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Study Protocol for a Randomized Controlled Feasibility Trial of a Virtual Intervention (STRIDE) for Symptom Management, Distress, and Adherence to Adjuvant Endocrine Therapy after Breast Cancer

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ABSTRACT

Introduction: Patient adherence to adjuvant endocrine therapy (AET) after a diagnosis of hormone-sensitive breast cancer is poor. Previous interventions have failed to produce changes in adherence, address patient preferences, or include theoretically informed and evidence-based components. Therefore, we iteratively developed a patient-centered, evidence-based, small-group, videoconference intervention to improve adherence and symptom management as well as reduce distress for patients taking AET after breast cancer (STRIDE).

Methods and Analysis: The current study is a non-blinded, randomized, controlled, feasibility trial of STRIDE compared to a medication monitoring control group. The primary objective is to examine the feasibility and acceptability of STRIDE, while secondary objectives are to assess changes in objective and subjective adherence, symptom distress, and satisfaction with AET. Patients will be recruited from the Massachusetts General Hospital Cancer Center in Boston, Massachusetts. The total number of patients accrued will be 75, with ≥60 patients completing the study. All patients will store their AET in an electronic pill bottle for objective adherence monitoring. Patients randomly assigned to the STRIDE intervention will receive six weekly one-hour sessions, in small groups of two, delivered via videoconferencing by a trained mental health professional. Patients assigned to the control group will store their medication in the electronic pill bottle and receive follow-up oncology care as usual. All participants will complete self-report psychosocial measures at baseline, 12 weeks, and 24 weeks post-baseline.

Ethics and Dissemination: The study is funded by the National Cancer Institute of the National Institutes of Health and is approved by the Dana-Farber/Harvard Cancer Center Institutional

Review Board (Protocol #18-603, version 1.2, first approval date 2/1/2019). The study will be reported in accordance with the Consolidated Standards of Reporting Trials statement for non-pharmacological trials. Results will be published in peer-reviewed academic journals, presented at scientific meetings, and disseminated to patient organizations and media outlets.

Trial Registration Number: Clinicaltrials.gov: NCT03837496; pre-results.

Keywords: adjuvant endocrine therapy, hormonal therapy, breast cancer, symptom management, adherence, distress, cognitive-behavioral intervention

Strengths and limitations of this study:

- This study employs a patient-centered, evidence-based, virtual videoconference intervention to improve adherence, enhance symptom management, and reduce distress for patients taking AET after breast cancer.
- Given the lack of efficacious interventions to date, this study design and intervention were informed by in-depth qualitative analysis and iterative intervention development to maximize patient-centeredness, feasibility, acceptability, and efficacy.
- To maximize scalability and dissemination, patients participate virtually for all study procedures including consent, intervention, and assessments; therefore, no hospital or in-person visits are necessary.
- The homogenous sample with respect to sociodemographic diversity will limit generalizability of the findings.

INTRODUCTION

Up to 75% of female patients diagnosed with early-stage breast cancer will require adjuvant endocrine therapy (AET) to prevent the likelihood of recurrence and improve survival.[1] AET (e.g., tamoxifen or an aromatase inhibitor) reduces recurrence and mortality by approximately 30 to 50%, for hormone receptor-positive breast cancer.[2,3] Despite the substantial, indisputable benefit, half of women are non-adherent (i.e., do not take the medication as prescribed) within five years of initiating AET.[4] In addition to greater risk of breast cancer recurrence[5,6] and breast cancer mortality,[7] non-adherence to AET is associated with higher rates of physician visits, hospitalizations,[8] and poorer patient-provider relationships.[9]

Several factors are known to contribute to suboptimal adherence for patients taking AET,[5,7,10] including substantial side effects (e.g., joint pain, hot flashes, sleep difficulties),[11-13] psychological distress during survivorship,[11] low perceived need for AET,[14] low self-efficacy for taking medication,[8] negative beliefs about AET and related side effects,[15] and low social support.[16] While several of these contributors are modifiable, patients receive virtually no formal support to promote medication-taking after breast cancer. Only four randomized controlled trials (RCTs) to date have investigated psychosocial interventions to promote AET adherence,[17] and they have failed to address the adherence challenges that patients face. Previous studies neglected to include theoretically-driven and empirically-based intervention components to target behavioral drivers of adherence, were not developed using guiding principles of behavioral intervention development,[18,19] have been methodologically flawed, and were not informed by patient preferences.

To address the significant need to optimize AET adherence, improve self-management of side effects, and reduce distress for patients taking AET, we iteratively developed a patient-

centered, small-group, evidence-based, videoconference intervention: STRIDE (**S**ymptom-**T**argeted **R**andomized **I**ntervention for **D**istress and Adherence to Adjuvant **E**ndocrine Therapy). Intervention development was informed by a comprehensive systematic literature review,[17] a qualitative in-depth analysis of patient experiences and preferences,[20] prior efficacious treatments,[21,22] and expert feedback from oncology clinicians and behavioral scientists. We then modified intervention content and duration, logistics, and study procedures using quantitative and qualitative feedback from exit interviews with five patients who participated in a run-in phase of the intervention. Patients were enthusiastic about the STRIDE intervention, described it as beneficial, preferred the group setting, and noted that the virtual delivery was a necessary convenience.

The current report outlines the details of the RCT that is currently underway comparing the finalized STRIDE intervention to a medication monitoring control condition. The primary objective is to establish the feasibility and acceptability of the STRIDE intervention compared to the medication monitoring control group. The secondary aims are to assess the effects of the intervention on objective and self-reported AET adherence, symptom distress, and satisfaction with AET. Finally, we will explore group differences on additional self-reported psychosocial constructs and examine potential mediators and moderators of any treatment outcomes.

METHODS AND ANALYSIS

Study Design

This is a single site, randomized, controlled, pilot feasibility study comparing a videoconference intervention (STRIDE) to standard care plus medication monitoring in 75 patients taking AET after breast cancer. Recruitment will occur at the Massachusetts General Hospital (MGH) Boston and three MGH community affiliates: MGH Newton-Wellesley, MGH

North Shore, and MGH Waltham. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is illustrated in Figure 1. The study is approved by the Dana Farber/Harvard Cancer Center's (DF/HCC) Institutional Review Board (Clinicaltrials.gov: NCT03837496).

Participant selection

To be eligible, patients must be female, be age 21 or older, have a diagnosis of early-stage (stage 0-IIIb), have hormone receptor-positive breast cancer, have completed primary treatment (i.e., chemotherapy, surgery, and/or radiation) for breast cancer, be within 1 week – 36 months of starting AET, be able to read and respond in English, and have an Eastern Cooperative Oncology Group performance status ≤ 2 (See Table 1). Patients will complete a 3-item distress screening using an adapted National Comprehensive Cancer Network (NCCN) Distress Thermometer (range = 0-10).[23] Those who report distress ≥ 4 on any of the three items will be eligible to participate (i.e., distress related to having to take AET, distress related to symptoms/side effects, and/or distress related to AET adherence). To ensure engagement and compliance with study procedures, patients with cognitive impairment, uncontrolled psychosis, active suicidal ideation, or a psychiatric hospitalization within the past year will not be eligible. In addition, exclusion criteria include enrollment in a clinical trial for breast cancer (due to additional medication monitoring), participation in another psychosocial intervention study, or current engagement in formal group psychotherapy.

