ECOG-ACRIN cancer research group
Reshaping the future of patient care

E1Z11

A Cohort Study to Evaluate Genetic Predictors of Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

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Addendum #2 – 11/13
Addendum #3 – 4/14
Addendum #4 - 12/14
Addendum #5

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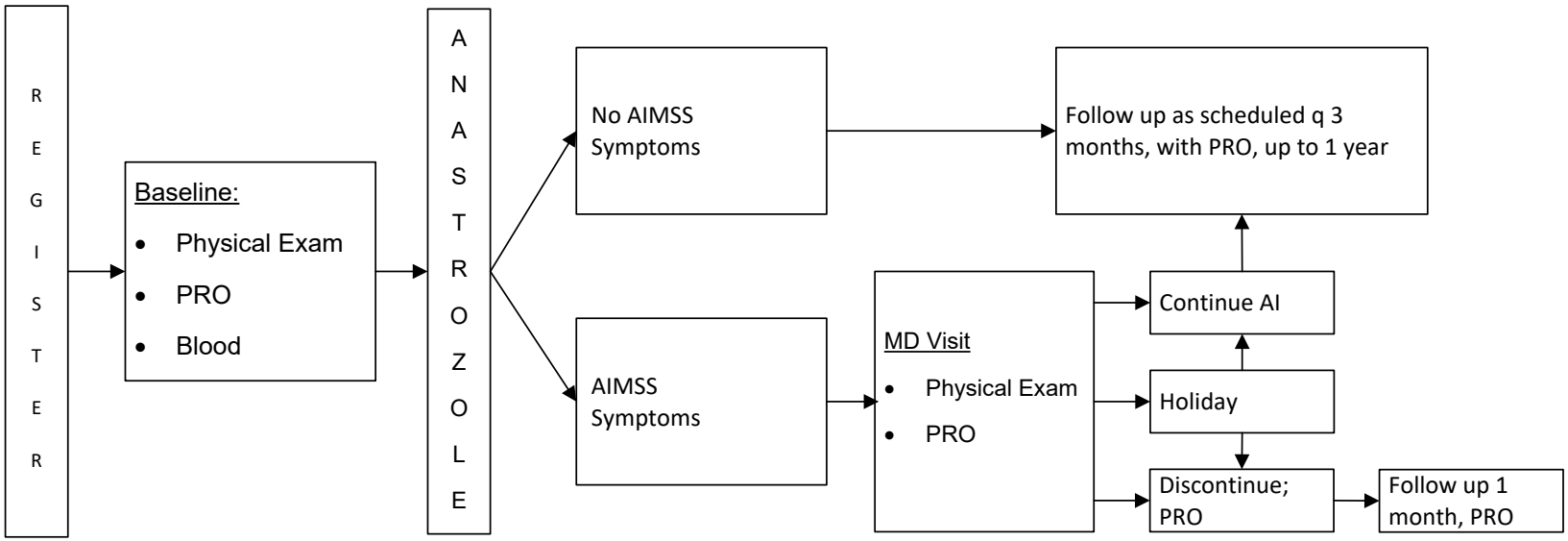
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Data collection will be performed in Medidata Rave and in Assessment Center™:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Please refer to the Forms Completion Guidelines for the Forms Submission Schedule.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility or treatment-related questions Contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Accrual = 1,000 patients

a. Anastrozole will be given 1mg, po daily for 12 months.
b. AIMSS diagnosis will be determined clinically by oncology MD or Nurse when patient complains of joint symptoms. See Section 5.
c. Decision whether to continue anastrozole or to start a treatment for AIMSS will be made by patient & MD discussion. See Section 5.
d. Blood collection is mandatory for pharmacogenomics as outlined in Section 10. If unable to collect at baseline, please collect at any other time point.

1. Introduction

1.1 Rationale for Proposed Study

1.1.1 Significance of the Condition

Breast cancer is one of the most prevalent cancers with 207,090 new cases of breast cancer and 39,840 deaths in women predicted for 2010 in the United States[1]. Aromatase inhibitors (AIs) are used as first-line adjuvant therapy for postmenopausal women with early stage breast cancer[2]. The effectiveness of current therapy is widely recognized to be compromised by poor compliance because of aromatase inhibitor-associated musculoskeletal symptoms (AIMSS), a syndrome that affects up to 40-50% of women who take these medications. The syndrome that was not recognized during the registration trials for this class of drugs[3], it can lead to discontinuation in up to 24% of women over 2 years [4,5]. Knowledge that can be used to prevent discontinuation of these important agents because of severe AIMSS is urgently needed.

The NCI Division of Cancer Prevention has recognized AIMSS as a priority area for future study. The symptoms are associated with a high rate of AI discontinuation and therefore compromise survival outcomes at great cost to both patients and society. Very little is known about AIMSS, or how to predict who is at risk for the condition, or for discontinuing therapy because of the symptoms. This study will provide a basis for comprehensive assessment of risk factors at the patient-reported outcomes, phenotypic, and laboratory levels. We will explore the natural history of AIMSS in different ethnic populations, and will validate previously reported genetic determinants of the development of AIMSS.

A common problem with multicenter GWAS studies of very large sample size, especially in the absence of measurable diagnostic parameters, is inclusion of heterogeneous groups of patients[6]. In addition to assessing pharmacogenomic predictors, this study involves specification of a pre-defined AIMSS phenotype and collection of patient-reported outcomes (PROs). As such, these data will have clinical utility by clarifying the factors associated with aromatase inhibitor discontinuation and thus guiding clinicians towards interventions to improve adherence. Coupled with other studies, the long-term goals are to develop a gene signature that will be used to better guide the selection of endocrine interventions for patients with breast cancer.

Etiology and Pathophysiology

The underlying physiology of AIMSS remains obscure. A small exploratory case control study did not find a role for commonly encountered cytokines in AIMSS [7]. The role of estrogen and estrogen metabolites remains a possible explanatory variable, as well as new cytokines such as IL-17. This newly described cytokine has been implicated in disorders such as rheumatoid arthritis and other

autoimmune diseases [8], and has been specifically linked to articular nociception in animal models of arthritis[9].

AIMSS Phenotype: The large studies to date of AIs (ATAC, BIG I-98, E1Z03) have been limited by the absence of a clearly defined phenotype for AIMSS [10]. Retrospective analyses have provided some information that clearly cannot replace (PROs). The lack of good prospective PROs represents a major gap as a well-defined phenotype is necessary in order to identify useful genomic associations. Methods evaluating possible predictors such as the use of MRI of the wrists for tenosynovitis are expensive and have not been definitive [11], and patient-reported symptoms are used and may represent the most useful clinical phenotype.

The exemestane and letrozole pharmacogenomics (ELPh) study, conducted by the Consortium on Breast Pharmacogenomics (COBRA), has provided important data not only regarding the prevalence of the symptoms and drug discontinuation but also for PRO by using the Health Assessment Questionnaire (HAQ), a commonly used rheumatology instrument. Dr. David Flockhart and Dr. Vered Stearns of ECOG are co-founders of the COBRA group. In this prospective comparison of exemestane and letrozole, patients were randomly assigned to either letrozole or exemestane and were evaluated at predefined intervals by study team members and referred to a rheumatologist based upon change in HAQ scores and pain ratings on a visual analog scale (VAS). The study showed that the predefined symptomatic criteria based on the HAQ and VAS successfully provided a means of case definition of an otherwise difficult-to-characterize syndrome [4, 5]. Improvement or worsening of HAQ score was defined as a decrease or increase, respectively, of more than 0.22 based on data provided from the rheumatology literature[12]. However, the sensitivity, specificity, and generalizability of the ELPh clinical criteria for defining AIMSS clearly need to be confirmed in a larger cohort of a diverse patient population and in other clinical settings. Data from the ELPh study for the first 100 patients showed that median time to onset of symptoms was 1.6 months (range 0.4-10 months), and median time to study discontinuation (for those who stopped taking AI) was 6.1 months (range 2.2-13 months) [4].

Anastrozole was not studied in the ELPh trial, representing a gap in knowledge both as it is a widely prescribed AI, and because anastrozole associated musculoskeletal symptoms have not been phenotypically characterized with the HAQ. Furthermore, as the patients studied by the ELPh and NCIC Clinical Trials Group MA.27 (described below) populations are predominantly Caucasian, further studies in minority populations are urgently needed.

Genetic Predictors of AIMSS: Pharmacogenomic predictors may help identify women at risk for AIMSS since genetic variants that are associated with AI pharmacokinetics, with the effects of estrogen deprivation on bone and other phenotypes have already been described. We briefly review recent important findings that emphasize the importance of this concept as well as its feasibility.

Previous studies by the PI with COBRA investigators identified genetic predictors, such as polymorphisms in estrogen receptors (ESR), or genes encoding for cytochrome P450 enzymes (CYP), of tamoxifen effects. Estrogen receptor subtypes may influence lipid metabolism [(13)] and bone density [(14)]. Furthermore, CYP polymorphisms are important in predicting discontinuation of tamoxifen [(15)], and hot flashes [(16)]. Our preliminary data suggest that variants in ESR predict development of AIMSS (Manuscript in preparation). These findings provide an important model for exploration of genetic predictors of side effects of AIs. Additional recent work has identified potential genetic determinants of the pharmacokinetics and pharmacodynamics of the AIs that may also explain variability in responses to AIs. [(17-21)].

