Official Title:	Increasing physical activity among breast cancer survivors: Use of the ORBIT Model to refine and test a novel approach to exercise promotion based on affect-regulation
NCT number:	NCT04903249
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	9/21/21

1.0 Study Summary

Setting: This study will be conducted within and supported by the strong research infrastructure at Dartmouth-Hitchcock Medical Center and the Dartmouth Cancer Center, an NCI- designated Comprehensive Cancer.

Purpose: Supportive care, behavioral intervention development. This research proposes to evaluate a novel intervention approach to prescribing exercise to stage 0-III breast cancer survivors based on affect regulation. The novel intervention is called "Affect-Rx."

Primary Objective: To modify and refine the Affect-Rx exercise prescription and study protocol to be acceptable for use with breast cancer survivors.

Study Specific Aim (i.e., Aim 1): To modify and refine the Affect-Rx exercise prescription and study protocol to be acceptable for use with breast cancer survivors. Modifications and refinements will be informed by semi-structured participant interviews and objective indicators of acceptability assessed using the Treatment Acceptability and Preferences (TAP) Measure,[67] accelerometer wear-time, and daily EMA survey completion.

2.0 Background

Exercise is medicine in cancer care,[11] but participation is lacking. The strategic plan set by the Health Behaviors Research Branch of the National Cancer Institute (NCI) identifies physical inactivity as a key cancer-related behavioral risk factor of interest.[10] There is strong epidemiological evidence of a dose-response relationship between exercise post-cancer diagnosis and cancer-related mortality risk.[6–8,12] While more exercise is better, even a modest amount of exercise produces a clinically meaningful reduction in cancer-related mortality.[7,12–15] For breast cancer survivors, cancer-related mortality risk has been shown to decrease by 2.5% for every additional ~15 mins/week of at least moderate-intensity physical activity completed under a threshold of ~150 mins/week.[6,12,16] The American College of Sports Medicine (ACSM) Exercise Guidelines for Cancer Survivors recommend all survivors avoid inactivity;[2,9] the guidelines also state exercise is safe for most cancer survivors, and ≥ 90 mins/week of at least moderate-intensity physical activity is associated with strong reductions in cancer treatment- related adverse effects (e.g., fatigue) and improvements in physical functioning and health- related quality of life.[2–5,17,18] However, few breast cancer survivors achieve these recommended guidelines, and rates of exercise engagement decline significantly starting from time of diagnosis, [19–21] with most breast cancer survivors never fully returning to pre-diagnosis activity levels.[19–21] Further, in rural areas, 50% of survivors engage in no leisure time physical activity.[22,23]

Among the general population, efforts to identify underlying determinants of physical activity have increasingly emphasized the contribution of affective (i.e., feeling- based) factors. For example, the "affective response to exercise" (i.e., feelings of pleasure and arousal directly resulting from exercise) has been shown to predict adherence to exercise regimens over time.[24–29] A 2015 systematic review found effect sizes ranging from r = .18 to r =.51 for the relationship between affective responses *during* exercise and future exercise.[30] Also, "incidental affect" (i.e., feelings of pleasure and arousal, *not* directly resulting from any specific behavior), has been shown to predict daily variation in physical activity levels.[31–38] The relationship between incidental affect and exercise is consistent with the "broaden-and-build theory of positive emotions," which postulates more positive feelings experienced throughout the day enable individuals to expand their bio-psycho-social resources and increase approach motivation for effortful tasks (e.g., exercise).[32,39–43] There is evidence that affective factors are amenable to influence by certain intervention strategies,[26,44] however, the data pertaining to affective determinants of physical

activity among cancer survivors are currently limited to only a few investigations.[33,45]

The ACSM Guidance for Prescribing Exercise Position Stand calls for additional research on the use of "affect-regulated" exercise prescriptions for physically inactive samples.[15,46] Prescribing affect-regulated exercise involves instructing individuals to *exercise at the highest pace that still feels good.*[46] The hedonic principle is the theoretical basis for this strategy: i.e., behavior that feels good is likely to be repeated.[29] This approach is in contrast to standard-of-care intensity-regulated exercise prescriptions that instructs individuals to regulate pace during exercise based on heart rate to achieve a relative exercise intensity (e.g., 64-76% of max heart rate).[15] Importantly, the affect-regulated prescription strategy is not simply a "hands-off" approach because studies have found that when physically inactive individuals are instructed to self-select their own pace of exercise, they do not prioritize feeling good by default.[47,48]

Why an affect-regulated exercise prescription? While some individuals experience positive shifts in affective response during moderate-vigorous physical activity, it is well documented that many people – especially those who tend to be the targets of exercise intervention programing (i.e., individuals who are more aerobically deconditioned, inactive, or overweight) – experience intensity-prescribed exercise as highly unpleasant.[27,48–50] Randomized studies have shown that compared to standard-of-care intensity-regulated prescriptions, affect- regulated prescriptions result in more pleasure during exercise (even when there is no statistically significant difference in actual intensity).[51–54] Furthermore, several independent research groups have shown that affect-regulated exercise prescriptions can produce health benefits equivalent to those achieved from intensity-regulated exercise prescriptions,[55] but with superior adherence rates over time[26,51] (thus increasing potential for long-term health benefits)[26,44,51] especially among those who are older[56] and the most aerobically deconditioned.[57]