Study Procedures

Trained study staff will review the electronic health record (EHR) to identify potentially eligible patients with upcoming appointments at the MGH Center for Breast Cancer or one of the MGH community affiliates. For those identified patients, study staff will then request permission from the respective oncology clinicians to approach the patients about study participation. After

receiving approval from the oncology clinicians, study staff will approach patients during their outpatient appointment to explain study procedures and gauge their interest in participating. Given the heavy volume of patients in the breast clinic on any given day, study staff can also contact patients by telephone if they are not able to approach them in person. Patients can also self-refer through advertisements on the online MGH study recruitment site or via posted flyers in the clinic. Finally, the oncology clinician or nurse practitioner can also directly refer interested patients.

Eligible patients approached in person will complete written informed consent with trained study staff, and those approached by telephone will complete electronic informed consent with trained study staff. Enrolled patients will complete a one-week baseline period during which they will use the Medication Event Monitoring System (MEMS Caps),[24] to electronically monitor medication-taking, as well as complete baseline self-report study questionnaires. Following one week of medication monitoring, study staff will randomly allocate patients 1:1 to either the STRIDE intervention or the medication monitoring control group via a computer-generated randomization scheme created by the study biostatistician; group allocation will be concealed for each patient until randomization occurs. Randomization will be stratified according to level of distress, determined by baseline scores on the Hospital Anxiety and Depression Scale (HADS),[25] (high distress ≥ 8; low distress <8). Patients will complete the same self-report measures at 12-week and 24-week follow-ups. Assessments will be conducted using mailed paper questionnaires or electronically via Research Electronic Data Capture (REDCap), a HIPAA compliant, web-based survey tool.[26] Given the virtual nature of the assessments and intervention sessions, patients will not need to travel to the hospital for any study-related visits and will receive $20 per assessment for their time and effort.

STRIDE Intervention

STRIDE is a brief, small group-based, videoconference intervention with six weekly one-hour sessions and two follow-up 15-30-minute telephone check-ins occurring approximately one and two months after the final intervention session. Groups will include two patients, matched according to schedules, and will take place via MGH-approved videoconference software, Zoom Video Communications, Inc (Zoom). The STRIDE intervention incorporates aspects of Cognitive Behavioral Therapy for Adherence and Depression [27] and Cognitive Behavioral Stress Management for Breast Cancer,[21] such as cognitive restructuring, behavioral activation, relaxation training, and skills-based coping strategies to address adherence and mood symptoms. The intervention also includes psychoeducation about the benefits and risks of AET, an assessment of barriers to adherence, and problem solving of individual barriers. Three of the six sessions focus entirely on addressing AET-related side effects and breast cancer treatment-related symptoms, such as hot flashes, pain, and fatigue, through specific behavioral coping strategies, evidence-based symptom management, and problem solving. As part of the intervention, participants will be asked to practice coping skills and relaxation training, using audio recordings, in between sessions.

Trained licensed psychologists, licensed social workers, and psychology doctoral students will administer the intervention and participate in weekly clinical group supervision with the principal investigator (PI). To monitor treatment fidelity, at least 10% of sessions will be randomly selected, stratified by study therapist, and reviewed by an independent assessor for percentage of key intervention topics covered, with a goal of 90% of possible topics covered per session.[28] Feedback will be discussed with the study therapists to maintain and enhance adherence to the intervention manual.

Medication Monitoring Control

Participants in the control condition will monitor medication-taking with MEMS Caps and otherwise receive follow up oncology care as usual. As medication monitoring can increase adherence in and of itself,[29] both groups will self-monitor medication, and only participants randomly assigned to STRIDE will receive the intervention.

Outcomes

Table 2 lists the self-report questionnaires and the time points at which they are administered.

Demographic and Clinical Characteristics

Participants will self-report their age, gender, race, ethnicity, marital status, education level, and relationship status. The following information will be collected from the EHR: MGH clinic site, breast cancer stage, node status, HER2/neu status, treatment type (e.g., surgery, chemotherapy, radiation), time since treatment completion, AET medication type, date of AET initiation, menopausal status, ovarian suppression (yes/no), oophorectomy (yes/no) and number of concomitant medications at study enrollment.

Primary Outcomes

Feasibility and Acceptability. Feasibility will be measured by the rate of enrollment (>50%), participant retention (>70%), and intervention attendance (≥70% of patients attending at least 4 of 6 sessions). Acceptability will be measured by intervention satisfaction, with >75% of patients reporting average satisfaction greater than the midpoint of the Client Satisfaction Questionnaire (CSQ) at the 12-week assessment.[30]

Secondary Outcomes

Adherence to AET. Objective adherence rates will be recorded using the MEMS Caps,[24] which are widely used in adherence monitoring, including for patients with breast

cancer.[31-33] Patients store their medication in the MEMS bottle, which records the date and time of any openings as a proxy for medication taking. The Supplemental Medication Diary will be used alongside the MEMS Caps to document any instance in which a patient takes the medication without opening the MEMS Cap. We will also make note of any physician-prescribed medication break during the patients' study participation. We will further assess self-reported adherence using the five-item Medication Adherence Report Scale (MARS-5).[34] The MARS-5 measures adherence to treatment with five questions concerning forgetting, changing doses, stopping, skipping, and using less than what is prescribed.

Symptom Distress. We will assess symptom distress using the Breast Cancer Prevention Trial Symptom Scale (BCPT),[35] a symptom checklist for which patients document how much they were bothered by several physical and psychological symptoms associated with AET use, such as hot flashes, weight gain, night sweats, and joint pain.

Satisfaction with AET. We will assess satisfaction with AET using the Cancer Therapy Satisfaction Questionnaire (CTSQ).[36] The CTSQ is a self-report measure that evaluates patients' beliefs about specific aspects of the medication, such as expectations of the effectiveness of AET therapy, feelings about side effects, and therapy adherence.

Exploratory Outcomes

The following measures will be administered to explore group differences on several psychosocial constructs, as well as possible mediators or moderators of intervention effects: quality of life measured by the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B),[37] medication-taking self-efficacy measured by the Self-Efficacy for Appropriate Medication Use Scale (SEAMS),[38] distress measured by the Hospital Anxiety and Depression Scale (HADS), [25] beliefs about AET measured by the Beliefs about Medicines Questionnaire –

Adjuvant Endocrine Therapy (BMQ-AET),[39] social support measured by the Multidimensional Scale of Perceived Social Support (MSPSS),[40] acquired coping skills measured by the Measure of Current Status –Part A (MOCS),[41] self-efficacy for symptom management measured by the Self-Efficacy For Managing Symptoms Questionnaire,[42] and cognitive functioning measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) – Cognitive Function – Short Form 4a.[43]

Safety and Adverse Events

Study staff will review self-report measures upon completion for missing data and to monitor distress levels. If a patient endorses a score ≥11 on the depression subscale of the HADS, the PI will be notified and either the PI or one of the trained study therapists will contact the patient via telephone to conduct a risk/safety assessment. If the patient requires further outpatient services (e.g., pharmacotherapy) or is at risk for self-harm, study staff will make the necessary referrals for treatment and/or urgent psychiatric care. If suicidality or risk of harm to others is otherwise discovered at any study visit, the patient will be referred to the appropriate services.

