PRE-OPERATIVE WINDOW OF ADJUVANT ENDOCRINE THERAPY TO INFORM RADIATION THERAPY DECISIONS IN OLDER WOMEN WITH EARLY-STAGE BREAST CANCER

Protocol ID: POWER

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Key Roles and Study Governance

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR), and the NIH Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Sponsor/Lead Principal Investigator

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Name (print) Signature Date

Investigator

_____

Name (print) Signature Date

ABBREVIATIONS

AE	Adverse Event
AI	Aromatase Inhibitor
BCS	Breast Conservation Surgery
BCT	Breast Conservation Surgery followed by Radiation Therapy
BCPT-SCL	Breast Cancer Prevention Trial Symptom Checklist
BIPQ	Brief Illness Perception Questionnaire
BMQ	Beliefs about Medicines Questionnaire
CESD	Center for Epidemiologic Studies Depression Scale
CESD-R	Center for Epidemiologic Studies Depression Scale Revised
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DCS	Decisional Conflict Scale
DHHS	Department of Health and Human Services
DRS	Decision Regret Scale
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ELPh	Exemestane and Letrozole Pharmacogenetics
EORTC	European Organisation for Research and Treatment of Cancer
EuroQOL VAS	EuroQOL Visual Analog Scale
ER	Estrogen Receptor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-related quality of life
IB	Investigator's Brochure
IBTR	Ipsilateral Breast Tumor Recurrence
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MOP	Manual of Procedures
NCCN	National Comprehensive Cancer Network

NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
PR	Progesterone Receptor
Pre-ET	Pre-operative endocrine therapy
PRO	Patient Reported Outcomes
PSM	Perceived Sensitivity to Medicine Scales
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOM	School of Medicine
SOP	Standard Operating Procedure
RT	Radiation Therapy
UP	Unanticipated Problem
US	United States
UVA MCRO	University of Virginia Multisite Clinical Research Office
VAS	Visual Analog Scale

1 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td>Title:</td><td colspan="2">Pre-Operative Window of Adjuvant Endocrine Therapy to Inform Radiation Therapy Decisions in Older Women with Early-Stage Breast Cancer</td></tr>
<tr><td>Study Description:</td><td colspan="2">This is a prospective multisite exploratory study for women ≥ 65 years of age with early stage estrogen receptor positive (ER^+) breast cancer. These individuals will be treated with 3 months of pre-operative endocrine therapy (pre-ET) with assessment of tolerance to the endocrine therapy by patient reported outcome (PRO) measures. The results of this study will be used to develop an algorithm for treatment recommendations in early stage geriatric breast cancer patients.
The following will be assessed:
1) The results of the tolerance assessments will change the treatment recommendations and decisions regarding adjuvant radiation therapy (RT);
2) Tolerance of pre-ET as measured by PROs will be predictive of long-term adjuvant endocrine therapy adherence;
3) Use of 3 months of pre-ET endocrine therapy in order to assess tolerance to the endocrine therapy will not negatively impact surgical completion.</td></tr>
<tr><td rowspan="8">Objectives & Endpoints</td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td>Primary</td><td></td></tr>
<tr><td>• To assess whether pre-ET changes an individual’s preference for adjuvant radiation treatment
• To assess whether pre-treatment with endocrine therapy changes the surgical oncologist’s preference for adjuvant radiation treatment</td><td>• Radiation preference question for participant pre and post pre-ET treatment
• Radiation preference question for the surgical oncologist pre and post pre-ET treatment</td></tr>
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• For those participants who agree to a radiation oncologist consultation, to assess whether pre-treatment with endocrine therapy changes the radiation oncologist’s preference for adjuvant radiation treatment</td><td>• PRO assessments
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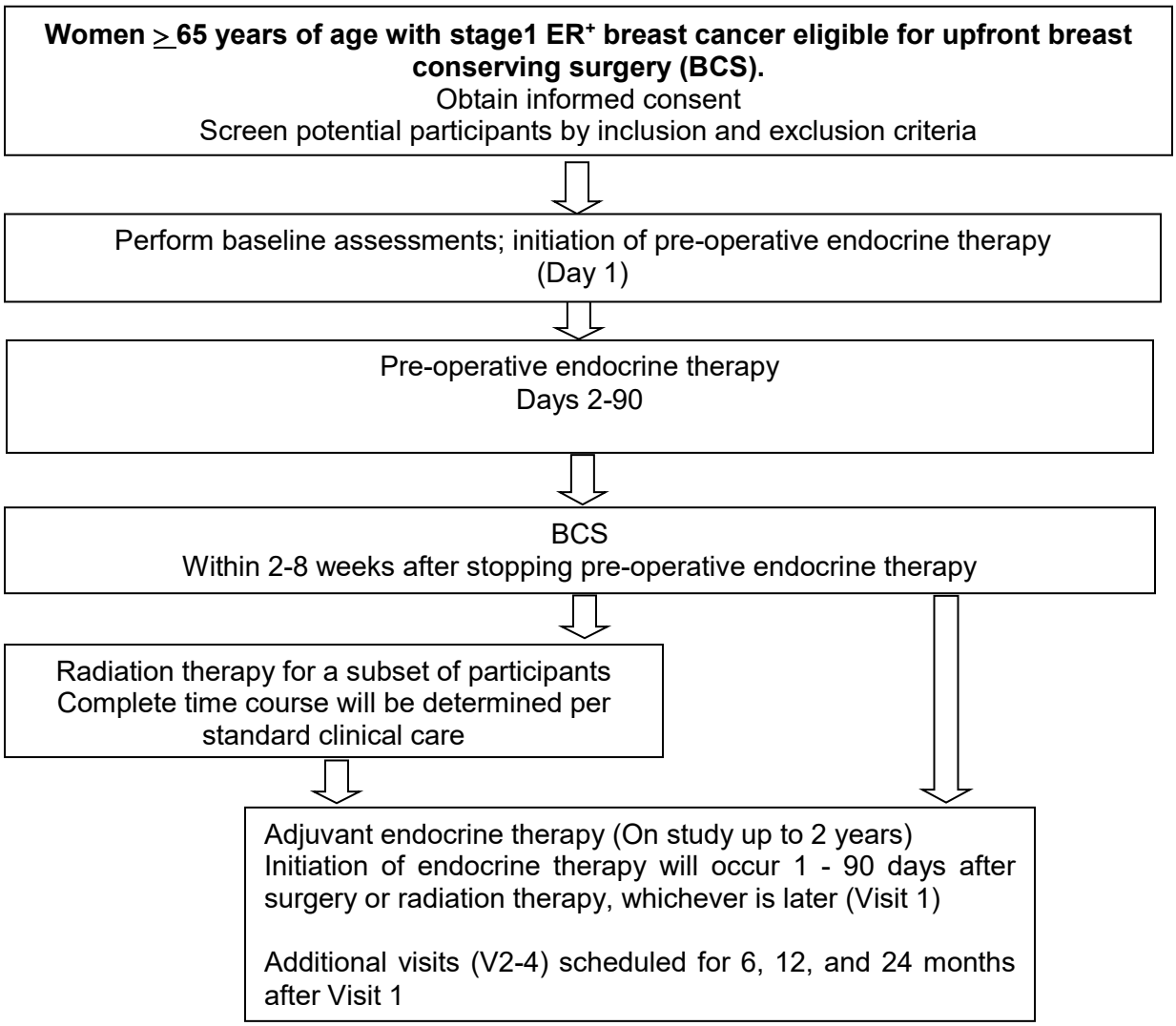
<tr><td>Exploratory</td><td></td></tr>
</table>

	• To obtain exploratory data on recurrence-free survival and overall survival	• Recurrence-free survival and survival through 24 months
Study Population:	Women ≥65 years of age with a diagnosis of clinical stage I, ER^+, progesterone positive (PR^+) or negative (PR^-), and HER2 non-amplified invasive breast cancer and clinically negative nodes. Any invasive breast cancer histologic subtype may be enrolled.	
Phase:	Pilot study	
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled at the University of Virginia Health System and Virginia Commonwealth University	
Description of Study Intervention:	Participants enrolled to the study will receive 3 months of endocrine therapy (e.g. tamoxifen or aromatase inhibitors (AIs) such as letrozole, anastrozole, or exemestane). The choice and dose of endocrine therapy will be at the discretion of the treating medical oncologist.	
Study Duration:	62 months	
Participant Duration:	30 months	

Note that before IRB approval of protocol v01-26-22, this study was referred to as “Breast 52.”

1.2 Schema



Please see Appendix 1 for a complete list of activities

2 INTRODUCTION

2.1 Study Rationale

Breast cancer is the most common cancer diagnosed in women in the United States and almost half of newly diagnosed breast cancer cases are in women 65 years and older[1]. Given this large number of geriatric breast cancer patients, it is paramount that research be conducted in this population so that treatment recommendations can be tailored to specific geriatric considerations. Historically, early stage breast cancer patients were treated with breast conserving surgery (BCS), followed by adjuvant radiation therapy (RT; delivered in the immediate postoperative period) and endocrine therapy (for 5-10 years) - both of which are known to decrease the risk of recurrence. However, recent data from randomized controlled trials in women ≥ 65 - 70 years of age with estrogen receptor (ER) positive, node negative, small (≤ 3cm) breast cancers have shown that omission of adjuvant radiation following BCS does not result in a decreased survival[2-4]. Despite these findings and inclusion of criteria for omission of radiation in NCCN guidelines, studies show that RT is still frequently used after BCS in this population[5-7]. There is increasing opinion that offering radiation to this patient population should be considered overtreatment. However, RT omission has not been widely accepted because of the concern that adherence to endocrine therapy is higher in the clinical trial setting than what is reported in clinical practice[8,9], and therefore adjuvant radiation therapy is offered to ensure acceptable recurrence rates. Without patient-level data regarding tolerance to endocrine therapy, physicians and patients are unable to make informed decisions regarding omission of RT. The rationale for this prospective analysis is to collect data on pre-ET tolerance as a criterion to better inform decision making on RT omission in the immediate post-operative period and to identify criteria to guide future additional adjuvant treatment.