The first evidence for the existence of genetic predictors of AIMSS came from an analysis of 293 cases and 585 controls from the MA.27 trial, a large study which compared exemestane and anastrozole. Genome wide associations (GWAS) and functional genomic studies identified novel single nucleotide polymorphisms (SNPs) and a gene related to IL-17 as associated with AIMSS[(17)]. These findings were recognized as important and should be confirmed in large prospective studies [(22)]. However, few studies conducted or planned to date have included a predefined phenotype, PROs or specimens evaluable for pharmacogenomics.

Review of available data from the MA27 and the ELPh studies has identified ten SNPs that may be relevant to AIMSS syndrome. In the MA27 dataset, the most striking P values (1E-06) were for three SNPs on chromosome 14, rs7158782, rs7159713, rs2369049, which were all close to the T Cell leukemia 1A (TCL1A) gene, a fourth SNP, rs11849538, was imputed. The ELPh study also identified the latter two SNPs, and four other SNPs. These were rs2296972, the serotonin receptor subtype 2A, rs2347868 and rs9340835 associated with estrogen receptor 1, and rs4646 associated with CYP19A1. An additional two SNPs have been identified in studies of severe large joint arthritis. These are rs2234693 in the ESR1 gene, and rs1062033 in the CYP19A1 gene [(22a).]

1.1.2 Studying the Decision to Discontinue Aromatase Inhibitors

Compliance is an important issue, as many patients do not fill their prescriptions for AIs [(23)]. The basis for the patient's decision to discontinue AI therapy has not been studied. On the basis of anecdotal observations of our community oncologists, patients are torn between their fear of recurrence and the perceived burden of treatment. AIs are one of the few agents that have pain as a side effect. Patient answers to questions about their fear of recurrence, perceived treatment burden, burden due to co-morbidities, and adherence behaviors may provide further insights to patient decision-making and compliance.

The significant role of patient reported outcomes as a possible determinant in the decision to discontinue AIs was a central finding in ECOG 1Z03 and presented by Dr. Lynne Wagner at the 2011 San

Antonio Breast Conference [24]. Further study of patient reported outcomes may lead to robust bedside assessments of the risk of discontinuation.

1.1.3 Studying the use of paper forms or the PROMIS electronic format for data entry

Collection of patient rated outcomes is a critical component of these kinds of studies, and incomplete data collection during follow-up represents a major challenge both logistically and to the validity of these studies. The NIH has developed a Web-based system for recording patient reported outcomes during clinical trials, the Patient Reported Outcomes Management Information System (PROMIS) that will enable the efficient collection of patient reported outcomes and decrease the logistical burdens on office practices for patients on clinical trials. The PROMIS Assessment Center is the web-based platform for dissemination of NIH PROMIS measures. The assessment center can be used to administer patient rated outcome instruments, monitor accrual, manage data, send reminders to patients, be used to deliver custom researcher developed content, and has numerous features that support both simple and complicated accrual designs (branching, multiple arms, multiple time points, etc.).[25] Dr David Cella, an ECOG member, has been a key participant in the development of the PROMIS system and is Director of the PROMIS Statistical Center. Studies undertaken by the PROMIS staff have shown there is excellent satisfaction with the PROMIS Assessment Center [26] for patients with visual and other impairments. There is no charge for using the PROMIS system. Data is kept secure behind firewalls. Data that is entered will be the property of ECOG and can be downloaded directly to the ECOG system. With the current popularity of smart phones in the breast cancer patient population, we think the time is ripe to test its' use in a cooperative group trial setting.

The symptom instruments used will build upon the work in the NIH Patient Reported Outcomes project to develop better symptom instruments, through use of the PROMIS Physical Function 20 Form and the PROMIS Assessment Center. This will support the development of better symptom and quality of life measurements and begin to integrate the PROMIS project within the Cancer Cooperative Groups. Experience in using the instruments and the PROMIS Assessment Center will lead to new ways for cooperative groups to collect patient rated outcome data and reduce attrition.

Secondary objective 2.2.6 is to assess the **feasibility** of the on-line **PROMIS** platform for collecting patient-reported outcomes in the setting of a cooperative group clinical trial. We plan to make all of the patient-reported quality of life instruments available through the PROMIS web site.

2. Objectives

2.1 Primary Objectives

To validate previously identified associations between 10 specific single nucleotide polymorphisms (SNPs) and discontinuation of treatment with AIs due to the development of musculoskeletal symptoms (MSS) among women with breast cancer.

2.2 Secondary Objectives

2.2.1 To determine whether other SNPs in CYP, UGT, Vitamin D, serotonin and other receptors are associated with discontinuation of treatment due to the development of severe AIMSS.

2.2.2 To determine whether other SNPs in CYP, UGT, Vitamin D, serotonin and other receptors are associated with the development of other potential complications of AI therapy.

2.2.3 To develop a gene signature that can identify patients at risk for developing severe anastrozole-related AIMSS and other potential complications of AI therapy.

2.2.4 To determine the epidemiology and predictors of severe AIMSS and of AI discontinuation.

2.2.5 To describe patient reported outcomes for minority patients with breast cancer treated with aromatase Inhibitors (AIs).

2.2.6 To assess the utility of the PROMIS system to collect patient reported outcomes in a cooperative group study, and validate the PROMIS Physical Function 20a form in patients with AIMSS.

2.2.7 To develop a model that incorporates patient ratings of treatment burden, fear of recurrence and adherence behaviors to describe patient decisions to continue or discontinue anastrozole.

2.2.8 To collect serum samples for future testing for biomarkers of AIMSS.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 Patients must be female and post-menopausal. Post-menopausal will be defined as women meeting any of the following criteria:

- ≥ 60 years of age; or
- < 60 years of age and amenorrheic for ≥ 12 months prior to day 1 if uterus/ovaries are intact; or
- < 60 years of age, and the last menstrual period 6-12 months prior to day 1, if intact uterus/ovaries and meets biochemical criteria for menopause (FSH and estradiol within institutional standard for postmenopausal status); or
- < 60 years of age, without a uterus, and meets biochemical criteria for menopause (FSH and estradiol within institutional standards for postmenopausal status); or
- < 60 years of age and history of bilateral oophorectomy. Surgery must have been completed at least 4 weeks prior to day 1; or
- Prior radiation castration with amenorrhea for at least 6 months.

Rev. 11/13 **NOTE:** Use of LHRH agonists (e.g., leuprolide or goserelin) is not allowed

_____ 3.1.3 Patients must have estrogen and/or progesterone receptor positive histologically confirmed Stage I-III adenocarcinoma of the breast.

Rev. 11/13 _____ 3.1.4 Patients must have completed planned local therapy (i.e., definitive surgery and radiation therapy) and adjuvant chemotherapy for breast cancer prior to registration. In addition, any prior local therapy and adjuvant chemotherapy should be completed prior to participant completion of baseline PRO instruments (i.e., HAQ, PROMIS Physical

Function, FACT Breast and ES, etc.) and collection of optional blood for banking for future research.

NOTE: Concomitant treatment with ongoing trastuzumab (Herceptin®) or other targeted/biologic agents is allowed. Concomitant treatment with any other type of chemotherapy or hormonal therapy is not allowed.

_____ 3.1.5 Patients must not have received prior AI therapy with exemestane, letrozole, or anastrozole as preoperative/adjuvant therapy or for prevention of breast cancer. Prior tamoxifen is allowed.

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_____ 3.1.6 Plan to treat with anastrozole for at least 12 months.

_____ 3.1.7 ECOG performance status between 0-2.

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_____ 3.1.8 Patients must be disease-free of other prior invasive malignancies for ≥ 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix. Prior early stage breast cancers are also allowed as long as prior treatment did not include aromatase inhibitors.

_____ 3.1.9 Patients must not be currently taking (or have taken in the past 6 months) medication for active, chronic conditions, including rheumatoid arthritis, carpal tunnel syndrome, tenosynovitis, systemic lupus erythematosus, gout, fibromyalgia, or severe osteoarthritis involving the hands, wrists, hips, knees, feet or ankles. This includes analgesic medications or medications being taken with the purpose of treating pain or that may have an effect on pain (e.g. anti-depressants for help with pain or neuropathy, corticosteroid shots for arthritis.) (Note: patients taking daily low dose aspirin are allowed to participate in this trial.)

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_____ 3.1.10 Patients must not have a prior history of deep vein thrombosis (DVT) or pulmonary embolism in the past 5 years.

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_____ 3.1.11 Patients must have worst pain rated as no worse than 3 out of 10 on the following question (i.e., a pain score of 0, 1, 2, or 3): “In the past week, how much pain have you had on a scale of 0 to 10, where 0 equals no pain and 10 means the worst pain you can imagine.”

NOTE: This question regarding patient’s pain should be completed within one week prior to registration. This question may be asked orally prior to consent up to 7 days prior to registration; the response will be recorded on the registration checklist.

_____ 3.1.12 Patients must have adequate hepatic, hematologic and renal functioning to be able to be administered anastrozole at the discretion of the treating physician.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for E1Z11 site registration:

CTSU IRB Certification

CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.

- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

The CTSU encourages you to go to the following CTSU RSS webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log in to http://www.ctsu.org and click on the Regulatory tab to access the RSS webpage. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 8:30pm.

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Patients must not start protocol treatment prior to registration.