At weekly meetings, the research team will discuss summaries of adverse events by treatment group, and all serious adverse events will be reported to the PI, the DF/HCC IRB, and the appropriate federal agencies (e.g., National Cancer Institute) regardless of any judgment of their relatedness to the study. The research team will also discuss summary reports of treatment retention and reasons for dropout or withdrawal by treatment group. Patients who withdraw will be asked if they are willing to complete assessment measures. The project will be stopped immediately if at any point the DF/HCC IRB or the study investigators judge that the risks of

study procedures outweigh the benefits. Furthermore, the DF/HCC IRB will conduct trial auditing if deemed necessary throughout the study.

Data Collection and Management

The study PI will oversee all aspects of data collection and management. All data management activities will utilize REDCap for electronic collection and management of data. Data management reports will be generated weekly and discussed during the study team meetings. Study source documents, including but not limited to signed consent forms, completed eligibility checklists, and any paper-based self-report questionnaires, will be scanned and stored digitally as certified copies on a secure drive within the encrypted MGH network accessible only to trained study staff. Physical source documents will be destroyed once they are scanned and the corresponding electronic document is confirmed to be viable. If a patient is consented electronically, their digital consent form will be saved as the original source document.

Statistical Analysis

The primary objective of this pilot study is to demonstrate feasibility, defined as (1) enrollment rate >50%, (2) retention rate >70%, and (3) intervention attendance rate ≥70% (i.e. ≥ 70% of participants complete at least 4 of 6 sessions). Five patients participated in a trial run-in phase, and 75 will participate in the RCT. We estimate that the enrollment rate will be approximately 60%. If 134 patients are approached and 80 (total) are enrolled, the lower limit for an exact, one-sided 95% confidence interval for the estimated enrollment rate will be 53%. Furthermore, we anticipate that the retention and attendance rates will both be at least 80%, and with 80 enrolled participants, the lower limit for an exact, one-sided 95% confidence interval for the retention and attendance rates will be 71%. Thus, based on our estimates of the feasibility

parameters, the study will demonstrate feasibility of the STRIDE intervention with a sample size of 75 in the RCT and five in the run-in.

For the analysis of secondary outcomes of the STRIDE intervention on objective and subjective adherence to AET, symptom-related distress, and satisfaction with AET, data will be first be assessed for patterns of missingness [44] and statistical assumptions. We will use the intention-to-treat principle for analyses with all randomized subjects and maximum likelihood with multiple imputation to account for missing data. We will then conduct mixed effects models with repeated measures data for secondary outcomes and relevant demographic and treatment-related factors as covariates (e.g., age, stage, time since AET initiation). Longitudinal analyses will include all time points and a cross-sectional analysis for each time point. Given that this pilot is not powered to detect statistically significant group differences, we will examine mean differences and sample variability on the secondary outcomes. Effect sizes (Cohen's d) will be calculated for changes in outcomes from baseline to 12 and 24 weeks, where 0.3 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect [45]. Effect sizes will be used in a power analysis to estimate the necessary sample size to conduct a full-scale efficacy trial with power >80%. We will also verify the needed sample size based on ability to detect a clinically meaningful difference and references to existing literature.[46] We will use the same statistical procedures to examine group differences on exploratory outcomes (e.g., QOL, distress). Finally, we will explore a) possible mediators of the intervention (e.g., coping ability) by examining the bootstrapped confidence intervals of the indirect effects and b) possible moderators (e.g., social support) of intervention effects by probing interactions between the moderator and group assignment that reach or approach significance ($p<.15$) when predicting patient-reported outcomes.

LIMITATIONS

Limitations of the current trial deserve mention. First, the study is limited to patients with breast cancer currently receiving care at a Boston area major medical center and its affiliate sites, limiting the generalizability of the results. Second, patients who have access to devices (e.g., smartphones, computers, tablets) with videoconferencing capability are more likely to participate, which may bias the sample to individuals with higher incomes and education. However, videoconference delivery does have the potential to increase accessibility for individuals for whom in-person sessions may be prohibitive due to travel and/or associated costs. Third, although we are using a randomized, controlled design, both the participants and the study therapists are aware of each patient's study group assignment after randomization, as it is not possible to conduct a blinded psychosocial intervention study. Fourth, while we considered an attention-matched condition to control for nonspecific intervention effects, we decided against this approach because medication monitoring is likely to improve adherence alone.[29] Additionally, requesting participation in a placebo intervention adds undue burden to patients who are coping with emotional and physical sequelae. Finally, an attention control should only be employed if attention (from the therapist) would affect the primary outcome. Since no data suggest that therapist attention would improve AET adherence, an attention control would be an added expense and potentially unethical.[29] Finally, while many patients continue to take AET for up to ten years, our assessment follow-ups are limited to approximately six months following enrollment. Future studies may benefit from a longer follow-up period.

Patient and Public Involvement

Patients were involved in an initial qualitative phase of this study, which informed the overall study design, intervention, and outcomes measures. Briefly, 30 patients enrolled and

engaged in semi-structured interviews with trained study staff to understand experiences with and perceptions of AET, barriers and facilitators to adherence, emotional and symptom-related distress.[20] Interviews also solicited feedback from patients about their preferences for a psychosocial intervention, such as whether they preferred videoconference vs. in person, individual vs. group, and session length, frequency, and duration. Recurrent themes from these interviews informed intervention content and procedures. In addition, five patients participated in a run-in trial of the intervention and assessment measures and quantitatively rated the acceptability, enjoyableness, and feasibility of the intervention while also completing semi-structured interviews to provide feedback about the intervention, assessments, and study procedures. The intervention and procedures were modified and refined based on feedback from these exit interviews. For example, an additional session was added to the intervention for a total of six sessions in the final intervention, and an outcome measure was added based on feedback about acceptability of the length of the assessment battery.

ETHICS AND DISSEMINATION

The trial is being conducted in compliance with this study protocol, which has been approved by the DF/HCC's IRB. Written informed consent is and will be obtained from every participant, either in-person or over the phone; if consented over the phone, participants are and will be provided with a secure electronic consent form that is digitally signed. All documents, investigative reports, and information relating to the participants are confidential. Participant data are de-identified and compliant with the Standards of Privacy of Individually Identifiable Health Information ("Privacy Rule") of Health Insurance Portability and Accountability Act (HIPAA). Significant modifications to the study protocol will be submitted to the DF/HCC IRB for approval and communicated to study participants and all relevant members of the research

team. Due to this being a low-risk, social/behavioral intervention, it is unlikely participants will be at any risk of physical harm because of study participation but they may experience increased emotional distress as a result of the intervention content. Participants may withdraw from the study at any time, and participants for whom distress is not adequately resolved will be offered additional psychological care through the primary site's cancer center. Any results from this study will be published in peer-reviewed journals and local and national conference proceedings, and a description of the trial and summary of results will be available on ClinicalTrials.gov. The investigative team will track the manuscript in accordance with authorship guidelines. Only the investigative team will have access to the trial dataset, and access will only be permitted upon reasonable request through a data usage agreement via the IRB. There are no plans for the use of professional writers. If a patient expresses interest in learning the results of the study, study staff will provide an abstract of the study results upon completion of data collection.

Current Trial Status

Recruitment of participants started on October 11, 2019, and as of March 15, 2020, 25 patients had enrolled. The trial was put on a temporary recruitment pause on March 26, 2020 due to the COVID-19 pandemic and plans to resume recruitment in June 2020.

CONCLUSION

Adherence to AET is suboptimal and associated with poorer outcomes for patients after treatment for early-stage hormone receptor-positive breast cancer. While barriers to adherence are modifiable, interventions thus far have failed to produce meaningful improvements in adherence. The study outlined in this protocol is the first to address adherence, distress, and symptom management with a theoretically informed and evidence-based psychosocial

videoconference intervention that also directly incorporates patients' preferences for intervention content and delivery. Ultimately, this study will contribute to the understanding of patients' needs related to AET and provide insights into the feasibility and acceptability of an intervention designed to improve adherence, symptom management, and distress. Future studies based on these findings have the potential to influence survivorship care plans, as videoconferencing is a modality that can be widely disseminated to overcome geographic and cost-related barriers to in-person care. Improved adherence to AET may prevent recurrence and mortality, extending the survival for patients after breast cancer on lengthy regimens while also improving their quality of life.

FIGURES AND TABLES

Figure 1: CONSORT flow diagram

Table 1. Eligibility Criteria

Inclusion Criteria
1. Female
2. Age 21 or older
3. Diagnosis of early-stage (Stage 0-IIIb), hormone receptor + breast cancer
4. Within 1 week-36 months of starting adjuvant endocrine therapy
5. Ability to read and respond in English
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7. Currently taking adjuvant endocrine therapy (i.e. if took recent break, has taken within the past 2 weeks)
8. Completed primary treatment (i.e., chemotherapy, surgery, and/or radiation) for early-stage breast cancer
9. Indicates a score ≥4 on one of the three NCCN adapted distress thermometer study screening questions
Exclusion Criteria
1. Uncontrolled psychosis, active suicidal ideation, or psychiatric hospitalization within the past year
2. Cognitive impairment that prohibits participation in the study
3. Enrollment in a different clinical trial for breast cancer
4.Current participation in formal group psychotherapy or other psychosocial intervention trial

Table 2. Study Instruments and Time Points

Instrument/Measure:	Screening	Baseline (4-week window from consent)	12-weeks post-baseline (+/- 2-week window)	*24-weeks post-baseline (+/- 2-week window)
Electronic health record review	X			
Adapted NCCN Distress Thermometer	X			
Medication Event Monitoring System (MEMS Caps)		To be used throughout the 24-week study period		
Demographics		X		
Medication Adherence Report Scale (MARS-5)		X	X	X
Breast Cancer Prevention Trial Symptom Checklist (BCPT)		X	X	X
Cancer Therapy Satisfaction Questionnaire (CTSQ)		X	X	X
Hospital Anxiety and Depression Scale (HADS)		X	X	X
Functional Assessment of Cancer Therapy (FACT-B)		X	X	X
Measure of Current Status (MOCS)		X	X	X
Beliefs About Medications Questionnaire – Adjuvant Endocrine Therapy (BMQ-AET)		X	X	X
Multidimensional Scale of Perceived Social Support (MSPSS)		X	X	X
Self-Efficacy in Appropriate Medication Use Scale (SEAMS)		X	X	X
Self-Efficacy For Managing Symptoms and Taking AET Questionnaire (Self-Efficacy For Symptoms)		X	X	X
Patient-Reported Outcomes Measurement Information System (PROMIS) – Cognitive Function – Short		X	X	X

Form 4a				
Client Satisfaction Questionnaire (CSQ)*			X	
Supplemental Medication Diary	To serve as optional as-needed supplement to MEMS Caps (e.g., on vacation)			
**CSQ will be administered to intervention participants only*				

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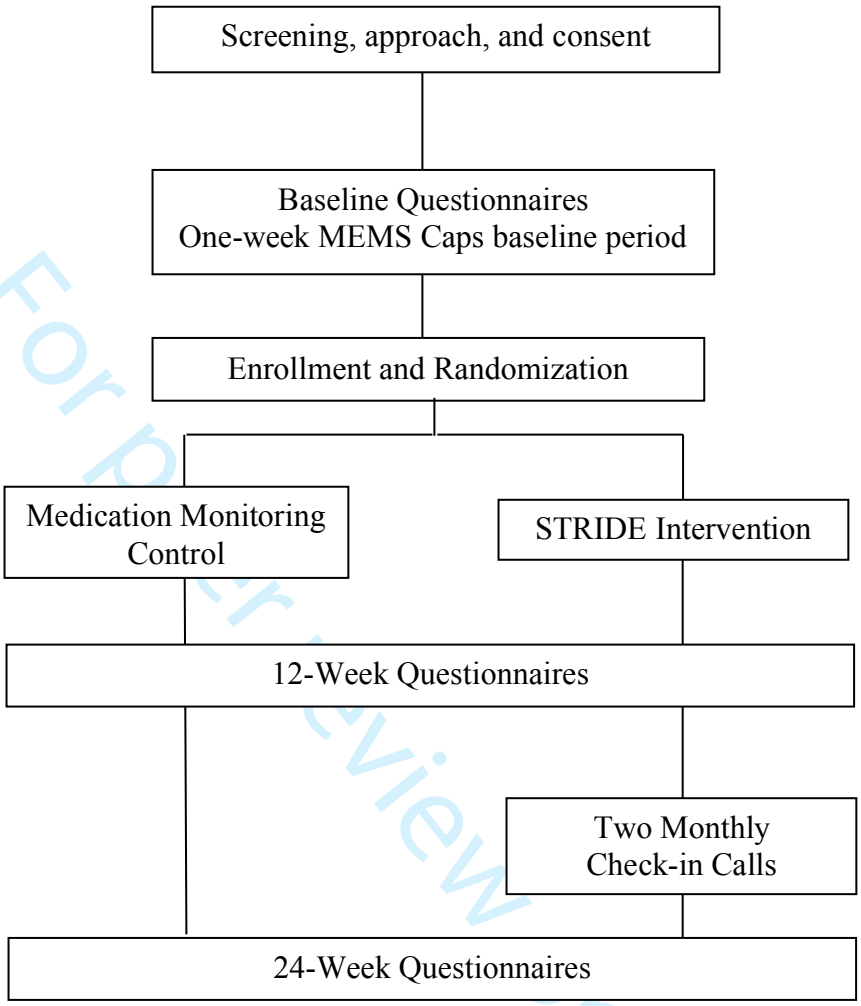
Figure 1: CONSORT flow diagram



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,9,20
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-10, 19, 21-22

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6, 13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8,16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13, 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12,17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Study Protocol for a Randomized Controlled Feasibility Trial of a Virtual Intervention (STRIDE) for Symptom Management, Distress, and Adherence to Adjuvant Endocrine Therapy after Breast Cancer

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Author Contributions: JJ, CR, AH, MC, EW, JP, JT, and JG contributed to the study conception and design. The protocol was developed by JJ, CR, AH, MC, EW, JP, JT, and JG, and written by JJ, EW, and CR. The first draft of the manuscript was written by JJ, CR, and AH, and JJ, CR, AH, MC, EW, JP, JT, and JG commented on previous versions of the manuscript. JJ, CR, AH, MC, EW, JP, JT, and JG read and approved the final manuscript.

Competing Interests Statement: JJ is a paid consultant from Blue Note Therapeutics. JG receives royalties from Springer Humana Press, has research funding from Gaido Health/BCG Digital Ventures, and is a paid consultant from Concerto HealthAI and Blue Note Therapeutics. JP has received research funding from Pfizer, is a paid consultant for Athenex, and JP's spouse is an employee of GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

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ABSTRACT

Introduction: Patient adherence to adjuvant endocrine therapy (AET) after a diagnosis of hormone-sensitive breast cancer is poor. Previous interventions have failed to produce changes in adherence, address patient preferences, or include theoretically informed and evidence-based components. Therefore, we iteratively developed a patient-centered, evidence-based, small-group, videoconference intervention to improve adherence and symptom management as well as reduce distress for patients taking AET after breast cancer (STRIDE).

Methods and Analysis: The current study is a non-blinded, randomized, controlled, feasibility trial of STRIDE compared to a medication monitoring control group. The primary objective is to examine the feasibility and acceptability of STRIDE, while secondary objectives are to assess changes in objective and subjective adherence, symptom distress, and satisfaction with AET. Patients will be recruited from the Massachusetts General Hospital Cancer Center in Boston, Massachusetts. The total number of patients accrued will be 75, with ≥60 patients completing the study. All patients will store their AET in an electronic pill bottle for objective adherence monitoring. Patients randomly assigned to the STRIDE intervention will receive six weekly one-hour sessions, in small groups of two, delivered via videoconferencing by a trained mental health professional. Patients assigned to the control group will store their medication in the electronic pill bottle and receive follow-up oncology care as usual. All participants will complete self-report psychosocial measures at baseline, 12 weeks, and 24 weeks post-baseline.

Ethics and Dissemination: The study is funded by the National Cancer Institute of the National Institutes of Health and is approved by the Dana-Farber/Harvard Cancer Center Institutional

Review Board (Protocol #18-603, version 1.2, first approval date 2/1/2019). The study will be reported in accordance with the Consolidated Standards of Reporting Trials statement for non-pharmacological trials. Results will be published in peer-reviewed academic journals, presented at scientific meetings, and disseminated to patient organizations and media outlets.

Trial Registration Number: Clinicaltrials.gov: NCT03837496; pre-results.

Keywords: adjuvant endocrine therapy, hormonal therapy, breast cancer, symptom management, adherence, distress, cognitive-behavioral intervention

Strengths and limitations of this study:

- This study employs a patient-centered, evidence-based, virtual videoconference intervention to improve adherence, enhance symptom management, and reduce distress for patients taking AET after breast cancer.
- Given the lack of efficacious interventions to date, this study design and intervention were informed by in-depth qualitative analysis and iterative intervention development to maximize patient-centeredness, feasibility, acceptability, and efficacy.
- To maximize scalability and dissemination, patients participate virtually for all study procedures including consent, intervention, and assessments; therefore, no hospital or in-person visits are necessary.
- The homogenous sample with respect to sociodemographic diversity will limit generalizability of the findings.

INTRODUCTION

Up to 75% of female patients diagnosed with early-stage breast cancer will require adjuvant endocrine therapy (AET) to prevent the likelihood of recurrence and improve survival.[1] AET (e.g., tamoxifen or an aromatase inhibitor) reduces recurrence and mortality by approximately 30 to 50%, for hormone receptor-positive breast cancer.[2,3] Despite the substantial, indisputable benefit, half of women are non-adherent (i.e., do not take the medication as prescribed) within five years of initiating AET.[4] In addition to greater risk of breast cancer recurrence[5,6] and breast cancer mortality,[7] non-adherence to AET is associated with higher rates of physician visits, hospitalizations,[8] and poorer patient-provider relationships.[9]

Several factors are known to contribute to suboptimal adherence for patients taking AET,[5,7,10] including substantial side effects (e.g., joint pain, hot flashes, sleep difficulties),[11-13] psychological distress during survivorship,[11] low perceived need for AET,[14] low self-efficacy for taking medication,[15] negative beliefs about AET and related side effects,[16] and low social support.[17] While several of these contributors are modifiable, patients receive virtually no formal support to promote medication-taking after breast cancer. Only four randomized controlled trials (RCTs) to date have investigated psychosocial interventions to promote AET adherence,[18] and they have failed to address the adherence challenges that patients face. Previous studies neglected to include theoretically-driven and empirically-based intervention components to target behavioral drivers of adherence, were not developed using guiding principles of behavioral intervention development,[19,20] have been methodologically flawed, and were not informed by patient preferences.

To address the significant need to optimize AET adherence, improve self-management of side effects, and reduce distress for patients taking AET, we iteratively developed a patient-

centered, small-group, evidence-based, videoconference intervention: STRIDE (**S**ymptom-**T**argeted **R**andomized **I**ntervention for **D**istress and Adherence to Adjuvant **E**ndocrine Therapy). Intervention development was informed by a comprehensive systematic literature review,[18] a qualitative in-depth analysis of patient experiences and preferences,[21] prior efficacious treatments,[22,23] and expert feedback from oncology clinicians and behavioral scientists. We then modified intervention content and duration, logistics, and study procedures using quantitative and qualitative feedback from exit interviews with five patients who participated in a run-in phase of the intervention. Patients were enthusiastic about the STRIDE intervention, described it as beneficial, preferred the group setting, and noted that the virtual delivery was a necessary convenience.

The current report outlines the details of the RCT that is currently underway comparing the finalized STRIDE intervention to a medication monitoring control condition. The primary objective is to establish the feasibility and acceptability of the STRIDE intervention compared to the medication monitoring control group. The secondary aims are to assess the effects of the intervention on objective and self-reported AET adherence, symptom distress, and satisfaction with AET. Finally, we will explore group differences on additional self-reported psychosocial constructs and examine potential mediators and moderators of any treatment outcomes. This pilot study will ultimately inform a future full-scale trial which will examine intervention efficacy.

METHODS AND ANALYSIS

Study Design

This is a single site, randomized, controlled, pilot feasibility study comparing a videoconference intervention (STRIDE) to standard care plus medication monitoring in 75

patients taking AET after breast cancer. Recruitment will occur at the Massachusetts General Hospital (MGH) Boston and three MGH community affiliates: MGH Newton-Wellesley, MGH North Shore, and MGH Waltham. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is illustrated in Figure 1. The study is approved by the Dana Farber/Harvard Cancer Center's (DF/HCC) Institutional Review Board (Clinicaltrials.gov: NCT03837496).

Participant selection

To be eligible, patients must be female, be age 21 or older, have a diagnosis of early-stage (stage 0-IIIb), have hormone receptor-positive breast cancer, have completed primary treatment (i.e., chemotherapy, surgery, and/or radiation) for breast cancer, be within 1 week – 36 months of starting AET, be able to read and respond in English, and have an Eastern Cooperative Oncology Group performance status ≤ 2 (See Table 1). Patients will complete a 3-item distress screening using an adapted National Comprehensive Cancer Network (NCCN) Distress Thermometer (range = 0-10).[24] Those who report distress ≥ 4 on any of the three items will be eligible to participate (i.e., distress related to having to take AET, distress related to symptoms/side effects, and/or distress related to AET adherence). To ensure engagement and compliance with study procedures, patients with cognitive impairment, uncontrolled psychosis, active suicidal ideation, or a psychiatric hospitalization within the past year will not be eligible. In addition, exclusion criteria include enrollment in a clinical trial for breast cancer (due to additional medication monitoring), participation in another psychosocial intervention study, or current engagement in formal group psychotherapy.

Five patients participated in a trial run-in phase, and 75 will participate in the RCT. We estimate that the enrollment rate will be approximately 60%. If 134 patients are approached and 80 (total) are enrolled, the lower limit for an exact, one-sided 95% confidence interval for the

estimated enrollment rate will be 53%. Furthermore, we anticipate that the retention and attendance rates will both be at least 80%, and with 80 enrolled participants, the lower limit for an exact, one-sided 95% confidence interval for the retention and attendance rates will be 71%. Thus, based on our estimates of the feasibility parameters, the study will demonstrate feasibility of the STRIDE intervention with a sample size of 75 in the RCT and five in the run-in.

Study Procedures

Recruitment

Trained study staff will review the electronic health record (EHR) to identify potentially eligible patients with upcoming appointments at the MGH Center for Breast Cancer or one of the MGH community affiliates. For those identified patients, study staff will then request permission from the respective oncology clinicians to approach the patients about study participation. After receiving approval from the oncology clinicians, study staff will approach patients during their outpatient appointment to explain study procedures and gauge their interest in participating. Given the heavy volume of patients in the breast clinic on any given day, study staff can also contact patients by telephone if they are not able to approach them in person. Patients can also self-refer through advertisements on the online MGH study recruitment site or via posted flyers in the clinic. Finally, the oncology clinician or nurse practitioner can also directly refer interested patients.

Enrollment and Randomization

Eligible patients approached in person will complete written informed consent with trained study staff, and those approached by telephone will complete electronic informed consent with trained study staff. Enrolled patients will complete a one-week baseline period during which they will

use the Medication Event Monitoring System (MEMS Caps),[25] to electronically monitor medication-taking, as well as complete baseline self-report study questionnaires. Following one week of medication monitoring, study staff will randomly allocate patients 1:1 to either the STRIDE intervention or the medication monitoring control group via a computer-generated randomization scheme created by the study biostatistician; group allocation will be concealed for each patient until randomization occurs. Randomization will be stratified according to level of distress, determined by baseline scores on the Hospital Anxiety and Depression Scale (HADS),[26] (high distress ≥ 8; low distress <8).

Assessments

Patients will complete the same self-report measures at 12-week and 24-week follow-ups. Assessments will be conducted using mailed paper questionnaires or electronically via Research Electronic Data Capture (REDCap), a HIPAA compliant, web-based survey tool.[27] Given the virtual nature of the assessments and intervention sessions, patients will not need to travel to the hospital for any study-related visits and will receive $20 per assessment for their time and effort.

STRIDE Intervention

STRIDE is a brief, small group-based, videoconference intervention with six weekly one-hour sessions and two follow-up 15-30-minute telephone check-ins occurring approximately one and two months after the final intervention session. Groups will include two patients, matched according to schedules, and will take place via MGH-approved videoconference software, Zoom Video Communications, Inc (Zoom). The STRIDE intervention incorporates aspects of Cognitive Behavioral Therapy for Adherence and Depression [28] and Cognitive Behavioral Stress Management for Breast Cancer,[22] such as cognitive restructuring, behavioral activation, relaxation training, and skills-based coping strategies to address adherence and mood symptoms.

The intervention also includes psychoeducation about the benefits and risks of AET, an assessment of barriers to adherence, and problem solving of individual barriers. Three of the six sessions focus entirely on addressing AET-related side effects and breast cancer treatment-related symptoms, such as hot flashes, pain, and fatigue, through specific behavioral coping strategies, evidence-based symptom management, and problem solving. As part of the intervention, participants will be asked to practice coping skills and relaxation training, using audio recordings, in between sessions.

Patient and Public Involvement

Patients were involved in an initial qualitative phase of this study, which informed the overall study design, intervention, and outcomes measures. Briefly, 30 patients enrolled and engaged in semi-structured interviews with trained study staff to understand experiences with and perceptions of AET, barriers and facilitators to adherence, emotional and symptom-related distress.[21] Interviews also solicited feedback from patients about their preferences for a psychosocial intervention, such as whether they preferred videoconference vs. in person, individual vs. group, and session length, frequency, and duration. Recurrent themes from these interviews informed intervention content and procedures. In addition, five patients participated in a run-in trial of the intervention and assessment measures and quantitatively rated the acceptability, enjoyableness, and feasibility of the intervention while also completing semi-structured interviews to provide feedback about the intervention, assessments, and study procedures. The intervention and procedures were modified and refined based on feedback from these exit interviews. For example, an additional session was added to the intervention for a total of six sessions in the final intervention, and an outcome measure was added based on feedback about acceptability of the length of the assessment battery.

Intervention Delivery

Trained licensed psychologists, licensed social workers, and psychology doctoral students will administer the intervention and participate in weekly clinical group supervision with the principal investigator (PI). To monitor treatment fidelity, at least 10% of sessions will be randomly selected, stratified by study therapist, and reviewed by an independent assessor for percentage of key intervention topics covered, with a goal of 90% of possible topics covered per session.[29] Feedback will be discussed with the study therapists to maintain and enhance adherence to the intervention manual.

Medication Monitoring Control

Participants in the control condition will monitor medication-taking with MEMS Caps and otherwise receive follow up oncology care as usual. As medication monitoring can increase adherence in and of itself,[30] both groups will self-monitor medication, and only participants randomly assigned to STRIDE will receive the intervention.

Outcomes

Table 2 lists the self-report questionnaires and the time points at which they are administered.

Demographic and Clinical Characteristics

Participants will self-report their age, gender, race, ethnicity, marital status, education level, and relationship status. The following information will be collected from the EHR: MGH clinic site, breast cancer stage, node status, HER2/neu status, treatment type (e.g., surgery, chemotherapy, radiation), time since treatment completion, AET medication type, date of AET initiation, menopausal status, ovarian suppression (yes/no), oophorectomy (yes/no) and number of concomitant medications at study enrollment.

Primary Outcomes

Feasibility and Acceptability. Feasibility will be measured by the rate of enrollment (>50%), participant retention (>70%), and intervention attendance (≥70% of patients attending at least 4 of 6 sessions). Acceptability will be measured by intervention satisfaction, with >75% of patients reporting average satisfaction greater than the midpoint of the Client Satisfaction Questionnaire (CSQ) at the 12-week assessment.[31]

Secondary Outcomes

Adherence to AET. Objective adherence rates will be recorded using the MEMS Caps,[25] which are widely used in adherence monitoring, including for patients with breast cancer.[32-34] Patients store their medication in the MEMS bottle, which records the date and time of any openings as a proxy for medication taking. The Supplemental Medication Diary will be used alongside the MEMS Caps to document any instance in which a patient takes the medication without opening the MEMS Cap. We will also make note of any physician-prescribed medication break during the patients' study participation. We will further assess self-reported adherence using the five-item Medication Adherence Report Scale (MARS-5).[35] The MARS-5 measures adherence to treatment with five questions concerning forgetting, changing doses, stopping, skipping, and using less than what is prescribed.

Symptom Distress. We will assess symptom distress using the Breast Cancer Prevention Trial Symptom Scale (BCPT),[36] a symptom checklist for which patients document how much they were bothered by several physical and psychological symptoms associated with AET use, such as hot flashes, weight gain, night sweats, and joint pain.

Satisfaction with AET. We will assess satisfaction with AET using the Cancer Therapy Satisfaction Questionnaire (CTSQ).[37] The CTSQ is a self-report measure that evaluates

patients' beliefs about specific aspects of the medication, such as expectations of the effectiveness of AET therapy, feelings about side effects, and therapy adherence.

Exploratory Outcomes

The following measures will be administered to explore group differences on several psychosocial constructs, as well as possible mediators or moderators of intervention effects: quality of life measured by the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B),[38] medication-taking self-efficacy measured by the Self-Efficacy for Appropriate Medication Use Scale (SEAMS),[39] distress measured by the Hospital Anxiety and Depression Scale (HADS), [26] beliefs about AET measured by the Beliefs about Medicines Questionnaire – Adjuvant Endocrine Therapy (BMQ-AET),[40] social support measured by the Multidimensional Scale of Perceived Social Support (MSPSS),[41] acquired coping skills measured by the Measure of Current Status –Part A (MOCS),[42] self-efficacy for symptom management measured by the Self-Efficacy For Managing Symptoms Questionnaire,[43] and cognitive functioning measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) – Cognitive Function – Short Form 4a.[44]

Safety and Adverse Events

Study staff will review self-report measures upon completion for missing data and to monitor distress levels. If a patient endorses a score ≥11 on the depression subscale of the HADS, the PI will be notified and either the PI or one of the trained study therapists will contact the patient via telephone to conduct a risk/safety assessment. If the patient requires further outpatient services (e.g., pharmacotherapy) or is at risk for self-harm, study staff will make the necessary referrals for treatment and/or urgent psychiatric care. If suicidality or risk of harm to

others is otherwise discovered at any study visit, the patient will be referred to the appropriate services.

At weekly meetings, the research team will discuss summaries of adverse events by treatment group, and all serious adverse events will be reported to the PI, the DF/HCC IRB, and the appropriate federal agencies (e.g., National Cancer Institute) regardless of any judgment of their relatedness to the study. The research team will also discuss summary reports of treatment retention and reasons for dropout or withdrawal by treatment group. Patients who withdraw will be asked if they are willing to complete assessment measures. The project will be stopped immediately if at any point the DF/HCC IRB or the study investigators judge that the risks of study procedures outweigh the benefits. Furthermore, the DF/HCC IRB will conduct trial auditing if deemed necessary throughout the study.

Data Collection and Management

The study PI will oversee all aspects of data collection and management. All data management activities will utilize REDCap for electronic collection and management of data. Data management reports will be generated weekly and discussed during the study team meetings. Study source documents, including but not limited to signed consent forms, completed eligibility checklists, and any paper-based self-report questionnaires, will be scanned and stored digitally as certified copies on a secure drive within the encrypted MGH network accessible only to trained study staff. Physical source documents will be destroyed once they are scanned and the corresponding electronic document is confirmed to be viable. If a patient is consented electronically, their digital consent form will be saved as the original source document.

Statistical Analysis

The primary objective of this pilot study is to demonstrate feasibility, defined as (1) enrollment rate >50%, (2) retention rate >70%, and (3) intervention attendance rate ≥70% (i.e. ≥ 70% of participants complete at least 4 of 6 sessions).

For the analysis of secondary outcomes of the STRIDE intervention on objective and subjective adherence to AET, symptom-related distress, and satisfaction with AET, data will be first be assessed for patterns of missingness [45] and statistical assumptions. We will use the intention-to-treat principle for analyses with all randomized subjects and maximum likelihood with multiple imputation to account for missing data. We will then conduct mixed effects models with repeated measures data for secondary outcomes and relevant demographic and treatment-related factors as covariates (e.g., age, stage, time since AET initiation). Longitudinal analyses will include all time points and a cross-sectional analysis for each time point. Given that this pilot is not powered to detect statistically significant group differences, we will examine mean differences and sample variability on the secondary outcomes. Effect sizes (Cohen's d) will be calculated for changes in outcomes from baseline to 12 and 24 weeks, where 0.3 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect [46]. Effect sizes will be used in a power analysis to estimate the necessary sample size to conduct a full-scale efficacy trial with power >80%. We will also verify the needed sample size based on ability to detect a clinically meaningful difference and references to existing literature.[47] We will use the same statistical procedures to examine group differences on exploratory outcomes (e.g., QOL, distress). Finally, we will explore a) possible mediators of the intervention (e.g., coping ability) by examining the bootstrapped confidence intervals of the indirect effects and b) possible moderators (e.g., social support) of intervention effects by probing interactions between the moderator and group

assignment that reach or approach significance ($p<.15$) when predicting patient-reported outcomes.

LIMITATIONS

Limitations of the current trial deserve mention. First, the study is limited to patients with breast cancer currently receiving care at a Boston area major medical center and its affiliate sites, limiting the generalizability of the results. Second, patients who have access to devices (e.g., smartphones, computers, tablets) with videoconferencing capability are more likely to participate, which may bias the sample to individuals with higher incomes and education. However, videoconference delivery does have the potential to increase accessibility for individuals for whom in-person sessions may be prohibitive due to travel and/or associated costs. Third, although we are using a randomized, controlled design, both the participants and the study therapists are aware of each patient's study group assignment after randomization, as it is not possible to conduct a blinded psychosocial intervention study. Fourth, while we considered an attention-matched condition to control for nonspecific intervention effects, we decided against this approach because medication monitoring is likely to improve adherence alone.[30] Additionally, requesting participation in a placebo intervention adds undue burden to patients who are coping with emotional and physical sequelae. In fact, an attention control should only be employed if attention (from the therapist) would affect the primary outcome. Since no data suggest that therapist attention would improve AET adherence, an attention control would be an added expense and potentially unethical.[30] While many patients continue to take AET for up to ten years, our assessment follow-ups are limited to approximately six months following enrollment. Future studies may benefit from a longer follow-up period. Finally, although the study is underpowered to examine group differences in secondary outcomes, the purpose of

including all study questionnaires is to also examine the feasibility of participants completing an assessment battery of this size. If participants do not complete the surveys, this may indicate an unacceptable lengthiness that would prohibit data collection and analysis in a future full-scale efficacy trial. Survey length was directly assessed in the run-in phase of this study.

