively closer to their long-term functional goals. The BA/PS framework integrates the cognitive-

behavioral therapies of Behavioral Activation[71, 72] and Problem-solving Treatment[73, 74] and incorporates concepts from an occupational therapy theory called the Person-Environment-Occupational Performance Model.[75]



Non-prescriptive. The BA/PS interventionist does not directly give advice or prescriptions. Behavioral Activation and Problem-solving Treatment were developed to treat depression and one active ingredient of those therapies is to teach patients to actively identify their own solutions to problems in living. We have found this technique is also beneficial when addressing participation because the cancer survivor is the expert in his or her lifestyle, routines, and environment. A participant in a pilot study of Behavioral Activation that we are conducting at Johns Hopkins (K23HL138206; PI: Parker) noted this emphasis was refreshing and in stark contrast to his post-hospitalization experiences of rehabilitation (i.e., "they mostly told me what I should do.").

Session 1. The interventionist presents the rationale for BA/PS, promotes a positive problem orientation, and educates about the framework for problem-solving and action planning. The interventionist then administers the Canadian Occupational Performance Measure[76] to elicit participant priorities, motivation, and long-term goals. The interventionist then guides the participant in using the BA/PS framework to set a goal, brainstorm solutions to challenges, and create a detailed action plan for the coming week.

Subsequent sessions (once a week for five more weeks, then once a month for three months). The interventionist begins by reviewing the rationale for BA/PS and the previous action plan and elicits information about goal attainment and satisfaction with effort and outcome. If the goal for that week was met, then the interventionist guides the participant to identify another short-term goal for the coming week that would continue the progress towards the long-term goal. If the goal was not met, then the interventionist troubleshoots with the participant to determine whether the challenge was not fully described, whether the goal was too hard, whether the chosen solution or action plan was not effective, or whether more practice is needed. The framework is then used to create a goal and action plan for the coming week.

Dose. The therapies that BA/PS is built upon typically show that six sessions allow sufficient exposure for participants to meet many of their goals and independently utilize the framework.[77, 78] The theoretical rationale for the three monthly sessions comes from the Transtheoretical Model[79] that suggests there is a maintenance stage of intentional behavior change where people need to actively solidify habits and develop confidence in their ability to sustain gains in activity engagement. As such, the three monthly follow-ups are booster sessions to enhance motivation, provide feedback, and keep the focus on continued incremental gains.

Attention Control Condition

Rationale for an attention control. This proposal explores the question, ""Is BA/PS efficacious in enhancing activity participation and quality of life of breast cancer survivors?" Using randomization and a usual care control condition would allow us to eliminate the threats to internal validity that arise with time and history (i.e., participants might improve naturally as time goes by or because of an event occurring at the sites). However, the BA/PS participants would be receiving more attention and support than would the usual care participants. We recognize that the attention experienced within a weekly telephone call from a warm and supportive therapist could lift the spirits of participants and it is theoretically plausible that feeling more hopeful or supported could allow and encourage participants to become more active and engaged in life. We feel it is important to control for this possibility so that we can determine that it is our specific BA/PS intervention and not general support or attention that drives any effects seen in our data.

Rationale for education within the attention control condition. Increased attrition can occur if participants feel that an attention placebo is not a meaningful use of time.[80] As such, we decided to provide education regarding nine cancer survivorship topics (i.e., healthy diets, physical activity, lymphedema management, smoking cessation, stress management, communication with providers, body image and sexuality, communication with social supports, work accommodations) during the control telephone contacts. The control condition will match the intervention in terms of the number of sessions, the delivery by telephone, use of an occupational therapist, and the use of "homework" between sessions (i.e., reading the education materials for the control condition versus executing the action plan for the BA/PS condition). This will allow us to determine the effect of the specific BA/PS elements (i.e., strategic goal setting, problem-solving, activity adaptation, environmental modification, and action planning) on participation and quality of life.

7. Risks and Discomforts

There are three potential risks involved in this study: (1) the risk of hurting oneself when trying to increase activity level (e.g., falling while exercising or performing home management tasks); (2) the risk of distress while talking about challenges with functional recovery after cancer treatment; and (3) risk of loss of confidentiality. The level of risk is generally quite low and strategies to minimize risks are incorporated into the BA/PS treatment manual.