Treatment should start within three working days after registration

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following information will be requested

4.1 Protocol Number

4.2 Investigator Identification

- 4.2.1 Institution and affiliate name (Institution CTEP ID)
- 4.2.2 Investigator's name (NCI number)
- 4.2.3 Cooperative Group Credit
- 4.2.4 Credit Investigator
- 4.2.5 Protocol specific contact information

4.3 Patient Identification

- 4.3.1 Patient's initials (first and last)
- 4.3.2 Patient's Hospital ID and/or Social Security number
- 4.3.3 Patient demographics
  - 4.3.3.1 Gender
  - 4.3.3.2 Birth date
  - 4.3.3.3 Race
  - 4.3.3.4 Ethnicity
  - 4.3.3.5 Nine-digit ZIP code
  - 4.3.3.6 Method of payment
  - 4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Additional Requirements

- 4.5.1 Patients must provide a signed and dated, written informed consent form.

  NOTE: Copies of the consent are not collected by the ECOG Coordinating Center.
- 4.5.2 Blood for DNA must be submitted for pharmacogenomic analysis as outlined in Section 10.
- 4.5.3 Blood for banking for future research studies should be submitted as outlined in Section 10 per patient consent.

NOTE: ECOG requires that biological samples submitted from patients participating in E1Z11 be entered and tracked via the online ECOG Sample Tracking System (STS). See Section 10.3.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG Coordinating Center regarding logistics for submission of fresh samples.

4.5.4 Data collection for this study will be done in Medidata Rave and in Assessment Center™. Prior to beginning data entry in Rave, study staff must be registered in Medidata and complete the required training modules. Study staff will receive an invitation to join the study in Rave after evidence of IRB approval is submitted to RSS.

4.5.5 Patients will have the option of completing quality of life assessments through the PROMIS Assessment Center, a web-based application. Prior to registering patients, the site should consider whether there are facilities in the clinic for this (e.g., a computer terminal available for patient use), or if the patient must make their own arrangements. If neither of these options is possible or if the patient prefers, QOL assessments can be done using paper forms, with responses entered by study staff into Medidata Rave. More information about how to use the PROMIS Assessment Center for this study is available at www.ecog.org/AIMSS_QOL.

4.6 Instructions For Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E1Z11 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

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Patient receives anastrozole 1 mg po daily, and completes the baseline and follow up questionnaires on the PROMIS study website, Assessment Center,™ or with pencil and paper. The questionnaires include Functional Assessment of Cancer Therapy (FACT) measures (FACT-General, Breast subscale and Endocrine subscale) and HAQ.

The patient will be asked not to discontinue the medication on her own. When the patient develops joint pain or stiffness and calls their treating physician, the patient will be encouraged to continue anastrozole medication until seen in an office visit.

5.1.1 Treatment

Anastrozole 1 mg, oral, daily for 12 months. Treatment should start within three working days after registration. The patient will be given a pill diary and instructed to complete it and bring it with them to their next MD visit.

5.1.2

Patients should be instructed that when they develop joint pain or stiffness that they should call their MD. Patients should be encouraged to stay on the medication until seen in an office visit.

MD or provider should see the patient within 2 weeks of the patient's call to assess for the likelihood of rheumatologic disease (joints are not red, hot, swollen, or deformed), and determines clinically if the patient has AIMSS, and records his/her impression. The patient completes the questionnaires.

Patient discusses with MD whether to continue or discontinue the drug or start a treatment for AIMSS. A holiday (defined as a drug-free interval of 6 weeks or less) is also an option, as is switching to a different AI, tamoxifen, or participating in a treatment study. The MD will record the recommendation.

5.1.3

If and when the patient decides to discontinue anastrozole, the patient will be asked to complete questionnaires. If this was part of a holiday plan, the drug will be considered discontinued if the patient refuses to restart the medication (off the medication for more than 6 weeks).

5.1.3.1

When a patient discontinues the medication, she will be asked for the reasons, and asked to rank them. If pain or other symptoms such as stiffness are the first or second reason, then it will be considered a discontinuation because of AIMSS.

5.1.3.2

The MD will check in with the patient 4-6 weeks later to see if symptoms have resolved, and if anastrozole is discontinued. The patient will complete questionnaires again.

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5.1.4 If the patient is to continue anastrozole beyond the 12 months on study, a final questionnaire will be completed at the 12 month time point.

NOTE: All notations of MD above refer to medical protocol (ie, MD, NP or PA); an oncology nurse may also make assessments if felt to be qualified by the Principal Investigator.

5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probably	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.2.3 Reporting Procedure

Rev. 4/14

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG (617-632-3610)
- the FDA (800-332-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Rev. 11/13

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

Rev. 4/14

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Expedited Reporting Requirements For Protocol E1Z11

Commercial Agent: Anastrozole

Attribution	Grade 5[a]	
	Unexpected	Expected
Possible, Probable, Definite	7 calendar days	7 calendar days

Rev. 4/14, 12/14

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment with an attribution of possible, probable, or definite.

NOTE: In addition, any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

5.2.5 Other Recipients Of Adverse Event Reports and Supplemental Data

Rev. 4/14

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.6 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG using Medidata Rave

- A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:

Rev. 11/13

1. Complete a Second Primary Form within 14 days in Medidata Rave
2. Upload a copy of the pathology report to ECOG via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG via Medidata Rave.

- A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:

Rev. 11/13

1. Complete a Second Primary Form within 14 days in Medidata Rave.

Rev. 4/14

2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

- Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

3. Upload a copy of the pathology report to ECOG via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG via Medidata Rave and submit a copy to NCI/CTEP.

Rev. 4/14

NOTE: The ECOG Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG Second Primary Form must be submitted for the most recent trial. ECOG must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG Second Primary Form.

Rev. 4/14

5.3 Patient Reported Outcome Administration

Rev. 11/13

5.3.1 PRO Instruments to be Administered

Participants will complete the Health Assessment Questionnaire (HAQ) and the PROMIS Physical Function 20 to assess AIMSS symptoms, the FACT Endocrine Subscale to assess estrogen deprivation symptoms, the FACT-Breast to assess breast cancer-specific concerns, the FACT-General (FACT-G) to assess health-related quality of life, the Assessment of Survivor Concerns (ASC) to assess fear of recurrence, a Treatment Burden scale, and the PROsetta Stone Comorbidity Form and SOAPP study Comorbidity

Rev. Add5

Bother Item. Participants will have a choice between completing these electronically with the NIH Assessment Center or pencil and paper versions of these instruments will be administered to the participants during office visits to their oncologist. It should take approximately 30 minutes for study participants to complete the battery of study instruments.

Rev. Add5

5.3.2 PRO Assessment Schedule

Patients will be assessed according to the following schedule:

1.) Baseline*
2.) 3 months
3.) 6 months
4.) 9 months
5.) 12 months
6.) At the time of symptom onset (if applicable)**

Rev. 4/14

7.) At the time the patient discontinues taking anastrozole due to AIMSS***

Rev. 4/14

8.) One month after discontinuing anastrozole due to AIMSS

The PRO assessment timepoints correspond to the standard office visits of routine clinic visits to minimize participant burden. However, in the event that a routine clinic visit is not planned or is missed, an attempt should be made to complete the questionnaires on schedule, either by mail or remote electronic entry.

* The Pain Item on the HAQ will be administered within one week prior to registration. It may be administered orally by staff.

** When a study participant has AIMSS symptoms, she should make an appointment to have a MD/provider visit within 2 weeks of onset of symptoms. At this visit it will be determined whether the patient has AIMSS and if it is related to anastrozole. The patient and her MD/provider will decide on a plan to either continue on anastrozole, take a holiday from taking it, or discontinue taking it.

Rev. 4/14

*** If the patient discontinues taking anastrozole due to AIMSS the MD should follow up within 1 month after discontinuation to have the patient complete an additional PRO assessment. All participants will continue PRO assessments as scheduled up until 12 months, including participants who discontinue anastrozole early for any reason.

Rev. 11/13

5.3.3 PRO Administration Instructions – Using Paper Forms

Rev. 12/14

5.3.3.1 The questionnaires must be administered at the time points listed above. The patient should be instructed to respond to the questionnaires in terms of her experience during the timeframe specified on each questionnaire.

5.3.3.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the

completion of the questionnaires as long as the staff person does not influence the patient's responses.

5.3.3.3 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how she is feeling. If a question was not answered, the patient should be asked if she would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that she declined to answer the item.

5.3.3.4 If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the E1Z11 Forms Completion Guidelines.

5.3.4 PRO Administration Instructions – Using Assessment Center ™

5.3.4.1 Electronic administration of PRO will be done using the study's website in the PROMIS Assessment Center www.assessmentcenter.net/ac1/Assessments/E1Z11.

5.3.4.2 Prior to accessing the website, each patient will need to be registered by the site. After registering the patient, the site staff member will be provided with a username and password to be given to the patient.

5.3.4.3 Patient-friendly instructions along with additional information about electronic submission of PRO can be found at www.ecog.org/AIMSS_QOL.

5.3.4.4 For patients who complete assessments using the Assessment Center, sites will log completion of these assessments in Medidata Rave. If the patient needed assistance or was unable to complete assessments at a given time point, the reason or type of assistance should be provided.

Rev. 12/14

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5.3.4.5 For sites with troubleshooting inquiries regarding the use of Assessment Center, the following steps should be followed: 1) All sites should direct troubleshooting inquiries directly to the E1Z11 Data Associate; 2) ECOG will forward unresolved inquiries to Northwestern University research staff; 3) Research staff at Northwestern University may forward unresolved inquiries to Assessment Center for final resolution. NOTE: Assessment Center should not receive any troubleshooting inquiries directly from sites.