2.2 Background

2.2.1 Breast Conservation Therapy is a Standard Treatment for Early Stage Breast Cancer

Early stage breast cancer is treated with surgery (mastectomy or BCS). There is no difference in long term survival between mastectomy and breast conservation therapy (BCS followed by radiation therapy (RT); BCT), and BCT is the preferred treatment approach based on decreased morbidity and higher associated quality of life[10,11]. Traditionally, a key part of BCS is the recommendation for adjuvant whole breast RT to decrease the risk of local recurrence[12-14]. Adjuvant RT is delivered in the immediate post-operative period as there is evidence of increased risk of local failure if RT is delayed beyond 8 weeks[15-17]. Patients with hormone receptor positive breast cancer are treated with adjuvant endocrine therapy (tamoxifen or an AI), which is typically started upon completion of RT. The duration of endocrine therapy is at least 5 years with evidence for extended duration in higher risk patients[18]. Adjuvant endocrine therapy is proven to decrease local recurrence, distant recurrence, and prolong survival [19].

2.2.2 Breast Cancer Incidence and Mortality in Geriatric Patients

The incidence of breast cancer is increasing as the population ages and nearly half of new diagnoses of breast cancer are in women ≥65 years of age. Thus, treatment specific to the geriatric population is increasingly relevant[1]. Elderly breast cancer patients have been shown to be more likely to have favorable tumor characteristics including lower histologic grade and hormone receptor positivity[20,21]. Despite this, there is evidence that suggests that increasing age is associated with higher disease-specific mortality[22]. Importantly, elderly breast cancer patients

compared to younger patients are known to be more likely to have deviations from standard of care in surgical management and adjuvant radiation, chemotherapy, and endocrine therapy management[23]. These non-standard treatment approaches for geriatric breast cancer patients reflect both physician recommendations and patient preference. Elderly patients are therefore both under- and over- treated in regards to established treatment recommendations, with each possibly contributing to higher rates of disease specific mortality. More studies are needed in the geriatric breast cancer population that will allow for age-specific evidence-based algorithms to guide clinical decision making.

2.2.3 Treatment of Early Stage Breast Cancer in Geriatric Patients

Radiation omission is a proven treatment option for older patients with low risk breast cancers, but implementation rates are low. Many trials have explored the utility of adjuvant radiation in hormone receptor positive early stage breast cancer and, while use of adjuvant RT leads to a decrease in ipsilateral breast tumor recurrence (IBTR), there is no difference in survival when compared to patients that omit RT[3,4,12-14,24]. Current NCCN breast cancer guidelines indicate that adjuvant radiation may be omitted in patients 70 years or older with ER^+, clinically node negative, T1 tumors who will receive adjuvant endocrine therapy[18]. This recommendation comes primarily from the evidence provided by two large, randomized clinical trials in geriatric patients[3,4].

Cancer and Leukemia Group B (CALGB) 9343

In CALGB 9343, 636 geriatric women with clinical stage 1, ER^+ breast cancer were randomly assigned to adjuvant treatment with tamoxifen plus RT or tamoxifen alone[3]. Long term follow up (median 12.6 years) confirmed 98% of patients in the RT plus tamoxifen arm and 90% of patients in the tamoxifen alone arm were free from local and regional recurrence with no difference in time to local or regional recurrence, frequency of mastectomy, breast cancer specific survival, time to distant metastasis, and overall survival[2]. Therefore, the authors concluded that RT has no significant impact on survival, and RT omission is a reasonable choice for low risk, ER^+ breast cancer patients ≥ 70 years who take adjuvant endocrine therapy after BC.

Prime II

The PRIME II trial included 1326 geriatric women aged 65 years or older with ER^+, node negative, T1-2 tumors treated with BCS and adjuvant endocrine therapy. Individuals were randomized to receive RT or no RT. Patients treated with adjuvant RT and endocrine therapy had an IBTR of 1.3% and those treated with adjuvant endocrine therapy without RT had an IBTR of 4.1% with median follow up of 5 years. There was no difference in regional recurrence, distant metastases, contralateral breast cancers, or new breast cancers and 5 year overall survival was 93.3% in both groups[4]. The authors concluded that postoperative RT resulted in a significant reduction in IBTR, but that the 5 year IBTR was low enough for omission of RT to be a rational treatment approach for select patients. Updated 10-year results were reported at the 2020 San Antonio Breast Cancer Symposium and confirm previous findings of increased local recurrence of 9.8% vs 0.9%, but no difference in overall survival[25].

The results of these two trials resulted in updates to the NCCN guidelines in 2004, which included the option for omission of RT in women over the age of 70 with ER^+ T1N0 breast cancer who will take adjuvant endocrine therapy. However, despite these recommendations, implementation of RT omission is low[5,7] and many providers still view RT omission as substandard care[6]. The

reasons for why providers do not offer RT omission is multifactorial. Providers overestimate the life expectancy of patients[6] and believe that healthy patients over age 70 do not fit the population of the CALGB 9343 study. In fact, the patients in CALGB 9343 were healthier and lived longer than women in the general population of similar ages[2]. A key part of the design of CALGB 9343 and PRIME II trials was that all patients were recommended to be treated with adjuvant endocrine therapy. Adjuvant endocrine therapy is shown to not only decrease distant recurrence, but also IBTR[12-14]. When recommending BCS with omission of immediate postoperative RT, neither the provider nor the patient knows whether the patient will tolerate and adhere to prescribed endocrine therapy. Early insight regarding an individual patient's tolerance and predicted adherence to endocrine therapy has potential to assist physicians to better formulate treatment plans and will allow patients to better accept and follow these recommendations. This would result in a patient specific treatment plan and decrease the risk of either over or under treatment of early stage breast cancer in the geriatric population.

2.2.4 Adherence to Endocrine Therapy in the Geriatric Population

Adherence to endocrine therapy in clinical practice is low. Non-adherence to endocrine therapy as documented in large adjuvant endocrine therapy trials is estimated between 23-28%, but it is even higher in studies examining non-adherence in clinical practice[8,9]. A systematic review of adherence to adjuvant endocrine therapy in clinical practice shows that adherence at 5 years ranges from 32 -73%. Within this systematic review, reports of 5-25% of women on AIs discontinued treatment within the first two years[9]. At year 5, 47.1% of patients discontinued tamoxifen and 31.3% discontinued AI treatment[26]. Non-adherence to adjuvant endocrine therapy results in increased recurrence and mortality[27] Capturing reasons for non-adherence is challenging with studies often reporting on demographic factors, but not identifying patient experience factors such as tolerability of the medication or a patient's perception of risk and benefit of therapy. Demographic factors identified as predictive of non-adherence include younger age, type of surgery (BCS), more comorbid conditions, and African American race[28].

There is a need to better define health related quality of life (HRQOL) and patient reported factors for non-adherence within clinical practice. Intolerable patient side effects is the most common patient reported reason for endocrine therapy non-adherence[29] with musculoskeletal symptoms being the primary reported toxicity leading to AI discontinuation[26,30]. Musculoskeletal side effects are estimated to occur in up to 50% of patients on adjuvant AI treatment[31]. The Exemestane and Letrozole Pharmacogenetics (ELPh) trial was a multicenter, prospective randomized study comparing adjuvant exemestane and letrozole that included patient reported outcomes (PROs) and adherence data. Within this study, 32.6% of patients discontinued adjuvant AI (median follow up 15.5 months +/- 9 months) with the primary reason being musculoskeletal symptoms. Of the entire study population, 24.4% discontinued adjuvant AI because of musculoskeletal symptoms. The median time to treatment discontinuation was 6.4 months[32].

2.2.5 Tolerance as a Predictor of Non-Adherence to Endocrine Therapy.

The ELPh trial reported on PROs and examined whether early changes in PROs predict AI discontinuation. In this study, health-related quality of life (HRQoL) was assessed using the EuroQOL Visual Analog Scale (EuroQOL VAS), depression was assessed using the Center for Epidemiologic Studies-Depression (CESD) tool, anxiety was assessed with the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), and symptom burden was assessed using the Breast Cancer Prevention Trial Symptom Checklist (BCPT-SCL). The BCPT-SCL was analyzed by symptom clusters of weight/body image, vasomotor, vulvovaginal, musculoskeletal,

cognitive, and mood. The PROs were assessed at regular intervals on adjuvant AI therapy. The musculoskeletal symptom burden assessment was noted to be rising at month 1 and significantly higher by month 3 and month 6 ($p = 0.023$, $p = 0.033$). Of the examined PROs, rising musculoskeletal scores and decreasing HRQOL scores were found to predict discontinuation of AI[33]. This study demonstrates that side effects develop early in patients on AIs and are predictive of early discontinuation and non-adherence. In the present study, we plan to assess if this can be looked at in a brief course of pre-ET to predict long term tolerance and adherence of adjuvant endocrine therapy.

2.2.6 Relevant Clinical Experience

The traditional approach to treatment of early stage breast cancer is local management with surgical resection via lumpectomy followed by adjuvant radiation and adjuvant endocrine therapy. There is significant clinical evidence that endocrine therapy can be safely and effectively used in a neoadjuvant approach in postmenopausal women[34]. Historically, neoadjuvant endocrine therapy was studied as a treatment approach for an elderly patient population that was not well suited to neoadjuvant chemotherapy or even surgery[35]. However, additional studies completed include multiple randomized trials that included healthier and younger postmenopausal patients randomized to neoadjuvant endocrine therapy or neoadjuvant chemotherapy. These studies have shown similar response rates between the two arms of treatment and improved toxicity profile in the endocrine therapy arms[36-38]. On the basis of this evidence, the NCCN Breast Cancer guidelines include “Neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor-positive tumors”[18]. While there is mounting clinical evidence for the use of neoadjuvant endocrine therapy in postmenopausal women with strongly ER positive breast cancer, the relatively small numbers within the trials and uncertain best endocrine therapy regimens in this setting has limited the routine use of this approach for a fit patient in clinical practice. It is for this reason that the present study is being conducted as an investigational approach.