Risk of injury: The goal of the BA/PS intervention is to assist participants in optimizing functional recovery and activity participation after cancer treatment. BA/PS may help the participant to change aspects about themselves, the task, or how it is performed in order to engage in valued activities. In general, there is a very low level of risk involved in the intervention. Regarding the risk of injury, the BA/PS program includes action planning in order to increase the safety and success of activity engagement to minimize the chances of this risk. Furthermore, we instruct participants to schedule the outcome assessments and the intervention sessions at times when they can be seated comfortably while writing in the workbook or looking at the response choice sheet during outcome assessment administration. We have found that staffing in evening hours as needed and using these clear instructions helps us to discourage and counteract some participants' desire to complete study procedures by telephone while driving.

Risk of distress: This is somewhat of a self-correcting problem because the objective of BA/PS is to provide a structured process to help people find ways to increase activity engagement. The interventionists are trained to validate feelings of frustration and distress while re-directing the participant to actionable ways to make immediate progress. Likewise, the coordinators who administer the outcome assessment are also trained in listening for signals of distress (e.g., long

pauses, weeping) and are trained handle distress tactfully (e.g., do not indicate verbally or non-verbally that they are uncomfortable with participant distress) and to remind the participants that they can discontinue the surveys at any time. If a participant is experiencing significant emotional distress, either because of their disease and its treatment or participation in the study, Mark Hegel, PhD (Co-investigator and licensed clinical psychologist) will be available for consultation and mental health services are available at both study sites (D-H and UAB).

Risk of privacy loss: Finally, to address a low-level risk of loss of privacy, participant confidentiality will be strictly protected. Hard copies of data will be maintained in locked files that can only be accessed by study personnel. Data forms will be identified using an identification (ID) number only. Access to the list cross-tabulating ID numbers with participant names will be kept in a password-protected data file behind the firewalls of D-H and UAB, accessible only to the project manager and coordinators. Hard copies of data files will likewise be kept in a locked file cabinets in locked offices and will include the ID number but no other unique identifier. All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Good computer security practice (shutting down computers after work hours, restricting physical access to machines, prohibition of password sharing) will be required of all study personnel. Virus protection software is installed on each study computer. The virus detection tools are used, maintained, audited and, if necessary, updated on all computers and pathways into the system. Redundant backups allow for quick restoration of data in the unlikely event that a hardware failure or security breach occurs. Data sharing between sites occurs via the secure Sharefile storage system housed behind the Dartmouth-Hitchcock firewall.

8. Benefits

Potential benefit. Participants who are randomized to the BA/PS intervention arm will receive elements of a problem-solving intervention that has been shown to improve function and quality of life in other populations. Therefore, participants may benefit from their participation in the study. If shown to be efficacious, the intervention model could be used to improve health outcomes for cancer patients across the country.

9. Statistical Analysis

Sample Size Determination

Minimally important differences. The minimally important differences (MID) between the two study arms are taken to be 10% of the practical range of the outcome variable[31] and thus the MIDs are 3.94, 3.95 and 11.2 for satisfaction with participation, ability to participate, and quality of life, respectively. Note that these MIDs are not data dependent, although standard deviations might change for different data sets. We will assume the standard deviation for the two PROMIS scales are both 10 according to the scoring manual and the standard deviation for FACT-B is 24, as estimated from our third pilot study.[29]

Estimated attrition. To estimate attrition, we examined the attrition seen in our three preliminary studies. One of the preliminary studies was an RCT,[25] two studies used a single arm design,[29] and each of the studies had at least three assessments. On average, 80% of our participants completed all study activities, and thus we expect an attrition of ~20% (if 300 people enroll, at least 240 participants will complete the study).

Power. Using a Time-Averaged Difference approach,[81] at a corrected significance level of .05/3=.017, and with three time-points post baseline, the required sample size to test for the minimally important effects of BA/PS on participation (PROMIS scales) ranges from 63 to 117 in each arm to achieve 80% power for within subject correlations ranging from 0.2-0.8. The required sample size to test for the minimally important effect of BA/PS on quality of life (overall FACT-B score) ranges from 45 to 83 in each arm to achieve 80% power for within subject correlations ranging from 0.2-0.8. An FDR correction (see section C.7.3) will be used at the time of analysis which will provide more power than a Bonferroni correction and adequate control to the number of Type I errors.

Statistical Methods

Data analysis will begin with descriptive statistics for baseline participant characteristics and outcomes by study group. We will calculate means, standard deviations, and percentiles for continuous variables (e.g., participation, quality of life, coping, goal adjustment, distress, age, etc.) and frequencies and proportions for categorical variables (e.g., clinical characteristics), at each time point as appropriate. We will plot and inspect the distributions of the outcome variables, and examine the validity of any extreme values (data entry errors will be minimized by logic checks in the Velos data collection system, and inspection of scheduled reports during data collection). We will examine balance between study groups with respect to baseline characteristics using effect sizes such as the standardized mean difference for numerical variables and Cramer's V for categorical variables. We will examine patterns of missing data due to dropout, and whether baseline characteristics are associated with dropout. Baseline factors showing non-trivial imbalances between groups or that are predictive of dropout, will be then used as adjusting covariates in the longitudinal group comparisons. We will use the latest versions of standard statistical packages (SAS and R) for all analyses.