5.4 Dose Modifications

See Section 5.1 for criteria for dose interruption, discontinuation, and/or resumption. The daily dose of anastrozole (1mg po daily) cannot be modified when it is taken.

5.5 Concomitant Treatment

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Concomitant treatment with ongoing trastuzumab (Herceptin®) or other targeted/biologic agents is allowed; treatment with any other type of chemotherapy or hormonal therapy is not allowed. Prior enrollment in any other clinical trial during chemotherapy or radiation therapy in the preoperative (i.e., neoadjuvant) or adjuvant setting is not an exclusion as long as all other eligibility criteria are met, and the planned assessments on this study can be completed as planned.

The enrollment of a participant in another clinical trial that may randomize to a hormonal therapy other than anastrozole or to anastrozole plus another therapeutic agent is not allowed.

Should the participant develop AIMSS and stay on anastrozole, concomitant enrollment on to a clinical trial for treatment of AIMSS is allowed (see Supportive Care)

5.6 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

Rev. 11/13

In participants who experience AIMSS, concomitant enrollment in other clinical trials evaluating the roles of medications or other interventions in the treatment of AIMSS is allowed. Any co-enrollment and interventions must be clearly documented in the medical record and reported on the electronic CRF.

NOTE: The co-enrollment of participants to a trial looking to PREVENT the development of AIMSS is not allowed.

5.7 Duration of Therapy

Patients will receive protocol therapy for 12 months from registration. After the 12-month study period is completed, patients should continue to take anastrozole or other endocrine therapies in accordance with standard practice guidelines if tolerated.

Patient will receive protocol therapy unless:

5.7.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit data through Medidata Rave according to the schedule in the E1Z11 Forms Completion Guidelines.

5.7.2 Patient withdraws consent.

5.7.3 Patient experiences unacceptable toxicity.

Rev. 11/13

5.7.4 Prohibited non-protocol therapies are administered.

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed until the month 12 visit, which should take place approximately 1 year (+/- 4 weeks) after the initiation of anastrozole therapy. For this protocol, all patients, including those who discontinue protocol therapy early,

will be followed **for survival and recurrence** for 5 years from the date of registration.

6. Study Measures

6.1 Patient Reported Outcome Measures Used In This Study Will Include The Following:

6.1.1 Health Assessment Questionnaire (HAQ)

Rev. 11/13

6.1.2 FACT -G, FACT-Breast subscale and FACT-Endocrine Subscale

6.1.3 Assessment of Survivor Concerns (ASC) and Rackovitch Risk Perception Scale – will be used to assess fear of recurrence and perceived risk of recurrence.

6.1.4 Treatment Burden

Rev. Add5

6.1.5 PROsetta Stone Comorbidity Form

6.1.6 SOAPP study Comorbidity Bother Item

6.1.7 PROMIS Physical Function 20 Form

6.2 Patient Reported Outcome Measures To Be Used In This Study

6.2.1 HAQ - AI arthralgias are not well defined, and the most careful work to date has been done with the Health Assessment Questionnaire (HAQ) [27], a patient reported instrument used by rheumatologists, and in the ELPh trial organized by COBRA. This instrument is designed for patients with more serious and debilitating arthritic conditions, and not as sensitive for patients with milder symptoms. Use of broader screening questions may detect milder disability but show ceiling effects for severe disability. We will follow the symptom assessment scheme of the COBRA study by Henry et al (4). This will allow us to gain experience with a published approach to case finding in a second population of patients, and for both clinical and genomic datasets to be compared with the ELPh study,

Rev. 11/13

6.2.2 FACT Breast and ES - The FACT-Breast and Endocrine Subscales are tailored for patients with breast cancer and includes specific questions related to endocrine therapy [28, 29]. The FACT-G measures overall health-related quality of life and consists of 4 subscales that measure physical, functional, emotional and social well-being. The FACT-B Trial Outcome Index (TOI) combines the Physical well-being (PWB) and functional well-being (FWB) subscales of the FACT-G with the breast cancer subscale (BCS). The FACT B+ES were used in the ATAC trial [30]. Normative data for interpreting results from this study will be available from E1Z03 for FACT Breast and ES data.

6.2.3 Fear of Recurrence - The Assessment of Survivor Concerns (ASC) is a 5-item questionnaire that has 2 subscales – worry about cancer recurring (3 items) and worry about general health (2 items). Each of the items has a Likert response. In the initial paper, Cronbach's alpha was 0.93 for the cancer worry subscale and 0.72 for the health worry subscale. The items are worry about future tests, new cancer, recurrence, death, and health. ECOG has used the 5-item Assessment of Survivor Concerns [31] for the TAILORx trial to assess fear of recurrence.

The Rakovitch Risk Perception Scale asks respondents to describe perception of the likelihood of breast cancer recurring in the breast, of breast cancer recurring elsewhere, of dying from breast cancer, and of dying from other cancers. It has 4 items [32].

6.2.4 Treatment Burden - While many factors may contribute to treatment burden, the concept of a single item for global burden has been used in European studies by the SAKK group[33].

Rev. Add5

6.2.5 PROsetta Stone Comorbidity Items - Clinical decision-making regarding cancer treatment takes on additional complexity in the presence of comorbidity [36]. Currently, no gold standard exists in the measurement of comorbidity in cancer patients[37]. Although comorbidity is often measured through provider checklists based on chart review, patient self-report of comorbidity yields similar information and includes chronic conditions that are sometimes overlooked on provider chart review. The Prosetta Stone comorbidity items have been used across several large NIH-sponsored projects (PROMIS, Neuro-QOL, Toolbox) and it has demonstrated good reliability and validity. An additional item to address cigarette smoking will be included on this measure for this study. This item is added in response to the need for better reporting of tobacco use as a potential factor influencing patient outcomes in NCI sponsored clinical trials[38].

6.2.6 The SOAPP Study Comorbidity Bother Item - Perception about a patient's capacity to tolerate treatment can influence treatment decisions. In the ECOG SOAPP study (E2Z02), a single item was used to assess the degree to which the patient reported being bothered by conditions other than cancer. In the breast cancer cohort of the SOAPP study, 65.9% of patients reported at least a little bit of bother due to comorbidities [39] There was a strong association seen between this self-reported bother due to comorbidity and symptom burden [40] This single item is thus included to better understand the impact of comorbidity in addition to the Prosetta Stone items.

6.2.7 PROMIS Physical Function (PF) Short Form 20a - The PROMIS PF 20a consists of 20 items that assess four subdomains of physical function: upper extremity, lower extremity, central, and activity. Responses to the 20 items are summed to create one single score. The PROMIS PF 20 was developed based on items selected from the PROMIS Physical Function 154 item bank. The PROMIS PF 20a contains IRT-based items selected from the PROMIS PF 154 item bank. The "IRT-based" PROMIS PF20 are selected using IRT information content data from over 21,000 subjects to identify the best items and minor qualitative input to ensure that all major areas of Physical Function/Disability were represented in the instrument, with their strongest items. In a study of 451 rheumatoid arthritis patients, the PF20 form was comparable to the HAQ [41]. The PF20 form has not been used in patients with AIMSS and will be validated against the HAQ in this study.

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NOTE: Please note, Spanish, Korean, Chinese and Japanese versions of the FACT-B form will be available on the ECOG website. Chinese and Spanish version of the HAQ

will be available on the ECOG website. Also, the Spanish version of the PROMIS Physical Function 20-item scale will be posted to the ECOG website.

7. Study Parameters

7.1 Data Collection

Rev. 11/13 Rev. 4/14 Rev.12/14		Baseline[1]	3, 6, 9 and 12 months[12,17]	Symptom onset/At diagnosis of AIMSS[13,17]	At discontinuation of Anastrozole due to AIMSS[12,17]	One month after discontinuation of Anastrozole due to AIMSS[14,12,17]	5 Years Post Registration[16]
	Demographics	X					
	Vital Status	X					X
	History & Physical Exam, ECOG PS	X					
	Physical Exam Joints[2]	X	X	X	X		
	Routine Blood Tests[3]	X					
	Medication Form[4]	X	X	X	X	X	
Rev. 4/14	The Stanford Health Assessment Questionnaire (HAQ) and PROMIS Physical Function- Short Form 20a[5,6]	X[5]	X	X	X	X	
	Patient-Reported Comorbidity Checklist	X					
	Provider Completed Comorbidity Form	X					
Rev. 4/14	FACT-G, FACT-B, and FACT-ES[6]	X	X	X	X	X	
Rev. 4/14	Quality of Life (QOL) Battery including Assessment of Survivor Concerns (ASC), Rakovitch Scale, SOAPP Comorbidity Bother, and SOAP Treatment Burden[6]	X	X	X	X	X	
Rev. 4/14	Physician Questionnaire[7]			X	X		
	Recurrence Status[15]	X	X	X	X		X
	Pill Calendar[8]		X		X		
	Biological Sample Submissions[9]	See Section 10					
	MANDATORY: Blood for Pharmacogenomics (one (1) 10cc yellow top tube)[10]	X					
	Blood for Banking for Future Research[11] (serum, [one (1) 10cc red top tube]	X	X	X	X		

Rev. 12/14 1. Baseline assessments and questionnaires must be completed by patients after consent is signed and prior to the start of study treatment, unless otherwise noted.

Rev. 11/13 2. The baseline physical exam is to include physical exam of the joints and should be done within 4 weeks prior to registration. Providers must document presence of any joint abnormalities (ie, deformity, edema, joint tenderness, effusions) and if any decrease in range of motion at each visit. In follow-up, assessment should include any diagnosis of AIMSS and recommendations on anastrozole dosing.