2.3 Summary

The present study is designed to assess whether a three month course of pre-ET is an appealing, safe, and informative strategy to assist in formulating treatment regimens for geriatric breast cancer patients. The ultimate goal of our research is to develop a novel and comprehensive tool that will allow patients and providers to make informed decisions about treatment regimens for early stage breast cancer patients. Our future intention is to expand upon this research by using the PROs in combination with other factors such as demographic and breast cancer histopathologic characteristics to generate a tool for recommendations on treatment for geriatric patients. This tool will guide decisions on breast surgery, adjuvant radiation, and choice of endocrine therapy and it will be based on evidence specific to the early stage geriatric breast cancer patient. This work may ultimately change the established order treatment is given to geriatric breast cancer patients and it will allow for patient-specific treatment plans without leading to under or overtreatment.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

The present study is felt to be of low risk of harm to potential participants. All patients will be recommended for standard breast conservation treatment based on available evidence and clinical practice guidelines. The potential for radiation omission is a current standard approach for patients eligible for this study and all patients will be counseled on the potential benefits and risks of radiation as in standard in clinical practice. The use of endocrine therapy is well established as a mainstay in ER positive breast cancer treatment and in general is a safe and effective practice. As noted in section 2.2.6, neoadjuvant endocrine therapy is a proven safe and effective treatment strategy. Within the present study, patients will be treated with a limited duration of pre-ET as a tool for better informing future treatment decisions. The present study is not intended to demonstrate that pre-ET is a more efficacious approach than upfront surgery, but rather that the information gained from the early exposure will ensure informed patient and physician decisions regarding adjuvant radiation therapy importance.

2.4.2 Known Potential Benefits

Breast cancer patients that opt for BCT are recommended to initiate breast RT within 4-12 weeks after completion of surgery. Adjuvant endocrine is not initiated until after completion of radiation. Therefore, providers and patients are currently forced to make a decision regarding RT without knowledge about endocrine therapy tolerance. This leads to the potential for omission of RT and nonadherence to endocrine therapy and a resultant higher risk of IBTR.

Data from prospective randomized controlled trials supports the omission of breast RT in elderly patients with early stage ER positive tumors. The patients in these trials were all treated with adjuvant endocrine therapy. However, outside of clinical trials, it is well established that adherence to adjuvant endocrine therapy is low and especially in elderly patients. The proposed study will provide necessary data regarding utilization of a short course of pre-ET to guide recommendations for post-operative RT.

While it is widely known that NCCN guidelines include RT omission for ER positive early stage breast cancer patients over 70, providers are not routinely offering this[5]. Within the present study, we propose a new treatment approach to try to better inform patients and providers on the decision to give or omit adjuvant RT. By treating patients with pre-ET for three months and assessing tolerance, the provider and the patient will have the opportunity for an informed discussion about the adjuvant treatment plan. Providers can educate patients on the role of endocrine therapy in decreasing IBTR with emphasis on the importance of this for patients omitting RT. Patients will know what sort of side effects they will experience on endocrine therapy and better assess their willingness and ability to tolerate five or more years of the medication. The goal is that careful assessment of PRO measurements while on three months of pre-ET can help the patient and provider better predict adherence to adjuvant endocrine therapy. Ultimately, this could result in a patient specific treatment plan that would decrease the risk of either over or under treatment of their disease.

2.4.3 Assessment of Potential Risks and Benefits

The present study is felt to be of low risk of harm to potential participants and may result in patient specific treatment plans that either decrease the risk of either over or under treatment of breast cancer in the geriatric population.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess whether pre-ET changes an individual's preference for adjuvant radiation treatment • To assess whether pre-treatment with endocrine therapy changes the surgical oncologist's preference for adjuvant radiation treatment	• Radiation preference question for participant pre and post pre-ET treatment • Radiation preference question for the surgical oncologist pre and post pre-ET treatment
Secondary	
• To obtain preliminary estimates to assess whether patient reported outcomes during pre-ET are predictive of long-term adjuvant endocrine therapy adherence • For those participants who agree to a radiation oncologist consultation, to assess whether pre-treatment with endocrine therapy changes the radiation oncologist's preference for adjuvant radiation treatment	• PRO assessments • Radiation preference question for the radiation oncologist pre and post pre-ET treatment
• To obtain preliminary data on the effect of pre-ET on decision outcomes for adjuvant therapy after BCS	• PRO assessments
Exploratory	
• To obtain exploratory data on recurrence-free survival and overall survival	• Recurrence-free survival and survival through 24 months

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter study of pre-ET tolerance to inform treatment decisions for adjuvant radiation in geriatric individuals with early stage, ER^+ breast cancer. Study therapy will include 90 days of pre-ET. Endocrine therapy options may include tamoxifen or AI (letrozole, anastrozole, or exemestane) and choice of endocrine therapy will be at the discretion of the treating physician. Following pre-ET, all individuals will undergo BCS. After BCS, enrolled participants and their physicians (surgical oncology, radiation oncology, and medical oncology) will finalize an adjuvant radiation and adjuvant endocrine therapy plan. Participants recommended for and accepting adjuvant RT will complete this as planned and then be recommended to re-start on adjuvant

endocrine therapy. Participants who do not have radiation will be recommended to restart on endocrine therapy after surgery. The choice and duration of adjuvant endocrine therapy will be determined by the treating medical oncologist. All participants regardless of their adjuvant therapy will be followed. Genomic profiling of the tumor may be performed if deemed clinically indicated by the treating medical oncologist and any recommended adjuvant chemotherapy will be completed prior to resumption of endocrine therapy in the adjuvant setting.

The primary objective is to assess whether pre-treatment with endocrine therapy changes an individual's or the surgical oncologist's preference for adjuvant radiation treatment. The secondary objective is obtain preliminary information to assess whether tolerance of pre-ET predicts adherence to adjuvant endocrine therapy.

Baseline assessment of patient beliefs and attitudes will be assessed using the Brief Illness Perception Questionnaire (BIPQ), the Beliefs about Medicines Questionnaire (BMQ) and BMQ Endocrine therapy subscale (BMQ ET), the Perceived Sensitivity to Medicine Scale (PSM), the Decision Regret Scale (DRS), and an additional novel survey of breast cancer and breast cancer medication specific patient beliefs.

Tolerance of pre-ET will be assessed using validated PRO assessments. Baseline and serial assessment of PROs will be conducted using the EORTC Quality of Life Questionnaire (QLQ-C30 and QLQ-BR23), the Breast Cancer Prevention Trial Symptom Checklist (BCPT-SCL), and the Center for Epidemiologic Studies Depression Scale Revised (CESD-R).

The Decision Regret Scale will be used to assess the effect of pre-ET on decision outcomes for adjuvant therapy after breast conservation surgery.

Adherence will be monitored throughout the endocrine therapy treatment period using patient report.

Up to 83 individuals will be enrolled.

4.2 Justification for Dose

Each of the endocrine therapy drugs will be used at standard doses described in the drug labels.

Radiation therapy will be completed in accordance with standard clinical practice.

4.3 End of Study Definition

Primary completion date is the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

Study completion date is the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

Collection and analysis of exploratory data may extend beyond the study completion date. The study may remain open with the IRB during this time.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. ECOG performance status 0-2
4. Females, aged ≥ 65 years
5. Diagnosed with anatomic stage I, ER positive, PR positive or negative, and HER2 non amplified invasive breast cancer and clinically negative nodes; any invasive breast cancer histologic subtype may be enrolled
6. Tumor size ≤ 2 cm
7. Patient has elected BCS as surgical choice
8. Eligible to receive tamoxifen or an aromatase inhibitor
9. Ability to take oral medication and be willing to adhere to the endocrine therapy for the 3 month period prior to BCS
10. Agreement to adhere to Lifestyle Considerations (see Section 5.4) throughout study duration

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior or current use of endocrine therapy for breast cancer
2. History of ipsilateral breast radiation
3. Pregnancy or lactation
4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
5. Current or planned use of a strong CYP2D6 inhibitor (e.g. Fluvoxamine, Paroxetine) and is not able to receive an endocrine therapy agent that does not use the CYP2D6 pathway.

5.3 Justification for Study Population

Each year, nearly half of newly diagnosed breast cancer cases are in women 65 years and older. Recent data from randomized controlled trials have shown that omission of adjuvant radiation following BCS does not result in a decreased survival in women 65+ years old with estrogen receptor (ER) positive, node negative, small (≤ 2 cm) breast cancers. Despite these findings and inclusion of criteria for omission of radiation in NCCN guidelines, studies show that RT is still frequently used after BCS in this population[5-7]. Without patient-level data regarding tolerance to endocrine therapy physicians and patients are unable to make informed decision regarding omission of RT. This study is limited to women ≥ 65 years of age to develop treatment

recommendations that can be tailored to specific geriatric considerations. On the basis that the initial studies supporting the omission of radiation in the geriatric population were conducted in women and that the surgical plans and side effect profiles from endocrine therapies differ between men and women, men will be excluded from this initial pilot study.

5.4 Lifestyle Considerations

Individuals will be educated on potential interactions between the endocrine therapies and other drugs. The prescribing information will be referenced by the treating physician to identify potential interactions. If a potential interaction exists (e.g. use of another strong CYP2D6 inhibitor with the use of tamoxifen), alternative endocrine therapies may be considered for the individual or the individual may be prescribed an alternative CYP2D6 inhibitor for the treatment of other conditions.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (for NIH studies) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

5.6 Strategies for Recruitment and Retention

Potentially eligible participants will be identified by treating clinicians. Participants who are interested in participating will have a consultation with a medical oncologist to discuss pre-ET.

6 STUDY INTERVENTION

6.1 Description of Study Intervention(s)

6.1.1 Endocrine Therapy

The choice of endocrine therapy will be determined by the medical oncologist. All endocrine therapy drugs are commercially available and will be prescribed at doses consistent with those described in the product label.

On the basis of the following criteria, the principal investigator has determined that the study meets the criteria for IND exemption.

1. **The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.**
   The present study is not intended to get a new FDA approval for any of the included endocrine therapy drugs.

2. **The study is not intended to support a significant change in the advertising for the product.**
   The present study is not intended to result in a change in the advertising for any of the included endocrine therapy drugs.