Group Comparisons (Aim 1, Aim 2, and Exploratory Aim)

Objective. Our objective is to compare the two groups' functional recovery over time in terms of participation (PROMIS scales; Aim 1), productivity (Disability Days and WLQ; Aim 1), quality of life (FACT-B; Aim 2) and coping style, distress, and goal adjustment (Brief COPE, HADS, and GDGRS; Exploratory Aim). All measures are collected at conceptually relevant time points of enrollment (T1), completion of the most intensive part of the intervention (T2), completion of the full intervention (T3) and six months after treatment completion (T4). The methods described below will be conducted upon each outcome variable.

Modeling. A longitudinal model fitted with linear mixed methods will be used for each outcome. Numerical outcomes with markedly non-normal distributions, if any, will be modeled with more appropriate error distributions than the default normal (e.g., lognormal or generalized beta distributions). The focus of inference will be the between-group difference in outcome trajectories over the study time points, modeled by a time by group interaction. A random effect for subject will be fitted to account for covariance among repeated measures on the same individuals. If necessary, we will conduct covariate adjustment for baseline factors unbalanced between the groups or predictive of dropout. Time will be modeled as a categorical variable, to avoid the strong assumption of linear trajectories, and therefore the single test for the interaction effect will be a multiple-degree of freedom test. Model-predicted outcome means (a.k.a. LS-Means) by group at each time point will be computed to facilitate interpretation. The overall treatment effect will be computed as the between-group difference in change from baseline (change from T1 averaged over T2 to T4) estimated with a linear contrast.

Handling of Missing Data

Mixed modeling techniques and covariate adjustment will reduce the impact of missing data, as the missingness is not assumed completely at random (MCAR) but conditionally (on the covariates) at random (i.e., MAR, a milder assumption).[82] Should dropout exceed the 20% allowed by the sample size (section C.7.5), non-parametric multiple imputation[83] will be employed to determine the robustness of the conclusions for the main analyses under the milder MAR assumption. Because missing data due to non-ignorable or non-random drop out (i.e., MNAR) does not depend on the observed data, it presents the most complex situation to handle. Because of the non-invasive, supportive nature of the BA/PS intervention, as well as the attention control condition, a priori, we do not expect to encounter non-random dropout (and therefore MNAR). However, we will examine the tracking system records and logs with regard to dropout, to determine the main reasons for dropout. If sufficient indication of an MNAR mechanism is found, sensitivity analyses under different assumptions for the missing data mechanism will be conducted, following the methodology described by Molenberghs and Kenward[84] in which the missing data mechanism needs to be modeled explicitly.

Adjustment for Multiple Inference

A False Discovery Rate (FDR) approach[85] will be utilized to adjust inferential results for multiple inferences on the same body of data, separately for the primary analyses and the exploratory analyses. The FDR is the expected proportion of true null differences among those that are declared "significant". The FDR will be set at 10%. All research products will disclose the number of inferences conducted and whether outcomes were primary or exploratory. As shown above , the sample is well powered to detect relevant effect sizes on the primary outcomes, even after multiplicity adjustment.

Heterogeneity of Intervention Effects

Rationale. We have developed the intervention to be flexible and responsive to the needs of a diverse group of breast cancer survivors. However, our diverse sample will give us the opportunity to identify any unanticipated moderator effects. Therefore, we will explore whether there are subgroups of participants who benefited most and least during the study, as per the primary outcomes.

Recursive partitioning. The classical approach to moderator or subgroup analysis consists of 3 steps: 1) pre-specifying some population characteristics of interest (e.g., site: UAB vs. D-H; race: minority vs. white; age: <65 vs. ≥65; source of participation restriction: primarily related to or unrelated to cancer; relapse vs. not, etc.); 2) analyzing one characteristic at a time, conducting inferences on differential intervention effects based on the characteristic's subgroups, using interaction tests adjusted for subgroup imbalances in other characteristics; and 3) applying an adjustment for multiple inference to account for the multiple analyses on the same body of data. Instead of implementing the classical approach, we propose using recursive partitioning, a.k.a. CART[86] (Classification and Regression Trees), a non-parametric modeling approach that allows extracting multivariate profiles from a sufficiently large dataset under minimal modeling assumptions, based on values of an outcome and participant characteristics. We propose this approach instead of the classical approach because multiple patient characteristics might be simultaneously associated with benefitting from the BA/PS intervention, therefore the multivariate approach can potentially provide more information and be more useful than the classical approach. Because CART is data-driven, these analyses will be considered exploratory. To avoid assuming that missing outcome data due to dropout is missing completely at random (i.e., MCAR), a Random Forest-based algorithm[83, 86] will be used to generate 3 imputed datasets comprising