Rev. 11/13, 12/14 Rev. 4/14 3. This refers to blood tests requested by the provider to assess appropriateness to begin hormonal therapy with anastrozole, if the provider would routinely perform any tests. There are no routine blood tests specifically required by the study.

Rev. 11/13 4. Include a list of interventions being used by the patient for pain or AIMSS on the Medication Form. MD/provider may allow the patient to complete the medication form as long as they check accuracy after patient completes this form.

Rev. 11/13 5. Patient's baseline pain rating must be completed within 7 days prior to registration. The response will be recorded on the registration checklist.

Rev. 11/13, 12/14 Rev. Add5 6. If patients want to use the Assessment Center for completing quality of life assessments, the site should complete the registration prior to asking the patient to complete QOL questionnaires so that their case number can be used as an identifier in Assessment Center. The baseline assessment should be done prior to starting treatment with anastrozole. For subsequent visits, if participant is not able to complete the questionnaires online, paper versions should be given for completion in clinic.

Rev. 11/13 7. Physician impressions and recommendations regarding AIMSS (stop, continue or holiday) should be recorded on the Physician Questionnaire in Medidata Rave. This can be completed by the physician either electronically or on paper, with information transferred to the electronic CRF by the study staff.

Rev. 11/13 8. Patient pill calendar/diary should be completed by patient and collected by the site at 3, 6, 9 and 12 month visits and at the time patient discontinues taking anastrozole.

Rev. 11/13 9. Kits are being provided for the collection and shipment of the blood samples. Please refer to Section 10.1.2.1 for instructions.

Rev. 11/13 10. Blood collection for DNA for pharmacogenomics is mandatory as outlined in Section 10. Blood is strongly encouraged to be collected at baseline [after registration, prior to treatment] but may be collected at any other time point if unable to collect at baseline.

Rev. 11/13 11. Blood (serum) should be collected at baseline (after registration, prior to treatment), at three (3) months **OR** onset of AIMSS (if prior to three [3] months), and at twelve (12) months **OR** discontinuation of anastrozole due to AIMSS. Submit from patients who answer **"Yes"** to *"I agree to provide additional blood for research."*

Rev. 11/13 Rev. 4/14 12. PRO assessments and clinic visits should be completed every 3 months until 1 year (-/+ 4 weeks) after the initiation of anastrozole therapy. In the event that anastrozole is discontinued due to AIMSS, two additional PRO assessments will be administered: At the discontinuation of Anastrozole due to AIMSS and 1 month after discontinuation of anastrozole due to AIMSS. All participants will complete PRO assessments up until 12 months, including participants who discontinue anastrozole early for any reason.

Rev. 11/13, 12/14 Rev. 11/13 13. Within two weeks after the patient first reports possible AIMSS, there must be an MD assessment/visit to confirm diagnosis and complete PRO's. If the decision is made to discontinue anastrozole due to AIMSS during the same visit as Symptom onset/At diagnosis of AIMSS only one additional MD assessment/visit and repeat PROs must occur one month after discontinuation. If discontinuation due to AIMSS occurs on a separate visit an MD assessment and PRO's must be done at discontinuation due to AIMSS and one month after discontinuation.

Rev. 4/14 14. If the decision is made to discontinue anastrozole due to AIMSS prior to 12 months, a one month follow-up visit after discontinuation must be completed.

Rev. 11/13 15. All patients will be followed for recurrence status and survival status until 5 years post study registration. No specific imaging or other assessments are required.

Rev. 4/14 16. Follow-up visits should be done yearly until 5 years post registration, starting after the patient has completed the 12 months of patient assessments.

Rev. 12/14 17. If the Symptom assessment(s), At discontinuation of Anastrozole due to AIMSS or 1 month after discontinuation of Anastrozole due to AIMSS visits are within one month (+ or -) of any of the regularly scheduled visit (3, 6, 9, 12) only one set of PRO's and one clinic visit are required. The Symptom assessment(s), At discontinuation of Anastrozole due to AIMSS and 1 month after discontinuation of Anastrozole due to AIMSS visits must trump the 3,6,9 and 12 month post registration visits.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG Pharmacy and Nursing Committees.

8.1 Drug Name Anastrozole

8.1.1 Other Names

Arimidex®

8.1.2 Classification

Antineoplastic agent

8.1.3 Mode of Action

Aromatase inhibitor

8.1.4 Storage and Stability

Store at 20-25° degrees Celsius in a dry environment.

8.1.5 Dose Specifics

1 mg by mouth daily.

8.1.6 Preparation

Oral tablet. Ready to use commercial preparation.

8.1.7 Route of Administration

Anastrozole is taken orally.

8.1.8 Incompatibilities

Not applicable.

8.1.9 Availability

Commercially available.

8.1.10 Side Effects

Vasodilation, hot flushes (flashes), diarrhea, nausea, vomiting, asthenia, pain (including back pain), arthritis, arthralgia, fractures, increased liver function tests, hypertension, osteoporosis, peripheral edema, lymphedema, pharyngitis, depression, rash, insomnia, headache, increased cough, dyspnea, fatigue

8.1.11 References

AstraZeneca. Arimidex (anastrozole) tablets prescribing information. Wilmington, DE; 2008 Dec.

9. Statistical Considerations

The primary endpoint is defined as discontinuation of treatment following development of AIMSS. A patient will be considered to have developed AIMSS if there is a 20% or greater decline in scores on the HAQ instrument from baseline within one year. At the time of treatment discontinuation, patients and providers will be asked to rank the reasons for treatment discontinuation. If either the patient or the provider lists pain as the first or second-ranked reason and discontinuation is within 3 months of symptom escalation, this will be considered an event. Patients who are lost to follow-up or whose reason for discontinuation is unknown will be considered to be event-free. From previous studies, it is estimated that 40% of patients will develop symptoms, and 25% of patients will discontinue treatment with AIs within 1 year due to development of musculoskeletal symptoms.

The enrollment plan is designed to assure adequate enrollment of minority (Asian and African-American) patients. After 600 patients are enrolled from other racial groups, closure of the study to those subgroups will be terminated and accrual will continue among only Asian and African-American patients. When 200 patients are enrolled from the first remaining racial subgroup, closure of accrual to that subgroup will terminate and all remaining patients will be enrolled from the final remaining subgroup. ECOG Minority CCOPs will be strongly encouraged to participate in order to meet targets for minority accrual. While not a separate accrual cohort, ethnicity (Hispanic/non-Hispanic) will also be considered in the analysis plan.

The approach we will use to conduct genetic analysis will be a comprehensive one that employs a range of technologies to examine germline genetic variants in the DNA of women in this study, the goal being to test for simple associations of these variants with AIs-induced events. Our GWAS approach builds upon data and techniques from genome wide trials already conducted as well as data from candidate gene studies. We will use a custom - designed series of variants tested using the ABI Biotrove Open Array™ system. This allows robust testing of 100-300 variants with a technology that has high reliability and reproducibility, since it is based on simple Taqman™ technology. The Indiana COBRA site has extensive experience in developing chips which can be used to screen for complex and difficult-to-identify ESR genotypes, CYP SNPs, and the other hypothesized candidate polymorphisms that will be tested for in this trial. The use of a flexible but robust technology like this is important since new variants are being identified all the time.

9.1 Statistical considerations for primary objective of SNP validation

Patients will be classified into two groups based on whether or not they discontinued treatment due to MSS. Hardy-Weinberg equilibrium will be evaluated within each racial subset. SNP genotypes will be coded as additive effects on the log odds ratio by coding as 0, 1 or 2 for the count of the minor allele. Logistic regression will be used to test the association between having a minor allele and the log odds of discontinuation of treatment, adjusting for covariates. We plan to enroll 1000 patients and follow them for development of symptoms. Minor allele frequencies reported by Ingle et al. were assumed for the 4 SNPs associated with the TCL1A gene, and preliminary results from the ELPH study were used to estimate minor allele frequencies associated with the ESR gene. A Bonferroni adjustment will be used to account for the simultaneous testing of 10 SNPs; a one-sided p-value of 0.0025 will be considered statistically significant. For purposes of illustrating statistical power, we assume that Hardy-

Weinberg equilibrium exists in the allele distribution and that the minor allele is associated with *higher* proportions of discontinuation of treatment due to development of symptoms. Table 1 shows the genes, SNPs, and representative minor allele frequencies observed in previous studies. Table 2 shows odds ratios for the effect of each minor allele that will be detectable with 80% power for overall discontinuation rates of 20% or 30% and a range of plausible minor allele frequencies, given a sample size of 1000 patients and using a one-sided Cochran-Armitage trend test. The table also shows detectable odds ratios for the subsets of Caucasian (n=600) and African-American and Asian patients (n=200 patients each).