3. **The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.**
   Each of the included endocrine therapy drugs within the present study will be used at standard dosing, route of administration and schedule as indicated in the package inserts. The only change of use from the label is that the endocrine therapy will be administered as 3 months of pre-ET in addition to adjuvant therapy recommended for at least 5 years. While the endocrine therapy labels do not include pre-ET use, there is sufficient clinical evidence in the literature documenting the safety of pre-ET in hormone receptor positive breast cancer. This has been prospectively studied and deemed to be an appropriate treatment approach in selected patients. Based on these studies, the NCCN Breast Cancer guidelines include a line stating that “Neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor-positive tumors.” It is the investigator’s opinion that three months of pre-ET does not result in increased risk to the targeted patient population of ER positive breast cancer patients.

4. **The study is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in parts 56 and 50 (21 CFR parts 56 and 50).**
   The present study is submitted for internal review by both the Protocol Review Committee and the IRB and will be monitored closely.

5. **The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).**
   The present study is conducted in compliance with promotion and charging for investigational drugs.

6.1.2 Radiation Therapy

Radiation therapy will be administered in accordance with standard clinical practice.

6.2 Dosing and Administration

6.2.1 Endocrine Therapy

The dosing and administration of endocrine therapy will be in accordance with the drug label for each drug prescribed by the medical oncologist.

Individuals will not switch endocrine therapies during pre-operative endocrine therapy; however, an individual may stop endocrine therapy at any time during pre-operative therapy. Individuals who stop neo-adjuvant therapy prior to 90 days may still be eligible to receive adjuvant endocrine therapy.

Individuals may take different endocrine therapies during neo-adjuvant and adjuvant therapy.

Individuals may also switch endocrine therapies (e.g. switch from an aromatase inhibitor to tamoxifen) during adjuvant therapy.

6.2.2 Radiation Therapy

The dosing and administration of radiation therapy will be in accordance with standard clinical practice guidelines for the treatment of breast cancer.

6.2.3 Dose Modifications and Delays for Endocrine Therapy

Dose Modifications

No dose modifications of endocrine therapy are permitted.

Dose Delays

Neo-adjuvant Endocrine Therapy

No dose delays will be prescribed during pre-operative endocrine therapy.

Adjuvant Endocrine Therapy

Individuals may temporarily discontinue adjuvant endocrine therapy if recommended by the treating medical oncologist. Interruptions in adjuvant endocrine therapy should not last longer than 12 weeks per year. This is based on evidence from the SOLE trial in which patients on intermittent endocrine therapy (defined as at least 9 months per year) had no difference in survival compared to those on continuous endocrine therapy[39].

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Acquisition and Accountability

All endocrine therapy drugs will be commercially available. Individuals will receive a prescription for the endocrine drugs and the drugs will be dispensed from a licensed pharmacy. The cost of the drugs will be billed to the participant or the participant's insurance provider.

6.3.2 Formulation, Appearance, Packaging, and Labeling

Details may be found in the prescribing information for each endocrine therapy drug.

6.3.3 Product Storage and Stability

Details may be found in the prescribing information for each endocrine therapy drug.

6.4 Study Intervention Compliance

Participants will be asked about compliance with taking endocrine therapies as part of patient reported outcomes.

6.5 Registration and Treatment Allocation

All participants must sign the consent form prior to determination of eligibility for this study.

When a site is ready to enroll a patient, the following documentation must be scanned and emailed to the UVA Coordinating Center:

- Patient and staff signed signature page of the current informed consent form (ICF)
- Completed Inclusion/Exclusion checklist demonstrating subject eligibility
- Supporting documentation needed to confirm eligibility (lab results, scan results etc.)

Consult with the MCRO for instructions on sending this information. The Coordinating Center will consult with the Overall Study PI if questions arise in confirming eligibility. The UVA Coordinating Center will communicate the subject number to the enrolling site.

Registration will occur following verification of eligibility by the treating physician.

Participants who are consented and accrued to the study should be registered in OnCore in accordance with the Clinical Trial Management System Policy via the UVa OnCore Resources link in OnCore. General guidelines are available in the OnCore User Manual and Data Entry Guide.

Participants should receive their first study treatment within 2 weeks of registration.

Treatment allocation to receive either radiation and adjuvant endocrine therapy or adjuvant endocrine therapy after BCS will be discussed with participants during the process of informed consent. At enrollment and at the pre-operative visit, the surgical oncologist will be asked the radiation recommendation survey question (section 8.2.2). If the patient is seen by UVA radiation oncology during this time, the radiation oncologist will be asked the radiation recommendation survey question at enrollment and at the time of the pre-operative visit (section 8.2.2). The participant will also answer a radiation preference survey question at enrollment and at the pre-operative visit (section 8.2.2). Individuals will proceed with/without radiation and adjuvant endocrine therapy per standard clinical practice.

This study does not involve any randomization, blinding or masking procedures. Participants will be told which treatment they are receiving.

6.6 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. The participant should be asked about all medications that were administered ≤ 28 days prior to screening and throughout study treatment.

6.6.1 Prohibited Concomitant Medications

- Endocrine therapy not prescribed for the treatment of the breast cancer
- Current use of strong CYP2D6 inhibitors if participant is receiving tamoxifen.

6.6.2 Rescue Medicine/Supportive Care

Any reported side effects from the endocrine therapy should be managed by the treating physicians per usual standard of care. This includes recommendations for non-medication

supportive interventions such as acupuncture, physical therapy, etc. Physicians may also choose to prescribe additional medication with evidence for improving endocrine therapy side effects such as venlafaxine, duloxetine, or Nonsteroidal anti-inflammatory drugs. Any prescription medications will be prescribed per package labeling. Patients on endocrine therapy should have any routine standard of care monitoring as recommended by the treating oncologist. This includes annual LFT evaluation and annual gynecology evaluation for patients on tamoxifen if recommended by treating oncologist. This includes periodic assessment of bone density and appropriate treatment of low bone density as recommended by the treating oncologist.

7 STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that would warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

For safety related concerns, the study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Principal Investigator, IRB, and Data and Safety Monitoring Committee.

Participants receiving study treatment at the time of study discontinuation should complete procedures described in section 7.3.

7.2 Participant Discontinuation/Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

A participant's study treatment would be discontinued for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant per the discretion of the principal investigator.
- Disease progression which requires discontinuation of the study intervention

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant decision to withdraw from study treatment and/or the study
- Initiation of prohibited intervention or medication
- Dose delays beyond those permitted in section 6.2.3

The reason for participant discontinuation or withdrawal from study treatment will be recorded on the CRF. Participants who sign the informed consent and who are registered will not be replaced. Participants that withdraw from the study (not only from study treatment, but all study follow-up) will not be contacted for any further study visits.

7.3 Procedures for Discontinuation of Study Intervention

Discontinuation from endocrine therapy or radiation therapy does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected and procedures to be completed at the time of study intervention discontinuation are included in the schedule of events (Appendix 1).

7.4 Lost to Follow-Up

A participant will be considered lost to follow-up if she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff. The study staff will attempt to contact the participant up to 3 times.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant by phone.
- These contact attempts should be documented in the study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Clinical Assessments

The study team will have access to tests and procedures conducted prior to the study that were completed as part of an individual's standard clinical care. These include information about medical history, results from prior physical exams or laboratory tests, pathology reports, and clinic notes.

The following evaluations will be performed on an outpatient basis. Please refer to Appendix 1 for the schedule of activities.

8.1.1 Exams and Evaluations

The following will be performed by a licensed clinician:

- Medical History
- Physical Exam -Breast exam and axillary lymph node exam.
- Vital signs (pulse, blood pressure)
- Start and stop dates of pre-ET and adjuvant endocrine therapy; reason for discontinuation

8.1.2 Assessment of Adverse Events

Each participant will be evaluated by a licensed clinician at each study visit. The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be used for the characterization and grading of adverse events.

Toxicities will be captured from the exams and evaluations. For each AE, date of onset, duration, grade, and attribution will be noted in the individual's study chart, or study documents, or in the clinic note and will be entered in the UVA Cancer Center database.

In the event of an AE, appropriate action will be taken to ensure adequate care for the participant. If the participant is still on protocol, treatment delay or withdrawal from the protocol will be considered according to the protocol guidelines (section 6.2.3).

8.2 Participant Questionnaires

8.2.1 Patient Belief Surveys

Baseline data regarding patient beliefs and perceptions about their breast cancer and endocrine therapy will be collected prior to starting pre-ET.

The Brief Illness Perception Questionnaire (BIPQ, Appendix 3) is a 9 item scale that measures patients' beliefs about their illness including consequences, timeline, personal control, treatment control, identity, coherence, emotional response, and causes[40]. Responses are on a 10 point Likert scale and patients also identify 3 causes of their breast cancer.

The Beliefs about Medicines Questionnaire (BMQ) is an 8 item scale that measures patients' beliefs about medicines using a 5-point Likert scale[41]. The BMQ-ET (Appendix 4) is an adapted version of the BMQ that includes 10 questions on a 5 point Likert scale that assess patients' beliefs about their endocrine therapy[42]. The BMQ-ET will be assessed at baseline.

The Perceived Sensitivity to Medicine Scale (PSM, Appendix 5) is a 5 item assessment of patients' perceived sensitivity to medications at baseline using a 5 point Likert scale[43].

The UVA Breast Cancer Belief Survey (Appendix 6*),* **a novel series of questions regarding patient beliefs about breast cancer and breast** cancer medications, will also be administered.

8.2.2 Radiation Preference Questions

The patient and the surgical oncologist will answer the radiation preference question at enrollment and at the pre-operative visit. If the patient has a radiation oncology consultation on or before Day 1, the radiation oncologist will answer the radiation preference question at Day 1 and at the pre-operative visit per Appendix 1. Answers to questions are measured on a 4 point Likert scale. Before IRB approval of protocol version 01-27-2021, radiation preference questions were asked at a post-operative visit and not the pre-operative visit. Subjects who have had their pre-operative visit but not their post-operative visit after protocol v 01-27-2021 is IRB approved should have their radiation preference questions asked post-operatively to ensure that this data point is collected.