An affect-regulated exercise prescription may be useful for promoting exercise to physically inactive breast cancer survivors for several reasons: Many breast cancer survivors are overweight or obese,[58–60] which increases the likelihood that exercise is experienced as unpleasant.[49] Further, peripheral neuropathy, a common chemotherapy-related adverse effect that can persist long after the conclusion of treatment,[61] is another factor that may contribute to worse affective experiences during exercise. Beyond these patient-level characteristics, research has shown that even small improvements in affective response during exercise can yield changes in exercise behavior that would be clinically meaningful for cancer survivors. Specifically, one recent study used ecological momentary assessment (EMA) methods to measure affective responses to exercise in-real-time as participants completed structured exercise over 6-months. Results showed that a 1-unit increase on the Feeling Scale[62] (e.g., moving from 0 = "neutral" to 1 = "fairly good"), resulted in approximately 90 extra minutes of moderate-vigorous physical activity one week later. Notably, a change of 90 extra exercise minutes per week would move a breast cancer survivor from 'completely sedentary' to 'meeting ACSM recommended guidelines for weekly exercise'.

3.0 Study Endpoints

Primary Outcomes:

1. **Acceptability of the affect-regulated exercise prescription measured using the Treatment Acceptability and Preferences (TAP) Measure.**

Description: A 4-item self-report questionnaire used to measure acceptability of the affect-regulated exercise prescription using a Likert scale ranging from 0 (not at all) to 4 (very much). Total scores range from 0 - 16. Higher scores indicate greater acceptability. *Time Frame:* 12-weeks follow-up assessment.

2. **Proportion of sample with valid accelerometer data at baseline.**

Description: The number of participants with valid accelerometer data out of the total number of participants in the sample at baseline. *Time Frame:* Baseline assessment

3. **Proportion of sample with valid accelerometer data at 2-weeks follow-up.**

Description: The number of participants with valid accelerometer data out of the total number of participants in the sample during the 2-week follow-up assessment. *Time Frame:* 2-weeks follow-up assessment

4. **Proportion of sample with valid accelerometer data at 6-weeks follow-up.**

Description: The number of participants with valid accelerometer data out of the total number of participants in the sample during the 6-week follow-up assessment. *Time Frame:* 6-weeks follow-up assessment

5. **Proportion of sample with valid accelerometer data at 12-weeks follow-up.**

Description: The number of participants with valid accelerometer data out of the total number of participants in the sample during the 12-week follow-up assessment. *Time Frame:* 12-weeks follow-up assessment

6. **Rate of ecological momentary assessment (EMA) survey prompt completion.**

Description: The number of Ecological momentary assessment (EMA) survey prompts completed by participants during the study out of the total number of EMA survey prompts delivered to participants. *Time Frame:* Baseline through 12-weeks follow-up assessments

7. **Acceptability of intervention content and study methods as measured via a semi-structured interview.**

Description: Semi-structured interview to assess participants perceptions regarding their experience participating in the study. *Time Frame:* 12-weeks follow-up assessments

Secondary Outcomes:

1. **Average minutes of daily moderate-vigorous physical activity measured using the ActiGraph wGT3X-BT accelerometer at 12 weeks follow-up.**

   Description: The research grade ActiGraph wGT3X-BT model is a valid measure of physical activity intensity and duration among multiple populations, including breast cancer survivors. Minutes of moderate-vigorous physical activity will be collected from the ActiGraph wGT3X-BT every day for 10-days. Average minutes of moderate-vigorous physical activity completed per day of valid wear time will be calculated. *Time Frame:* 12-weeks follow-up assessment

2. **Satisfaction with study participation as measured by the Participant Satisfaction Questionnaire.**

   Description: An 8-item self-report questionnaire used to assess participant satisfaction with study participation using a Likert scale ranging from 1 to 4. Scores are summed and then averaged; total scores range from 1- 4. Higher scores indicate greater satisfaction. *Time Frame:* 12-weeks follow-up assessment

3. **Study retention at 2-weeks follow-up.**

   Description: Number of participants who complete the 2-week follow-up assessment out of the number of participants who enroll in the study. *Time Frame:* 2-weeks follow-up assessment

4. **Study retention at 6-weeks follow-up.**

Description: Number of participants who complete the 6-week follow-up assessment out of the number of participants who enroll in the study. *Time Frame:* 6-weeks follow-up assessment

5. **Study retention at 12-weeks follow-up.**

Description: Number of participants who complete the 12-week follow-up assessment out of the number of participants who enroll in the study. *Time Frame:* 12-weeks follow-up assessment

Other Pre-specified Outcomes:

1. **Change overtime in cancer-related fatigue measured using the PROMIS Fatigue Short Form 8a**

Description: An 8-item self-report measure with response options 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. Total scores range from 8 - 40. Higher scores reflect more fatigue. *Time Frame:* Baseline and 12-weeks follow-up assessments.

2. **Change overtime in health-related quality of life measured using the PROMIS Global Health Scale**

Description: A 10-item self-report measure with response options ranging from 1 (poor/never/not at all) to 5 (excellent/completely/always) for items 1-9 and 0 (no pain) to 10 (worst pain imaginable) for the item 10. Total scores range from 9 - 45. Higher scores represent better health-related quality of life. *Time Frame:* Baseline and 12-weeks follow-up assessments.

3. **Change overtime in physical functioning measured using The PROMIS Physical Function Short Form 8a**

Description: An 8-item self-report measure with response options ranging from 1 (unable to do) to 5 (without any difficulty) and the degree to which health limits specific activities on a scale from 1 (cannot do) to 5 (not at all). Total scores range from 8 - 40. Higher scores reflect better physical function. *Time Frame:* Baseline and 12-weeks follow-up assessments.