baseline characteristics, group assignment, and longitudinal outcome variables. CART modeling will be implemented on each imputed dataset and results will be compared as a form of sensitivity analysis. The target variables for the CART modeling will be the average change from baseline in each primary outcome. Regression tree models for these target variables will be fitted using as predictors the group assignment and selected baseline characteristics. These baseline characteristics will include indicators of pertinent subpopulations of interest: site, race, income, age, etc. We will implement the conditional inference approach[87] to fit the tree models and use repeated 10-fold cross-validation to determine the final tree size. The tree model is a decision-tree-like structure that is interpreted based on the characteristics of the resulting groups of participants.

Intent to treat. Our main analyses will utilize an intention-to-treat approach. As the BA/PS intervention is not part of standard practice, cross-over events are not expected to occur. All available data from all participants who undergo randomization will be included in the analyses according to the group assigned, regardless of any post-randomization protocol deviations.

10. Monitoring and Quality Assurance

Safety and Adverse Events

Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect

- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Investigator reporting: notifying the IRB

The IRB requires reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The IRB requires researchers to submit reports of *any incident, experience, or outcome that meets each of the following criteria:*

- ***Unanticipated*** *in terms of nature, severity, or frequency given: (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and consent document; and (b) the characteristics of the subject population being studied; and*
- ***Possibly related*** *to participation in the research means there is a reasonable possibility that the incident, experience, or outcome may have been associated with research participation; and*

- *The problem suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, emotional, economic, legal, or social harms) than was previously known or recognized.*

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB using the form: "Unanticipated Problem Involving Risks to Subjects or Others (UPR)."

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical trials, the following events are also reportable to the IRB:

- Any adverse experience, defined as an untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research), that is considered:
  - Serious: Death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; and
  - Unexpected: Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure or consent form; and
  - Possibly related: There is a reasonable possibility that the incident, experience, or outcome may have been associated with the procedures involved in the research; and
  - Is experienced by a participant in a trial open at a site subject to Dartmouth IRB review
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol deviation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

Stopping Rules

Significant risk is not anticipated in this study due to the supportive and non-invasive nature of the intervention. However, we will summarize adverse event data annually to the D-H Data Safety Monitoring and Accrual Committee for consideration of study continuation. The study design does not include planned interim analyses to identify the need to stop early due to significant benefit, i.e., inferential analyses will be conducted when data collection has been completed.

Internal Data and Safety Monitoring Board

This project will involve enrolling 300 breast cancer survivors into a randomized controlled trial within the year after they complete their treatment. After enrollment, participants will complete a baseline assessment. Participants randomized to the BA/PS intervention arm will engage in 9 individual sessions delivered via telephone by an interventionist (who is an occupational therapist or nurse). Participants randomized to the attention control arm will engage in 9 individual education sessions delivered via telephone by an interventionist. The intervention and assessments are not invasive and do not involve pharmacological agents. The informed consent process, the recruitment process, and the timeliness and quality of the data will be monitored by the principal investigator, the Institutional Review Board, and the Data Safety Monitoring and Accrual Committee (DSMAC) of the D-H. The DSMAC meets quarterly to review accrual rates and information for studies that have accrued participants. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the MGH IRB office. The last DSMAC report will be filed in January 2023 as all enrollment and intervention activities have been completed and the only remaining study activity is data collection.

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11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens

☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research

☒ Additional privacy and/or confidentiality protections

Data sharing between D-H, MGH IHP, and UAB will occur via the D-H Sharefile site, as described in the data use agreements as part of the subcontracting award process. Data sharing will be bi-directional between D-H and UAB (e.g., UAB sends participant enrollment information to D-H and receives outcome data from D-H for analysis) and bi-directional with MGH IHP as Dr. Lyons will provide a de-identified data set to UAB where the statistician is located..

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
There are 8 standing members of the DSMAC, representing different disciplines and laboratories.

☒ Describe planned frequency of meetings:
Data is submitted and reviewed annually

☒ DMC/DSMB reports with no findings (i.e., “continue without modifications”) will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.