Table 1. SNPs to be validated

SNP	Gene	Rank (Ingle)	Rank (ELPH)	Minor Allele Frequency (MAF)
rs7158782	TCL1A	1		0.189 among cases, 0.109 among controls (0.2 ELPH)
rs7159713	TCL1A	2		0.189 (0.19 ELPH)
rs2369049	TCL1A	3	4	0.176 (.18 ELPH)
rs11849538	TCL1A	4	9	0.15 (ELPH)
rs2296972	HTR2A		1	0.37 (ELPH)
rs2347868	ESR1		2	0.23
rs9340835	ESR1		3	0.35
rs2234693	ESR1			0.45 (Riancho)
rs1062033	CYP19A1			0.44 (Riancho)
rs4646	CYP19A1		5	0.28

Table 2. Odds Ratios for Effect of Each Minor Allele Detectable with 80% Power (Additive Model)

Proportion Discontinuing	MAF	N=1000	N=600	N=200
20%	10%	1.88	2.23	3.89
30%	10%	1.78	2.10	3.65
20%	20%	1.63	1.87	2.94
30%	20%	1.55	1.76	2.70
20%	30%	1.55	1.76	2.66
30%	30%	1.47	1.65	2.42
20%	40%	1.52	1.72	2.59
30%	40%	1.44	1.61	2.33

9.2 Secondary Endpoint Analyses

The association of other SNPs in the ESR, TCL1A, and CYP19A1 genes with discontinuation of treatment due to MSS will be explored using a candidate gene approach. In this exploratory analysis, the prevalence of treatment

discontinuation will be compared between patients who do and do not have the variant genotype, modeling the effects as additive, dominant, and recessive. Correlations among SNPs will be estimated, and linkage disequilibrium among pairs of SNPs will be characterized. Logistic regression models, with treatment discontinuation as the outcome variable, will be used to explore the association with SNPs, adjusting for important clinical factors. No adjustment for multiple comparisons is planned, but only the top ranking SNPs that were not part of the primary validation study will be further explored.

Other endpoints, including the proportions of patients with treatment discontinuation for any reason, the proportion of patients with symptoms determined not to be from other known etiologies, and the proportion of patients whose symptoms improve when the AI is discontinued, will be similarly explored. Time to discontinuation of treatment and time to development of symptoms will be explored using proportional hazards models adjusting for significant genotypic and clinical predictors. Kaplan-Meier plots will be used to graphically portray the associations. Hispanics are the fastest growing demographic group in the US population, and there are 17,100 new breast cancer cases and 2400 breast cancer deaths expected in this demographic group in 2012[37]. The Hispanic demographic group may have unique attitudes, beliefs and behaviors related to medication adherence with AI.[38-40] Exploratory analyses to determine whether effects are different in patients with Hispanic ethnicity will also be performed.

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Previous studies have suggested that patients who experience specific adverse events associated with endocrine therapy may have improved recurrence-free (RFS) and overall survival (OS) compared to those who do not develop these symptoms ([42,43]). RFS ad OS will be described for the entire study population and for racial and ethnic subsets. Differences in RFS and OS between patients who do or do not develop AIMSS will be explored.

9.3 Statistical Considerations For Patient-Reported Outcomes

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We propose to include all 1000 patients in assessment of patient-reported outcomes. Linear mixed effects models will be used to evaluate changes in symptoms over time on these instruments. For purposes of estimating available statistical power, we consider a hypothetical analysis comparing changes in endocrine symptoms from baseline to 3 months between Caucasian and African-American patients. Total score on the FACT-ES (FACT-B plus ES subscale) will be calculated. Psychometric properties of FACT-ES were reported by Fallowfield et al. [(29).] In that report, mean scores of 61.61 at baseline (standard deviation 6.65) and 57.03 at 12 weeks (standard deviation 9.03) were reported among 32 women (a decline of 4.52 points). Table 3 shows statistical power and differences in change from baseline that will be detectable assuming a two-sided t-test with 5% Type I error, 85% power, baseline standard deviation of 6.65, intra-patient correlations of 0.4 or 0.6, and QOL completion rates of 90% and 75% across the two time points. There will be good power to detect reasonable differences between groups in changes from baseline.

Table 3. Detectable Differences for an Example Patient-Reported Outcomes Analysis (85% Power)

Intra-Patient Correlation	Standard Deviation of Change	Completion Rate	N Caucasian Patients	N African-American Patients	Detectable Difference
0.4	7.285	90%	540	180	1.88
0.6	5.948	90%	540	180	1.54
0.4	7.285	75%	450	150	2.06
0.6	5.948	75%	450	150	1.68

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Similar analyses will be done for the FACT-B subscale and for the Trial Outcome Index, consisting of the FACT-B subscale along with the FACT-G Physical Well-being and Functional Well-Being subscales.

In E1Z03, the quality of life companion study to MA27, patients who reported being bothered by side effects of treatment were more likely to discontinue treatment. The impact of patient-reported outcomes, both side effects in general and joint pain in particular, on treatment discontinuation will be examined along with the genotype information to assess the relative significance of both.

Patients will be given a choice regarding their preference for submitting QOL instruments in paper form or electronically. If 90% or more of patients choose the electronic system and if the completion rate among those patients is greater than 90%, then the web-based system would be considered for future trials.

If fewer than 90% of patients choose the system but the completion rate among these patients is greater than 90%, then the web-based system would be offered as an alternative in future trials.

If the completion rate among web-based users is significantly lower than the rate for paper forms, then paper forms would be retained for future studies. Assuming that 80% of the 1000 patients opt for the web-based system, there will be adequate power (91%) to detect a difference in completion rates of 12% (for example, 80% vs. 68%), using a one-sided Fisher's exact test with 2.5% Type I error. Given that access issues may exist in racial subgroups, differences in the rates of preference of the on-line system and in the completion rates by racial subgroup will be explored. Within minority subgroups there will be 90% power to detect a difference in completion rates of 28% (for example, 80% vs. 52%) for paper- and web-based processes. A plan to carry electronic capture of QOL data forward would not be considered if this was a barrier to participation in minority communities.

As described in Objective 2.2.6 and Section 6.2.7, a goal of the study is to validate the PROMIS Physical Function (PF) Short Form 20a in patients with AIMSS. We plan to employ both instruments until 480 English-speaking patients have enrolled, assuming that the incidence or AIMSS among these patients is 25%, resulting in 120 symptomatic patients with assessments on both instruments. Validation will include assessment of internal consistency using Cronbach's alpha. Test-retest reliability will be assessed by calculating a bivariate correlation on scores for the first and second administrations among patients whose scores on the HAQ assessment did not change. Associations

between scores on the HAQ and the PROMIS PF20a will be used to evaluate external validity. The ability of the instrument to discriminate between patients with/without symptoms will also be evaluated. Assuming 480 patients, a completion rate of 90% at 3 months, and 25% of patients with symptoms at 3 months, there will be adequate power to detect an effect size of .35, using a two-sided t-test with 90% power and 5% Type I error.

9.4 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG studies. Reports of these analyses are sent to the ECOG Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.

9.5 Gender and Ethnicity

Based on prespecified accrual targets the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	100	0	100
Not Hispanic or Latino	900	0	900
Ethnic Category: Total of all subjects	1000	0	1000
Racial Category			
American Indian or Alaskan Native	5	0	5
Asian	200	0	200
Black or African American	200	0	200
Native Hawaiian or other Pacific Islander	5	0	5
White	590	0	590
Racial Category: Total of all subjects	1000	0	1000

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.6 Accrual Rates

We expect to accrue 500 patients per year for 2 years. Accrual of African American and Asian cohorts may take longer, but targeted strategies will be used to encourage enrollment to these cohorts.

10. Correlative Studies

NOTE: An informed consent must be signed prior to the submission of any samples, including future laboratory studies.

NOTE: ECOG requires that all biological samples submitted be entered and tracked via the online ECOG Sample Tracking System. An STS Shipping Manifest Form must be generated and shipped with the sample submissions. See Section 10.3.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG Coordinating Center regarding logistics for submission of fresh samples.

10.1 DNA Polymorphisms Associated with AIMSS and Discontinuation of Aromatase Inhibitors

Pharmacogenomic predictors may be able to identify women at risk for AIMSS since genetic variants have already been identified that are associated with AI pharmacokinetics, with the effects of estrogen deprivation on bone and other phenotypes.

The goal of the correlative study is to validate previously identified associations between ten specific single nucleotide polymorphisms (SNPs) and discontinuation of treatment with aromatase inhibitors (AIs) due to the development of musculosketal symptoms (MSS) among women with breast cancer. If these associations are confirmed, a marker could be identified that may serve as an indicator of increased risk for treatment discontinuation and related poor therapeutic outcome.

10.1.1 Sample Submission Schedule

Instructions to order kits are outlined below in Section 10.1.2.1.

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NOTE: Due to funding restrictions multiple kit requests are not permitted. Additionally patients must be registered to or being worked up for the trial before submitting your kit requests.

Questions are to be directed to the ECOG Immunological Monitoring and Cellular Products laboratory (IMCPL) ECOG study coordinator at (412) 624-0078.

10.1.1.1 Blood for DNA must be collected at baseline (blood is strongly encouraged to be collected at baseline [after registration, prior to treatment] but may be collected at any other time point if unable to collect at baseline)for the mandatory genotyping assays outlined in Sections 1.1.2 and 10.2.

Dr. David Flockhart's Laboratory at the Indiana University Division of Clinical Pharmacology will perform the analysis.

10.1.1.2 Blood (serum) for banking for future research studies should be submitted at the following time points:

- Baseline

- At Three (3) Months **OR** Onset of AIMSS (if prior to three [3] months)
- At Twelve (12) Months **OR** Discontinuation of Anastrozole due to AIMSS

NOTE: Blood samples are to be submitted from patients who answer "YES" to "I agree to provide additional blood for research."

10.1.2 Sample Preparation Guidelines

1. At Baseline ONLY the following MUST be submitted:

- One (1) FULL 10 cc YELLOW top ACD tube

2. At EACH time point listed above in Section 10.1.1.2 please submit the following (OPTIONAL):

- One (1) FULL 10 cc RED top tube

Please completely fill all blood tubes as full as possible.