4. **Average minutes of daily moderate-vigorous physical activity measured using The Godin Leisure-Time Exercise Questionnaire at 2 weeks follow up**

Description: The Godin Leisure-Time Exercise Questionnaire is a brief self-report measure that asks participants to report how many minutes they spent participating in moderate and vigorous physical activity on a given day. Participants will report total minutes of moderate-vigorous physical activity completed per day for 10-days. Average minutes of moderate-vigorous physical activity completed per day will be calculated. *Time Frame:* 2-weeks follow-up assessment.

5. **Average minutes of daily moderate-vigorous physical activity measured using The Godin Leisure-Time Exercise Questionnaire at 6 weeks follow up**

Description: The Godin Leisure-Time Exercise Questionnaire is a brief self-report measure that asks participants to report how many minutes they spent participating in moderate and vigorous physical activity on a given day. Participants will report total minutes of moderate-vigorous physical activity completed per day for 10-days. Average minutes of moderate-vigorous physical activity completed per day will be calculated. *Time Frame:* 6-weeks follow-up assessment.

6. **Average minutes of daily moderate-vigorous physical activity measured using The Godin Leisure-Time Exercise Questionnaire at 12 weeks follow up**

Description: The Godin Leisure-Time Exercise Questionnaire is a brief self-report measure that asks participants to report how many minutes they spent participating in moderate and vigorous physical

activity on a given day. Participants will report total minutes of moderate-vigorous physical activity completed per day for 10-days. Average minutes of moderate-vigorous physical activity completed per day will be calculated. *Time Frame:* 12-weeks follow-up assessment.

7. **Average minutes of daily moderate-vigorous physical activity measured using the ActiGraph wGT3X-BT accelerometer at 2 weeks follow-up**

Description: The research grade ActiGraph wGT3X-BT model is a valid measure of physical activity intensity and duration among multiple populations, including breast cancer survivors. Minutes of moderate-vigorous physical activity will be collected from the ActiGraph wGT3X-BT every day for 10-days. Average minutes of moderate-vigorous physical activity completed per day of valid wear time will be calculated. *Time Frame:* 2-weeks follow-up assessment.

8. **Average minutes of daily moderate-vigorous physical activity measured using the ActiGraph wGT3X-BT accelerometer at 6 weeks follow-up**

Description: The research grade ActiGraph wGT3X-BT model is a valid measure of physical activity intensity and duration among multiple populations, including breast cancer survivors. Minutes of moderate-vigorous physical activity will be collected from the ActiGraph wGT3X-BT every day for 10-days. Average minutes of moderate-vigorous physical activity completed per day of valid wear time will be calculated. *Time Frame:* 6-weeks follow-up assessment.

9. **Change in voluntary exercise behavior measured using The Voluntary Exercise Questionnaire**

Description: A 3-item self-report measure of exercise performed over the last month and week. Two items range from 1 (never) to 7 (often) and four items range from 0 (0 days per week) to 7 (7 days per week). Total scores range from 2-21. Higher scores reflect higher levels of voluntary exercise behavior. *Time Frame:* Baseline and 12-weeks follow-up assessments.

10. **Change in physical activity category completed in the past month measured using the Stanford Leisure-Time Activity Categorical Item (L-Cat)**

Description: A single item self-report measure that present six statements describing various levels of monthly physical activity. Response options range from 1 (I did not do much physical activity) to 5 (I did vigorous activities almost daily). Total scores range from 1-5. Higher scores reflect more vigorous, more frequent physical activities completed in the past month. *Time Frame:* Baseline and 12-weeks follow-up assessments.

11. **Change in intentions to engage in physical activity measured using The Exercise Intentions Scale**

Description: A 5-item self-report measure of intentions to engage in physical activity. Response options range from 1 (not at all likely) to 7 (very likely). Responses are summed and then averaged; total scores range from 1-7. Higher scores represent stronger intentions to engage in physical activity. *Time Frame:* Baseline and 12-weeks follow-up assessments.

12. **Change in self-efficacy for exercise measured using The Barriers Specific Self-Efficacy for Exercise Scale**

Description: A 13-item self-report measure of one's perceived capability to exercise regularly despite commonly identified barriers to participation. Response options range from 0 (not at all confident) to 100 (highly confident). Responses are summed and then averaged; total scores range from 0% - 100%, higher scores represent greater self-efficacy for exercise. *Time Frame:* Baseline and 12-weeks follow-up assessments.

13. **Change in intrinsic motivation for exercise measured using The Behavioral Regulations in Exercise Questionnaire (BREQ-2)**

Description: A 4-item self-report scale depicting intrinsic motivation for exercise. Response options range from 0 (not true for me) to 4 (very true for me). Responses are summed and then averaged; total scores range from 0-4. Higher scores indicate greater intrinsic motivation for exercise. *Time Frame:* Baseline and 12-weeks follow-up assessments.

14. **Change in affective attitudes about exercise using The Instrumental and Affective Attitudes about Exercise Scale**

Description: A 4-item self-report measure of affective attitudes for exercise. Response options range from -5 to 5. Responses are summed and then averaged; total scores range from -5 to 5. Higher scores more favorable affective attitudes about exercise. *Time Frame:* Baseline and 12-weeks follow-up assessments.

