The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Randomized Multicenter Placebo-Controlled Trial of Omega-3-Fatty Acids for the control of Aromatase Inhibitor-Induced Musculoskeletal Pain (S0927)

Hershman, et al

DOI: 10.1200/JCO.2014.59.5595

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Distribution Date: February 1, 2013
E-mailed Date: January 22, 2013

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swog.org

TO: ALL SWOG MEMBERS, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S0927**, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III." Study Coordinators: Drs. D. Hershman, K.D. Crew, and C. Moinpour.

STATUS NOTICE

Study Coordinator: Dawn Hershman, M.D., M.S.
Phone number: 212/305-1945
E-mail: dlh23@columbia.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The above-referenced study has met its accrual goal and will permanently close to accrual effective **February 1, 2013 at 11:59 p.m. Pacific.**

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Frank Meyskens, D.O.
Dawn Hershman, M.D., M.S.
Katherine D. Crew, M.D., M.S.
Carol Moinpour, Ph.D.
Lisa Hansen, R.N., M.S.
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January 1, 2013

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL INVESTIGATORS AND CLINICAL RESEARCH ASSOCIATES

FROM: SWOG Operations Office

RE: Eligibility Affirmation

MEMORANDUM

By signing the FDA 1572, every SWOG investigator has agreed to conduct studies in compliance with the protocol, and to personally conduct or supervise the investigation. A critical step in this process is verification of patient eligibility.

Effective January 1st, 2013, every registering investigator or another SWOG investigator designate is required to sign a statement on the Registration Worksheet that the eligibility criteria have been confirmed. This worksheet will not be submitted to Data Operations Office but must be maintained at the local institution for review during audits.

As part of this transition, forms and the forms list (Section 18.2) are being removed from active studies and will be posted separately on the individual protocol abstract page for each study. Subsequent pages have been renumbered accordingly. No other form, protocol, or consent form changes have been made as part of the transition.

If you have any questions, please contact the SWOG Operations Office at 210/614-8808.

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Distribution Date: July 15, 2012
DCP Submission Date: July 2, 2012

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TO: ALL SWOG MEMBERS, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S0927**, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III." Study Coordinators: Drs. D. Hershman, K.D. Crew, and C. Moinpour.

REVISION #1

Study Coordinator: Dawn Hershman, M.D., M.S.
Phone number: 212/305-1945
E-mail: dlh23@columbia.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

The above-referenced protocol has been revised as follows:

1. Title page: The version date has been updated

2. Section 3.1c, Page 12: Under "Distribution", the following sentence was added: The institution will automatically receive a resupply of omega-3-fatty acid/placebo based on the patient's registration date.

3. Section 5.16, Page 17: This eligibility criterion was added to exclude patients with a known soy allergy. Subsequent sections have been renumbered accordingly.

4. Section 7.1a, Page 19: In the first sentence, “general physical exam” was removed as this is required at pre-study and not the initial study visit. The bullet for the **S0927** Brief Pain Inventory Short Form (BPI-SF) (Form #54223) was removed as this is required prior to registration and not at the initial visit.

5. Section 9.0, Page 22: Added the ∆ footnote to clarify that the history and physical exam must be completed within 28 days prior to registration. The "X" under Prestudy for the **S0927** Omega-3-Fatty Acid Dietary Intake Questionnaire has been moved to baseline.

6. Section 15.2d, Page 30: Clarified that kits may be ordered "for the baseline, 12 week and 24 week collection" by the SWOG Specimen Repository Management Application.

7. Model Consent Form, Page 56: Under “Future Use of Specimens” added “I agree for my blood to be used in the additional studies.” as it was on the **S0927** Registration Worksheet (Form #7067), but was missing from the consent form.

Please append this notice to the front of your protocol and insert the replacement pages referenced above.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Frank Meyskens, D.O.
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April 1, 2012

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TO: ALL SWOG MEMBERS, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S0927**, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III." Study Coordinators: Drs. D. Hershman, K.D. Crew, and C. Moinpour.

MEMORANDUM

Study Coordinator: Dawn Hershman, M.D., M.S.
Phone number: 212/305-1945
E-mail: dlh23@columbia.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

Change #9 of the Activation Revision is incorrect. Kits for the Week 12 and Week 24 collections **will not** be automatically sent to the site. Kits must be ordered through the SWOG Specimen Repository Management Application for each collection timepoint. Please see Section 15.2d for online access to the application. This will be clarified in the protocol in a future revision.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Frank Meyskens, D.O.
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February 1, 2012

TO: ALL SWOG MEMBERS, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S0927**, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III." Study Coordinators: Drs. D. Hershman, K.D. Crew, and C. Moinpour.

STATUS NOTICE

Study Coordinator: Dawn Hershman, M.D., M.S.
Phone number: : 212/305-1945
E-mail: dlh23@columbia.edu

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate; for institutions that have not received approval of the protocol)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed (for institutions that have received approval of the protocol version distributed for IRB review only)

( ) No review required

ACTIVATION

The study referenced above is open for participation **effective February 1, 2012 at 2:00 p.m. EST**. The entire protocol is attached for your use.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Frank Meyskens, D.O.
Dawn Hershman, M.D., M.S.
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Distribution Date: February 1, 2012
DCP Submission Date: January 11, 2012

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S0927**, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III" Study Coordinators: Drs. D. Hershman, K.D. Crew, and C. Moinpour.

STATUS NOTICE

Study Coordinator: Dawn Hershman, M.D., M.S.
Phone number: 212/305-1945
E-mail: dlh23@columbia.edu

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate; for institutions that have not received approval of the protocol version distributed for IRB review only)
- ( ) Increased risk to patient
- ( ) Complete study redesign
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- ( ) Study closure due to new risk information

(√) Expedited review allowed (for institutions that have received approval of the protocol version distributed for IRB review only)

( ) No review required

ACTIVATION REVISION

Institutions should update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients who have signed a consent form but not yet started treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The above referenced protocol has been revised as follows:

1. Title page: The version date has been updated and the activation date has been added to the top right corner.

2. Section 9.0, Page 22: Under “Physical”, “BMI” has been removed from the physical exam line and “height” has been added. Under "Procedures", "Fasting" has been removed from blood for DNA, "Fasting blood for serum" has been changed to "Fasting blood for biomarker analysis", and "Blood for banking (optional) †" has been added. In the “**” footnote, Section 15.2 has been updated to Section 15.2d and “SWOG Repository/University of Colorado” has been updated to “SWOG Specimen Repository”. The "†" footnote was added to reference Section 15.1 for information about the optional blood submission for banking.

3. Section 15.1, Page 29: The name and lab number of the SWOG Specimen Repository have been updated to “SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201”.

4. Section 15.1a, Page 29: The word “whole” has been added before “blood” for clarification in the first sentence, "(10 cc's)" has been added to specify the quantify of blood required, and "at baseline" has been added to specify the required time point.

5. Section 15.2, Page 30: The word “whole” has been added before “blood” for clarification.

6. Section 15.2a, Page 30: The previous Section 15.2a that referenced collection and submission instructions has been deleted. Subsequent sections have been renumbered accordingly. In the new Section 15.2a, “samples” has been replaced with “whole blood specimens” in the first sentence. The end of the sentence has been changed from “…at the following times” to “…at the timepoints listed below.” The second sentence has been added to direct sites to the SWOG Specimen Submission webpage for specimen collection and submission instructions.

7. Section 15.2b, Page 30: This section has been added to contain the information regarding the required whole blood sample for DNA analysis for clarification that it is a separate submission. Subsequent sections have been renumbered accordingly. The second sentence has been added to direct sites to the SWOG Specimen Submission webpage for specimen collection and submission instructions. Information has been included to state that whole blood for DNA must be submitted in a purple top EDTA tube, as this is not part of standard submission instructions.

8. Sections 15.2c and 15.2d, Page 30: The previous Section 15.2c with specimen collection procedures and the previous Section 15.2d containing notes to avoid hemolysis, have been removed. Subsequent sections have been renumbered accordingly.

9. Section 15.2d, Page 30: The details of this section have been deleted and it now references the SWOG Specimen Repository Management Application which will allow sites to order kits online. Kits for Week 12 and Week 24 collections will be automatically sent to the site.

10. Section 15.2f, Page 30: This section with shipping instructions has been deleted as all shipping information can be found on the SWOG Specimen submission webpage.

11. Section 15.3a.2, Page 30: “At the 6 month assessment” has been replaced with “Week 24” to be consistent throughout the protocol.

12. Section 15.3b, Pages 30-31: In the first paragraph, “8-10mL” has been replaced with “5mL”. In the last sentence of the second paragraph, “repository in Colorado” has been replaced with “Specimen Repository”.

13. Section 15.4, Pages 31-34: The previous Section 15.4 containing instructions for shipping samples has been deleted as this information can be found on the SWOG Specimen submission webpage. Subsequent sections have been renumbered accordingly. The deletion has caused the redistribution of information throughout Pages 31-34.

14. Section 15.4c.4, Page 32: This section was added to include additional information about the quality of life training program on the SWOG website.

15. Section 16.1c, Page 35: The reference to Table 16.2 has been corrected to Table 16.1.

16. Model Consent Form, Page 59: Under “How am I protected?”, the address of the Solid Tumor Specimen Repository has been removed.

17. The activation date, 2/1/2012, has been added to all **S0927** protocol specific forms.

18. **S0927** Prestudy Form (Form #54663): On Page 2 under "Prior treatment related to this cancer", the question "Has the patient received prior taxane therapy for any reason?" has been removed. This question is a duplicate from the **S0927** Registration Worksheet (Form #7067).

19. **S0927** Treatment Form (Form #15208): Page 2 was missing and has been added. Subsequent pages have been renumbered accordingly.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Frank L. Meyskens, Jr., M.D.
Dawn Hershman, M.D., M.S.
Katherine D. Crew, M.D., M.S.
Carol Moinpour, Ph.D.
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Distribution Date: October 15, 2011
E-mailed Date: October 7, 2011

TO: ALL SWOG MEMBER INSTITUTIONS, CCOP INSTITUTIONS AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S0927**, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III". Study Coordinators: Drs. D. Hershman, K.D. Crew, C Moinpour and L Hansen.

MEMORANDUM

Study Coordinator: Dawn Hershman, M.D., M.S.
Phone number: 212/305-1945
E-mail: dlh23@columbia.edu

IRB Review Requirements

(√) Full board review required. Reason:
(√) Initial activation (should your institution choose to participate)
( ) Increased risk to patient
( ) Complete study redesign
( ) Addition of tissue banking requirements
( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

MEMORANDUM

This protocol is being distributed at this time **for Institutional Review Board (IRB) review only**. Once drug is ready for shipment, institutions will be informed that the study is active for patient registrations.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Laurence Baker, D.O.
Frank L. Meyskens, Jr., M.D.
Powel Brown, M.D., Ph.D.
Carol Moinpour, Ph.D.
James L. Wade, III, M.D.
Dawn Hershman, M.D., M.S.
Katherine Crew, M.D.
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Joseph Unger, M.S.
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Nathan Eriksen
Dana Sparks, M.A.T.

SWOG

A RANDOMIZED PLACEBO-CONTROLLED TRIAL OF OMEGA-3-FATTY ACID FOR THE CONTROL OF AROMATASE INHIBITOR-INDUCED MUSCULOSKELETAL PAIN AND STIFFNESS IN WOMEN WITH EARLY STAGE BREAST CANCER, PHASE III

PARTICIPANTS: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

STUDY COORDINATORS:

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AGENTS:

Omega-3-Fatty Acid

NURSE COORDINATOR:

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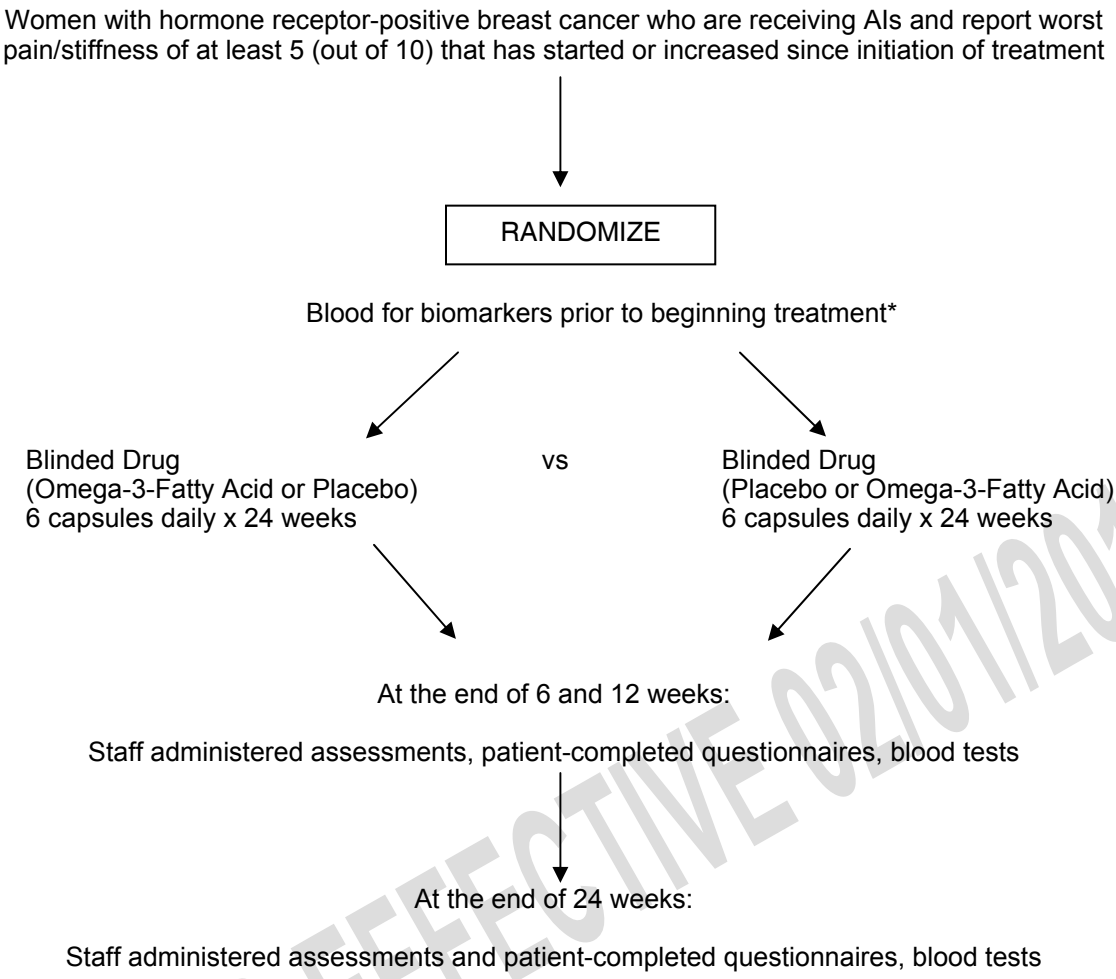
(Version Date: 07/2/12)

SCHEMA



* See Section 15.0 for specimen submission requirements.

1.0 OBJECTIVES

1.1 To assess if omega-3-fatty acid as compared to placebo causes a reduction in worst joint pain/stiffness in women with aromatase inhibitor (AI) associated arthralgias as measured at 12 weeks by the modified Brief Pain Inventory (BPI).

1.2 Secondary Objectives (measured at 6, 12 and 24 weeks)

a. To assess the proportion of patients who report improved versus deteriorated joint pain for patients receiving omega-3-fatty acid compared to those receiving placebo as measured by the modified BPI.

b. To assess the proportion of patients who report improved versus deteriorated joint stiffness for patients receiving omega-3-fatty acid compared to those receiving placebo as measured by the modified BPI.

c. To assess whether patients receiving omega-3-fatty acid compared to placebo have decreased analgesic use and increased AI adherence.

d. To assess whether patients receiving omega-3-fatty acid compared to placebo have improved functioning, pain, and stiffness in the knees/hips (as measured by the Western Ontario and McMaster Universities Osteoarthritis, WOMAC) score.

e. To assess whether patients receiving omega-3-fatty acid have improved functioning, pain, and stiffness in the hands (as measured by the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands, M-SACRAH).

f. To assess whether patients receiving omega-3-fatty acid compared to placebo have improved functional quality of life as measured by the Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES) Trial Outcome Index (TOI).

g. To assess whether patients receiving omega-3-fatty acid report changes for the better versus worse compared to patients receiving placebo as measured by the Global Rating of Change Scale.

h. To identify minimally important change in the WOMAC, M-SACRAH, and the FACT-ES Trial Outcome Index (TOI) using “a little better” or “a little worse” responses on the patient-reported global rating of change in joint pain and joint stiffness.

i. To assess whether patients receiving omega-3-fatty acid compared to placebo have an improved lipid profile as measured by triglycerides, HDL and LDL.

j. To assess the toxicity of omega-3-fatty acid compared to placebo in this setting.

k. To assess whether there is a difference in serum free and total estradiol levels before and after treatment with omega-3-fatty acid compared to placebo.

l. To explore whether CYP19A1 genotype correlates with severity of joint symptoms or predicts response to omega-3-fatty acid.

m. To explore changes in hormonal and inflammatory serum biomarkers such as IL6, TNF-α, CRP, and urine biomarkers for joint degradation CTX-II.

n. To assess whether there is a relationship between change in serum DHA and EPA and resolution of joint symptoms.

o. To establish a cohort (placebo group) to better characterize the natural history of the syndrome.

2.0 BACKGROUND

Endocrine treatments, including tamoxifen and aromatase inhibitors, are widely prescribed for all stages of hormone-responsive breast cancer. These agents are primarily directed at inducing estrogen deprivation through blocking estrogen at the receptor level (tamoxifen), or by inhibiting estrogen biosynthesis (aromatase inhibitors). Tamoxifen, the previous gold standard of care, is both an antagonist and a partial agonist of the estrogen receptor. *(1)* Tamoxifen may cause hot flashes, vaginal bleeding and discharge, and serious long-term side effects, including endometrial cancer and thromboembolism. *(2-4)*

Third-generation aromatase inhibitors (AIs), namely anastrozole, letrozole and exemestane, markedly suppress plasma estrogen levels in postmenopausal women by inhibiting the enzyme responsible for the conversion of androgens to estrogens in peripheral tissues (skin, muscle, fat, benign and malignant breast tissue). *(5-7)* Treatment of hormone receptor-positive breast cancer in postmenopausal women with third-generation AIs has been shown to be superior to tamoxifen with respect to disease-free survival, distant and local recurrence rates, and incidence of contralateral breast cancer. *(8-13)*

The Arimidex (anastrozole), Tamoxifen, Alone or in Combination (ATAC) trial compared five years of anastrozole to 5 years of tamoxifen in 9,366 postmenopausal women with localized breast cancer. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (HR 0.87, 95% CI 0.78-0.97), time-to-recurrence (HR 0.79, 95% CI 0.70-0.90), and contralateral breast cancers (42% reduction, 95% CI 12-62%). *(10)* The Breast International Group (BIG) 1-98 study compared 5 years of hormonal treatment in 8,010 postmenopausal women with hormone receptor-positive breast cancer. After a median follow-up of 25.8 months, letrozole as compared with tamoxifen significantly prolonged disease-free survival (HR 0.81, 95% CI 0.70-0.93) and reduced the risk of distant recurrence (HR 0.73, 95% CI 0.60-0.88). *(11)* The MA.17 trial was designed to determine whether extended adjuvant therapy with letrozole after 5 years of tamoxifen reduces the risk of late breast cancer recurrence. The trial was stopped early after an interim analysis showed that letrozole improved disease-free survival, and 5 year data showed that after a median follow-up of 30 months, women in the letrozole arm had significantly better disease-free survival (HR 0.58, 95% CI 0.45-0.76) and distant disease-free survival (HR 0.60, 95% 0.43-0.84). Here, overall survival was the same in both arms, however, among lymph node-positive patients, overall survival was significantly improved with letrozole (HR 0.61, 95% CI 0.38-0.98). *(12)* The Intergroup Exemestane Study tested the effect of switching to exemestane after 2-3 years of tamoxifen, compared to remaining on tamoxifen for 5 years. After a median follow-up of 30.6 months, women receiving exemestane had increased disease-free survival (HR 0.68, 95% CI 0.56-0.82), but overall survival remained the same (HR 0.88, 95% CI 0.67-1.16). *(13)* Recent studies have evaluated the presence of a SNP in the 3' untranslated region of the CYP19 aromatase gene, and found that it is associated with improved AI treatment efficacy. Less is known about its relationship to toxicity. *(14, 15)*

As a result of these studies, AIs are used at some point for all hormone receptor-positive cancers in postmenopausal women. They are currently the first-line hormonal therapy in postmenopausal women and standard of care for women who have received 2 ½ years to 5 years of tamoxifen in the adjuvant settings. They are also undergoing evaluation as chemopreventive agents in several large clinical trials.

Side Effects Caused by Aromatase Inhibitors

Despite the well-proven efficacy of AIs for the treatment of hormone-sensitive breast cancer, some patients suffer from side-effects or even stop treatment early due to undesirable side effects. The most common side effects of AIs are hot flashes, vaginal dryness, musculoskeletal pain and headache, and possibly alterations in serum lipid profiles. *(8)* In addition, all third-generation AIs increase bone resorption and may predispose to osteoporosis and fractures. *(16,17)* In one study, 16% of metastatic breast cancer patients complained of joint pain within 2 months of starting anastrozole and 5% had to discontinue therapy because of severe arthralgia. *(18)* Discontinuation of anastrozole resulted in resolution of pain related symptoms. In large adjuvant trials involving AIs, the incidence of musculoskeletal disorders was 20% to 30% and nearly 5% of patients discontinued therapy in the AI group because of toxic effects. *(8,9)* In a study evaluating menopausal symptoms in breast cancer patients receiving endocrine therapy, there was a significant change in musculoskeletal pain in women receiving AIs. *(19)* Fifty percent of women who were asymptomatic at baseline reported variable degrees of pain after one month of treatment. There was a marked increase in the number of patients reporting severe to intolerable symptoms after three months of therapy, which led to treatment interruption in 11% of patients. Patients usually present with polyarthralgia affecting the hands, knees, hips, lower back or shoulders, which is often refractory to conventional pharmacological interventions. *(18)* The musculoskeletal pain appears to be specific for this class of compounds, regardless of the AI prescribed.

Observational studies, however, have shown that AI-related arthralgias are more prevalent than originally reported. *(20,21)* In a cross-sectional survey of 200 consecutive postmenopausal women receiving adjuvant AI therapy for breast cancer, 94 (47%) reported AI-related joint pain and 88 (44%) reported joint stiffness, with the bulk of the symptoms reported in the hands and knees. *(20)* Risk factors include since cessation of menstrual function, previous taxane chemotherapy, body mass index, and prior hormone replacement therapy. *(20,22,23)*

Mechanism of Aromatase Inhibitor-Induced Musculoskeletal Pain

Estrogen deficiency after menopause has been linked to an increase in several chronic inflammatory conditions, including osteoporosis and osteoarthritis. *(24,25)* In terms of preclinical evidence, conjugated equine estrogen demonstrated significant anti-inflammatory activity in a rat model. *(26)* Several investigators have reported the presence of estrogen receptors in cartilage. *(27-29)* When adult monkeys were treated with conjugated equine estrogens, chondrocytes incorporated higher levels of sulfate in proteoglycans compared to baseline. *(30)* Decreased estrogen results in increased release of proinflammatory cytokines from monocytes and macrophages. *(31)* The proinflammatory cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF alpha) promote cartilage reabsorption, inhibit synthesis of proteoglycans and cause inflammation. *(32-34)* From these preclinical results, it seems clear that close interactions exist between estrogen and inflammation as well as cartilage metabolism.

The identification of the two estrogen receptors alpha and beta in human articular chondrocytes provided further evidence that cartilage is sensitive to estrogens. *(27,35-37)* Various animal and in vitro studies suggest that estrogen may play a role in the regulation of cartilage turnover and development of joint disease. In an experimental model of postmenopausal osteoarthritis (OA) with ovariectomized rats, estrogen deficiency accelerated cartilage turnover and increased cartilage surface erosion, whereas administration of estrogen or selective estrogen-receptor modulators significantly suppressed cartilage degradation. *(38)* In ovariectomized rats, estrogen prevented the cartilage breakdown caused by interleukin, a proinflammatory cytokine that plays a critical role in the pathogenesis of OA. *(39,40)* In a sheep model of OA, estrogen replacement therapy reduced the loss of proteoglycans from cartilage adjacent to OA lesions, providing evidence for a chondroprotective effect of estrogen. *(41)*

Estrogen can influence chondrocyte formation on multiple levels by interacting with cellular growth factors, adhesion molecules, and cytokines. In vitro studies showed a dose-dependent change in

matrix protein turnover when cultured chondrocytes were exposed to estradiol. *(28,29,42,43)* Production of interleukin-6 (IL-6) and Type II collagen in articular chondrocytes was affected by estradiol, suggesting possible mechanisms whereby it may affect cartilage metabolism. *(44,45)* In addition, estrogens may decrease the acceleration in subchondral bone remodeling, which is a key factor in the pathophysiology of osteoarthritis. *(46)*

The exact mechanism of AI-related arthralgia is unclear, but is thought to be related to estrogen deprivation. The effects of estrogen on bone, endometrium, and breast tissue have been extensively studied. Cartilage is not generally viewed as an estrogen responsive tissue, however, several epidemiological studies and a few intervention studies support that estrogen may have a role in osteoarthritis (OA). OA is a disease of joints, involving both cartilage and bone. Progressive and permanent articular cartilage degeneration is the hallmark of OA. *(47)* Factors influencing the incidence of radiological OA include obesity and female gender, especially after entering the menopause. *(48,49)* Over 80 years ago, Cecil and Archer first described "arthritis of the menopause" as the rapid development of hand and knee osteoarthritis coinciding with cessation of menses. *(50)* Various studies report larger increases in women than in men in the incidence and prevalence of hip, knee, and hand osteoarthritis after 50 years of age. *(51)* Sowers et al. reported significant associations of lower serum estradiol and urinary metabolites with the development of knee OA in women. *(52)* However, other studies have not found a consistent link between OA and sex hormone levels. *(53-55)*

Observational studies of the incidence and prevalence of osteoarthritis in postmenopausal women with and without hormone replacement therapy (HRT) has provided strong support for a protective effect of estrogens in osteoarthritis. *(51,56,57)* Two studies found that HRT tended to reduce the incidence of radiological knee osteoarthritis. *(58)* In a study of women without osteoarthritis, HRT taken for longer than 5 years was associated with a larger volume of tibial cartilage as compared to women who were not taking HRT. *(47)* The number of years since menopause was more strongly related to diminished knee cartilage volume than age per se, suggesting an effect of hormonal status on knee cartilage. In a randomized controlled trial of HRT, the Heart and Estrogen/progestin Replacement Study (HERS) found no difference in the prevalence of knee pain with or without HRT (24.1% and 26.1%, respectively). However, another intervention trial, the Women's Health Initiative (WHI) recently reported a difference in the incidence of any joint pain or swelling in postmenopausal women on estrogen compared to those who were not on estrogen (70.6% versus 77.2%, p=0.01). *(59)*

Imaging studies assessing AI-induced arthralgias have shown that inflammation may be a key component. Morales et al. demonstrated that the subjective symptoms of AI-induced arthralgias in the hands are associated with physiologic changes to the joint and functional impairments. *(60)* The patients in this study were assessed with serial MRIs of the hands, measurements of grip strength, and symptoms self-assessments. In a 6-month period, women taking AIs were more likely than those on tamoxifen to have an increase in tenosynovial changes as seen on MRI, a decrease in grip strength as measured by a sphygmomanometer, as well as increased pain and stiffness as measured by self-administered questionnaire. *(60)*

<u>Current Treatment for Aromatase Inhibitor Induced Joint Pain</u>

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common medications used to treat pain associated with AI-induced musculoskeletal pain, with over 50% of patients using them, however their efficacy has not been formally tested. *(61)* It is well known that NSAIDS may lead to serious renal and gastrointestinal toxicity, particularly in older adults. *(62,63)* Selective cyclooxygenase-2 (COX-2) inhibitors, such as rofecoxib (Vioxx) and celecoxib (Celebrex), are effective analgesics with fewer gastrointestinal side effects but have recently been shown to elevate the risk of cardiovascular events. *(64)* Non-toxic treatments that effectively relieve AI-induced musculoskeletal pain are needed.

Acupuncture is a popular non-pharmacological modality used for treating a variety of conditions, including musculoskeletal pain. The analgesic properties of acupuncture may be mediated by the

release of opioid peptides and serotonin. *(65,66)* Acupuncture has been shown to have short-term analgesic effects for musculoskeletal pain, and clinical trials have found that patients with knee osteoarthritis have less pain when acupuncture is used as an adjunct to conventional treatments. *(67,68,69)* Since research in this area is limited, researchers at Columbia initially conducted a small pilot study evaluating the use of acupuncture to relieve symptoms of AI-associated arthralgias. In this study of 21 women treated with a 6 week course of acupuncture, improvements were reported in pain severity, pain-related functional outcomes, and physical well-being, and no significant adverse events were reported. *(70)* This study was limited due to its small sample size and lack of a control group. The Columbia group then went on to conduct a randomized, sham-controlled, blinded study to assess the efficacy of acupuncture. True acupuncture was associated with about a 50% decrease in mean BPI-SF scores. *(96)* No change from baseline was observed for the sham arm. At 6 weeks, the mean BPI-SF worst pain scores were lower for true acupuncture compared to sham acupuncture (3.0 vs.5.5, $p<0.001$), as well as pain severity (2.6 vs.4.5, $p=0.003$) and pain-related interference (2.5 vs.4.5, $p=0.002$). Similar findings were seen for the WOMAC and M-SACRAH scores. *(99,100,105)* The Columbia group found that acupuncture is an effective and well-tolerated strategy for managing this common treatment-related side effect. Other approaches have been switching classes of AIs, Vitamin D and exercise. *(71, 72)*

Efficacy of Omega-3-fatty acid in Rheumatoid Arthritis

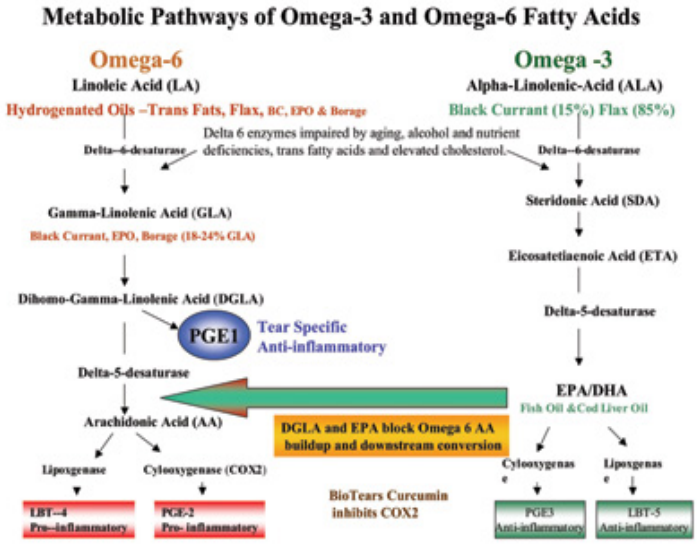
The use of omega-3-fatty acid for rheumatoid arthritis as well as other inflammatory conditions has been studied for more than 20 years. In a mouse model, fish oil, which is a rich source of omega-3-fatty acids particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), decreased the incidence as well as severity of joint pain and inflamation. In addition it resulted in delayed onset of symptoms. *(73)* In another mouse model, administration of EPA and DHA produced resolvins and protectins, anti-inflammatory lipids, which are known to have anti-inflammatory effects. *(74)*

Approximately 25% of the population over the age of 55 years is affected by joint pain and about half of them will have some restriction of normal daily activities. *(48,75)* Conventional approaches to controlling pain and minimizing loss of function include analgesics and exercise. *(76,77)* About two-thirds of individuals who suffer from joint pain have used complementary and alternative treatments to control their symptoms. *(78)* However, due to the dearth of prospective clinical trials evaluating efficacy, most third party payers do not reimburse patients for the cost of many of these procedures or supplements.

Since 1985, several randomized controlled trials studied the effect of omega-3-fatty acids on the pain of patients with rheumatoid arthritis. *(79-93)* A meta-analysis in 2007 of these studies found significant changes at 3-4 months in patient-assessed pain, morning stiffness, number of painful and/or tender joints, and NSAID consumption. *(74)* The majority of the studies in the 2007 meta-analysis monitored omega-3-fatty acid supplementation for 3-4 months, but the studies lasting more than 5 months found significant improvements in physician assessed pain and number of painful and/or tender joints; the effect sizes were notably larger in these longer studies. *(74)* Similarly, a meta-analysis in 1995 found that dietary fish oil supplementation for 3 months significantly improved the number of tender joints and the duration of morning stiffness. *(94)*

Given the proposed anti-inflammatory effects of omega-3-fatty acid and the paucity of therapeutic options for AI-induced arthralgia, it is therefore reasonable to test the efficacy of omega-3-fatty acid in a population of breast cancer patients with moderate to severe joint symptoms related to AIs.

The doses of omega-3-fatty acid vary among studies though it has been found that doses greater than 2.7g/day of EPA and DHA show greater improvements in pain outcomes than lower doses. *(74)*



Sundrajun et al. conducted a 24-week randomized, double-blind, placebo-controlled study on the use of omega-3-fatty acid, 4g/day, in 35 patients with RA. *(92)* Although omega-3-fatty acid significantly reduced inflammation and disease activity markers (serum CRP level, IL-6, TNF-1α, and the soluble form of the TNF-1α receptor sTNF-Rp55), there were no statistically significant differences in clinical outcomes measured as tender and swollen joint count assessed by a rheumatologist, visual analog score (VAS) pain score, patient global assessment of pain, and modified health assessment questionnaire (MHAQ) administered by a nurse. *(92)*

Mechanisms of Action of Omega-3-fatty acid

Fish oils are a natural source of omega-3-fatty acids, specifically EPA and DHA. Cold-water, fatty fish such as albacore tuna are particularly high in EPA and DHA. The human body does not directly synthesize omega-3-fatty acids.

The mechanisms by which omega-3-fatty acids reduce pain are not fully understood. One possibility is that omega-3-fatty acids compete with arachidonic acid (AA) for production of inflammatory eicosanoids resulting in an increased production of mediators formed from omega-3-fatty acids, such as LTB_5, and decreased production of more potent and more inflammatory mediators formed from AA, such as LTB_4. *(95)* Another proposed mechanism of action of omega-3-fatty acids is their production of resolvins and protectins, a newly discovered group of anti-inflammatory lipids. *(95)* Omega-3-fatty acids also affect inflammatory cytokine production. In cell culture studies, EPA and DHA inhibited the production of proinflammatory IL-1 and TNF-α by monocytes and IL-6 and IL-8 by venous endothelial cells. *(95, 96)* In humans, there are conflicting studies regarding the effect of EPA and DHA on the production of TNF, IL-1, and IL-6 by mononuclear cells. It is also possible that omega-3-fatty acids exert their anti-inflammatory and pain-reducing effects by decreasing activation of the pro-inflammatory transcription factor NFκB, up-regulating the anti-inflammatory transcription factor PPAR-γ and thus altering inflammatory gene expression. *(95)*

Pharmacokinetics of Omega-3-fatty acid

Omega-3-fatty acids are well-absorbed orally and stored primarily in adipose tissue. Serum concentrations of EPA and DHA have been found to increase as dietary consumption increases. Elimination of omega-3-fatty acids occurs primarily through oxidative catabolism to carbon dioxide and water though small quantities are eliminated when skin and digestive cells are sloughed.

Safety and Tolerability of Omega-3-fatty acid

Studies of omega-3-fatty acids have found them to be well-tolerated. In 8 placebo-controlled, randomized clinical trials of omega-3-fatty acids 4g/day for the treatment of hypertriglyceridemia, adverse events led to discontinuation of omega-3-fatty acids in 3.5% of patients treated with omega-3-fatty acids compared to 2.6% of patients on placebo. The most common side effects of omega-3-fatty acids are halitosis (a fishy odor to the breath), dysgeusia, and gastrointestinal disturbance (eructation and dyspepsia). Additional adverse events found in clinical trials were: back pain (2.2% fish oil vs. 1.3% placebo), flu syndrome (3.5% fish oil vs. 1.3% placebo), infection (4.4% fish oil vs. 2.2% placebo), unspecified pain (1.8% fish oil vs. 1.3% placebo), and angina pectoris (1.3% fish oil vs. 0.9% placebo). *(97)*

A potentially rare but serious side effect of omega-3-fatty acid due to its inhibition of platelet aggregation is prolonged bleeding time although studies have not shown bleeding time to exceed normal limits or to cause clinically significant bleeding episodes. Nonetheless, caution should be used, particularly in patients on anticoagulant or thrombolytic therapy. In some patients taking omega-3-fatty acid, alanine aminotransferase (ALT) levels increase, so ALT should be monitored. *(97)* Omega-3-fatty acid is widely in use and has not been found to interfere with NSAIDs.

Validated Questionnaires for Collection of Patient Reported Outcomes

No published scales have been established or validated to specifically measure the effects of treatments for AI-induced joint pain and stiffness. Therefore, we have chosen to make use of a combination of scales to assess the effect of omega-3-fatty acid on AI-induced joint pain and stiffness. Patients will complete self-reported questionnaires including the Brief Pain Inventory – Short Form (BPI-SF) to assess severity of pain/stiffness, the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index to assess joint and pain stiffness, and the Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) to measure changes in symptoms of the hands. *(96,99,100,105).* The Functional Assessment of Cancer Therapy-Breast Endocrine System (FACT-ES) Trial Outcome Index (TOI) will be used to measure functional well-being as perceived by the patient and the Global Ratings of Change (GRCs) will be used to identify overall improvement versus deterioration in these outcomes as well as patient reported minimally important differences in joint pain and stiffness. *(106-108)* Patients will also complete an Omega-3-fatty acid Dietary Intake Questionnaire at baseline and Week 24 which includes 4 items from a standard food frequency questionnaire that has been previously validated. *(109)*

Inclusion of Minorities

This clinical trial was designed to include minorities, but was not designed to measure differences of intervention in minority subgroups. We expect that the participants accrued to this trial will reflect the minority representation in the local population of the participating sites. Anticipated accrual to this study by race and ethnicity, based on previous Group trials in this disease type, follows:

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	9	+	0		9
Not Hispanic or Latino	213	+	0		213
Ethnic Category: Total of all subjects	222	+	0	=	222
Racial Category					
American Indian or Alaskan Native	2	+	0	=	2
Asian	4	+	0	=	4
Black or African American	18	+	0	=	18
Native Hawaiian or other Pacific Islander	2	+	0	=	2
White	196	+	0	=	196
Racial Category: Total of all subjects	222	+	0	=	222

Differences among treatment arms are not expected to be a function of race or ethnicity. Thus the study is not designed to detect differences within race or ethnicity subsets. This will be explored as a part of the final analysis.

3.0 DRUG INFORMATION

3.1 Omega-3 Fatty Acid, Omega-3 Fish Oils (Ocean Nutrition Canada Limited)

a. DESCRIPTION

Omega-3-fatty acids are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) used as add on treatment for patient with persistently high triglycerides. Taking omega-3-fatty acids orally, alone or in combination with naproxen (Naprosyn), seems to significantly decrease the duration of morning stiffness in patients with rheumatoid arthritis (RA).

Molecular Formula: EPA: $C_{22}H_{34}O_2$ DHA: $C_{24}H_{36}O_2$
Molecular Weight: EPA = 330.51 DHA = 356.55

b. PHARMACOLOGY

The mechanism of action of omega-3-fatty acids to reduce pain is not completely understood. Omega-3- fatty acids have anti-inflammatory effects. They seem to suppress COX-2 expression and the inflammatory cytokines interleukin (IL)-1 alpha and tumor necrosis factor (TNF)-alpha. Other clinical research suggests omega-3-fatty acids decrease endothelial activation by reducing intercellular adhesion molecule 1 (ICAM-1) and thrombomodulin levels, indicating a reduction in inflammation. Omega-3-fatty acids seem to be beneficial in rheumatoid arthritis due to anti-inflammatory effects, and epidemiological data that suggests EPA levels are decreased in total plasma fatty acids and synovial fluid, and DHA is decreased in the synovial fluid of patients with rheumatoid arthritis.

Pharmacokinetics: Omega-3-fatty acids are well absorbed orally and stored primarily in adipose tissue. Serum concentrations of EPA and DHA have been found to increase as dietary consumption increases. Elimination of omega-3-fatty acids occurs primarily through oxidative catabolism to carbon dioxide and water though small quantities are eliminated when skin and digestive cells are sloughed.

Formulation of omega-3-fatty acid: Each 1,000 mg capsule contains a combination of 560 mg ethyl esters of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) in a 40:20 ratio. Omega-3 fatty acid capsules also contain mixed natural tocopherols. Capsules are colored with carob and flavored with natural lemon-lime.

Formulation of placebo: The matching placebo capsules are a blend of soybean: corn oil, in a 1:1 ratio. All capsules are colored with carob and flavored with lemon-lime.

c. TOXICOLOGY

Adverse effects by Body System:

Gastrointestinal: Fishy aftertaste; halitosis; heartburn; dyspepsia; nausea; loose stools; weight gain

Hematologic: inhibition of platelet aggregation; increase risk of bleeding; potential increase risk of stroke, T- and B-cell function suppression, reduce production of cytokines, increase in LDL cholesterol

Dermatologic: rash

Miscellaneous: Back pain (2.2%), flu syndrome (3.5%); infection (4.4%); unspecified pain (1.8%); and angina pectoris (1.3%).

Pregnancy and lactation: Likely safe, when used orally and appropriately. Maternal intake of fish oil does not appear to adversely affect the fetus or nursing infant.

Drug interactions:

Anticoagulant/Antiplatelet: (aspirin, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, ticlopidine, warfarin, and others)	High doses of fish oils have antiplatelet effects. Theoretically, concomitant use of fish oil with anticoagulant or antiplatelet drugs may increase the risk of bleeding.
Antihypertensive drugs:	Fish oils can lower blood pressure and might have additive effects in patient treated with antihypertensives; use with caution
Contraceptive drugs:	There is some evidence that contraceptive drugs might interfere with the triglyceride lowering effect of fish oils.
Orlistat (Xenical)	Orlistat binds lipase in the gastrointestinal tract and reduces fat absorption.

Storage and Stability: Stable at room temperature. Omega-3-fatty acid and placebo have a 3 year shelf-life from the date of manufacture.

Administration: Oral.

Supplier: Omega-3-fatty acid and placebo, manufactured by Ocean Nutrition Canada, are supplied as liquid-filled gel capsules.

Distribution: Omega-3-fatty acid or matching placebo will be packaged and distributed by Uinta Vision Inc. (UVI). Blinded drug will be supplied to the institution in kits of 3 bottles containing 180 capsules each for a total of 540 capsules – sufficient to provide a 12 week supply. The institution will automatically receive a resupply of omega-3-fatty acid/placebo based on the patient's registration date. UVI will label each bottle with a bottle number. The packing slip will specify the ID number of the patient who will receive each kit. The receiving institution will label each bottle with the subject's SWOG Patient Number, Patient initials, and date dispensed. No supply of unassigned omega-3-fatty acid or matching placebo will be maintained at the institution. Rather omega-3-fatty acid or matching placebo will be supplied to the site in a "just in time" manner.

The SWOG Statistical Center will notify UVI electronically early each morning of the randomizations from the previous day. This notification will result in an order for a patient specific kit. Orders will be shipped daily by overnight courier. Therefore patient kits will arrive at the institution between 2 to 5 working days after UVI receives notification of a randomization. Institutions should consider this timing when randomizing a patient and planning for the initiation of therapy.

Since the study agent is a commercially available nutritional supplement, an NCI drug accountability form is not required. However the bottle number should be recorded in the participant's medical record and **S0927** Drug Accountability Record Form – Blinded Study for auditing purposes. The **S0927** Drug Accountability Record Form is available on the **S0927** abstract page of the SWOG website (http://swog.org). See Drug Accountability below.

If a patient requires a replacement bottle (Emergency Bottle) for lost (etc.) bottles of blinded study drug, the institution should immediately notify UVI of the need for an emergency bottle by calling 800/370-2508 so a bottle can be prepared and shipped to the site in an expedited manner.

When calling UVI, the caller will be asked which study they are calling in regards to. To facilitate the caller being transferred to the correct pharmacy staff, the caller should indicate the "SWOG **S0927**" or the "SWOG Omega-3 Study". UVI will require the following information:

- The SWOG Patient ID Number of the patient;
- The name of the receiving individual;
- Complete street address and phone number;
- Email address of the receiving individual

The patient must be registered to the study before study drug can be obtained.

UVI, Inc. office hours are 8:00 a.m. to 12:00 p.m. Pacific Time; phone messages may be left at other times.

Orders received by 12:00 p.m. Pacific Time Monday through Friday will be shipped for next day delivery. Shipments to each study site will be delivered by 3:30 p.m. Orders received by 3:00 p.m. Eastern Time on Friday will be shipped for receipt the following Monday, unless the institution specifically requests Saturday delivery and can guarantee their institution will accept delivery. Participants must be registered to the study before study drug can be obtained.

Questions about drug orders, transfers, returns, or accountability should be addressed to the general UVI phone number, 800/370-2508.

d. Drug Accountability**:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and return of all study drugs received from distributor using the **SWOG S0927 Drug Accountability Record Form - Blinded Study,** available at http://swog.org. A separate record must be maintained for each patient on this protocol.

Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the Drug Accountability Record form – Blinded Study; the date(s) and quantity of drug received, the dose, the date and quantity of drug dispensed to the subject, lot number, the balance forward, the number of capsules returned, and recorder's initials. These Drug Accountability Records must be readily available for inspection and are open to NCI inspection or SWOG audit at any time. Questions about drug orders, transfers, returns or accountability should be addressed to the distributor at:

UVI, Inc.
Phone: 800/370-2508
FAX: 650/745-3877
E-mail: orders@uintavision.com

e. Drug Transfer: Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating institution to another participating institution) must be approved **in advance** by calling the distributor.

f. Drug Disposal**:** All unused drug (unopened and unused bottles remaining when a subject goes off treatment, and expired bottles) should be destroyed on-site in accordance with institutional policy. Opened bottles with remaining capsules should be documented in the patient-specific accountability record (i.e., logged in as "# of capsules returned") and destroyed on-site in accordance with institutional policy.

4.0 STAGING CRITERIA

STAGING CRITERIA, AJCC 6th Edition, 2002

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2 or T3). If other measurements, such as mammographic or pathologic measurements are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor

NOTE: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but no more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below:
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis

STAGE GROUPING

Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0

*T1 includes T1mic

NOTE: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Prestudy Form (Form #54663) and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

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. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

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

_____ 5.1 Patients must be women with histologically confirmed primary invasive adenocarcinoma of the breast (Stage I, II or III) with no evidence of metastatic disease (M0) (see Section 4.0). Patients must have undergone modified radical mastectomy or breast sparing surgery. Patients must have recovered from all side-effects of the surgery.

_____ 5.2 Patients must be post-menopausal, as defined by at least one of the following:

a. ≥ 12 months since the last menstrual period OR

b. prior bilateral oophorectomy OR

c. previous hysterectomy with one or both ovaries left in place (or previous hysterectomy in which documentation of bilateral oophorectomy is unavailable) AND FSH values consistent with the institutional normal values for the post menopausal state. FSH levels must be obtained within 28 days prior to registration.

_____ 5.3 Patients must be positive for either estrogen receptor (ER) and/or progesterone receptor (PgR) as determined by institutional standard.

_____ 5.4 Patients must currently be taking a third-generation aromatase inhibitor (AI) -anastrazole (Arimidex®), letrozole (Femara®), or exemestane (Aromasin®) for at least the previous 90 days prior to registration with plans to continue for at least an additional 180 days after registration.

_____ 5.5 Patients must have completed the **S0927** Brief Pain Inventory-Short Form within 14 days prior to registration. Patients must have a worst pain/stiffness of at least 5 on the Brief Pain Inventory (item #2). The pain/stiffness must have started or increased since starting AI therapy.

_____ 5.6 Patients must have a Zubrod performance status of 0 to 2 (see Section 10.3).

_____ 5.7 Patients must not have taken omega-3-fatty acid supplements within the past 3 months prior to registration and must agree to refrain from use of omega-3-fatty acid supplements from sources outside of this study.

_____ 5.8 Patients must be willing to submit blood for serum free estradiol, total estradiol, serum inflammatory markers (IL6, TNF-α, CRP), DHA and EPA, lipid profile (LDL, HDL, triglycerides), DNA analysis (CYP19A1) and to submit urine for markers of joint degradation (CTX-II), and must be given the option to consent for specimen submission for banking and future translational medicine studies as outlined in Section 15.0. Baseline samples must be obtained prior to beginning treatment.

SWOG Patient No. _____

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

_____ 5.9 Patients must be able to complete study questionnaires in English.

_____ 5.10 Individuals must not have participated in a clinical trial with an investigational agent within 28 days prior to registration.

_____ 5.11 Patients must not be on anticoagulation medication (i.e., heparin/warfarin) because of increased risk of bleeding within 28 days prior to registration.

_____ 5.12 Patients must not have a history of bone fracture or surgery of the afflicted knees and/or hands within 6 months prior to registration.

_____ 5.13 Patients must not be on narcotics within 14 days of registration.

_____ 5.14 Patients may have received corticosteroid treatment however the following criteria apply:

a. Patients must not have received oral corticosteroids within the 28 days prior to registration.

b. Patients must not have received intramuscular corticosteroids within 28 days prior to registration.

c. Patients must not have received intra-articular steroids to the study joint within 28 days prior to registration.

d. Patients must not have received intra-articular steroids to any other joint within 28 days prior to registration.

_____ 5.15 Patients must not have received topical analgesics (e.g., capsaicin preparations) to the study joint or any other analgesics (e.g., opiates, tramadol; with the exception of NSAIDs and acetaminophen) within 14 days prior to registration.

_____ 5.16 Patients must not have a known allergy to soy, given that the placebo is suspended in soybean oil.

_____ 5.17 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, DCIS, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

_____ 5.18 All participants must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ 5.19 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the database.

6.0 STRATIFICATION FACTORS

Patient randomization will be dynamically balanced according to the following stratification factors: prior history of diagnosed osteoarthritis (yes vs. no); and prior taxane use (yes vs. no).

7.0 TREATMENT PLAN

For treatment or dose modification questions related to study drug, please contact Dr. Dawn Hershman at 212/305-1945 or Dr. Katherine Crew at 212/305-1732. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

7.1 Treatment Schedule

Please note that it is recommended that patients do not have concurrent medical/arthritic disease that could confound or interfere with evaluation of pain or efficacy including: inflammatory arthritis (e.g. rheumatoid arthritis, systemic lupus, spondyloarthropathy, psoriatic arthritis, polymyalgia rheumatica), gout, episodes of acute monarticular arthritis clinically consistent with pseudogout, Paget's disease affecting the study joint (knees/hands), a history of septic arthritis or avascular necrosis or intra-articular fracture of the study joint, Wilson's disease, hemochromatosis, alkaptonuria, or primary osteochondromatosis.

Patients will be randomized to receive 6 capsules (at 1,000 mg each) of omega-3-fatty acid or placebo. Blinded drug will be ordered upon registration (randomization). Treatment with blinded drug may start up to 10 working days after registration.

During Week 1, patients will take 2 capsules of blinded drug two times per day. This period will allow patients to adjust to the omega-3-fatty acid or placebo.

Dosage:

AGENT	DOSE	ROUTE	SCHEDULE
Blinded Drug (Omega-3-fatty acid* or placebo**)	2 capsules*** two times per day (BID)	oral taken with food	Daily 1 week
Blinded Drug (Omega-3-fatty acid* or placebo**)	3 capsules*** two times per day (BID) **or** 2 capsules*** three times per day (TID) (total of 6 capsules per day)	oral taken with food	Daily for 23 weeks starting Week 2

* Each 1,000 mg omega-3-fatty acid capsule = 560 mg of the ethyl esthers of omega-3-fatty acids (EPA+DHA)

** Each placebo capsule contains = 1,000 mg of soybean and corn oil

*** Capsules may be taken either way per patient preference, however, patients are encouraged to choose one regimen and stay on that schedule for the duration of the study.

NOTE: All participants will receive a maximum of 24 weeks of blinded omega-3-fatty acid/placebo treatment, even if there are delays in AI therapy beyond 24 weeks post-registration. No additional blinded drug will be administered to accommodate delays in AI therapy.

a. Initial Visit

Before beginning the intervention, participants will have a fasting blood draw for serum and urine collection (see Section 15.2). Participants will complete the following self-administered questionnaires prior to beginning treatment with blinded study drug:

- **S0927** Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1) (Form #61225)
- **S0927** Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) (Form #34375)
- **S0927** FACT – ES Trial Outcome Index (Version 4) (Form #53333)
- **S0927** Omega-3-fatty acid Dietary Intake Questionnaire (Form #36668)

It should take the patient about 20-25 minutes to complete the assessments. **See Section 15.3 for instructions for administration of the questionnaires.** The nurse or CRA must complete the **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634).

b. Follow-Up Visits

Follow-up visits will occur at 6, 12, and 24 weeks after registration. Drug adherence will be ascertained by the nurse or CRA by review of the patient-completed **S0927** Intake Calendar (see Appendix 19.3) and count of blinded drug capsules. Counts of blinded drug capsules should be recorded on the **S0927** Treatment Form and the participant's medical record. Adverse events will be assessed and recorded on the **S0927** Adverse Event Summary Form (Form #39275) Use of pain medications and steroids will be recorded on the **S0927** Supplemental Agents Reporting Form (Form #28384).

Patients will be instructed to complete the following self-administered questionnaires at these three timepoints. It takes about 20-25 minutes to complete the assessments. **See Section 15.5 for instructions for administration of the questionnaires.**

- **S0927** Brief Pain Inventory Short Form (BPI-SF) (Form #54223)
- **S0927** Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1) (Form #61225)
- **S0927** Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) (Form #34375)
- **S0927** FACT – ES Trial Outcome Index (Version 4) (Form #53333)
- **S0927** Omega-3-fatty acid Dietary Intake Questionnaire (Form #36668) – Baseline and Week 24 only
- **S0927** Global Ratings of Change in Joint Pain and Stiffness (Form #45914) – No baseline assessment

The nurse or CRA will also complete the **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634).

Additionally, at 12 and 24 weeks, fasting blood will be drawn for serum estradiol/hormonal levels, serum inflammatory markers, and cholesterol levels (see Section 15.2).

c. Additional Instructions for Patient-Completed Questionnaires

If a patient goes off protocol treatment before the schedule for patient-completed questionnaires has been completed, please administer all patient-completed questionnaires at the scheduled assessment times, even if the patient has begun another treatment. The 6, 12, and 24 week assessment times as well should be defined from registration.

The **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634) is required with each set of patient-completed questionnaires indicating whether or not the assessment occurred, if assistance was required, and the location of the assessment. If one or all of the questionnaires were not administered, an overall reason must be indicated on the **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634). Please see Section 15.5 for more detailed instructions for the questionnaires.

7.2 Criteria for Removal from Protocol Treatment:

a. Evidence of new cancer or cancer recurrence at any time

b. Unacceptable toxicity (see Section 8.2)

c. Delay of 30 days of study intervention due to any reason.

e. The participant may withdraw from the study at any time for any reason.

f. Completion of 24 weeks of treatment.

g. Discontinuation of AI therapy. (Note: a delay of 30 days or more will be considered discontinuation of AI therapy.)

7.3 All reasons for discontinuation of treatment must be documented on the Off-Treatment Notice-Prevention Studies Form (Form #57439).

7.4 No further follow-up will be required once the patient completes 24 weeks of treatment.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Guidelines for Monitoring of Expected and Unexpected Symptoms/Toxic Events

Grade 1 and Grade 2 Toxicity
If Grade 1 or 2 toxicities occur that are felt to be possibly, probably, or definitely related to study drug, monitor as needed until problem has resolved (i.e., Grade 0), stabilized (i.e., remains as Grade 1 or Grade 2), or is otherwise explained. If Grade 1 or Grade 2 symptoms persist, the nurse will assess whether symptom management should be initiated, or whether the dose should be reduced from 6 capsules per day to 4 capsules per day. Follow-up will be conducted at the intervals specified in the protocol.

Grade 3 or Grade 4 Toxicity
If patient develops any Grade 3 toxicity possibly, probably, or definitely related to the study drug, the patient should go on a drug holiday (for no longer than 7 days). If the symptoms resolve, the dose should be reduced from 6 capsules per day to 4 capsules per day. This

dose is to be maintained if no further Grade 3 toxicity is noted. If at the 4 capsule a day dose, the participant is still experiencing problems, the participant can be given a 1 week drug holiday from the blinded study drug. Subsequently, the participant may be re-challenged at the 4 capsule per day dose for one month. Follow-up will continue at the intervals specified in the protocol. If symptoms do not recur (i.e., if symptoms resolve to Grade 0), the dose should be maintained. If Grade 3 drug-related toxicity does not resolve to a Grade 0, 1, or 2 level within 1 week at the reduced dose, the patient should be removed from all protocol treatment per Section 7.2b. If the patient develops any Grade 4 toxicity possibly, probably, or definitely related to the study drug, the patient will be removed from protocol treatment. Patient will be removed from protocol treatment if there is a delay of study intervention > 30 days.

If patient discontinues use of AI for > 30 cumulative days, patient is removed from study.

If patient discontinues use of AI for < 14 days patient should continue blinded study drug.

8.3 For study related questions, please contact Dr. Hershman at 212/305-1945 or Dr. Crew at 212/305-1732.

8.4 Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and NCI via AdEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR S0927, "Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer"

REQUIRED STUDIES	Prestudy	Baseline %	Week 6 √	Week 12 √ β	Week 24 √
PHYSICAL					
History (demographics, comorbidities, medications) Δ	X				
Physical Exam (Height, Weight, Performance Status) Δ	X				
LABORATORY					
ER/PgR	X				
FSH (if necessary)	X				
PATIENT-REPORTED QUESTIONNAIRES					
S0927 BPI-SF	X		X	X	X
S0927 WOMAC		X	X	X	X
S0927 M-SACRAH		X	X	X	X
S0927 FACT-ES/TOI		X	X	X	X
S0927 Global Rating of Change Scale			X	X	X
S0927 Omega-3-Fatty Acid Dietary Intake Questionnaire		X			X
STAFF ADMINISTERED FORMS					
S0927 Prestudy		X			
S0927 Treatment Form ≠			X	X	X
S0927 Supplemental Agents Reporting Form ©	X		X	X	X
S0927 Adverse Events Reporting Form (toxicity notation)			X	X	X
Review of Intake Calendar ≠			X	X	X
S0927 Cover Sheet for Patient Completed Questionnaires		X	X	X	X
PROCEDURES					
Blood for DNA (CYP19A1) **		X			
Fasting blood for biomarker analysis		X		X	X
Urine for joint degradation (CTX-II)		X			X
Blood for banking (Optional) †		X			
TREATMENT					
Dispense blinded study drug		X		X	
Omega-3 fatty acid/placebo treatment π			X	X	X

NOTE: Forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

≠ Aromatase inhibitor use and pill counts are recorded on the treatment form.
© Pain treatments received in the past 6 weeks are recorded on this form.
β Treatment continues daily for 84 days.
√ Because there is a 4-10 day allowance for receipt of blinded study drug, there will be a 7-day window in which to perform study assessments. Please administer all patient-completed questionnaires at the scheduled assessment times, even if the patient goes off protocol treatment early.
** See Section 15.2d and order kit from SWOG Specimen Repository.
π See Section 7.1.
% The baseline patient reported forms should be completed prior to initiation of treatment with blinded drug.
† See Section 15.1.
Δ Must be completed within 28 days prior to registration.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Primary Outcome

Reduction in worst joint pain/stiffness: A difference of two points in the modified Brief Pain Inventory worst pain/stiffness score (item #2) has been identified as a clinically meaningful difference at 12 weeks. *(108)* This item has a scale of 0 to 10 with 0 indicating "No pain/stiffness" and 10 indicating "Pain/stiffness as bad as you can imagine".

10.2 Secondary Outcomes (at 6, 12, and 24 Weeks)

a. Differences between the two study arms of at least two points on the WOMAC Index and on the M-SACRAH at 24 weeks are of interest for these two outcome measures. *(105, 108)* We will also evaluate clinically meaningful change for the WOMAC Index and M-SACRAH with respect to the 1/3 to ½ standard deviation during the study period of 24 weeks.

b. Differences between the two arms of at least five to seven points on the FACT-ES TOI at 24 weeks will be of interest. *(106, 107)* Clinically meaningful change in FACT-ES TOI scores will also be based on 1/3 to ½ of a standard deviation. *(107,109,111)*

c. Global Ratings of Change (GRCs) for joint pain and joint stiffness. The GRCs for joint pain and for joint stiffness will be used to identify patients who report they are worse (combining scores of -1 through -3), the same score (score of 0), or better (combining scores of +1 through +3) since the last time they completed the questionnaire. *(109-111)* Mean scores for the WOMAC Index, BPI, M-SACRAH, and FACT-ES TOI will be compared for groups based on those patients who select "a little better" and "a little worse" on the GRC ratings to identify minimally important change. *(109-111)*

d. For the Omega-3-fatty acid Dietary Intake, we will use 4 items from a standard food frequency questionnaire that have been previously validated. *(118)* The Four fish items will ask about: dark-meat fish such as bluefish (1.37 g of n-3 fatty acids per 3-4 ounce portion); canned tuna (0.69 g per 3-4 ounce portion); other fish (0.17 g per 3-5 ounce portion); and shrimp, lobster, or scallops (0.46 g per portion). We will calculate the average daily intake during that year of marine n-3 fatty acids as the sum of the daily consumption of each type of fish multiplied by the n-3 content of the specified portion. *(98)*

e. We will also describe adverse events, frequency of analgesics consumed, frequency of pain treatments used, serum free and total estradiol levels (measured with Liquid Chromatography combined with a special form of Mass Spectrometry), serum biomarkers of inflammation, biomarkers of joint degradation, fasting cholesterol levels, the association between CYP19A1 genotype and treatment response, as well as patient withdrawal and compliance rates.

10.3 Performance Status: Participants will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.

2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary hypothesis of the study is that omega-3-fatty acid will decrease joint pain and/or stiffness associated with the use of aromatase inhibitors in breast cancer patients compared to placebo at 12 weeks. Joint pain/stiffness will be assessed using "worst pain and/or stiffness" according to the BPI. Enrollees must currently be taking AIs and must exhibit joint pain/stiffness with a minimum BPI worst pain/stiffness score of 5; scores of 5 to 10 are considered to reflect moderate to severe pain. *(112)* Patients will be stratified at randomization by the use of prior history of arthritis (yes vs. no) and prior taxane use (yes vs. no). The primary endpoint of 12 weeks was chosen based on concerns that there would be differential drop-out if no effect was seen by 12 weeks in the placebo group.

This study stipulates an alpha=.05 two-sided test, with an estimated 5% non-adherence (reducing the nominal effect size) and 20% dropout rate (increasing the total required sample size) at the primary endpoint evaluation time of 12 weeks after randomization. In addition, the design will incorporate a 10% contamination rate (which also reduces the nominal effect size) based on the assumption that a portion of the patients will have joint pain/stiffness with a different etiology (that is, not biologically associated with AI treatment and therefore not amenable to the specified intervention). The proposed sample size incorporates adjustments for loss, non-adherence, and contamination. Data on the use of the BPI to assess joint pain/stiffness from AIs is limited. The power for the design will be a function of the difference detected and the standard deviation at 12 weeks after randomization. A difference of 2 points in the BPI has been identified as a clinically meaningful difference. *(108)* One study of intervention for AI-induced joint pain/stiffness found the standard deviation for BPI "worst pain/stiffness" at 12 weeks on the control arm to be 2.5 points. However, this study was small (n=18); for design purposes, a more conservative estimate of standard deviation of 3.5 points will be assumed. For a two point difference and a 3.5 point SD at 12 weeks, with other parameters as specified above, 222 eligible patients would be required for 90% power under a two-arm normal design. Power will be higher with lower observed standard deviation. A multiple linear regression analysis of the primary endpoint will include the baseline score as well as the pre-specified stratification factors. To allow for a typical rate of ineligibility of 10%, a total of 246 patients will be enrolled to achieve 222 eligible patients.

11.2 Secondary Endpoints

The secondary endpoints also include changes in the WOMAC Index, M-SACRAH, FACT-ES TOI, Global Ratings of Change (GRCs) for joint pain and joint stiffness, adverse events, frequency of new pain medications used, serum free and total estradiol levels (measured with Liquid Chromatography combined with a special form of Mass Spectrometry), serum biomarkers of inflammation, fasting cholesterol levels, as well as patient withdrawal and compliance rates. *(105-107)* Mean scores will be calculated for other outcome measures (e.g., WOMAC Index, BPI interference score, FACT-ES TOI, M-SACRAH). In addition, we will identify the minimally important difference for these measures by examining mean scores for patients who select "a little better" and "a little worse" on the two anchor measures of change. *(110,111)* A 1/3 to ½ standard deviation will serve as a second criterion for clinically important change.

Exploratory analyses will be done to evaluate the relationship between the aromatase inhibitor gene polymorphism (CYP19A1) and response to treatment. Additional analyses will explore the potential interaction of the intervention with stratification factors as well as other baseline factors (e.g., age, BMI, physical activity) with respect to outcome.

The frequency and severity of each adverse event, as measured by the NCI Common Terminology Criteria Version 4.0 between patients treated with omega-3-fatty acid and placebo, will be summarized and tabulated.

11.3 Sample Size/Accrual Rate

Accrual is expected to be rapid given the common use of AIs for adjuvant therapy in post-menopausal women with breast cancer. Allowing for 6 months ramp-up and IRB approval time, accrual of 12 patients/month would allow completion of the study in approximately 2 years. Accrual will be assessed at 1.5 years after study activation. If monthly average accrual in quarters 5-6 after study activation is < 50% of projected accrual, efforts will be made to increase accrual over the succeeding 6 month period. If after 2 years, monthly accrual remains < 50% of projected accrual, study revision will be considered.

11.4 A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study. Given the anticipated rapid accrual to this protocol (≤ 2 years total), insufficient data will be available while the study is still accruing to conduct an interim analysis. Thus no formal interim analysis is planned.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Participants must be registered prior to initiation of treatment with blinded drug (no more than 10 working days prior to planned start of treatment).

13.2 The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.3 Registration procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and 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, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. 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 on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

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

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the 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.

13.4 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** participants registered, whether or not assigned treatment is administered, including participants deemed to be ineligible. Participants for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the CRA Workbench link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

14.4 AFTER REGISTRATION BUT PRIOR TO BEGINNING TREATMENT:

Submit urine and fasting baseline blood samples as described in Section 15.0. The SWOG Specimen Tracking System must be used for sample submission.

14.5 WITHIN 7 DAYS OF INITIAL REGISTRATION:

Submit the following:

a. **S0927** Prestudy Form (Form #54663).

b. **S0927** Supplemental Agents Reporting Form (Form #28384)

c. **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634)

d. **S0927** Brief Pain Inventory Short Form (BPI-SF) (Form #54223)

e. **S0927** WOMAC Index (Version 3.1) (Form #61225)

f. **S0927** M-SACRAH (Form #34375)

g. **S0927** FACT-ES TOI (Version 4) (Form #53333)

h. **S0927** Omega-3-fatty acid Dietary Intake Questionnaire (Form #36668)

i. Institutional surgical pathology report to confirm staging.

14.6 WITHIN 14 DAYS OF THE WEEK 6, 12 AND 24 STUDY ASSESSMENTS:

Submit the following:

a. **S0927** Treatment Form (Form #15208)

b. **S0927** Adverse Event Summary Form (Form #39275)

c. **S0927** Supplemental Agents Reporting Form (Form #28384)

d. **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634)

e. **S0927** Brief Pain Inventory Short Form (BPI-SF) (Form #54223)

f. **S0927** WOMAC Index (Version 3.1) (Form #61225)

g. **S0927** M-SACRAH (Form #34375)

h. **S0927** FACT-ES TOI (Version 4) (Form #53333)

i. **S0927** Global Ratings of Change in Joint Pain and Stiffness Form (Form #45914)

14.7 AT THE 12 AND 24 WEEK ASSESSMENT:

Submit fasting blood sample as described in Section 15.0.

14.8 AT THE 24 WEEK ASSESSMENT:

a. Submit the **S0927** Omega-3-fatty acid Dietary Intake Questionnaire (Form #36668)

b. Submit urine sample as described in Section 15.0.

14.9 WITHIN 14 DAYS OF REMOVAL
14.10 FROM PROTOCOL TREATMENT:

Submit a copy of the Off Treatment Notice-Prevention Studies (Form #57439) along with the final copies of the **S0927** Treatment Form (Form #15208) and the **S0927** Adverse Event Summary Form (Form #39275).

14.10 WITHIN 14 DAYS OF A DIAGNOSIS OF NEW OR RECURRENT CANCER OCCURRING UP TO 24 WEEKS AFTER REGISTRATION:

Submit copies of:

a. Pathology report documenting cancer

b. If participant was on protocol treatment, submit all forms in Section 14.6.

c. Follow-Up Form (Form #64587)

14.11 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH OCCURRING UP TO 24 WEEKS AFTER REGISTRATION:

If patient was on **S0927** protocol treatment, submit a copies of the Notice of Dea
th (Form #49467) documenting death information AND all forms in Section 14.8. If patient was off **S0927** protocol treatment, submit copies of the Notice of Death (Form #49467) documenting all death information and the Follow-Up Form (Form #64587).

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for banking (submitted to the SWOG Specimen Repository - Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (Optional for patients)

a. **Institutions are required to seek additional patient consent to bank whole blood (10 cc's) for future translational medicine studies (including genotyping and biochemical assays).** If the participant agrees, the institution is required to collect at baseline and submit per the repository guidelines.

b. Blood specimen collection and submission instructions can be accessed on the SWOG Specimen submission webpage (http://swog.org/members/clinicaltrials/specimens/STSpecimens.asp).

15.2 Whole Blood Specimens for Translational Medicine (required for patients)

a. Patients are required to submit whole blood specimens for serum free estradiol, total estradiol, serum inflammatory markers (IL6, TNF-α, CRP) DHA and EPA, lipid profile (LDL, HDL, Triglycerides) at the timepoint listed below. Specimen collection and submission instructions are outlined on the SWOG Specimen Submission webpage (see Section 15.1b). **(NOTE: Blood draws should be preferably 8 hour fasting or morning blood draws)**

1. At baseline (after registration but prior to start of study drug)
2. at 12 weeks
3. at 24 weeks

b. Patients are additionally required to submit a whole blood sample for DNA analysis (CYP19A1) at the timepoint listed below. Specimen collection and submission instructions are outlined on the SWOG Specimen Submission webpage (see Section 15.1b) **with the exception that the DNA specimen must be submitted in a purple top EDTA tube.**

1. At baseline (after registration but prior to start of study drug)

NOTE: Fasting is not required for DNA sample

c. If the patient agrees, left over blood will be banked for future translational medicine studies. **Institutions are required to seek additional patient consent to bank blood for future translational medicine studies (see Section 15.1).**

d. Specimen collection kits may be ordered for the baseline, 12 week, and 24 week collection by the SWOG Specimen Repository Management Application at http://ricapps.nationwidechildrens.org/BPCKitManagement.

15.3 Urine Specimens for Translational Medicine (required for patients)

a. Urine for CTX-II testing is required at the following times:

1. Baseline (after registration, but prior to beginning treatment

2. Week 24

b. Specimen collection and submission

The sample must be inverted gently 2-3 times to mix well. Urine is then transferred for storage using a disposable pipette into two specimen tubes, with 5 mL in each tube, which are then securely capped.

Sample should be shipped within 24 hours of collection. Sample can be stored at 4°C until ready for shipment. Be sure tube is closed securely. If the sample will be stored for more than 24 hours at the local site, the specimen should be stored at -70°C prior to shipment on dry ice to the SWOG Specimen Repository.

15.4 Patient Questionnaires: Instructions for Administration

a. Time frame for questionnaires

It is important to note that the time frame for providing ratings differs depending on the scale the patient is completing. The **S0927** BPI-SF (Form #54223), **S0927** WOMAC Index (Form #61225), **S0927** M-SACRAH (Form #34375), and **S0927** FACT-B/ES TOI (Form #53333) should be rated with respect to the past 7 days. The **S0927** Global Ratings of Change (Form #45914) for joint pain and joint stiffness are answered with respect to the last time the patient filled out the questionnaire. **S0927** Omega-3-fatty acid Dietary Intake Questionnaire (Form #36668) uses a 6 month time frame.

If treatment is delayed due to toxicity, the assessment schedule for the Week 6, 12 and 24 assessments should be defined from registration.

b. Administration of Questionnaires

1. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each patient questionnaire. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.

2. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Note on the cover sheet what assistance was required and indicate reason (e.g., elderly, too sick, etc.). Discourage family members from; 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.

3. It is very important to review the questionnaires after the patient has completed it to be sure all of the questions have been answered and that only one answer is marked. a) If the patient has marked more than one answer per question, ask the patient which answer reflects how he is feeling. b) If the patient has skipped a question, tell the patient that a question was not answered and ask if he would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question.

4. If a patient refuses or cannot complete the questionnaire for some reason, then this must be documented on the cover sheet and faxed to the Data Operations Center in Seattle (see Section 14.3b).

5. If a patient misses an appointment or is too sick to complete the questionnaires on the scheduled date, the questionnaire can be mailed to the patient or sent home with her. A telephone interview must be scheduled and completed within one week of the originally scheduled time. Patient responses to questionnaire items are to be obtained during the telephone interview while the patient is looking at his copy of the questionnaire. The date of the telephone interview is to be noted on the cover sheet.

c. Additional quality control procedures:

1. When a patient is registered on **S0927**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed before receiving treatment. You may wish to photocopy the Study Calendar, Section 9.0, and include the patient's name and specific dates. A copy of this should be kept in the patient file.

2. If a patient goes off omega-3-fatty acid or placebo treatment prior to the protocol-defined end of treatment at 24 weeks, administer the patient-completed questionnaires according to the protocol-defined assessment schedule (timed from registration date).

3. If a patient refuses or cannot complete the patient questionnaires at one time point, she should be asked to do so at the next scheduled administration time.

4. The Quality of Life Coordinator, Lisa Hansen, R.N., M.S., will monitor compliance on a regular basis, having been provided with timely reports from the Statistical Center. The Expectation Report also provides a reminder of upcoming quality of life assessments for a patient.

Anyone involved in the collection of quality of life data in SWOG trials should review the training program available on the SWOG website (www.swog.org). Please log on as a member and go to the **CRA Workbench**. Inside the Workbench, click on **Tools of the Trade** and select training program: **Patient-Reported Outcome Questionnaires Training Program**. This program is a narrated set of slides designed to standardize the way quality of life data is collected from patients; it takes the place of the Quality of Life Training Video. Questions regarding the quality of life assessments can be addressed to Lisa Hansen (503/413-6285) or to Dr. Carol Moinpour at the SWOG Statistical Center (206/667-4604).

d. **S0927** Cover Sheet for Patient-Completed Questionnaires

For each time point, the nurse or CRA completes the **S0927** Cover Sheet for Patient-Completed Questionnaires (Form #16634). The Cover Sheet is submitted with the set of patient-completed forms at each scheduled assessment. The Cover Sheet is very important for tracking how and when the patient forms were completed. When a patient-completed form is not administered at a scheduled time point, it is important to know the why the assessment did not occur; the form includes potential reasons for a patient not completing a form. See Section 14.0 for data submission guidelines.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 19.1 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be sent to the SWOG Operations Office by electronically submitting the report via the AdEERS Web-based application located at http://ctep.cancer.gov.

c. When to report an event in an expedited manner

Some adverse events may require 24-hour notification (refer to Table 16.1) via AdEERS and/or to desired recipient(s) and method of reporting, i.e., phone or fax.

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study.

Attribution	**Grade 4**		**Grade 5[a]**	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**AdEERS**	**AdEERS**
Possible, Probable, Definite	**AdEERS**		**AdEERS**	**AdEERS**

AdEERS: Indicates an expedited report is to be submitted via NCI AdEERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution (except deaths clearly due to progressive disease which require routine reporting only). Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line AdEERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.

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18.0 MASTER FORMS SET

18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

Informed Consent Model for **S0927**

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	62 (targeted above 55)
Flesch-Kincaid Grade Level	8.5 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S0927, "A Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Women with Early Stage Breast Cancer, Phase III"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have been identified as having a history of stage I, II, or III hormone receptor positive breast cancer, are post-menopausal and are being treated with an aromatase inhibitor.

Who is doing this study?

SWOG is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of almost four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of the nutritional supplement omega-3-fatty acid against placebo (contains no active ingredient) on the joint pain and stiffness that is associated with taking aromatase inhibitors.

How many people will take part in the study?

About 200 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular health care for postmenopausal women and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam
- Blood work to check your menopausal status (if necessary).

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following procedure.

- Blood sample – Blood (about 2 tablespoons) will be taken before starting the study drug. You will need to be fasting (no food or drink for 8 hours) before the sample is taken. The blood sample is not part of the usual medical care. The blood sample will be submitted to look at hormone levels, specific biomarker, cholesterol levels and DNA (genetic) studies. (A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.) You will be asked if remaining blood from the sample can be kept for future research purposes. Please see separate consent form at the end of this document.
- Urine sample – Urine (about 4 tablespoons) will be collected before starting the study drug and at the end of the study. The urine sample will be submitted to look at markers in the urine that may indicate a breakdown of tissue in your joints.
- Questionnaires- Five self-administered questionnaires (which will take about 20 minutes to complete) will be given at the beginning of the study to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to rate joint pain and stiffness, and will be asked to respond to questions regarding aromatase inhibitors, pain medications and fish consumption. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private.

Randomization

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

You will receive omega-3-fatty acid (the study drug), or you will receive placebo (which contains no drug). During the first week, you will take 2 capsules two times per day. Starting the second week, you will take 6 capsules per day (either 3 capsules two times a day or 2 capsules 3 times a day depending on your preference), for a total of 24 weeks (168 days). However, once you choose a regimen, you should stick with that schedule for the rest of the time you are on the study.

You will be supplied with study drug when you start the study and during Week 12, and will return any unused supply.

At Week 6….

The medical team or staff will record:

- Side effects you may be having
- Pain treatments you are receiving
- Aromatase inhibitor use
- Number of pills remaining in your container

- Questionnaires- Five self-administered questionnaires (which will take about 20 minutes to complete) will be given at six weeks to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to rate joint pain and stiffness, and will be asked to respond to questions regarding aromatase inhibitors and pain medications. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private.

At Week 12….

You will have the following procedure:

- Blood sample – Blood (about 1 tablespoon) will be taken at Week 12. You will need to be fasting (no food or drink for 8 hours) before the sample is taken. The blood sample is not part of the usual medical care. The blood sample will be submitted to look at hormone levels, specific biomarker, and cholesterol levels. You will be asked if remaining blood from the sample can be kept for future research purposes. Please see separate consent form at the end of this document.
- Questionnaires- Five self-administered questionnaires (which will take about 20 minutes to complete) will be given at twelve weeks to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to rate joint pain and stiffness, and will be asked to respond to questions regarding aromatase inhibitors and pain medications. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private.

The medical team or staff will record:

- Side effects you may be having
- Pain treatments you are receiving
- Aromatase inhibitor use
- Number of pills remaining in your container

At Week 24….

You will have the following procedure:

- Blood sample – Blood (about 2 tablespoons) will be taken at Week 24. You will need to be fasting (no food or drink for 8 hours) before the sample is taken. The blood sample is not part of the usual medical care. The blood sample will be submitted to look at hormone levels, specific biomarker, cholesterol levels and genetic studies. You will be asked if remaining blood from the sample can be kept for future research purposes. Please see separate consent form at the end of this document.
- Urine sample – Urine (abut 4 tablespoons) will be taken at Week 24. The urine sample will be submitted to look at markers in the urine that may indicate a breakdown of tissue in your joints.

- Questionnaires- Six self-administered questionnaires (which will take about 25 minutes to complete) will be given at week 24 to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to rate joint pain and stiffness, and will be asked to respond to questions regarding aromatase inhibitors, pain medications and fish consumption. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private.

The medical team or staff will record:

- Side effects you may be having
- Pain treatments you are receiving
- Aromatase inhibitor use
- Number of pills remaining in your container

How long will I be in the study?

You will be asked to take the study drug for 24 weeks. After you are finished taking the study drug, there will be no follow-up visits.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to omega-3-fatty acid/placebo include those which are:

Likely

- **Fishy aftertaste**
- **Heartburn**
- **Nausea**
- **Bloating**
- **Belching**
- **Loose stools**
- **Diarrhea**

Less Likely

- **Prolonged bleeding time**
- **Elevations in LDL-Cholesterol**
- **Weight gain**
- **Back pain**
- **Flu-like symptoms**

Rare but serious

- **Increased risk of stroke**
- **Lower white blood counts**
- **Heart pain**

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. We hope that the information from this study will help doctors learn whether omega-3-fatty acids reduce joint pain and stiffness in patients receiving aromatase inhibitors. This information could help patients in the future.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment without being in a study**
- **Taking part in another study**
- **Getting no treatment**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- SWOG
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Ocean Nutrition Canada (the company that provides the omega-3-fatty acid)

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of associated with this study (except for the research studies done on your blood and tissue as discussed below). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular care.

The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (Local institutions must choose the option that best fits the hospital's situation)*

Ocean Nutrition Canada will provide omega-3-fatty acid (and placebo) free of charge while you are participating in this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.
Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/

- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/ You will get a copy of this form. If you want more information about this study, ask your study doctor.

Future Contact

Occasionally, researchers working with SWOG may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact by circling "yes" or "no".

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

Consent Form for Future Use of Specimens

We would like to keep some of the blood specimens that are left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Are Specimens Used for Research" to learn more about tissue research.

The research that may be done with your specimens are not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While SWOG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

Future Use of Specimens *(section updated 7/2/12)*

a. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.

Yes No

b. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

c. Someone may contact me in the future to ask me to allow other uses of my specimens.

Yes No

d. I agree for my blood to be used in the additional studies.

Yes No

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted by your study doctor to the SWOG Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

Signature _____

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered regarding specimen use.

Participant _____

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, tissue from a biopsy, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

(section deleted 1/11/12)

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

19.0 APPENDIX

19.1 Determination of Expedited Adverse Event Reporting Requirements

19.2 Guidelines for Emergency Unblinding

19.3 Intake Calendar

19.4 Instructions for Patient-Completed Questionnaires

19.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the Phase (I, II, or III) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- Concurrent administration: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- Sequential administration: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE version specified.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. 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 only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.

Step 6: Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions above.

19.2 Guidelines for Emergency Unblinding of Coded Drug

a. The following events MAY require emergency unblinding of Coded Drug:

- A compelling medical need as determined by a physician, e.g., occurrence of a severe or life-threatening reaction, inclusive of an adverse drug reaction, which may have been attributable to Coded Drug, or existence of a condition where the knowledge of the patient's treatment assignment would directly influence or affect his/her immediate care;
- ingestion of the Coded Drug by persons other than the patient or in excessive quantity;
- exposure of a pregnant woman to the Coded Drug;
- exposure of a child to the Coded Drug;

  Note: Adverse drug reactions should be reported as required per Section 16.0 of this protocol.

b. Procedure for Emergency Unblinding

The procedure for unblinding the treatment assignment for a patient is as follows:

- All unblinding must be done by the registering physician or designee.
- Call the Washington Poison Control (WPC) collect at 206/526-2121 or at 800/732-6985 if calling from within Washington State. The WPC is accessible 24 hours per day, 365 days per year for unblinding calls. Informational calls should be directed to the Data Operations Center in Seattle during standard business hours.
- Provide the WPC with the following information:

  Study number: **S0927**
  SWOG patient number
  Patient name
  Coded Drug ID number and bottle number
  Name and telephone number of the caller
  Reason unblinding is required

- Unblinding for ingestion of the Coded drug by a pregnant woman will not require the authorization of a resource physician. (The resource physicians for this study are listed at the end of this section.)
- Unblinding for ingestion of the Coded Drug by a child will not require the authorization of a resource physician.
- Unblinding for ingestion of the drug either in excessive amounts or by a person other than the patient will be done ONLY when a compelling medical need exists and/or unblinding has been authorized by a resource physician.
- Unblinding for a "compelling medical need" must be authorized by a physician designated as a resource physician for this protocol.

The treating physician (or designee) would provide the WPC with the information needed to determine if unblinding is required for the patient. The WPC would contact the resource physician, provide the required information, and obtain the authorization to unblind, if necessary. Based on the decision of the resource physician, the WPC would call the treating physician with either the unblinded treatment assignment or a treatment recommendation from the resource physician.

If a resource physician cannot be reached by the WPC, treatment of the patient should proceed as if the drug ingested were an active agent.

- Unblinding of Coded Drug for any reason must be documented on the **S0927** Treatment Form (Form #15208) and the **S0927** Off Treatment Notice-Prevention Studies (Form #57439).

All unblinded participants are taken off treatment and followed per the requirements of the SWOG protocol.

Any questions regarding unblinding may be directed to one of the following resource physicians:

Dawn Hershman, M.D., M.S. (Medical Oncology)
Columbia University
161 Fort Washington Avenue
10-1068
New York, NY 10032
Phone: 212/305-1945
FAX: 212/305-0178
E-mail: dlh23@columbia.edu

Katherine D. Crew, M.D. (Medical Oncology)
Columbia University
161 Fort Washington
10-1072
New York, NY 10032
Phone: 212/305-1732
FAX: 212/305-0178
E-mail: kd59@columbia.edu

SOUTHWEST ONCOLOGY GROUP
INTAKE CALENDAR

SWOG Patient ID | | | | | | | **SWOG Study No.** S | | | | **Registration Step** |

Patient Initials (L, F, M) _____

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions for the Nurse or Research Coordinator:

Give this intake calendar to the participant for use with contact information filled in. Instruct the participant to bring the intake calendar to each visit.

This form does not need to be returned to the Data Operations Center.

If you have any questions contact: _____ Telephone: _____

Your next appointment is: _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

Special instructions:

Month: _____ **Year:** _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

19.4 Instructions for Patient-Completed Questionnaires

a. Brief Pain Inventory – Short Form (BPI-SF): At baseline and clinic visit weeks 6, 12 and 24, the BPI-SF will be used to assess the severity of pain/stiffness, evaluate the impact of pain on daily functions and monitor the effects of treatment The instrument gives several ratings of the intensity and severity of pain and the degree of pain interference on activity, mood, sleep, relations with others and work. *(96)* This self-administered questionnaire uses 0-10 scales for subject ratings and takes approximately five minutes to complete. The BPI-SF responds to both behavioral and pharmacological pain interventions and has been well-validated. *(96)* Note that we consider a reduction of two or more points on the BPI-SF worst pain item (#2) to correspond to a clinically meaningful decrease in pain. *(101)* Patients will answer questions about pain and its interference with daily activities with respect to the past 7 days.

b. Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index: At baseline and clinic visits weeks 6, 12 and 24, the WOMAC index Version 3.1 will be used to assess joint pain and stiffness. *(99,100)* The WOMAC index is a validated questionnaire that consists of 24 questions related to three subscales: pain (0-50), stiffness (0-20) and physical function (0-170). *(99,100)* Five questions assess joint pain, 2 questions assess stiffness, and 17 questions assess limitation of physical function in a specific time period prior to assessment. We are using the 11-point numerical rating scale format, which has been validated for the WOMAC. *(99,100)* Although originally developed as a standardized assessment to evaluate osteoarthritis, WOMAC has been used as a generalized symptom scale to evaluate musculoskeletal pain from conditions such as rheumatoid arthritis, total knee replacements, rotational malalignment due to a femoral shaft fracture, and osteonecrosis of the femoral head. *(101-104)* Patients will provide ratings with respect to the past 7 days.

Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH): The M-SACRAH will be used to measure changes in symptoms of the hands at baseline and at Weeks 6, 12 and 24. *(105)* This scale has been validated in patients with rheumatoid arthritis and hastraditionally used a VAS format. An even shorter version of the M-SACRAH is the Short Form M-SACRAH (SH-SACRAH). This measure uses a 0-10 numeric scale and has been found to correlate highly with VAS version of the M-SACRAH. *(113)* Because SWOG's Teleform system for forms cannot accommodate the traditional 0-100 VAS format, we selected the 0-10 numerical rating format for the M-SACRAH. Zero to 10 response scales have been shown to be as responsive as 0-100 scales. *(114-116)*. Nunnally noted that not much was gained in the amount of discrimination beyond 11 levels for single-item measures. *(117)* Patients will rate their symptoms with respect to the past 7 days.

d. Functional Assessment of Cancer Therapy-Endocrine System Trial Outcome Index (FACT-ES TOI): At baseline and clinic visits at weeks 6, 12 and 24, the FACT-ES TOI will be used to measure functional well-being as perceived by the patient. *(106,107)* The FACT-ES TOI consists of three subscales; the Physical Well-Being, Functional Well-Being and the ES symptom module (endocrine side effects associated with AI agents; endocrine side effects include hot flashes, night sweats, etc. *(107)* The FACT scales have five response levels ("not at all" to "very much"), where higher scores reflect better well-being and fewer symptom problems. The time frame for the FACT-ES TOI is "the past seven days". The psychometric properties of the FACT questionnaires have been amply documented. *(106,107)*

e. Global Ratings of Change (GRCs) will be used to identify minimally important differences in joint pain and joint stiffness. *(109-111)* The items on this questionnaire are answered with respect to the last time the patient filled out the questionnaire and is administered at weeks 6, 12, and 24 (not at baseline).

f. Omega-3-fatty acid dietary intake: At baseline and Week 24, omega-3-fatty acid dietary intake will be recorded on the **S0927** Omega-3-fatty acid Dietary Intake Questionnaire. The Four fish items will ask about are dark-meat fish such as bluefish (1.37 g of n-3 fatty acids per portion); canned tuna (0.69 g); other fish (0.17 g); and shrimp, lobster, or scallops (0.46 g). *(118)* We will calculate the average daily intake during that year of marine n-3 fatty acids as the sum of the daily consumption of each type of fish multiplied by the n-3 content of the specified portion. *(98)*