Enrollment Patient Question: Based on the conversations you have had with your breast cancer doctors thus far, how likely are you to decide to do radiation after your surgery?

1 = Extremely Unlikely	2 = Unlikely	3 = Likely	4 = Extremely Likely

Enrollment Surgical/Radiation Oncologist Question: Based on your current knowledge of this patient's breast cancer and discussions with her about her treatment plan, how would you characterize the strength of your recommendation for adjuvant radiation therapy?

1 = Extremely weak	2 = Weak	3 = Strong	4 = Very Strong

Pre-operative Patient Question: Based on the conversations you have had with your breast cancer doctors thus far and your experience with the breast cancer medicine taken before surgery, how likely are you to decide to do radiation after your surgery?

1 = Extremely Unlikely	2 = Unlikely	3 = Likely	4 = Extremely Likely

Pre-operative Surgical/Radiation Oncologist Question: Based on your current knowledge of this patient's breast cancer, discussions with her about her treatment plan, and her experience with pre-ET, how would you characterize the strength of your recommendation for adjuvant radiation therapy?

1 = Extremely weak	2 = Weak	3 = Strong	4 = Very Strong

8.2.3 Patient Reported Outcome Surveys

Patient reported outcomes will be assessed as indicated in Appendix 1.

Health related quality of life (HRQOL) will be assessed using the EORTC QLQ-C30 and QLQ-BR23 (Appendix 7), which is a validated and reliable 53 question assessment of general health and wellbeing[44].

Depression will be assessed using the Center for Epidemiologic Studies Depression Scale Revised (CESD-R, Appendix 8), which is a 20 item assessment to measure symptoms of depression in nine different groups as defined by the American Psychiatric Association Diagnostic and Statistical Manual, fifth edition. The score ranges from 0 to 60 and scores greater than 16 indicate depressive symptoms[45].

General symptom burden while on endocrine therapy will be assessed using the Breast Cancer Prevention Trial Symptom Checklist (BCPT-SCL, Appendix 9) in which 47 symptoms are assessed on a scale of 0 to 4 (high burden) with plans to follow symptom clusters used in the ELPh trial of weight/body image, vasomotor, vulvovaginal, musculoskeletal, cognitive, and mood[33,46,47].

Data will be collected on patient adherence to endocrine therapy using patient report via two simple questions (Appendix 10).

8.2.4 Treatment Decision Survey

A survey to assess treatment decision will be given as indicated in Appendix 1. The survey can be found in Appendix 11.

8.2.5 Decisional Conflict and Decision Regret Scales

The Decisional Conflict Scale (DCS)[48] and Decision Regret Scale (DRS)[49] are patient reported outcome surveys that will be used to assess subjects' perceptions related to their medical choices (Appendix 12 and Appendix 13). The DRS does not need to be completed at baseline because it relates to past decisions related to a medical choice (radiation and endocrine therapy) that is not made at baseline.

8.3 Recurrence and Survival

Recurrence is defined as a biopsy-proven diagnosis of breast cancer in the index quadrant of the previously treated breast cancer. Patients will be evaluated routinely post-treatment to assess for local recurrence, loco-regional recurrence, contralateral breast cancer recurrence and distant disease. Clinical breast exams will be performed per standard of care every 3-6 months by the treating physicians. Mammography will be performed annually if patient is still eligible for breast cancer screening based on standard practice guidelines and images will be reviewed for evidence of recurrence.

9 DATA AND SAFETY MONITORING PLAN

In the following section, there are references to "days", "calendar days", and "working days". References to "days" should be interpreted as calendar days. Working days include Monday through Friday with the exception of the following federal holidays (New Year's Day, Marin Luther King Jr.'s birthday, Washington's birthday, Memorial Day, Independence Day, Labor Day, Columbus Day, Veteran's Day, Thanksgiving Day, Christmas Day). Please note that the difference in reporting between the FDA required reporting (10 working days) and the UVA IRB requirement of 10 calendar days for Unanticipated Adverse Device Effects (UADEs)(for device studies only). For reporting to the IRB, follow the more conservative guideline (e.g. calendar days).

9.1 Adverse Events and Serious Adverse Events

9.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

9.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: A planned medical or surgical procedure is not, in itself, an SAE

9.1.3 Classification of an Adverse Event

9.1.3.1 Severity of Event

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be used for the characterization and grading of adverse events.

9.1.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely

to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal

  relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.1.3.3 Expectedness

Pre-operative Endocrine Therapy

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention in the prescribing information for each drug.

9.1.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition (including a laboratory abnormality) that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the

study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

A member of the study team will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days (for non-serious AEs) or anytime (for SAEs considered related to the study intervention) after the last day of neo-adjuvant endocrine therapy, or until another therapy is started. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.1.5 Adverse Event Reporting

AEs must be recorded into the University of Virginia Cancer Center (UVA Cancer Center) database per guidelines in Table 1.

Table 1: Recording Guidelines for UVA

Cancer Center Database

Medium Risk Studies Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment									
	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected	Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 15 days	OnCore 15 days
Possible Probable Definite	OnCore 30 days	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 15 days	OnCore 15 days	OnCore 15 days	OnCore (24-hrs)* 7 days
*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours									

9.1.6 Serious Adverse Event Reporting

The study clinician will report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or drug labels, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the UVA Multisite Clinical Research Office (UVA MCRO/Sponsor) and should be provided as soon as possible

Site Reporting Requirements

- Report to the UVA MCRO within 24 hours from the time the study team received knowledge of the event according to UVA MCRO requirements.
- Report to your IRB in accordance with your IRB guidelines.

Multi-Site Principal Investigator / UVA MCRO Reporting Requirements

- The Sponsor (or the UVA MCRO on behalf of the sponsor) is responsible for notifying the UVA IRB-HSR of any event resulting in death that is deemed DEFINITELY related to (caused by) study within 24 hours from the time the study team received knowledge of the event. Report using IRB Online and by telephone.

- The Sponsor (or the UVA MCRO on behalf of the sponsor) is responsible for notifying the UVA IRB-HSR of any serious, unexpected, related adverse event within 7 calendar days from the time the study team receives knowledge of the event. Timeline includes submission of signed hardcopy of AE form. Report using IRB online.

9.2 Reporting Events to Participants

If there is any new information relevant to the participant's willingness to continue to participate in the study, such as if there are new risks of the study treatment identified that were not included on the consent form that the participant signed, the study team will contact the participant to discuss this information. If the participant is still receiving study treatment, the study team will present the participant with an updated consent and confirm that he or she wants to continue receiving study treatment. The Principal Investigator will determine whether new risks are applicable to participants who are in follow-up, whether participants need to be notified, and whether re-consenting is required.

9.3 Unanticipated Problems

9.3.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs)(may include a data breach) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.3.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

Site Reporting Requirements

- UPs that are SAEs will be reported in accordance with the guidelines for SAE reporting.

- UPs that are not adverse events, protocol deviations or data breaches (see section 9.4.2 for reporting for data breaches)
    - Report to the UVA MCRO within 2 calendar days from the time the study team receives knowledge of the event.
    - Report to your IRB of record in accordance with your IRB guidelines.

Multi-Site Principal Investigator/UVA MCRO/Study Team Reporting Requirements

- Report UPs that are not adverse events or protocol deviations to the UVA IRB-HSR within 7 calendar days from the time the study team receives knowledge of the event. Report using the Unanticipated Problem Report form.

- All UPs will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with institutional policies.

9.3.3 Reporting Unanticipated Problems to Participants

If during the course of the study there is an unanticipated problem that affects current or past participants, affected participants will be contacted if needed.

9.4 Data Breach

9.4.1 Definition of Data Breach

An unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

9.4.2 Reporting a Data Breach

Site Reporting Requirements

- Report to the UVA MCRO within 24 hours from the time the study team receives knowledge of the event.

- Report to your IRB of record in accordance with your IRB guidelines.

Multi-Site Principal Investigator (or UVA MCRO on behalf of the sponsor) Reporting Requirements

- Report to the UVA Corporate Compliance and Privacy Office as soon as possible and no later than 24 hours from the time the incident is identified. Report by telephone.

- Report to ITC if the breach involves electronic data. Report as soon as possible and no later than 24 hours from the time the incident is identified. Refer to the following for details: *http://security.virginia.edu/report-information-security-incident*.

- Report to UVA police if the breach includes such things as stolen computers. Report by telephone.

9.5 Protocol Deviation

9.5.1 Definition of Protocol Deviation

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or site staff. These protocol violations may be major or minor violations.

9.5.2 Reporting of a Protocol Deviation

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents.

Site Reporting Requirements

- Report major deviations to the UVA MCRO within 4 calendar days from the time the study team receives knowledge of the event. Consult the MCRO for instructions on recording minor deviations.

- Report to your IRB of record in accordance with your IRB guidelines.
  (For sites that use the UVA IRB-HSR as the IRB of record, the UVA MCRO will report to the UVA IRB-HSR as required—see sponsor reporting requirements)

Multi-Site Principal Investigator Reporting Requirements

- Report to the UVA IRB-HSR major deviations within 7 calendar days from the time the study team received knowledge of the event. Report using the Protocol Deviation and Protocol Exception Reporting Form.

For minor deviations, please reference the UVA IRB-HSR website for tips for recording minor deviations

9.6 Participant Withdrawals/Dropouts Prior to Study Completion

Participants who withdraw consent and those dropping out of the study secondary to an AE will be reported to the IRB yearly on the IRB continuation form.

10 STATISTICAL CONSIDERATIONS

10.1 Study Design Overview

This is a prospective multicenter study to obtain preliminary information on whether pre-treatment with endocrine therapy changes preference for adjuvant radiation treatment as considered by the participant or the surgical oncologist. In addition, we aim to capture a range of patient reported outcomes over time to explore the possibility that these measures will be useful predictors of adherence to post-operative endocrine therapy.

10.2 Endpoints, Statistical Hypotheses and Estimation

Assessment of the primary study objectives will be based upon answers to the radiation preference question for study participants and surgical oncologists separately. Change in preference is measured as a binary variable (yes/no) with a coding of ‘yes’ if answers between the pre-op and on-study (baseline) response differ (no to yes; or yes to no). No difference in response is coded as ‘no’.