15. **Change in instrumental attitudes about exercise using The Instrumental and Affective Attitudes about Exercise Scale**

Description: A 4-item self-report measure of instrumental attitudes for exercise. Response options range from -5 to 5. Responses are summed and then averaged; total scores range from -5 to 5. Higher scores more favorable instrumental attitudes about exercise. *Time Frame:* Baseline and 12-weeks follow-up assessments.

4.0 Study Intervention

Core Exercise Promotion Intervention

Intervention type: Behavioral

Intervention description: The core exercise promotion intervention is intentionally designed to be minimal and reflective of exercise promotion conversations that might occur between oncology care team providers and breast cancer survivors during survivorship planning visits. During the Tele-Visit 1, all participants will be given the goal of increasing weekly time spent exercising to ≥90 minutes, consistent with recommended guidelines.[2,9] Exercise will be defined as "activities that use large muscle groups, increase heart rate and breathing rate, and are performed intentionally for the purpose of exercise (as opposed to physical activities of daily living, e.g., housework)."[15,86] Safety guidelines will be discussed as well as strategies for overcoming potential barriers to exercise. Participants will not be instructed to perform specific forms of exercise, however, brisk walking for exercise will be encouraged because it does not require extra burdens of expense (e.g., the need for a gym membership) or equipment. Further, brisk walking is a moderate-intensity activity that is safe for most individuals without contraindications for exercise to perform. All participants will be given a wearable activity tracker (Fitbit). Providing participants a Fitbit watch arguably extends beyond standard-of-care procedures, but activity monitors are now ubiquitous,[87,88] and some health insurance plans provide activity monitors as rebate incentives; therefore, this choice does not drastically depart from standard-of-care consistent.

Affect-regulated exercise prescription (Affect-Rx).

Intervention type: Behavioral

Intervention description: Consistent with past research employing the affect-regulated exercise prescription strategy, participants assigned to Affect-Rx will receive instructions to adjust their pace of exercise so that they feel "fairly good" or better (i.e., a rating of +1 or higher on the Feeling Scale) while exercising and to avoid any increases in pace that result in feeling "fairly bad" or worse (i.e., a rating of -

1 or lower on the Feeling Scale). If no pace of exercise feels at least "fairly good" participants will be told to change their pace so that they feel "as positive as possible." We expect most participants will be able to achieve a pace that feels at least "fairly good" (+1) as recent studies have shown that, on average, participants receiving these instructions for regulating affect during exercise report feeling between a +2 and +3 ("good") on the Feeling Scale.

5.0 Procedures Involved

Study Design Overview: Physically inactive breast cancer survivors be recruited to participate in a pilot study promoting adherence to recommended weekly physical activity guidelines for breast cancer survivors. All participants will receive a core exercise promotion intervention and their daily activity levels and feeling states (affect) will be measured using EMA and accelerometry over a 12-week period with measurement burst assessment at baseline and 2-, 6-, and 12-weeks follow- up.

Study 1. *N* = 30 participants will receive the core exercise promotion intervention plus an affect-regulated exercise prescription (Affect-Rx) in this single-arm pilot. The ORBIT model recommends patient stakeholders be involved in the development of interventions intended to serve them as early as possible in the translational process;[1,63,64] thus, this study will be used to modify and refine the intervention protocol and study assessment schedule to be acceptable to the target population of physically inactive, stage 0-III breast cancer survivors.

Overview of Study Procedures:

Delivery Modality: All study procedures following enrollment will take place remotely to reduce participant travel burden as the Dartmouth Cancer Center serves a geographically large rural area. Accelerometer devices will be mailed to participants with return postage included, consistent with past work.[26,32,78,89]

Study Enrollment: Individuals who express interest in participating will meet with a member of the study team in-clinic or via videoconferencing, e.g., Zoom, (or by phone if necessary) to complete additional eligibility screening. If appropriate, informed consent procedures will be initiated. After participants provide their informed consent to participate, they will receive instructions for wearing the accelerometer device and installing the app that will be used to collect EMA data. Additionally, participants will be asked to complete the T1 (Baseline) survey, administered using REDCap.

Tele-Visit 1: Eligible participants will be contacted using videoconferencing services (e.g., Zoom) to complete the Tele-Visit 1 procedures, which include delivery of the core exercise promotion intervention and 12-week exercise prescription and is expected to take approximately 45 minutes to complete. Based on individual circumstances, this visit may also be completed by phone.

Follow-Up Assessments, Weeks 2, 6, and 12: Accelerometry and EMA assessments will be collected over 10-day periods at weeks 2, 6, and 12. To enhance compliance with study procedures, a member of the study team will give participants a phone call and/or send an email before participants' data collection periods are set to begin (at each time point). Additionally, a "check-in" email will be sent on day 2 or 3 of the 10-day data collection to inquire about any potential difficulties the participant may be experiencing following study instructions. EMA response completion rates will be monitored and participants will be called if they do not complete any EMA prompts in a 24-hour period during one of their data collection days.

Tele-Visit 2: At the end of the 12-week study period, participants will be emailed a secure link to complete the T2 (Follow-up) REDCap survey. Next, participants will be contacted to complete the Tele-Visit 2 procedures, which involve exit interviews and participant debreifing, to be completed over

videoconferencing or telephone.

How research material will be obtained and source materials: The information collected for this study will only be used for the study as described. This will be made clear during the consent process and included in all written consent forms. Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Any identifiable participant information will be secured behind the D-H firewall on password-protected computers and servers. All participants enrolling will be entered into the OnCore software system for Clinical Trials, which is Dartmouth-Hitchcock's clinical trial monitoring software in real-time (i.e., once the participant is consented, they will subsequently be entered).