ETHICS AND DISSEMINATION

The trial is being conducted in compliance with this study protocol, which has been approved by the DF/HCC's IRB. Written informed consent is and will be obtained from every participant, either in-person or over the phone; if consented over the phone, participants are and will be provided with a secure electronic consent form that is digitally signed. All documents, investigative reports, and information relating to the participants are confidential. Participant data are de-identified and compliant with the Standards of Privacy of Individually Identifiable Health Information ("Privacy Rule") of Health Insurance Portability and Accountability Act (HIPAA). Significant modifications to the study protocol will be submitted to the DF/HCC IRB for approval and communicated to study participants and all relevant members of the research team. Due to this being a low-risk, social/behavioral intervention, it is unlikely participants will be at any risk of physical harm because of study participation but they may experience increased emotional distress as a result of the intervention content. Participants may withdraw from the study at any time, and participants for whom distress is not adequately resolved will be offered additional psychological care through the primary site's cancer center. Any results from this study will be published in peer-reviewed journals and local and national conference proceedings, and a description of the trial and summary of results will be available on ClinicalTrials.gov. The investigative team will track the manuscript in accordance with authorship guidelines. Only the investigative team will have access to the trial dataset, and access will only be permitted upon

reasonable request through a data usage agreement via the IRB. There are no plans for the use of professional writers. If a patient expresses interest in learning the results of the study, study staff will provide an abstract of the study results upon completion of data collection.

Current Trial Status

Recruitment of participants started on October 11, 2019, and as of March 15, 2020, 25 patients had enrolled. The trial was put on a temporary recruitment pause on March 26, 2020 due to the COVID-19 pandemic and plans to resume recruitment in June 2020.

FIGURES AND TABLES

Figure 1: CONSORT flow diagram

Table 1. Eligibility Criteria

Inclusion Criteria
1. Female
2. Age 21 or older
3. Diagnosis of early-stage (Stage 0-IIIb), hormone receptor + breast cancer
4. Within 1 week-36 months of starting adjuvant endocrine therapy
5. Ability to read and respond in English
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7. Currently taking adjuvant endocrine therapy (i.e. if took recent break, has taken within the past 2 weeks)
8. Completed primary treatment (i.e., chemotherapy, surgery, and/or radiation) for early-stage breast cancer
9. Indicates a score ≥4 on one of the three NCCN adapted distress thermometer study screening questions
Exclusion Criteria
1. Uncontrolled psychosis, active suicidal ideation, or psychiatric hospitalization within the past year
2. Cognitive impairment that prohibits participation in the study
3. Enrollment in a different clinical trial for breast cancer
4.Current participation in formal group psychotherapy or other psychosocial intervention trial

Table 2. Study Instruments and Time Points

Instrument/Measure:	Screening	Baseline (4-week window from consent)	12-weeks post-baseline (+/- 2-week window)	*24-weeks post-baseline (+/- 2-week window)
Electronic health record review	X			
Adapted NCCN Distress Thermometer	X			
Medication Event Monitoring System (MEMS Caps)		To be used throughout the 24-week study period		
Demographics		X		
Medication Adherence Report Scale (MARS-5)		X	X	X
Breast Cancer Prevention Trial Symptom Checklist (BCPT)		X	X	X
Cancer Therapy Satisfaction Questionnaire (CTSQ)		X	X	X
Hospital Anxiety and Depression Scale (HADS)		X	X	X
Functional Assessment of Cancer Therapy (FACT-B)		X	X	X
Measure of Current Status (MOCS)		X	X	X
Beliefs About Medications Questionnaire – Adjuvant Endocrine Therapy (BMQ-AET)		X	X	X
Multidimensional Scale of Perceived Social Support (MSPSS)		X	X	X
Self-Efficacy in Appropriate Medication Use Scale (SEAMS)		X	X	X
Self-Efficacy For Managing Symptoms and Taking AET Questionnaire (Self-Efficacy For Symptoms)		X	X	X
Patient-Reported Outcomes Measurement Information System (PROMIS) – Cognitive Function – Short		X	X	X

Form 4a				
Client Satisfaction Questionnaire (CSQ)*			X	
Supplemental Medication Diary	To serve as optional as-needed supplement to MEMS Caps (e.g., on vacation)			
**CSQ will be administered to intervention participants only*				

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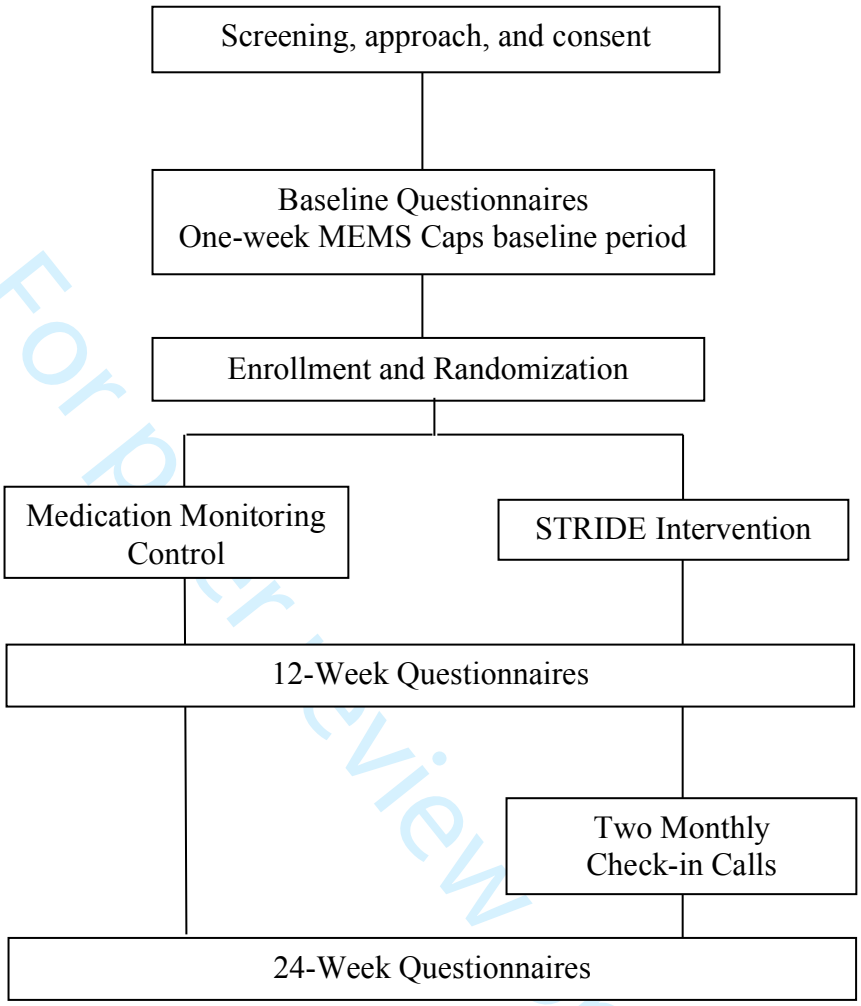
Figure 1: CONSORT flow diagram



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,9,20
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-10, 19, 21-22

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6, 13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8,16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13, 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12,17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.