Hypothesis test 1: To determine if pre-treatment with endocrine therapy changes participant preference for adjuvant radiation treatment in the participant study population by at least 10% with a one-sided binomial test.

Hypothesis test 2: To determine if pre-treatment with endocrine therapy changes surgical oncologist preference for participant specific adjuvant radiation treatment in the participant study population by at least 10% with a one-sided binomial test.

Estimation: To estimate the association of pre-treatment PRO measures on the probability of long-term adjuvant endocrine therapy adherence.

10.3 Sample Size Determination

Sample size estimation is based upon accruing a sufficient number of participants to assess the primary objective separately for participants and surgical oncologist responses with an overall one-sided 10% type I error rate (5% for each individual test). Accrual of 70 evaluable participants provides 90% power to test for a change in adjuvant radiation treatment preference between the pre-op visit and on-study in the participant study population from a null difference of 5% to an alternative of at least 15% with a target one-sided 5% level binomial test (by exact numeration). Accrual of 70 evaluable participants also provides 90% power to independently test for a change

in adjuvant radiation treatment preference of the surgical oncologist between the pre-op visit and on-study in the participant study population from a null difference of 5% to an alternative of at least 15% with a one-sided 5% level binomial test. For fixed target size and power, the detectable difference increases from 10% to 15% when the assumed null varies within the expected range of 5% to 20%.

This is a pilot study to obtain preliminary data to estimate which if any PRO measures are associated with adherence to post-operative endocrine therapy. With n=70, a logistic regression of the dependent variable of adherence or not to endocrine therapy by year 2 on a continuous PRO measure score achieves 80% power at a 5% significance level to detect an odds ratio of 2 when the probability of adherence is 25%. These error rate estimates assume no adjustment for multiple comparisons among the different PRO.

10.4 Accrual

Maximum target sample size is estimated at 83 eligible participants which adjusts for a 15% lost to follow-up/dropout rate. In 2018 and 2017, 70 and 78 patients, respectively, met the basic inclusion criteria at UVA. Assuming 60% of future patients will agree to enroll in the study, target accrual to the study should be achieved in less than two years.

10.5 Statistical Analyses

10.5.1 Analysis populations

a) Safety: All study participants who start protocol defined pre-ET.
b) Primary objective: All eligible study participants who start protocol defined pre-ET for which there is an answer to both the on-study and pre-op radiation question. A participant is considered ‘eligible’ if she satisfies all inclusion and exclusion criteria.
c) Secondary objective for adherence: All eligible study participants who start protocol defined pre-ET and who provide PRO measures at on-study and have information on post-op adherence to endocrine therapy.
d) Secondary objective for radiation oncologist’s preference: The subset of eligible study participants who start protocol defined pre-ET for which there is an answer to both the on-study and pre-op radiation question from a radiation oncologist.

10.5.2 Analyses

Primary analyses will not adjust for center. Summary measures will be described overall and by center. Demographics and baseline characteristics will be described for all study participants. Characteristics to be examined include: race/ethnicity, age, performance status, stage, ER, PR and HER-2 status, histologic subtype, tumor size date of diagnosis.

Adverse events will be coded based upon the NCI CTCAE v5.0. Safety will be reported by frequency and severity of adverse events.

The primary analysis will be based upon responses from a) study participants and b) surgical oncologists to the radiation questions, separately, without adjustment for center. For each response group, the proportion of responses that differ from the pre-op visit compared to the on-study (baseline) response (yes to no; or no to yes) will be calculated along with 95% confidence intervals. For each group, we will test that pre-ET resulted in a change in preference for adjuvant

radiation therapy in more than 10% of participants compared to no change with a one-sided 5% level exact binomial test.

Graphical methods will be used to display the PRO outcomes over time. On the most basic level, logistic regression models with adherence to post-op endocrine therapy at 2 years as the dependent outcome and the range of PRO measurement as independent factors will be used to obtain initial estimates of the predictive value of the protocol defined PRO to determine adherence. Other exploratory repeated measures models will be explored to determine if changes over time are also associated with determination of non-adherence. Exploratory analyses could include the assessment of PRO for quality adjusted life years or healthy-year equivalents. In all exploratory models, individual or simultaneous associations will be deemed promising for factors with $p < 0.1$.

The secondary analysis related to the radiation oncologist's preference will be based upon the subset of pre and post pre-ET responses from for the consulting radiation oncologist. The proportion of responses that differ from the pre-op visit compared to the on-study (baseline) response by at least one point (in either direction) will be calculated along with a 95% confidence interval.

Descriptive summaries and simple tabulations will be used to describe results from the preliminary data on justification of participant response for those whose preference changed.

At final analysis the Product-Limit method of Kaplan & Meier will be used to estimate recurrence-free survival and overall survival, along with 90% CIs. Recurrence-free survival is defined as the time from start of pre-ET to time of recurrence or death from any cause, whichever occurred first. Participants who do not experience an event (recurrence or death) will be censored at date of last clinical assessment. Overall survival is defined as the time from start of pre-ET to time of death from any cause. Participants who do not experience an event (death) will be censored at date of last contact.

10.5.3 Interim Analyses and Pausing Guidelines

There will be no planned interim analyses for testing the primary hypotheses. Participants will be monitored for adherence to pre-ET and for pre/post response data capture. Pre-operative ET treatment adherence is expected to be close to 100% thus an indication of a lower rate would be cause for pause. After accrual of 50% of eligible participants, if the upper limit of a 90% CI around the adherence rate does not contain 80% then the study will be paused to assess the cause, which may result in no modification, study modification or closure. Similarly, the study will be monitored for any indication that use of 3 months of pre-ET negatively impacts surgical completion with the same decision guideline.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory and Ethical Considerations

11.1.1 Informed Consent Document

Consent forms will be written in accordance with federal regulations and will be reviewed and approved by the IRB-HSR prior to use. Participants will be given a consent form to review and a

member of the study team will be available to answer any questions. Informed consent will be obtained from each participant prior to conducting any study-specific procedures or administering study treatment.

Signed consent forms and other research records will be retained in a confidential manner.

11.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. A member of the study team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Informed consent may be done via Telemedicine. Results from procedures completed prior to consent for standard of care purposes may be used for research purposes. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests (if applicable) in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA. When possible, specimens will be coded with IDs (not MRN or name). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Principal Investigator, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure

location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in OnCore. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the University of Virginia Cancer Center, Office of Clinical Research research staff will be secured and password protected.

To further protect the privacy of study participants, a Certificate of Confidentiality will automatically be issued by the National Institutes of Health (NIH) and an application is not necessary. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

11.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the University of Virginia.

At the end of the study, all study data will be archived and maintained by the PI in accordance with institutional policies.

11.1.5 Safety Oversight and Monitoring

The University of Virginia Cancer Center Data and Safety Monitoring Committee (CC DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The UVA CC DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The UVA CC DSMC will meet every month for aggregate review of data. Tracking reports of the meetings are available to the PI for review. Issues of immediate concern by the DSMC are brought to the attention of the Principal Investigator (and if appropriate to the PRC and IRB) and a formal response from the Principal Investigator is requested. Per the UVA Cancer Center NIH approved institutional plan, this study will be audited approximately every 6 months. The audit may include direct access to source data/documents.

Any study under the purview of the University of Virginia HSR-IRB is subject to review. Studies are chosen for Post-approval Monitoring either a) at random or b) requested by a study team member or any member of the IRB-HSR.

The purpose of Post-approval Monitoring audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled. Post-approval monitoring is done by staff within the office of the Vice President for Research (VPR) in accordance with their Standard Operating Procedures. The conduct of an on-site review may include but is not limited to:

- requests for progress reports from investigators,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- contacts with research subjects, or
- observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:
    - Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
    - IRB is made aware of a complaint or concern with regard to the informed consent process; or
    - IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

Additionally, clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The UVA Coordinating Center will implement ongoing monitoring activities for this study to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion.

- Monitoring may be conducted either remotely or on-site. For remote visits, each institution will be required to provide redacted source documents for review or appropriate access to the EMR. The UVA MCRO will provide the Participating Institution with a follow-up letter following completion of the monitoring visit which should be maintained in the site regulatory files. The schedule for monitoring may be adjusted according to subject accrual and data quality. The Investigator will be notified in advance of each visit.

- Independent audits may be conducted by each institution according to institutional guidelines. Results of these audits may be requested by the UVA Coordinating Center.

11.1.6 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct and data, documentation and completion according to institutional policies.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the study team for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

11.2 Data Handling and Record Keeping

11.2.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data will be collected using a password-protected, centralized electronic case report form called **ON**-line **C**linical **O**ncology **R**esearch **E**nvironment = **Oncore**.] Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

11.2.2 Study Records Retention

Record retention will be in accordance with IRB-HSR and institutional policies.

11.3 Publication and Data Sharing Policy

This trial will be registered at clinicaltrials.gov, and results information from this trial will be submitted to clinicaltrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. This study will be conducted in accordance with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

11.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have

a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the institution has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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13 APPENDICES

Appendix 1: Schedule of Events

Procedures	**Screening**	**Pre_ET Period**[c]			**Pre-Op Visit**	**Surgery**[j]	**Radiation**	**Adjuvant Treatment Period**			
Timeframe	≤ 21 days prior to registration unless otherwise noted	Day 1	Day 30 (+/- 7 d)	Day 90 (+/- 7 d)		2-8 weeks after Day 90[j]		Visit 1 (1-90 days after surgery, chemotherapy completion, or RT completion [b] whichever is later)	Visit 2 (6 months after visit 1) (+/- 30 d)	Visit 3 (12 months after visit 1) (+/- 30 d)	Visit 4 (24 months after visit 1) (+/- 30 d)
Informed consent	X										
Demographics	X										
Medical history	X										
Physical exam /vitals	X		X	X	X			X	X	X	X
Endocrine Therapy		Taken daily as directed[i]						--Taken daily as directed[d]--			
BCS						X					
Radiation Therapy							X[b]				
Adverse event review and evaluation			X	X	X[g]						
Patient Beliefs Qs		X									
PRO Surveys		X[a]	X	X				X	X	X	X
Treatment Decision Survey								X			
Subject RT preference question		X			X						
Surgeon RT preference question		X[h]			X						
Radiation Oncologist RT preference question		X[f,h]			X[f]						
Decisional Conflict Scale		X			X						
Decision Regret Scale									X	X	X
Recurrence/Survival[e]								X	X	X	X

[a] Patient reported outcome surveys should be completed prior to first dose of endocrine therapy.
[b] Radiation therapy will be scheduled and administered in accordance with standard clinical practice and as recommended by the treating radiation-oncologist.
[c] For patients who do not tolerate pre_ET and discontinue early, they will continue to be followed as indicated in the schedule above beginning at the pre-op visit.