Clinical characteristics and variables will be collected by medical record extraction (breast cancer stage, prior treatment, and other co-morbidities). Questionnaire and demographic data will be collected using REDCap, a research data collection platform. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: a) an intuitive interface for validated data entry; b) audit trails for tracking data manipulation and export procedures; c) automated export procedures for seamless data downloads to common statistical packages; and d) procedures for importing data from external sources.

Ecological momentary assessment (EMA) data will be collected using LifeData software via the RealLife Exp mobile app (Android and iOS compatible). This app will be installed on participants personal cell phones at the time of study enrollment. Once installed, the RealLife app will deliver daily EMAs over 10-day periods during the baseline, 2-, 6-, and 12-week follow-up assessments, concurrent with accelerometry data collection procedures.[73,78] This EMA collection schedule was found to be acceptable to a sample of breast cancer survivors in a recent study.[78] Daily EMAs will include: a morning report, within 2 hours of a participant's stated wake time, and 2 additional prompts during the afternoon and evening.

Consistent with procedures established in the research team's prior work, participants will be expressly instructed to use the RealLife mobile app to indicate when they start an exercise session.[26,91] The RealLife mobile app will prompt participants to complete ratings of affective response to exercise at the start, during, and end of exercise. Specifically, once participants indicate that they have started their exercise session, the app will send alerts to report on three variables [affective valence, measured via the Feeling Scale (FS), affective arousal, measured via the Felt Arousal Scale (FAS), and perceived exertion, measured via the Ratings of Perceived Exertion scale (RPE), every 5-minutes up until 30 minutes]. After 30 minutes, the app will send alerts to report on these three measures every 10 minutes. Participants will indicate when they have ended their exercise session and the app will send an alert to report on FS/FAS/RPE 10 minutes after the end of exercise is reported.

Exercise behavior will be measured in terms of minutes of moderate-vigorous physical activity measured by the ActiGraph wGT3X-BT accelerometer. Participants will be instructed to wear the research-grade ActiGraph accelerometer wGT3X-BT (ActiGraph, LLC) on their non-dominant hip during all waking hours, except when bathing or swimming, for 10 consecutive days during data collection periods at baseline and 2-, 6-, and 12-weeks follow-up. The research grade ActiGraph wGT3X-BT model is a valid measure of physical activity intensity and duration among multiple populations, including breast cancer survivors.[92,93]

Participants will further be asked to record all periods of accelerometer non-wear time in a paper log and to describe reasons for non-wear (e.g., swimming, illness, etc.). If the accelerometer was not worn during times when they performed physical activity, participants will be asked to specify (in both the paper log and on the daily EMA assessments) what the activity was (e.g., swimming laps), the level of

effort (e.g., light, moderate, vigorous), and how long the activity was performed in minutes.

Semi-structured exit-interviews will be conducted with participants by the Study PI or Research Assistant during the Tele-Visit 2 appointment. Data regarding participants' perceptions of intervention methods and study content acceptability will be measured using the Treatment Acceptability and Preferences Measure[77] during the Tele-Visit 2 appointment.

6.0 Data and Specimen Banking

In accordance with DHH IRB policy, we will maintain our study records, including signed and dated consent documents that include HIPAA authorizations for at least six years after completion of the research.

7.0 Sharing of Results with Subjects

A plain language summary of the study results will be sent to participants at the conclusion of all data collection and cleaning. This plain language summary will be sent via email to the email contact participants provided to the study team for communication purposes. Participants will be informed that the study and the study results will be posted on ClinicalTrials.gov. The PI (Stevens) will be responsible for submitting the information to ClinicalTrials.gov. Additionally, the data generated by this research will be submitted to peer-reviewed journals. NIH policy requires final peer-reviewed journal manuscripts that arise from NIH funds to be submitted to PubMed Central immediately upon acceptance for publication; PubMed Central is a free digital repository that archives open access full-text scholarly articles that have been published in biomedical and life sciences journals.

8.0 Study Timelines

Subject Participation Duration: 13 total weeks, this includes the 10-day baseline assessment that occurs after enrollment, but prior to the start of the 12-week intervention period.

9.0 Subject Population*

Study Population (Studies 1 and 2): According to the ORBIT Model, for early-phase studies in the refinement and proof-of-concept stages, "the sample can be selected from accessible subjects, rather than be representative, because this initial test will determine only whether the treatment merits more rigorous testing" (pg. 977).[1] Therefore, eligibility criteria will be kept intentionally broad. Participants will be physically inactive, stage 0-III breast cancer survivors within 5-yrs of completing primary cancer treatment (surgery, chemotherapy, and radiation) for Stage 0-III breast cancer. Physical inactivity status will be defined as <60 minutes of structured moderate-vigorous intensity physical activity per week, with no changes for the past 6-months.[9,94]

This research is focused on increasing exercise engagement among adult breast cancer survivors; therefore, only survivors ≥18 years will be included. Current ACSM guidelines recommend the same weekly volume of exercise for older adults as adults under age 65,[86,95] therefore, an upper limit on age eligibility will not be imposed. In support of this decision, recent research suggests that age may moderate the effect of the affect-regulated exercise prescription strategy on exercise engagement such that older adults (those >50 years old) benefit more (have a greater increase in exercise engagement) than younger adults.[56] Further, exercise during cancer survivorship is expected to yield health benefits for both sexes,[2,9,96] and therefore, exclusion criteria based on sex will not be imposed. However, the

Cancer Center at Dartmouth treats, on average, fewer than 4 male breast cancer patients annually, thus, likelihood of male representation in the study sample is low.