Each tube must be clearly labeled to include:

- ECOG protocol number E1Z11
- ECOG five digit patient sequence number
- Patient initials
- Originating institution/investigator name
- Date and time drawn
- Collection time point

10.1.2.1 Shipping Kits

Specimen shipping kits must be requested from the IMCPL. Please fax the request using the Shipping Kit Request Facsimile Form (Appendix VI) to (412) 623-6625 or call the IMCPL at (412) 624-0078. Please allow ten days for shipment and provide the following information:

- Study Number
- Participating Site Number
- Contact Person and Telephone Number

The kits will be shipped via FedEx Express Saver. Please plan ahead, priority overnight shipment is not possible.

All blood samples should be shipped the day of collection using the shipping kit. Follow shipping instructions provided in the kit carefully.

The shipping kit consists of the following:

- Insulated shipping container and packing material
- FedEx Priority Overnight return label
- Shipping Instructions
- Shipping Kit Request Form

10.1.3 Shipping Procedures

Log the samples into the ECOG STS the day of shipment. If the STS is unavailable, an ECOG Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

If the STS is unavailable, notify the IMCPL ECOG study coordinator by fax (412-623-6625) using the Specimen Shipment/Requisition Form (Appendix V). If you are unable to get through to the laboratory by fax, telephone the ECOG study coordinator at (412) 624-0078 and provide the tracking number.

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Blood collected into the appropriate tubes should be sealed, wrapped and placed in the specimen shipper kit and shipped on the same day they are drawn by Federal Express Priority overnight courier using the return label provided in the kit. The yellow and red top tubes should be refrigerated immediately. Cool packs are not required as the Styrofoam shipper should protect the tubes for overnight shipment. Shipments must be timed to arrive during normal working hours and should be shipped in one box.

The laboratory will be open Monday through Friday to receive samples. Do NOT ship on Fridays or Saturdays, or the day before a legal holiday. Ship by overnight courier Monday - Thursday only to:

Immunologic Monitoring and Cellular Products Laboratory
University of Pittsburgh Cancer Institute
UPCI-IMCPL
ECOG Study Coordinator
Hillman Cancer Center
5117 Centre Avenue, L 1.26
Pittsburgh, PA 15213
Tel: (412) 624-0078
Fax: (412) 623-6625

An STS Shipping Manifest Form must be generated and shipped with all sample submissions.

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NOTE: Blood should **NOT** be collected on Fridays. Please contact the IMCPL for further instruction.

10.1.4 Federal Guidelines for the Shipment of Blood Products:

Sites should follow IATA regulations for Packaging UN3372 shipments. Please refer to FedEx guidelines.

10.2 Pharmacogenomic Study Methods

10.2.1 Specimen Acquisition

Blood will be collected at baseline using yellow top tubes. Specimens will be shipped to the ECOG IMCPL at the University of Pittsburgh where DNA will be isolated and stored for subsequent shipment to Dr. David Flockhart's Laboratory at the Indiana University School of Medicine for genotyping assays. DNA concentrations will be determined using the Picogreen DNA quantification assay (Life

Technologies, Inc). This assay is based on the SYBR green fluorescence and provides the most accurate total DNA quantification measurements. DNA quality will be assessed by 260:280 nanometers absorbance and a subset of samples will be run on an agarose gel to assure that high quality high molecular weight DNA is being isolated.

10.2.2 Assay

The Flockhart Laboratory will use the OpenArray™ platform for the genotyping assays. The instrument to be used has been purchased from Applied Biosystems, Inc. The custom designed genotyping arrays are mini Taqman™ assays plated on the OpenArrays™ in 33 nanoliter reaction volumes. The thermocycling is done in an ABI 9600 thermocycler and the resulting allele specific fluorescence is read in the OpenArray™ reader. All equipment and reagents are purchased from Applied Biosystems, Inc. (a division of Life Technologies, Inc).

10.2.3 Assay Performance

The Flockhart Laboratory's previous studies using the OpenArray™ format have yielded call rates of >95% with accuracy of >98%. For quality control purposes, approximately 10-15% of the samples are re-genotyped. Concordance rates of >98% are expected, but are usually 100%. Any discrepancies are resolved by DNA sequencing. Every assay contains a no template control (water in place of the DNA sample). The assays are not performed in a CLIA laboratory, and thus no results will be returned to patients or health care providers.

10.2.4 Scoring

Genotyping data results will yield one of three possible classifications: Homozygous wild-type (2 wild-type alleles), heterozygous (1 wild-type and 1 variant allele), or homozygous variant (2 variant alleles). The classification is determined based on the fluorescent values obtained from the allelic discrimination plots of the Taqman™ assays. These are standard assays used widely in the field for genotyping. Minor allele frequencies are expected to range from 10% to 38% based on prior studies in similar populations. This range of frequencies is high enough that an association between the polymorphism and the phenotype of treatment discontinuation due to AIMSS has potential utility. The rate of treatment discontinuation due to AIMSS is expected to be 20 to 30%.

10.3 ECOG Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG Sample Tracking System (STS). The software will allow the use of either 1) an ECOG user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A

user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated Shipping Manifest Form should be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

10.3.1 Study Specific Notes

An ECOG Generic Specimen Submission Form (#2891) will be required only if STS is unavailable at the time of sample submission. Indicate the appropriate Lab ID # on the submission form:

- 0009= ECOG Immunologic Monitoring and Cellular Products Laboratory
    - The day of shipment, notify the IMCPL ECOG study coordinator by fax (412-623-6625) using the Specimen Shipment/Requisition Form (Appendix V). If you are unable to get through to the laboratory by fax, telephone the ECOG study coordinator at (412) 624-0078 and provide the FedEx tracking number.

      Retroactively enter all collection and shipping information when STS is available.

10.4 Banking

Blood samples collected will be retained at the ECOG IMCPL for use in future ECOG approved studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.5 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned correlative studies will be submitted electronically via secure data portal to the ECOG Coordinating Center by the central laboratory on a quarterly basis.

10.6 Sample Inventory Submission Guidelines

Inventories of all specimens collected and aliquoted will be submitted electronically by secure web application to the ECOG Coordinating Center on a monthly basis or upon request by any laboratory holding and/or using specimens associated with this study.

11. Electronic Data Capture

Please refer to the E1Z11 Forms Completion Guidelines for the forms submission schedule. Data Collection will be performed in Medidata Rave and in Assessment Center™.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG Coordinating Center to CTEP by electronic means.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin.60(5):277-300.
2. Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol. 2010;28(23):3784-96.
3. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol. 2007;25(25):3877-83.
4. Henry NL, Giles JT, Ang D, Mohan M, Dadabhoy D, Robarge J, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat. 2008;111(2):365-72.
5. Henry NL, Azzouz F, Desta Z, Li L, Nguyen AT, Lemler S, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol.30(9):936-42.
6. Klein C, Lohmann K, Ziegler A. The Promise and Limitations of Genome-wide Association Studies. J Am Med Assoc.1-2.
7. Henry NL, Pchejetski D, A'Hern R, Nguyen AT, Charles P, Waxman J, et al. Inflammatory cytokines and aromatase inhibitor-associated musculoskeletal syndrome: a case-control study. Br J Cancer. 2010;103(3):291-6. PMCID: 2920022.
8. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med. 2009;361(9):888-98.
9. Pinto LG, Cunha TM, Vieira SM, Lemos HP, Verri WA, Jr., Cunha FQ, et al. IL-17 mediates articular hypernociception in antigen-induced arthritis in mice. Pain.148(2):247-56.
10. Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer. 2003;98(9):1802-10.
11. Henry NL, Jacobson JA, Banerjee M, Hayden J, Smerage JB, Van Poznak C, et al. A prospective study of aromatase inhibitor-associated musculoskeletal symptoms

and abnormalities on serial high-resolution wrist ultrasonography. Cancer.116(18):4360-7. PMCID: 2936686.

12. Wolfe F, Michaud K, Strand V. Expanding the definition of clinical differences: from minimally clinically important differences to really important differences. Analyses in 8931 patients with rheumatoid arthritis. J Rheumatol. 2005;32(4):583-9.
13. Hayes DF, Skaar TC, Rae JM, Henry NL, Nguyen AT, Stearns V, et al. Estrogen receptor genotypes, menopausal status, and the effects of tamoxifen on lipid levels: revised and updated results. Clin Pharmacol Ther. 2010;88(5):626-9.
14. Henry NL, Nguyen A, Azzouz F, Li L, Robarge J, Philips S, et al. Lack of association between oestrogen receptor polymorphisms and change in bone mineral density with tamoxifen therapy. Br J Cancer.102(2):294-300. PMCID: 2816645.
15. Rae JM, Cordero KE, Scheys JO, Lippman ME, Flockhart DA, Johnson MD. Genotyping for polymorphic drug metabolizing enzymes from paraffin-embedded and immunohistochemically stained tumor samples. Pharmacogenetics. 2003;13(8):501-7.
16. Henry NL, Rae JM, Li L, Azzouz F, Skaar TC, Desta Z, et al. Association between CYP2D6 genotype and tamoxifen-induced hot flashes in a prospective cohort. Breast Cancer Res Treat. 2009;117(3):571-5. PMCID: 2746261.
17. Ingle JN, M. L, Wickerham DL, Schaid DJ, Mushiroda T, Kubo M, et al., editors. Genome-Wide Associations of Breast Events and Functional Genomic Studies in High-Risk Women Receiving Tamoxifen or Raloxifene on NSABP P1 and P2 Prevention Trials. A Pharmacogenomics Research Network-RIKEN-NSABP Collaboration. San Antonio Breast Cancere Symposium; 2010; San Antonio, Texas.
18. Kamdem LK, Liu Y, Stearns V, Kadlubar SA, Ramirez J, Jeter S, et al. In vitro and in vivo oxidative metabolism and glucuronidation of anastrozole. Br J Clin Pharmacol.70(6):854-69. PMCID: 3014069.
19. Garcia-Casado Z, Guerrero-Zotano A, Llombart-Cussac A, Calatrava A, Fernandez-Serra A, Ruiz-Simon A, et al. A polymorphism at the 3'-UTR region of the aromatase gene defines a subgroup of postmenopausal breast cancer patients with poor response to neoadjuvant letrozole. BMC Cancer.10:36. PMCID: 2830181.
20. Desta Z, Kreutz Y, Nguyen AT, Li L, Skaar T, Kamdem LK, et al. Plasma letrozole concentrations in postmenopausal women with breast cancer are associated with CYP2A6 genetic variants, body mass index, and age. Clin Pharmacol Ther.90(5):693-700.
21. Kamdem LK, Flockhart DA, Desta Z. In vitro cytochrome P450-mediated metabolism of exemestane. Drug Metab Dispos.39(1):98-105. PMCID: 3014267.
22. Offit K, Robson ME. New pharmacogenomic paradigm in breast cancer treatment. J Clin Oncol.28(31):4665-6.