[d] Some individuals may choose to refuse adjuvant endocrine therapy, but will continue to be followed as indicated in the schedule above. Some Individuals will continue beyond 24 months of endocrine therapy as directed by their oncologist based on standard of care recommendations.
[e] Tumor imaging will not be required at visits 1-4 to assess recurrence. Recurrence will be assessed using data from breast examinations conducted during the visit and prior results from imaging completed as part of standard clinical practice.
[f] This is not applicable if participant has not been seen by Radiation Oncology prior to starting pre-ET (radiation oncology consultation on or before Day 1).
[g] After the day 90 visit but prior to surgery.
[h] Questionnaire to be completed on day 1 or within +7 days.
[i] After the day 90 visit, participants may continue the pre-operative endocrine therapy until 2 weeks before surgery per clinician discretion based on standard of care recommendations for the pre-operative treatment.
[j] Participants need to be off endocrine therapy for at least 2 weeks and no more than 8 weeks prior to surgery

Appendix 2: Protocol Amendment History

Version Date	Description of Change	Brief Rationale
V25 February 2023	Title page, Statement of Compliance: Updated to add NIH as a funding source and to require following the terms and conditions of the award 11.1.3: Added language regarding a Certificate of Confidentiality 11.3: Added language regarding abiding by the NIH Public Access Policy	The study has received an NIH R21 grant to fund the study
	8.2.5: Added a sentence excluding the DRS from baseline	The decision that is of interest hasn't occurred yet at baseline
	1.2 Schema: Changed "14" to "1 - 90" days after surgery or radiation for adjuvant endocrine therapy	Internal consistency
V24 June 2022	Revised TOC and made formatting changes	To correct TOC and formatting
	In Section 6.6, removed language indicating the concomitant medications need to be recorded in the case report forms	To reduce study team burden by reducing extraneous information collection
V23 March 2022	In the study calendar, revised the follow-up Visit 1 to broaden the window from 60 days +/- 30 days to any time 1-90 days past surgery, chemotherapy completion, or RT completion, whichever is later.	To align with clinical practice
V26 January 2022	Updated TOC and made formatting revisions	To correct formatting
	Changed the title of the study from "A Pilot Study of Neoadjuvant Endocrine Therapy Tolerance to Inform Treatment Decisions for Adjuvant Radiation in Geriatric, Early Stage ER+ Breast Cancer" to "Pre-Operative Window of Adjuvant Endocrine Therapy to Inform Radiation Therapy Decisions in Older Women with Early-Stage Breast Cancer." Changed the Study ID from "Breast 52" to "POWER"	To differentiate this study from a different study with a similar title, and to give the study a more recognizable ID.
	Added information to include sites external to UVA. This includes additional reporting requirements, addition of information for VCU, and addition of information regarding the MCRO	To expand this study in allowing additional sites to participate in this clinical trial

	Replaced “neoadjuvant” with “pre-operative endocrine therapy (pre-ET)” in most places when referencing this study therapy	For clarity
	Added language to the first secondary endpoint	Clarity
	Added a secondary endpoint to include assessment of the effect of pre-ET on decisional outcomes for adjuvant therapy after BCS	To expand the study endpoints/objectives
	Removed UVA-specific language from Section 5.6 regarding process for recruitment.	To allow external site(s) to follow their established procedures
	Clarified that radiation oncologists should see subjects on or at Day 1 to answer the radiation preference questions, and that the questions should be answered at Day 1 and at the pre-operative visit.	Clarity
	Added the Decisional Conflict Scales and Decision Regret Scale to the study, including in the calendar and appendices	To assess subjects’ perceptions related to their medical decisions
	Added a Treatment Decision Survey at Day 1 of adjuvant therapy and added this survey to the appendix	To assess why participants made decisions about their treatment
	Removed the mild, moderate, and sever grading guidelines in section 9.1.3.1	AEs should be graded according to the CTCAE. Events that do not have their own term should be graded with the “other” category
	In Section 10.2, clarified that the pre-op and on-study responses measuring change in preference can be no to yes or yes to no	Clarity
	In the study calendar, lengthened the window for Visit 1 in the adjuvant treatment period and clarified the timeframe for this visit relative to chemotherapy completion	For clarity, and to make the calendar easier to follow
	In the study calendar, clarified with a footnote that after the day 90 visit, participants may continue the pre-operative endocrine therapy until 2-8 weeks before surgery based on clinician discretion and SOC. Clarified that the surgery should occur 2-8 weeks after Day 90. Fixed a footnote at Rad Onc RT preference day 1 (changed from “i” to “h). Clarified footnote “h” to specify that the footnote applies to the questionnaires. Added footnote “j” to Surgery visit to clarify that participants should be off of	For clarity and correctness.

	endocrine therapy for at least 2 weeks and no longer than 8 weeks prior to surgery.	
	In the study calendar, expanded the visit timeframe windows to 30 days for adjuvant treatment visits 2, 3, and 4	To reduce unnecessary restrictions
V27 January 2021	Updated TOC	To reflect shifted page numbers
	Formatting revisions throughout document	To correct formatting
	Updated the title sheet with the NCT number	To update NCT information
	In Sections 1, 2 and 5, updated the Prime II data and changed age inclusion criteria from females ≥ 70 to females ≥ 65	To reflect updated data presented from the PRIME II trial which includes patients ages 65 and above
	In Sections 6.5, 8.2.2, 10, and 13, revised the schedule of the radiation preference questions to occur at the pre-op visit instead of the post-op visit	To increase compliance with this study procedure
	In Section 11.1.2, added that consent may occur via Telemedicine	To allow for the use of telemedicine
	In Appendix 1 Schedule of Events, added physical exam/vitals to the Pre-Op Visit	Physical exam/vitals are part of the pre-op visit (standard of care)
	In Appendix 1 Schedule of Events and schema, removed the Post-Op visit	Visit is not needed, as no study procedures are performed at the Post-Op visit
	In Section 13 (Appendix 10), updated the adherence questions	To update the adherence questions
V18 March 2020	Listed additional radiation oncologist sub-investigators on the coverpage.	To address secondary endpoint regarding radiation oncologist RT therapy preference
	Updated TOC.	To address use of CESD-R and sections shifted with described revisions
	CESD-R added in abbreviations, section 4.1, 8.2.3 and appendix 8.	To replace the HADS for assessment of depression
	Added details regarding radiation oncologist RT preference questions in synopsis, section 3, 6.5, 8.2.2 and appendix 1.	To address secondary endpoint regarding radiation oncologist RT therapy preference
	Added pre-operative visit and footnotes in appendix 1	To address AE assessment prior to surgery and RT preference questions window
	Added “not applicable” response option in appendix 10 question 1 regarding how often subjects take ET.	For day 1 of pre-ET and visit 1 of adjuvant ET
	Reformatted surveys in appendix 3, 4, 5, and 6.	To improve readability and mimic participant surveys.

V04 November 2019	Table 1 (recording guidelines for high-risk studies) was revised to include recording guidelines for medium risk studies. Updated page numbers in TOC	The PRC reviewed this study and determined the study meets the criteria for a medium risk study.
	Formatting revisions throughout document	Formatting corrections
	Updated page numbers in TOC	Sections shifted with described revisions

Appendix 3: The Brief Illness Perception Questionnaire (BIP-Q)

Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. J of Psycho Res 2006;60: 631-637.

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?											
No affect at all	0	1	2	3	4	5	6	7	8	9	10	**Severely affects my life**
How long do you think your illness will continue?											
A very short time	0	1	2	3	4	5	6	7	8	9	10	**Forever**
How much control do you feel you have over your illness?											
Absolutely no control	0	1	2	3	4	5	6	7	8	9	10	**Extreme amount of control**
How much do you think your treatment can help your illness?											
Not at all	0	1	2	3	4	5	6	7	8	9	10	**Extremely helpful**
How much do you experience symptoms from your illness?											

No symptoms at all	0	1	2	3	4	5	6	7	8	9	10	**Many severe symptoms**
How concerned are you about your illness?												
Not at all concerned	0	1	2	3	4	5	6	7	8	9	10	**Extremely concerned**
How well do you feel you understand your illness?												
Don't understand at all	0	1	2	3	4	5	6	7	8	9	10	**Understand very clearly**

How much does your illness affect you emotionally (e.g. does it make you angry, scared, upset or depressed)?

Not at all affected emotionally	0	1	2	3	4	5	6	7	8	9	10	**Extremely affected emotionally**

Please list in rank-order the three most important factors that you believe caused <u>your illness</u>. *The most important causes for me*:

1.

2.

3.

Appendix 4: Beliefs about Medicines Questionnaire

General:

Horne R, Weinman J. Patients beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psycho Res 1999;47(6): 555-567.

For the following questions, please circle the number that best corresponds to your views:

1. Doctors use too many medicines.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
2. People who take medicines should stop their treatment for a while every now and again.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
3. Most medicines are addictive.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
4. Natural remedies are safer than medicines.				

1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
5. Medicines do more harm than good.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
6. All medicines are poisons.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
7. Doctors place too much trust on medicines.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
8. If doctors had more time with patients, they would prescribe fewer medicines.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree

Endocrine Therapy:

Brett J et al. Psychometric properties of the Beliefs about Medicine Questionnaire-adjuvant endocrine therapy (BMQ-AET) for women taking AETs following early-stage breast cancer. Health Psychol Open 2017:1-8

9. My health depends on my hormone treatment.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
10. My life will be impossible without my hormone treatment.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
11. Without my hormone treatment I will be very ill.				