Inclusion Criteria:

- ≥18 years old
- Within 5 years of completing primary cancer treatment (surgery, chemotherapy, and radiation) for Stage 0-III breast cancer
- <60 mins/week moderate-vigorous physical activity (MVPA) with no major changes for the past 6- months
- Own an Android or iPhone smartphone and willing to use the smartphone to complete app-based surveys during assessment periods
- Willing to wear the ActiGraph monitor during assessment periods
- Access to internet to complete REDCap survey assessments

Exclusion Criteria:

- Non-English speaking/not able to read English
- Evidence of major contraindications for exercise (informed by the 2020 Physical Activity Readiness-Questionnaire (PAR-Q)+)[112]
- Currently pregnant
- History of severe mental illness or currently taking mood stabilizing medications (antipsychotics, anticonvulsants, or lithium)
- Evidence of moderate-severe depressive symptoms (indicated by a score≥ 10 on the Patient Health Questionnaire-8)[114]
- Evidence of moderate-severe cognitive impairment (indicated by a score < 3 on a 6-item cognitive screener)[113]
- Evidence of clinically significant substance use as indicated by a scoreof ≥ 2 on the CAGE-AID screener.[128, 129]

10.0 Vulnerable Populations

No involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals or others who may be considered vulnerable, will be included in this research.

11.0 Local Number of Subjects

Based on the PI's experience conducting exercise intervention studies, we conservatively estimate a 30% rate of attrition.[97] Thus, in order to ensure we hit our target of *N* = 20 intervention completers, recruitment will continue until *N* = 30 participants provide informed consent to participate in the intervention portion of the study (see Consent Form Part 2).

12.0 Recruitment Methods

The research team has established a successful process by which study team members collaborate with DH clinicians to identify eligible patients each week. The PI (Stevens) will apply for a Health Insurance Portability and Accountability Act (HIPAA) waiver to allow members of the study team to screen clinic schedules to identify potential study participants. Medical oncology members of the research team may also independently identify potential participants for the study team to contact. The PI and/or a study coordinator will consult with clinicians to confirm eligibility based upon clinical characteristics. If a patient appears to be eligible per initial review of stage and treatment regimen, a study coordinator will ask the provider to mention the study/provide a recruitment flyer/letter from the patient's care team

and obtain permission for the study team to contact her in clinic, by phone, or by postal mail in order to explain the study, determine eligibility, and initiate informed consent procedures.

Strategies to minimize bias in sampling: Eligibility criteria will be clearly defined so that the sample is not biased by relying on clinicians' determinations of a given patient's "appropriateness" or need for the study. Remote delivery of all study intervention and data collection procedures along with flexible staffing (i.e., the PI and/or Research Assistant available during early evening hours) will help address barriers to participation that may be experienced by participants who do not live locally and/or individuals with clinic appointments outside of regular business hours.

Procedures to monitor enrollment and track and retain participants: The Research Assistant will prepare weekly enrollment reports that will be reviewed at weekly meetings with the PI. The reports will summarize the number of individuals identified, screened, and enrolled. The Research Assistant will work with the recruiters to elicit and summarize any patient feedback and bring it to the PI to discuss with the research team and determine if adjustments to recruitment procedures or materials are warranted. Should attrition rates be higher than expected, the research team will strategize alternative retention strategies (e.g., higher participant compensation incentives, reduced assessment burden).

Participant Incentives: Participant payments will be provided at a rate of $20 for completing each of the REDCap surveys (i.e., T1 REDCap survey and T2 REDCap survey). Additionally, participants will be compensated $1 for each of the morning report and random EMA prompts completed during the 10-day assessment periods at baseline, 2-, 6-, and 12-weeks follow-up; thus, a total of $120 can be earned for completing EMA assessments ($1 X 3 EMA prompts/day X 10 days X 4 data collection periods). (Note, participants will not be paid for completing the during exercise EMAs reports to avoid encouraging over-reporting of exercise).[89] Each participant, can earn a total of $160* for completing all study assessments.

At the Tele- Visit 1 appointment, participants will also be given a Fitbit activity tracker (to keep) as compensation for their participation and to encourage behavioral self-monitoring as part of the core exercise intervention. If participants decide to terminate their participation in the study early (before the week 12 follow-up assessment), we will ask that they return the Fitbit monitor given to them at the Tele- Visit 1 appointment. In this case, we would provide them a pre-paid envelope and ask they follow instructions to mail the Fitbit back at their earliest convenience. This will be explained to participants during the consent process.

13.0 Withdrawal of Subjects

Participants will be withdrawn from the study at their request. The research team will continue attempts 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 14 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. Participants may be withdrawn from the research without their consent if they experience any medical events (after enrollment) that would make it unsafe for them to continue participation in an unsupervised exercise intervention (e.g., myocardial infarction).

14.0 Risks to Subjects

The study intervention procedures and assessments are not invasive and do not involve pharmacological agents, thus, we anticipate that there will be a low risk of adverse events associated with participation in the proposed research. Potential risks involved with participation include:

i. Breach of Confidentiality
ii. Exercise-Related Injury or Discomfort
iii. Risk of Distress

Breach of Confidentiality: To address potential loss of confidentiality, study ID numbers will be used on all study documents, in place of personally identifying information, and all electronic data will be saved on a server protected by the Dartmouth Cancer Center's firewall.

Exercise-Related Injury or Discomfort: Regarding risks related to exercise, the study Control intervention (intensity-regulated exercise prescription) reflects the current standard for prescribing exercise during cancer survivorship and the experimental Affect-Rx intervention (affect-regulated exercise prescription) *explicitly instructs participants to avoid experiences of discomfort/displeasure during exercise*. Participants will be provided their assigned exercise prescription and encouraged to increase their weekly activity levels to be commensurate with recommended guidelines, but the study will not expose participants to in-person exercise sessions or classes, and participants will not be required to use any exercise-related equipment. Therefore, the study does not expose participants to additional risks related to exercise. However, there is always some inherent risk of injury when engaging in exercise (e.g., a participant could fall while walking). To manage this risk, participants will be informed of both the risks and benefits of exercise. Further, study inclusion criteria (i.e., medical clearance for exercise) are designed to identify and exclude patients for whom exercise will be unsafe.

Risk of Distress: It is not anticipated that participants are likely to experience distress in response to the nature of the assessments collected for this research; however, it is conceivable that completing some survey measures or reflecting on one's behavioral patterns could elicit distress or cause participants to feel uncomfortable. The PI is a licensed clinical psychologist and is trained to validate feelings of frustration and distress while re-directing participants to actionable ways of making immediate progress. Likewise, the Research Assistant will be trained to listen for signals of distress (e.g., long pauses, crying) and respond tactfully (e.g., do not indicate verbally or non-verbally that they are uncomfortable with participant distress) and to remind the participants participation is voluntary and assessments can be paused or returned to a later time if needed.

15.0 Potential Benefits to Subjects

Participants will not be promised benefits as a result of their participation in the proposed research. However, all participants will receive a core exercise intervention designed to promote exercise engagement consistent with recommended guidelines. Thus, all participants may benefit by learning about recommended guidelines for exercise during cancer survivorship and meeting with the study team to discuss goals and plans for increasing their exercise behavior. Participants may also notice a reduction in cancer-related adverse effects (e.g., fatigue) or improvements in physical functioning and/or health-related quality of life as a result of increasing their exercise behavior. The risks of the study are minimal to individuals in relation to the potential benefits they may receive from increased exercise participation.

16.0 Statistical Analysis Plan

Analysis Plan & Power Analysis : There are no definitive guidelines for determining the size of a pilot study in healthcare research,[98] and, according to guidelines provided by ORBIT, for this early phase of intervention development, *"The sample size can be small because clinical, not statistical, benefit is sought and sample size calculations are unnecessary"* (pg. 977).[1] Nevertheless, our target sample size of

N = 20 intervention completers is consistent with typical sample size targets used in similar early-phase open pilot studies.[99]

Aim 1 (ORBIT Phase Ib). To modify and refine the Affect-Rx exercise prescription and study protocol to be acceptable for use with breast cancer survivors. Modifications and refinements will be informed by semi-structured participant interviews and objective indicators of acceptability assessed using the Treatment Acceptability and Preferences (TAP) Measure,[67] accelerometer wear-time, and daily EMA survey completion.

Analysis of Aim 1 Quantitative Data: Responses to the Treatment Acceptability and Preferences TAP Measure[77] will be scored, distributions will be examined, and data will be assessed for completeness. Rates of accelerometer wear-time compliance and daily ecological momentary assessment (EMA) completion will similarly be examined for completeness and described as percentages and proportions.

Analysis of Aim 1 Qualitative Data: Qualitative data will be transcribed and analyzed in accordance with guidelines specified by NIH-Best Practices for Qualitative Research in the Health Sciences[101] for applicability, preferences, clinical relevance, intervention length/timing, and challenges. Coding and categorizing the data will be followed by comparing and contrasting categories to identify overarching themes and similarities and dissimilarities among patients' experiences and perspectives. The evolving analysis will be tracked using memos and shared during regular study team meetings to enhance rigor and develop the findings and interpretations.

Analysis Plan for Exploratory Outcomes: Patient reported outcome measures[2,9] collected on the T1 and T2 REDCap surveys will be scored and distributions will be examined and assessed for completeness. Pre/post intervention change on these measures will be evaluated using t-tests and ANCOVA tests, when appropriate, to control for covariates. These analyses are for exploratory purposes to inform effect size estimates for a future fully-powered efficacy trial.

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Overall Framework for Data and Safety Monitoring and Information to Be Monitored: All study data will be kept confidential during all study phases. A password-protected dataset will cross-reference study ID numbers and study data. The HIPAA-compliant Citrix Sharefile cloud- based platform will serve as backup and storage of files and data. The Dartmouth-Hitchcock electronic medical record system (EPIC) and REDCap platform are backed up daily. Integrity and privacy of data entered into an electronic database will be achieved using industry-standard encryption and a granular security permission scheme down to information at the individual level. Data safety will be ensured by redundant server hardware deployment and database backups. Several levels of password protection will be implemented and passwords will be changed regularly. Transcripts from exit interviews will be digitally recorded and transcribed. Any data-related paper records will be kept in a locked filing cabinet. In order to ensure fidelity to the study protocol and integrity of data, the following procedures will be implemented: a) frequent meetings between the PI and Co-Investigators to troubleshoot recruitment and data collection issues, b) use of data entry software (i.e., REDCap) that provides entry validation range tests and is designed to minimize missing data by flagging missed items before surveys are submitted, c) weekly monitoring of the completeness of data collected from the LifeData mobile app, d) accelerometer data download and back up upon return by mail.

This research involves no more than minimal risk to participants. Nevertheless, we have carefully thought through our procedures for monitoring the data to ensure the safety of participants. In order to ensure participant safety, data integrity, and validity, the PI (Stevens) will be responsible for reviewing the following information on a monthly basis: number of participants completing the protocol; subject

withdrawal and sources of data loss; any serious or minor adverse consequences and actions taken to remedy the issue; new, timely information that could impact efficacy and/or safety of the program or procedures. The PI will assure that informed consent is obtained prior to performing any research procedures, that all participants meet eligibility criteria, and that the study is conducted according to the IRB-approved research protocol.

Reporting of Adverse Events: All members of the study team will be trained to report all adverse events. In addition, screening for adverse events potentially related to the study procedures will occur during the routine administration of study assessment measures. The course of each adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. The PI will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum, events that will be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

Significant Adverse Events: If a significant adverse event occurs, the PI will report the event to the Cancer Center's CCRC and Dartmouth-Hitchcock IRB using the online reporting system and the team will follow institutional protocols with respect to reporting within 14 days of the PI's knowledge of the significant adverse event. The PI, in consultation with study co-investigators, will review the adverse event report and gather other information as needed to investigate the event and determine the need for subsequent action. Any subsequent action will be documented and reported to the IRB. The IRB will review each reported adverse event to determine whether: the participants in the study should receive additional information related to continuing their participation; the protocol, study plan or consent form should be modified; or the study should be temporarily suspended. If the IRB determines that some action in response to the adverse event is necessary, the IRB will promptly inform the PI. All deaths will bereported in an expedited manner within 24 hours of the PI's knowledge. The report of death will be submitted to the NIH Program Officer, Dartmouth-Hitchcock IRB, and DSMAC Chair.

Post-study adverse event: All unresolved adverse events will be followed by the PI until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the PI will instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. Serious adverse events that are still ongoing at the end of the study period will 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 intervention or study participation will be recorded and reported immediately.

Stopping Rules: Significant risk is not anticipated in this study due to the supportive and non- invasive nature of the intervention. However, the PI will summarize adverse event data annually to the DSMAC for consideration of study continuation. Interim analyses will only be conducted as requested by the DSMAC. The trial will be stopped only should there be IRB-related issues pertaining to unexpected safety risks.

18.0 Provisions to Protect the Privacy Interests of Subjects

Study ID numbers will be used in place of all personally identifying information on all study documents. All members of the study team, PI (Stevens), Research Assistant, and any other volunteer research assistants subsequently added to the IRB study protocol (e.g., students, trainees), will complete the Human Subject's Protection Training required by the Dartmouth-Hitchcock Institutional Review Board.

All members of the study team will abide by HIPAA policies and possess full comprehension of privacy rules. All members of the research team who interact with participants for this research will be trained to listen for and respond to signals of distress. Further, participants will be reminded (continuously) that their participation is voluntary, and assessments can be paused or returned to a later time if needed.

All study data will be kept confidential during all study phases. To facilitate recruitment, the PI (Stevens) will apply for a Health Insurance Portability and Accountability Act (HIPAA) waiver to access medical records of breast cancer survivors to provisionally determine eligibility prior to recruitment. We will maintain the name and medical record number of patients who decline to enroll so that we do not continue to approach them about the study on subsequent appointments at the Dartmouth Cancer Center, but the datafile will be password protected and names and medical record numbers will be deleted once active recruitment to the study is closed. Only members of the study team will be permitted to access identifiable participant data and only for the purpose of contacting participants to complete follow-up assessments and/or to respond to unanticipated problems or adverse events.

19.0 Compensation for Research-Related Injury

Not applicable. This research involves no more than minimal risk to participants.

20.0 Economic Burden to Subjects

There are no anticipated costs associated with participation in this research for participants.

21.0 Consent Process

The consent process will follow procedures in accordance with "*SOP: Informed Consent Process for Research (HRP-090)*." The study team will collaborate with clinical providers at the Dartmouth Cancer Center to identify potentially eligible participants on the clinic schedule through medical record chart review. Individuals who express interest in participating will be contacted by the study PI or Research Assistant in-clinic or by phone, whichever is preferred by the participant, to complete additional eligibility screening; if appropriate, informed consent procedures will be initiated. When the informed consent discussion is initiated by telephone, we will use DHH-approved document signing software (e.g., DocuSign) to obtain an electronic signature and written documentation of consent.

Study team members who perform the informed consent discussion for this study will have appropriate education, expertise, and background to understand and relay the concepts in the study and answer questions from potential participants. The PI and Research Assistant will have documented protocol specific training, so they are familiar with the research project.

Written consent will be obtained after the protocol has been fully explained and all questions have been answered. The teach-back method of evaluating comprehension will be used: Participants will be asked to describe in their own words the key aspects of study participation. There will be ongoing evaluation of consent at each study interactiron (i.e., re-confirm what steps happen next, solicit questions, and remind participants that their participation is voluntary).

22.0 Process to Document Consent in Writing

This research will follow *"SOP: Written Documentation of Consent (HRP-091)."* Informed consent will be collected at two points in time for this study: At the time participants initially enroll in the study, they are provisionally eligible for the intervention portion of the study pending verification of physical

inactivity status, which occurs during week 1. Thus, informed consent will be collected at two points in time: once prior to completing the week 1 physical inactivity verification period (see Consent Form Part 1) and again prior to completing the Tele-Visit 1 appointment (see Consent Form Part 2).