22 a Riancho JA, García-Ibarbia C, Gravani A, et al. Common variations in estrogen-related genes are associated with severe large-joint osteoarthritis: a multicenter genetic and functional study. Osteoarthritis Cartilage. 2010;18:927-33. PMID: 20417295.)

23. Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai WY, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of

8,769 early-stage breast cancer patients. J Clin Oncol.28(27):4120-8. PMCID: 2953970.

24. Wagner LI, Zhao F, Chapman J-AW, Cella D, Shepherd LE, Sledge GW, et al., editors. Patient-reported predictors of early treatment discontinuation: NCIC JMA.27/E1Z03 quality of life tudy of postmenopausal women with primary breast cancer randomized to exemestane or anastrozole. San Antonio Breast Cancer Symposium; 2011; San Antonio, Texas.
25. Gershon RC, Rothrock N, Hanrahan R, Bass M, Cella D. The use of PROMIS and assessment center to deliver patient-reported outcome measures in clinical research. J Appl Meas.11(3):304-14.
26. Gershon R, Rothrock NE, Hanrahan RT, Jansky LJ, Harniss M, Riley W. The development of a clinical outcomes survey research application: Assessment Center. Qual Life Res.19(5):677-85.
27. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003;30(1):167-78.
28. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol. 1997;15(3):974-86.
29. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. Breast Cancer Res Treat. 1999;55(2):189-99.
30. Cella D, Fallowfield L, Barker P, Cuzick J, Locker G, Howell A. Quality of life of postmenopausal women in the ATAC ("Arimidex", tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer. Breast Cancer Res Treat. 2006;100(3):273-84.
31. Gotay CC, Pagano IS. Assessment of Survivor Concerns (ASC): a newly proposed brief questionnaire. Health Qual Life Outcomes. 2007;5:15. PMCID: 1828718.
32. Rakovitch E, Franssen E, Kim J, Ackerman I, Pignol JP, Paszat L, et al. A comparison of risk perception and psychological morbidity in women with ductal carcinoma in situ and early invasive breast cancer. Breast Cancer Res Treat. 2003;77(3):285-93.
33. Bernhard J, Maibach R, Thurlimann B, Sessa C, Aapro MS. Patients' estimation of overall treatment burden: why not ask the obvious? J Clin Oncol. 2002;20(1):65-72.

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34. Ritchie CS, Kvale E, Fisch MJ. Multimorbidity: an issue of growing importance for oncologists. J Oncol Pract.7(6):371-4. PMCID: 3219463.
35. Sarfati D. Review of methods used to measure comorbidity in cancer populations: No gold standard exists. J Clin Epidemiol.65(9): 924-33.
36. Peters EN, Torres E, Toll BA, Cummings KM, Gritz ER, Hyland A, et al. Tobacco assessment in actively accruing national cancer institute cooperative group program clinical trials. J Clin Oncol.30(23):2869-75. PMCID: 3410402.
37. Kvale EA, Manola J, Ritchie CS, Snyder CF, Fisch MF. Concordance between patient and clinician regarding perception of comorbidity burden. Supp Care Cancer 2012;20(Suppl 1)(S197, Abstract 827).
38. Ritchie C, Manola J, Kvale E, Snyder CF, Fisch M. The relationship between symptom burden and perceived comorbidity in outpatients with common solid tumors. J Clin Oncol. 2012;30 suppl(Abst 6080).

39. Fries JF, Krishnan E, Rose M, Lingala B, Bruce B. Improved responsiveness and reduced sample size requirements of PROMIS physical function scales with item response theory. Arthritis Res Ther.13(5):R147. PMCID: 3308075.

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40. CuzickJ, Sestak I, Cella D, et al. Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial. Lancet Oncol 2008; 9: 1143-1148.

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41. Fontein DBY, Seynaeve C, Hadji P, et al. Specific adverse events predict survival benefit in patients treated with tamoxifen or aromatase inhibitors: an International Tamoxifen Exemestane Adjuvant Multinational Trial analysis. J Clin Oncol 2013; 31: 2257-2264.

A Cohort Study to Evaluate Genetic Predictors for Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

Appendix I

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Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in *Addendum #3*]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

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Appendix I was removed from the protocol document in Addendum #*3* and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

A Cohort Study to Evaluate Genetic Predictors for Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Cohort Study to Evaluate Genetic Predictors for Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

Appendix III

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.

NOTE: Local study teams may use a different calendar format as long as drug dates/doses are recorded for study reporting/data completion.

Patient Pill Calendar

This is a calendar on which you should record taking the study tablet, anastrozole. You should take your anastrozole as directed by your doctor. Write in the date and your initials for each day during the month you took anastrozole. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided.

DAY	Date			Patient Initials	Number of pills taken	Did you take brand or generic anastrozole	Side effects (including unusual symptoms), other medications you have taken, or other notes for your doctor.
	Month	Day	Year				
1							
2							
3							
4							
5							
6							
7							
8							
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A Cohort Study to Evaluate Genetic Predictors for Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

A Cohort Study to Evaluate Genetic Predictors for Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

Appendix V

Specimen Shipment Requisition Form

ECOG – PROTOCOL E1Z11

It is required that samples submitted from patients participating in E1Z11 be entered and tracked via the online ECOG Sample Tracking System. This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Immunologic Monitoring and Cellular Products Laboratory	UPCI Research Pavilion at the Hillman Cancer Center Room L 1.26 5117 Centre Avenue Pittsburgh, PA 15213-1863 Tel: 412-624-0078 Fax: 412-623-6625

Ship specimens by overnight express to arrive the next morning unless otherwise directed by the protocol. Do NOT ship on Friday or Saturday, or the day before a legal holiday.

Call the IMCPL ECOG Study Coordinator at 412-624-0078 with questions on shipping.

Please complete the following information and include this form in the shipment.

ECOG Patient Sequence Number: _____ ECOG Patient Initials: _____
Last First

Clinical Site:_____ Site Contact: _____

Telephone Number: _____ Fax Number: _____

Federal Express® Air Bill No.: _____ Date of Shipment: _____

Specimen
Collection Date __ __/__ __/__ __
mm dd yy

Specimen
Collection Time: ____ ____:____ ____
(24 hour clock)

Time Points (check one):

☐ Baseline One (1) ACD yellow top tube, One (1) red top tube

☐ Month 3 One (1) red top tube
(or onset of AIMSS)

☐ Month 12 One (1) red top tube
(or discontinuation of treatment)

Shipping Checklist: (kits will be shipped / delivered to you from UPCI IMCPL upon request)

____ Label vials with patient initials/ECOG sequence number, and date and time of draw.

____ Seal, wrap, and place specimen tubes in specimen shipper kit.

____ STS Shipping Manifest Form. Make a copy for your records and place the original form inside the specimen shipper kit.

To be completed by IML Staff:	IML Study Number
IML Accession Number:	Specimen Type received (if different from above):
Specimen Acceptability:	Comment:

A Cohort Study to Evaluate Genetic Predictors for Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

Appendix VI

Shipping Kit Request Facsimile Form

ECOG – PROTOCOL E1Z11

Immunologic Monitoring and Cellular Products Laboratory	UPCI Research Pavilion at the Hillman Cancer Center Room L 1.26 5117 Centre Avenue Pittsburgh, PA 15213-1863 Tel: 412-624-0078 Fax: 412-623-6625

To: ECOG Study Coordinator Fax: 412-623-6625

From: Name: _____

Institution:_____

Telephone: _____

Fax: _____

Number of Kits Requested:

Baseline (1RT/1ACD) _____

Month 3/Onset of AIMSS (1RT) _____

Month 12/End of Treatment (1RT) _____

Shipping Address: _____

_____

_____

_____

PLEASE ALLOW 10 WORKING DAYS FOR RECEIPT OF SHIPPING KITS

NOTE: To order collection and shipping kits for E1Z11, patients must be registered to or in the process of being worked up for the E1Z11 trial. Due to funding restrictions institutions cannot order multiple collection and shipping kits in advance.