1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
12. My health in the future will depend on my hormone treatment.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
13. Having to use my hormone treatment worries me.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
14. I sometimes worry about the long-term side effects of my hormone treatment.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
15. My hormone treatment is a mystery to me.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
16. My hormone treatment will disrupt my life.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
17. I sometimes worry about becoming too dependent on my hormone treatment.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
18. My hormone treatment protects me from getting worse.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree

Appendix 5: Perceived Sensitivity to Medicine Scale

Horne R, Faasse K, et al. The perceived sensitivity to medicines (PSM) scale: an evaluation of validity and reliability. Br J Health Psychol 2012;18 (1):18-30.

1. My body is very sensitive to medicines.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
2. My body overreacts to medicines.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
3. I usually have stronger reactions to medicines than most people.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
4. I have had a bad reaction to medicines in the past.				
1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree
5. Even very small amounts of medicines can upset my body.				

1 Strongly Disagree	2 Disagree	3 Uncertain	4 Agree	5 Strongly Agree

For the following questions, please circle the number that best corresponds to your views:

Appendix 6: UVA Breast Cancer Belief Survey

For the following questions, please circle the number that best corresponds to your views:

1. I worry a lot about a return of breast cancer at some point in my life.			
1 Strongly Disagree	2 Disagree	3 Agree	4 Strongly Agree
2. Getting breast cancer again would be devastating to me.			
1 Strongly Disagree	2 Disagree	3 Agree	4 Strongly Agree
3. The side effects of a medicine prescribed by my doctor are important when I consider if I will continue taking the medicine.			
1 Strongly Disagree	2 Disagree	3 Agree	4 Strongly Agree
4. If I know a medication can help lower my risk of getting breast cancer again, I will continue to take it even if I have side effects.			
1 Strongly Disagree	2 Disagree	3 Agree	4 Strongly Agree

Most medicines prescribed by your doctor can have side effects. Sometimes these side effects are very minor and sometimes they can be severe. Thinking about the medicine that will be prescribed for your cancer please consider how the side effect would impact you taking the medicine.

For each possible side effect please circle whether you would stop for mild, moderate, or severe symptoms or whether you would not stop at all.

Joint pains, general aches, muscle stiffness…	Mild	Moderate	Severe	I would not stop
Vaginal dryness, pain with intercourse, difficulty with bladder control…	Mild	Moderate	Severe	I would not stop

Weight gain, unhappy with appearance of my body…	Mild	Moderate	Severe	I would not stop
Difficulty concentrating, forgetfulness, easily distracted…	Mild	Moderate	Severe	I would not stop
Nausea, vomiting…	Mild	Moderate	Severe	I would not stop

Appendix 7: EORTC QLQ

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ | | | ⌋

Your birthdate (Day, Month, Year): ⌊ | | | | | | | | ⌋

Today's date (Day, Month, Year): 31 ⌊ | | | | | | | | ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 8: Center for Epidemiologic Studies Depression Scale Revised

Below is a list of the ways you might have felt or behaved. Please check the boxes to tell me how often you have felt this way in the past week or so.	LAST WEEK				
	Not at all *or* Less than 1 day	1-2 days	3-4 days	5-7 days	Nearly every day for 2 weeks
My appetite was poor.	☐	☐	☐	☐	☐
I could not shake off the blues.	☐	☐	☐	☐	☐
I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐	☐
I felt depressed.	☐	☐	☐	☐	☐
My sleep was restless.	☐	☐	☐	☐	☐
I felt sad.	☐	☐	☐	☐	☐
I could not get going.	☐	☐	☐	☐	☐
Nothing made me happy.	☐	☐	☐	☐	☐
I felt like a bad person.	☐	☐	☐	☐	☐
I lost interest in my usual activities.	☐	☐	☐	☐	☐
I slept much more than usual.	☐	☐	☐	☐	☐
I felt like I was moving too slowly.	☐	☐	☐	☐	☐
I felt fidgety.	☐	☐	☐	☐	☐
I wished I were dead.	☐	☐	☐	☐	☐
I wanted to hurt myself.	☐	☐	☐	☐	☐
I was tired all the time.	☐	☐	☐	☐	☐
I did not like myself.	☐	☐	☐	☐	☐
I lost a lot of weight without trying to.	☐	☐	☐	☐	☐
I had a lot of trouble getting to sleep.	☐	☐	☐	☐	☐
I could not focus on the important things.	☐	☐	☐	☐	☐

Eaton WW, Muntaner C, Smith C, Tien A, Ybarra M. Center for Epidemiologic Studies Depression Scale: Review and revision (CESD and CESD-R). In: Maruish ME, ed. The Use of Psychological Testing for Treatment Planning and Outcomes Assessment. 3rd ed. Mahwah, NJ: Lawrence Erlbaum; 2004:363-377.

Appendix 9: Breast Cancer Prevention Trial Symptom Checklist

EVERYDAY PROBLEMS DURING THE PAST 4 WEEKS

We are interested in knowing how much you have been bothered by any of the following problems during the **PAST 4 WEEKS.** *(Circle one number on each line. If you do not have the problem, circle "not at all".)*

During the **past 4 weeks,** how much were you bothered by:	Not at all	Slightly	Moder-ately	Quite a bit	Extremely
1. Hot flashes…….	0	1	2	3	4
2. Nausea……...	0	1	2	3	4
3. Vomiting……...	0	1	2	3	4
4. Difficulty with bladder control when laughing or crying.	0	1	2	3	4
5. Difficulty with bladder control at other times……....	0	1	2	3	4
6. Vaginal dryness……	0	1	2	3	4
7. Pain with intercourse..……..……	0	1	2	3	4
8. General aches and pains..……..…..……...	0	1	2	3	4
9. Joint pains……...……..……	0	1	2	3	4
10. Muscle stiffness……..……	0	1	2	3	4
11. Weight gain……	0	1	2	3	4
12. Unhappy with the appearance of my body...……...	0	1	2	3	4
13. Forgetfulness...……	0	1	2	3	4
14. Night sweats..……	0	1	2	3	4
15. Difficulty concentrating...……...	0	1	2	3	4
16. Easily distracted...……...	0	1	2	3	4
17. Arm swelling (lymphedema)..……..	0	1	2	3	4
18. Decreased range of motion in arm on surgery side..…...	0	1	2	3	4

Stanton, A. L., Bernaards, C. A., & Ganz, P. A. (2005). The BCPT Symptom Scales: A measure of physical symptoms for women diagnosed with or at risk for breast cancer. Journal of the National Cancer Institute, 97, 448-456.

Appendix 10: Adherence Questions

UVA IRB-HSR 22040: POWER Trial
Health-Related Quality of Life Questionnaires

Adherence Questions

In an average week, how often do you take your hormone treatment for breast cancer? Choose the best answer from the options below? **Note: On Day 1, please mark N/A**

Every Day	Most Days	Some Days	Rarely	I stopped taking it.
(7 out of 7 days)	(5 out of 7 Days)	(3-4 out of 7 Days)	(1-2 out of 7 Days)	

N/A

At this time, how likely is it that you will complete the entire recommended duration (i.e. 7-10 years) of your hormone treatment for breast cancer?

1	2	3	4
=Extremely Unlikely	=Unlikely	=Likely	=Extremely Like

Appendix 11: Treatment Decision Survey

UVA IRB-HSR 22040: POWER Trial
Treatment Decision Questionnaire

1. Why did you decide to have or not to have radiation therapy?

2. Why are you deciding to restart or not to restart the endocrine therapy pill?

Appendix 12: Decisional Conflict Scale

Decisional Conflict Scale (DCS)

My difficulty in making this choice

A. Which treatment option do you prefer? Please check one.

- ☐ Surgery only (no radiation and no endocrine therapy after surgery)
- ☐ Surgery plus radiation therapy alone (no radiation after surgery)
- ☐ Surgery plus endocrine therapy alone (no radiation after surgery)
- ☐ Surgery plus radiation therapy AND endocrine therapy
- ☐ Unsure

B. Considering the option you prefer, please answer the following questions:

	Strongly Agree [0]	Agree [1]	Neither Agree Nor Disagree [2]	Disagree [3]	Strongly Disagree [4]
1. I know which options are available to me.	☐	☐	☐	☐	☐
2. I know the benefits of each option.	☐	☐	☐	☐	☐
3. I know the risks and side effects of each option.	☐	☐	☐	☐	☐
4. I am clear about which benefits matter most to me.	☐	☐	☐	☐	☐
5. I am clear about which risks and side effects matter most to me.	☐	☐	☐	☐	☐
6. I am clear about which is more important to me (the benefits or the risks and side effects).	☐	☐	☐	☐	☐
7. I have enough support from others to make a choice.	☐	☐	☐	☐	☐
8. I am choosing without pressure from others.	☐	☐	☐	☐	☐
9. I have enough advice to make a choice.	☐	☐	☐	☐	☐
10. I am clear about the best choice for me.	☐	☐	☐	☐	☐
11. I feel sure about what to choose.	☐	☐	☐	☐	☐
12. This decision is easy for me to make.	☐	☐	☐	☐	☐
13. I feel I have made an informed choice.	☐	☐	☐	☐	☐
14. My decision shows what is important to me.	☐	☐	☐	☐	☐
15. I expect to stick with my decision.	☐	☐	☐	☐	☐
16. I am satisfied with my decision.	☐	☐	☐	☐	☐

Appendix 13: Decision Regret Scale

Decision Regret Scale

Please think about the decision you made about the treatment of your breast cancer (radiation and endocrine therapy) after talking to your doctors. Please show how you feel about these statements by circling a number from 1 (strongly agree) to 5 (strongly disagree).

1.	It was the right decision	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
2.	I regret the choice that was made	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
3.	I would go for the same choice if I had to do it over again	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
4.	The choice did me a lot of harm	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
5.	The decision was a wise one	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree