

CLINICAL STUDY PROTOCOL

Double-blind, randomized phase II clinical trial of sulindac for reducing breast density in postmenopausal women at risk of developing breast cancer

Sponsor

Stony Brook University and National Cancer Institute



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Synopsis

Primary Objective

The primary objective of this study is to determine if sulindac at a dose of 150 mg BID for 12 months reduces breast density in postmenopausal women at elevated risk of breast cancer when compared to a placebo control.

Secondary Objectives

The secondary objective of this study is to determine if sulindac at a dose of 150 mg BID for 6 months decreases breast tissue collagen straightness in postmenopausal women at elevated risk of breast cancer when compared to a placebo control.

Study Duration

The study is expected to open to enrollment in March 2020 with a target for completion of study December 2024.

The actual duration was from 12/02/2020 to 05/16/2025.

Study Design

To test the primary study hypothesis that sulindac reduces breast density, we will conduct a randomized, double-blind, placebo-controlled phase II clinical trial of sulindac (150 mg BID) or placebo PO BID for 12 months.

Study Population

The study population includes postmenopausal women at elevated risk of developing breast cancer with at least one unaffected, non-radiated breast with breast density defined as *heterogeneously dense* or *dense* (incl. *extremely* or *mostly dense*), or a minimum percent breast density of 10% within 12 months of randomization.

Number of Participants

The target number of participants is 150 with 75 randomized to each of two study arms.

The actual number of patients consented was 108, with 62 total participants randomized to either arm.

Number of Study Sites

This clinical part of the study will be conducted at multiple sites:

- Stony Brook University
- Cedars Sinai Medical Center
- University of Arizona

These sites will conduct only some aspects of the study

- University of South Carolina (exploratory tissue testing)

- Emory University (centralized MRI reads)
Primary Outcome Variables Primary Outcome Change in breast density as measured by magnetic resonance imaging (MRI based breast density or MRD) within individuals and between treatment arms at 12 months.
Secondary and Exploratory Outcome Variables (if applicable) Secondary Endpoints 1. Change in MRD within individuals and between treatment arms at 6 months. 2. Change in breast density within and between treatment arms at 12 months and stratified on use of aromatase inhibitors. Exploratory Endpoints 1. Change in MRI-acquired R2* in breast adipose tissue and percentage of CD68+, CD163+, CD80+, CD203+ macrophages in breast tissue biopsies within individuals and between treatment arms. 2. Test if MRI-acquired R2* correlates with increased percent and number of CD68+, CD163+, CD80+, CD203+ M2 macrophages in breast tissue biopsies. 3. Effect of sulindac on measures of pain and quality of life for all and separately for women on AIs and those who are not. 4. Change in breast tissue collagen type expression measured by whole tissue matrix assisted laser desorption ionization (MALDI) mass spectrometry within individuals and between treatment arms at 12 months 5. Change in breast tissue collagen alignment and collagen type expression measured by second resonance generated harmonics within individuals and between treatment arms at 12 months.
Visit Schedule Table (Optional)
Study Flow Chart (optional)

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Schedule Table

Timeline	Screening & Consent	Baseline (end of washout) Treatment start	Every 4 weeks ± 7 days on treatment	6 months on treatment	9 months on treatment	12 months on treatment	13 months (1 month off treatment)
# time since screening	0	30 + 30 days, as needed*	monthly	6 months ± 28 days	40 weeks ± 28 days	12 months ± 28 days	13 months ± 7 days
Eligibility Assessment	X						
Informed Consent	X						
Medical History	X						
Vital signs (blood pressure, pulse, height, weight, temperature) ^{2,6}	X ⁶	X ⁶	X (optional) ² , 6	X ⁶		X ⁶	
Review concomitant medication use within the past 30 days	X	X	X ¹	X	X ¹	X	X ³

Timeline	Screening & Consent	Baseline (end of washout) Treatment start	Every 4 weeks $\pm$ 7 days on treatment	6 months on treatment	9 months on treatment	12 months on treatment	13 months (1 month off treatment)
BPI-SF, WOMAC, & FACT-G	X	X		X		X	
Blood/Urine for Research ⁴	X ⁴	X ⁴		X ⁴		X ⁴	
Fecal Occult Blood Test (optional)	X ⁸						
Blood for CBC w diff and CMP ⁵	X			X		X	
Blood for Estradiol and/or FSH (as needed) ⁹	X						
Non-contrast MRI		X		X		X	
Breast Biopsy		X (optional)		X (optional)			
Review Adverse Events ¹		X	X ¹		X ¹	X	X ³

Timeline	Screening & Consent	Baseline (end of washout) Treatment start	Every 4 weeks $\pm$ 7 days on treatment	6 months on treatment	9 months on treatment	12 months on treatment	13 months (1 month off treatment)
Dispense/Return/ Reconcile Study Agents		X		X		X ⁷	
Phone Call ¹			X ¹		X ¹		X ³

* Eligible participants who did not regularly take NSAIDs (except aspirin $\leq$ 81 mg QID) in the 30 days prior to consenting to the study do not need to complete a washout and can proceed to the Baseline Visit right away.

¹All study subjects will receive a telephone call monthly for the first 6 months and again at 36 weeks (~9 months) after initiating study agent for medication use and review of adverse events. New onset adverse events will be followed weekly by telephone or clinic visit, as appropriate, until resolution. Vital signs will also be collected if subjects opt, and are allowed under institutional COVID-19 guidelines, to visit the research clinic in person during the first 6 months of treatment. At the time of the monthly phone calls, a study team member should make at least three attempts to contact the participant, within approximately a two-week time frame. Each attempt will be documented with the date and the method of communication (eg. phone, voicemail, email, etc.) in a log or research note. If a participant cannot be reached after three attempts, the team will initiate contact again at the next planned touch base, without documenting a deviation.

²All subjects will visit the research center site at baseline, then 6, and 12 months after initiating study agent. A clinic visit with study personnel (treating physician or nurse practitioner) at 3 months will be offered as an optional visit for participants who would feel more comfortable coming in more frequently. At this visit, the study personnel will review any AEs, any changes in medications, and check vital signs as indicated above.

³These procedures will be done via phone approximately 1 month after stopping study agent.

⁴Study subjects provide a blood sample (for serum and plasma) and urine sample (up to 100 ml) at baseline and at 6 and 12 months for research related biomarkers. Up to 10 ml of blood will be collected in a lavender top tube (K2 EDTA) for plasma and up to 10 ml in a red speckled serum separator tube. To minimize the number of blood draws, research blood and urine samples can be obtained at the time of screening from subjects who do not regularly use NSAIDs (i.e., NSAID use not to exceed one day per week in the preceding 4 weeks).

⁵ Each study subject will have blood drawn for a CBC with differential and for a Comprehensive Metabolic Panel (Chem8: glucose, calcium, albumin, total protein, sodium, potassium, CO₂, chloride, BUN, creatinine; hepatic panels: ALP, ALT, AST, bilirubin) baseline, 3 months (optional), 6 and 12 months. Existing bloodwork results can be used to assess eligibility if performed within 6 months of eligibility assessment.

⁶Subjects' blood pressure will be measured at rest. To account for white coat syndrome, any subject observed to have a BP>160/90 will be provided an in-home blood pressure monitor and asked to record her blood pressure at three times points each day over the subsequent 2 days. The study nurse will contact the subject and record the readings. If the study subject has persistently elevated blood pressure during screening for enrollment with in-home monitoring, the subject will not be eligible. If a study participant exhibits persistent elevation in blood pressure with in-home measures during the treatment phase, study drug will be stopped, and the subject asked to see her primary care or study physician prior to study continuation. Study drug can be restarted at full or dose-reduced after blood pressure control is achieved on recommendation of the treating physician.

⁷No study drug will be dispensed at this visit

⁸ A fecal occult blood test will be recommended to participants during screening, but is optional.

⁹ Testing for either follicular stimulating hormone (FSH) and/or estradiol may be ordered at baseline to confirm participants' menopausal status, if unclear.

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1 - Introduction

1.1 Introductory Statement

The proposed clinical trial is a randomized, double-blinded, placebo-controlled Phase II study to test the effect of sulindac, a non-selective, non-steroid anti-inflammatory drug (NSAID) on breast density in postmenopausal women at elevated risk of developing breast cancer. Breast density is an imaging and intermediate biomarker of breast cancer risk. Change in breast density is the primary outcome of the study.

2 - Background

2.1.1 Preclinical Experience

NSAIDs, including aspirin (ASA), consistently demonstrate anti-cancer activity in preclinical and observational studies of breast cancer. In the Women's Health Initiative Observational Study, NSAID use (ibuprofen or ASA) of ≥ 2 tablets/week in postmenopausal women was associated with a 21% and 28% reduction in breast cancer incidence with 5—9 and 10+ years of use, respectively. (1) Other studies support 20—30% lower risk with ASA use with some reporting stronger effects for hormone responsive (i.e., ER+) breast cancers. (2) (3) (4) (5) For example, analyses of the Nurse's Health Study found no main association between ASA or NSAID and lower incidence of breast cancer but higher dose and longer use was associated with a non-significant risk reduction for strongly hormone responsive cancer subtypes (i.e., ER+/PR+). (6) (7) In a more recent meta-analysis of data from ~900,000 women, ASA was associated with breast cancer risk reduction that was proportional to duration of use; 14%, 27% and 46% for 5, 10 and 20 years use, respectively. (8) This finding is similar to the observed NSAID benefit for colorectal cancer where ASA is recommended for use in high-risk patient populations.

Though individually distinct, drugs in the NSAID class share the ability to inhibit cyclooxygenase 2 (COX2) and suppress the metabolism of arachidonic acid (ARA) to the pro-inflammatory/pro-tumorigenic prostaglandin E2 (PGE2), which has experimentally been linked to their class specific anti-cancer activity. In breast cancer, COX2 expression is deregulated early and has been reproducibly shown to be increased in dense breast tissue (a risk factor for breast cancer) (9) and in the transition of the normal to malignant phenotype. (10) (11) (12) (13) (14) Inhibition of COX2 in breast cancer cell lines and PGE2, both in vitro and in vivo in xenograft models, is associated with tumor growth suppression and increased apoptosis (15). In earlier work, Barnes et al., (16) demonstrated that celecoxib, a selective COX2 inhibitor, inhibited growth and promoted apoptosis in ER+ MCF7 and ER-MDA-MB-231 xenograft human breast tumor models in immune compromised mice. More recent, Yin et al., (17) demonstrated that sulindac, a pro-drug with COX2 and non-COX inhibitory activity in cancer models, increased the survival of immune competent mice engrafted with the aggressive 4T1 murine basal-like (ER-) mammary tumor cell line but showed no effect on survival in athymic nude mice engrafted with the 4T1 model. Further, Yin associated the effect of sulindac on 4T1 tumor growth in the immune competent model to T cell function where the effect of sulindac on the T cell compartment was mediated via macrophage recruited into the tumor microenvironment.

These newer findings support effects of sulindac (possibly other NSAIDs) in the tissue microenvironment; findings that raise new immunomodulatory mechanisms of NSAID effects in cancer prevention.

2.1.2 Clinical Experience

In addition to the evidence that regular use of NSAIDs is associated with lower risk of cancer, several reports of lower breast cancer relapse rates and deaths in regular NSAID

users have been published. (15) These observational findings motivated efforts as early as the late 1990s and early 2000's to test NSAIDs and particularly, the COX2 selective and presumably better tolerated inhibitors for secondary prevention of breast cancer recurrence. (18) Unfortunately, all of the early studies that elected to test COX2 selective agents (i.e., celecoxib and Vioxx) were suspended early into accrual secondary to concerns around emerging cardiovascular risk. From these early studies, the Canadian Cancer Trials Group MA.27(19) failed to provide evidence for a celecoxib benefit on event free and overall survival. However, as discussed in an accompanying editorial (20), interpretation of MA.27, a 2 x 2 factorial of aromatase inhibitor (exemestane or anastrozole) and celecoxib or placebo in postmenopausal, ER+ patients was ultimately limited by the early suspension and resultant short median celecoxib exposure of only 4.6 months (range 0.03-17.5 months) and reduced sample size. Unpublished findings from the more contemporary and completed REACT trial of celecoxib at a safer dose of celecoxib for 2 years vs. placebo in early-stage patients, showed no overall effect on recurrence or early survival endpoints, but a benefit in secondary analyses for lower risk patients i.e., patient who did not receive chemotherapy that was independent of tumor subtype (21). Current efforts to advance NSAIDs for breast cancer secondary prevention include the ongoing trials of ASA (300mg QD) (the Alliance's Aspirin for Breast (ABC) Trial and the United Kingdom's Add-Aspirin Study) on disease recurrence.

Importantly, while these studies demonstrate the general interest in the potential benefit of NSAIDs in the setting of secondary prevention, these studies are not testing NSAIDs for primary BC prevention. To our knowledge, there are no ongoing studies of NSAIDs and specifically, sulindac for primary breast cancer prevention.

2.2 Background/prevalence of research topic

Current status of Breast Cancer Chemoprevention. The demonstration that inhibiting estrogen, via aromatase inhibitors [AIs] or selective estrogen receptor modulators (SERMs), prevents ~50% of breast cancers has provided proof of concept that breast cancer is a preventable disease. However, toxicities and undesirable side effects of AIs and SERMs, coupled with unclear benefit to lower cancer deaths and no effect on the more aggressive and deadly ER- cancers, has limited implementation clinically to only ~5% of high-risk patients outside of clinical trials. (22)(23) Thus, while there is clear potential to prevent breast cancer, (24) 1 in 7 to 8 women in the US will still be affected by breast cancer and it remains the leading cause of death in women ages 35—54 yrs.

Non-steroidal anti-inflammatory drugs and Cancer Chemoprevention: Changing

Landscape. ASA and NSAIDs for the prevention of epithelial cancers, including breast, is an old concept but one that has been slow to translate. NSAIDs are inexpensive, safe, widely used and generally well-tolerated drugs. As noted above, interest in NSAIDs for primary and secondary breast cancer prevention remains an area of active research. Focus on the COX2-specific (coxib) NSAID class of drugs in the late 1990s and early 2000s on presumed greater tolerability (particularly gastrointestinal) and safety relative to other NSAIDs detracted from interest in older, non-selective NSAIDs including sulindac for cancer prevention. This occurred despite compelling preclinical evidence supporting potent anti-

cancer activity of sulindac that included a non-COX2 pro-apoptotic activity attributable to a primary drug metabolite that did not demonstrate COX2 inhibitory activity. As discussed above, early, and unexpected cardiotoxicity associated with the daily dosing of coxibs prompted early closure of several trials of selective inhibitors and set the field back. This included a handful of studies for breast cancer prevention.

Subsequent findings from the PRECISION Trial (25) and polyp prevention trials, (26)(27) including those of the SEL/CEL published by study PI Thompson (28), served to quantify the rare but serious cardiovascular and hypertensive effects of all drugs with COX-2 inhibitor activity i.e., selective or non-selective. Further, these and other trials have led to the recognition that presence or history of cardiovascular disease, early rise in blood pressure and more advanced age largely account for the excess risk of serious cardiovascular risk with NSAID use; findings that led to refined exclusion criteria for their use in patients. With the demonstration that proton pump inhibitors and H2-receptor antagonists (29)(30) dramatically reduce common NSAID-associated GI toxicities, interest in NSAIDs as chemopreventive agents in the right target population (patients at risk of developing cancer) re-gained enthusiasm especially for colon, breast and head and neck cancers. With a better understanding of NSAID risks at the individual patient level and recognition of their clinical efficacy for cancer prevention, clinical guidelines now include use of ASA and sulindac for colorectal cancer prevention in patient groups at high-risk of developing colorectal cancer. (31)

Revisiting Sulindac for Breast Cancer Prevention — New Evidence. Among the NSAIDs, sulindac (Clinoril®), has more than 30 years of history as a candidate cancer prevention drug based on more potent and durable anti- cancer activity in experimental models of colorectal cancer than ASA. (32)(33) Sulindac — a substituted indene-3-acetic acid prodrug — is enzymatically converted to sulindac sulfide and sulindac sulfone (a.k.a exisulind). The analgesic and anti-pyretic activity is attributed to non-selective COX inhibitor activity and inhibition of PGE₂; though the exact mechanism of action remains unknown. In addition, sulindac metabolites have been shown to exhibit COX independent activities. (34) These are hypothesized to explain its unique anti- cancer activity profile and provide an explanation for the significant efficacy of sulindac when given in combination with diflouromethylornithine (DFMO) for colorectal adenoma prevention, findings that renewed interest in its use for prevention.(35) Some of the better characterized mechanisms of action for sulindac include pro- apoptotic activity attributed to induction of GDF-15, (36) inhibition of NFKB, activity as a PPAR_γ agonist 16 and evidence for RXR_α antagonism,(17) that may explain reported inhibition of PI3K/AKT pathway activation (18, 19, 20) . These molecular effects may underlie findings from several large clinical studies demonstrating stronger NSAID effects in PI3K mutant cancers, a common driver mutation of high relevance in head and neck, breast, and colon cancers. (21)

While the exact anti-cancer mechanism of sulindac remains unknown, strong evidence demonstrates pleotropic effects of sulindac that include immune cell activity. As noted above and important, Yin et al 22 demonstrated sulindac's activity to inhibit the growth of metastatic 4T1 basal-like (e.g., triple negative like tumor) mouse tumors in immune

competent but not athymic mouse orthotopic studies and attributed the activity to immunomodulatory effects of sulindac on macrophages (MACs) and CD8+ T cells. Our own preliminary results – discussed below – support a multiplicity of sulindac effects on breast tissue including direct effects on normal tissue architecture and breast density – a major risk factor for breast cancer. For example, in our study of early stage breast cancer patients on aromatase inhibitors receiving sulindac [150 mg BID] for 12 months, sulindac reduced breast density (an established risk factor for breast cancer ²³ with evidence for independent effects on adipose tissue and on extracellular matrix (ECM) proteins (i.e., collagen). The latter effects on the ECM, and particularly collagen, are exciting given experimental evidence of COX2 effects on collagen that link stromal features of breast density to tumorigenesis in the mammary gland of mice. ²⁴ Earlier studies (1980's) suggested sulindac was more renal sparing than other NSAIDs in subjects with normal or mildly impaired renal function. ²⁵ This 'sparing' of effects on renal prostanoid synthesis was thought to explain reduced pressor effects with sulindac compared to other NSAIDs. This has been attributed to metabolism of sulindac to the sulfone, which exhibits no COX2 activity, in the kidney. (26) Sulindac's COX2 activities are extra renal and are thought to explain its better performance in hypertensive patients. Unfortunately, all studies have been small and of short duration limiting interpretation on the relative safety of sulindac and the inability to clear sulindac sulfide in individuals with renal insufficiency makes renal status (27) persist as an important consideration in patient selection. While limited, sulindac has been recommended as a better drug choice for older patients based on lower pressor effects than other drugs in its class in healthy subjects. (28, 29) To further explore these effects, including effects on circulating and tissue bioactive oxylipins and their role in drug action and toxicities ³⁰ urine, blood and fresh biopsy will be banked for future work and blood pressure routinely monitored among participants on study.

Results of a single arm, open-label study of sulindac to reduce breast density with a non-randomized, observational control group for comparison. We recently completed a non-randomized, open label study of 150 mg sulindac BID given for 12 months for effects on breast density in the contralateral breast of patients receiving aromatase inhibitors for treatment of breast cancer. On published evidence that sulindac at this dose achieved higher breast tissue levels and on xenograft studies supporting decreased tumor growth related to pro-apoptotic effects at higher doses, we selected 150 mg BID (i.e., 300 mg per day) as an investigational dose for effects on breast density. For the completed study (manuscript in preparation), we originally proposed a randomized, placebo control design and were funded (5RO1 CA161534) to assess sulindac effects on breast density using a novel MRI method with change in tissue biomarkers using core needle biopsy of the breast (pre and post intervention). Secondary to funding cuts to our grant, we modified and simplified the study aims, with agreement from NCI, to initially obtain evidence for sulindac action on breast density using our novel MRI method and assessment of tolerability and safety of sulindac in the target population. Blinding was eliminated and the placebo arm was replaced with an observational (non-randomized) control group comprised of similar breast cancer patients on aromatase inhibitors who were unwilling or unable to participate in the intervention. The inclusion of the observation arm was for the purpose of assessing whether

aromatase inhibitors alone had effects on reducing breast density when measured by a more sensitive MRI approach. The primary study objectives were modified to assess whether sulindac at 150 mg BID for 12 months was well tolerated, demonstrated any adverse effects on blood pressure, improved symptoms of pain associated with AI use and showed evidence for any effect on breast density. Secondary objectives were modified to assess whether baseline breast density was an important factor for detecting agent effect by MRD and whether repeated needle biopsy was feasible. The trial closed to accrual and the last subject completed study in April 2019. The study is in final data analysis. The final study consort diagram is shown in Figure 1.

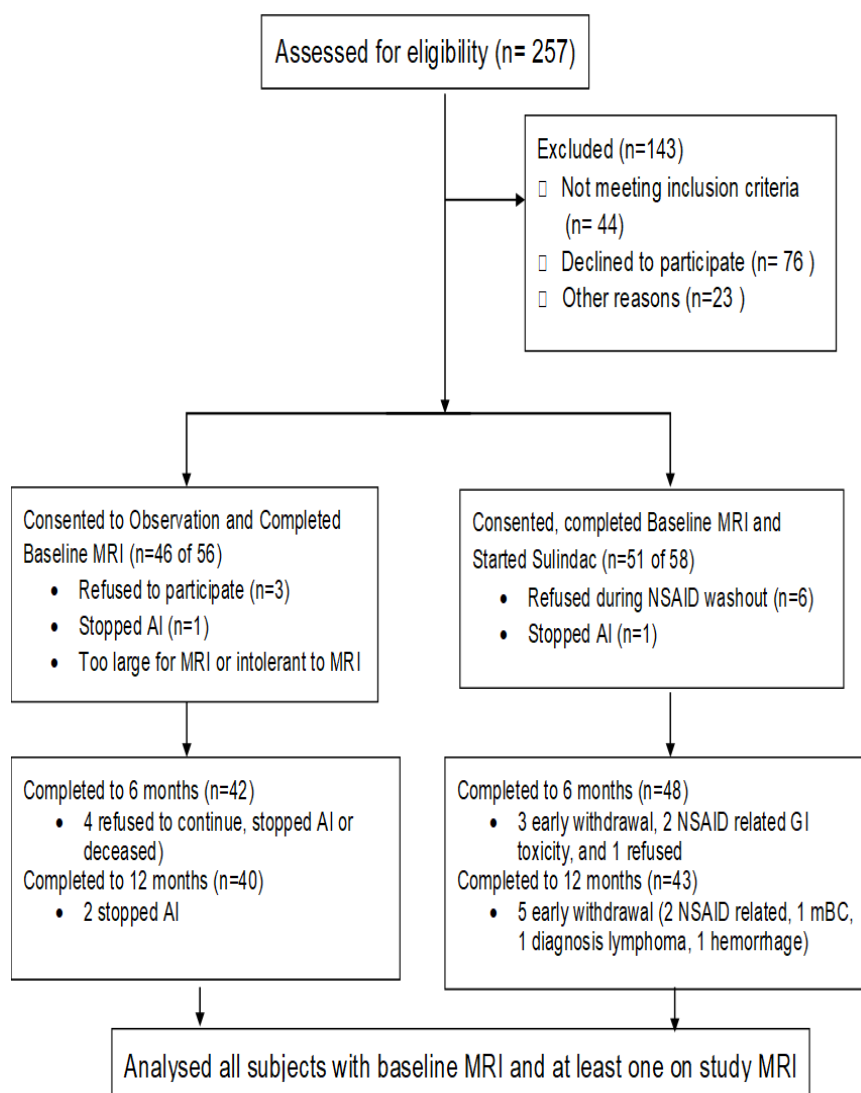


Figure 1. Study Consort Diagram

Results of the planned analyses of this study are shown in Tables 1 and 2. Table 1 shows the results of breast density change in all subjects (n=114 consented subjects) by sulindac intervention and observation group at 6 and 12 months using linear mixed effect for longitudinal data with percentage change in breast density the outcome. As shown, at both 6

and 12 months, breast density significantly decreased in the sulindac group, whereas breast density did not change at 6 months in the observation group and the decrease at 12 months was not significant.

Table 1. Adjusted estimate of relative change in breast density between two time points for Sulindac and Observation Arm at 6 and 12 months.

		Adjusted model 1	
Group	Time (Months)	Relative Change in BD (95% CI)	P-value ²
Obs n=46	6 vs 0	1.6 (-2.8, 6.1)	0.4857
	12 vs 0	-3.6 (-8.9, 2.0)	0.2011
Sul n=48	6 vs 0	-4.2 (-8.1, -0.1)	0.0464
	12 vs 0	-9.8 (-14.6, -4.7)	0.0003

¹Adjustments included were: baseline log(BD), month on AI at baseline, BMI at each visit, and site.

²P-values were based on T-test from linear mixed model.

Table 2 shows the results for participants with baseline breast density stratified on the study median (17.7% at baseline). While the % decrease from baseline in the sulindac group (and the observation arm) were greater at 6 and 12 months in women whose breast density was higher at baseline, the differences did not reach statistical significance.

Table 2. Adjusted estimate of relative change in breast density between two time points for Sulindac and Observation Arm at 6 and 12 months for study group by baseline breast density.

		Baseline BD ≤17.7%	Baseline BD >17.7%	
Group	Time (Months)	% Relative Change in BD (95% CI)	% Relative Change in BD (95% CI)	P-value ³
Obs	6 vs 0	5.7 (-0.7, 12.6)	-1.1 (-6.6, 4.7)	0.4857
	12 vs 0	-1.8 (-9.3, 6.4)	-5.2 (-11.6, 1.7)	0.2011
Sul	6 vs 0	-2.7 (-7.8, 2.8))	-5.8 (-11.2, 0)	0.0464
	12 vs 0	-9.8 (-14.6, -4.7)	-13.1 (-19.5, -6.1)	0.0003

Adjustments included were: baseline BD group, month on AI at baseline, BMI at each visit, and site.

³P-values were based on T-test from linear mixed model to test whether the relative change in BD by baseline BD within groups were different.

In addition to finding sulindac significantly decreased breast density, we employed second harmonic generation (SHG) microscopy to analyzed breast tissue collagen 'architecture' (31, 32) using tissue sections obtained from subjects in the sulindac only arm who provided a biopsies at baseline and between 6 and 12 months on treatment. SHG occurs when the laser field undergoes a nonlinear, second-order polarization on passing

through noncentrosymmetric ordered structures like fibrillary collagen on the slide. SHG is currently being applied to breast, ovarian, prostate and other cancer tissues where fiber orientation, including more aligned collagen orientation or 'straightness', is emerging as a feature of the invasive phenotype. Using this technique, important work from the late Patricia Keely demonstrated that bundles of straightened and aligned collagen oriented perpendicular to the breast tumor boundary is a poor prognostic factor. (33) As COX2, a major target of NSAIDs, has been shown to promote collagen deposition, a more dense appearing tissue and mammary tumor development in mouse models, 24 we hypothesized that sulindac may mediate its effects on breast density through inhibition of COX2 effects on collagen. To test this, we analyzed collagen fiber alignment by SHG in 30 paired samples blinded to pre and post sulindac status. For these studies, three random areas of the blinded tissue were imaged on a Zeiss LSM 510 META NLO Two-Photon laser scanning confocal microscope system and processed using the computer-assisted image feature extraction software, CT-FIRE. 31 Using this approach and analysis of the distribution (histogram) of 'straight' fibers in three randomly selected areas of the tissue with ≥ 100 fibers per area of interest, we observed a significant decrease in straight fibers between the pre and post sulindac samples ($p=0.01$). While preliminary, it is notable that this difference (decrease in collagen straightness) correlated with a decrease in breast density in the same subject by MRD ($\rho=0.66$, $p=0.01$). Our findings are further supported by recent work from McConnell et al., 34 using atomic force microscopy who demonstrate evidence that stromal collagen microarchitecture, and in particular aligned fibers, correlate positively with mammographic density.

The findings from this first in women, open label study of sulindac effects on breast density demonstrate the feasibility of the planned intervention as well as provide supporting evidence from human studies for effects of sulindac on breast density as well as for effects on collagen. In the new study, we are seeking to formally test the hypothesis that sulindac decreases breast density and does so through effects on tissue collagen using the more rigorous randomized, placebo-controlled study design where participants and study investigators are blinded to the study agents.

3 - Rationale/Significance

3.1 Problem Statement

Based on our preliminary findings that sulindac reduces breast density and alters the alignment of tissue collagen in postmenopausal women with breast cancer favoring chemopreventive activity in the breast, there is a need to confirm the effect of sulindac in a placebo controlled and randomized clinical trial in a patient population most likely to benefit.

3.2 Purpose of Study/Potential Impact

The purpose of this study is to rigorously test the hypothesis that the NSAID sulindac reduces breast density and alters tissue collagen in postmenopausal women at elevated risk of developing breast cancer. The potential impact of the study would be the demonstration

that sulindac has cancer prevention activity through effects on breast density. Positive findings would support a larger, more costly, phase III clinical trial to assess the effect of sulindac to reduce the risk of breast cancer in women at elevated risk. In addition, positive findings from the randomized placebo-controlled trial would provide compelling evidence in support of inflammation and prostaglandin E2 in breast density and open additional opportunities for interventions aimed at lowering breast cancer risk through their modulation.

3.3.1 Potential Risks

Adverse Events

Sulindac, marketed as the Merck drug Clinoril, was approved for the treatment of arthritis by the FDA in 1978. Currently, there are approximately 300,000 prescriptions for sulindac annually in the United States down from 1.3 million in 2006. The following adverse reactions have been reported in clinical trials or have been reported postmarketing. The probability exists of a causal relationship between sulindac and these adverse reactions. The adverse reactions which have been observed in clinical trials encompass observations in 1,865 patients, including 232 observed for at least 48 weeks.

1. Incidence greater than 1 to 10 in 100 (COMMON), RARELY SERIOUS

Gastrointestinal

The most frequent types of adverse reactions occurring with sulindac are gastrointestinal; these include gastrointestinal pain (10%), dyspepsia, and nausea, with or without vomiting, diarrhea, constipation, flatulence, anorexia and gastrointestinal cramps.

Dermatologic. Rash, pruritus.

Central Nervous System Dizziness, headache, nervousness.

Special Senses Tinnitus.

2. Incidence Less Than 1 in 100 (OCCASIONAL), SOME MAY BE SEVERE

Gastrointestinal. Gastritis, gastroenteritis or colitis. Peptic ulcer and gastrointestinal bleeding have been reported. GI perforation and intestinal strictures (diaphragms) have been reported rarely ageusia (change in taste) and glossitis (inflammation of tongue) have been reported rarely. Serious GI events, most notably peptic ulcer and GI bleed are more common among elderly patients.

Liver function abnormalities; jaundice, sometimes with fever; cholestasis; hepatitis; hepatic failure. Chronic therapy with sulindac is associated with a low rate of serum aminotransferase elevations, which are rarely severe and usually self-limited. Clinically apparent acute liver injury from sulindac is well known, but rare (~5 cases in 100,000 prescriptions and ~0.1% of users). The clinical pattern suggests an allergic hepatitis and is somewhat similar to the hepatotoxicity of the sulfonamides.

Pancreatitis. The annual incidence of acute pancreatitis (AP) in the United States is approximately 17 cases per 100,000. Of these, medications are thought to account for 0.1-2% of all AP cases with recent estimates of up to 5% with 500 suspect medications. While

rare, among the NSAID-associated AP, sulindac and ibuprofen are among the most reported drugs from the class for which, there is a single case report of symptom recurrence after rechallenge (i.e., positive rechallenge).

Dermatologic. Stomatitis, sore or dry mucous membranes, alopecia, photosensitivity. While rare, as with other NSAIDs, Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and exfoliative dermatitis have been reported (estimate for NSAIDs that include sulindac at 1-2 per million users per week).

Cardiovascular. NSAIDs including sulindac are associated with an increased risk of serious cardiovascular events. The most important adverse cardiovascular events include cardiovascular death, myocardial infarction (MI), and stroke. Other patient-important events include heart failure (HF), blood pressure elevation, atrial fibrillation, and venous thromboembolism. In one large study, major adverse cardiovascular events occurring within 30 days of initiating a NSAIDs ranged from 0.7/1000 to 1.3/1000 and were higher among patients with existing cardiovascular disease or with significant risk for cardiovascular disease. NSAIDs increase the risk for CV death and recurrent MI in the post-MI patient population, and, therefore, these agents should be avoided in these populations.

Hematologic. Thrombocytopenia; ecchymosis; purpura; leukopenia; agranulocytosis; neutropenia; bone marrow depression, including aplastic anemia; hemolytic anemia; increased prothrombin time in patients on oral anticoagulants.

Genitourinary. Urine discoloration; dysuria; vaginal bleeding; hematuria; proteinuria; crystalluria; renal impairment, including renal failure; interstitial nephritis; nephrotic syndrome. Renal calculi containing sulindac metabolites have been observed rarely.

Metabolic. Hyperkalemia.

Musculoskeletal. Muscle weakness.

Psychiatric. Depression; psychic disturbances including acute psychosis.

Nervous System. Vertigo and insomnia, Somnolence; paresthesia; convulsions; syncope. While rare, aseptic meningitis has been reported with high doses of NSAIDs, including sulindac and for which patients with systemic lupus erythematosus and other rheumatoid diseases are thought to be at greater risk. Nervous system symptoms are associated with sulindac overdose.

Special Senses. Blurred vision; visual disturbances; decreased hearing; metallic or bitter taste. These are symptoms associated with sulindac overdose.

Respiratory. Epistaxis, Hypersensitivity Reactions, Anaphylaxis; angioneurotic edema; bronchial spasm; dyspnea. These symptoms are associated with sulindac overdose.

Hypersensitivity vasculitis. A potentially fatal apparent hypersensitivity syndrome has been reported. This syndrome may include constitutional symptoms (fever, chills, diaphoresis, flushing), cutaneous findings (rash or other dermatologic reactions), conjunctivitis, involvement of major organs (changes in liver function including hepatic failure, jaundice, pancreatitis, pneumonitis with or without pleural effusion, leukopenia,

leukocytosis, eosinophilia, disseminated intravascular coagulation, anemia, renal impairment, including renal failure), and other less specific findings (adenitis, arthralgia, arthritis, myalgia, fatigue, malaise, hypotension, chest pain, tachycardia).

3. RARE CASE REPORTS AND CAUSAL RELATIONSHIP UNKNOWN (SOME MAY BE SEVERE)

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A β -hemolytic streptococcus, has been described in persons treated with NSAIDs, sometimes with fatal outcome. Observational studies however indicate that the association may be caused by delayed initiation of antibiotic therapy in NSAID users due to masking of symptoms.

Other reactions have been reported in clinical trials or since the drug was marketed but occurred under circumstances where a causal relationship could not be established. Therefore, these observations are listed solely to serve as alerting information to physicians.

Metabolic. Hyperglycemia.

Nervous System. Neuritis.

Special Senses. Disturbances of the retina and its vasculature.

Miscellaneous. Gynecomastia.

3.3.2 Potential Benefits

Expected Benefits to Research Subjects. Because a subset of the population are postmenopausal women on aromatase inhibitor therapy for the treatment of breast cancer, daily therapy with sulindac may result in improved tolerability and decreased musculoskeletal symptoms for patients on the trial. In our current study we have observed a decrease in the number of patients reporting severe pain on the sulindac arm with no such decrease observed in the observation arm. This may result in improved adherence or quality of life. The risks posed by sulindac exposure are minimized by selection and continued monitoring of our patient population.

Benefit of knowledge gained for society. The knowledge to be gained may also lead to a better understanding of the mechanism of action of NSAIDs, which are widely used in the general population. We anticipate that women at highest risk of breast cancer and particularly those with a personal history of breast cancer or premalignant lesion in the breast are more likely to consent to breast biopsy. It is our experience that these women in particular have a sense of helping to advance research and in taking an active part in fighting their disease as a positive experience. This is consistent with the evidence that altruism is a major reason that patients participate in clinical trials.

4 - Study Objectives

4.1 Hypothesis

Our primary hypotheses is that sulindac 150mg BID will demonstrate greater reduction in BD at month 12 than placebo control.

Our secondary hypothesis is that sulindac 150 mg BID will decrease breast tissue collagen straightness compared to placebo control.

4.2 Primary Objective

The primary objective of this study is to determine if sulindac at a dose of 150 mg BID for 12 months reduces breast density in postmenopausal women at elevated risk of breast cancer when compared to a placebo control.

Primary Endpoints

Change in breast density as measured by magnetic resonance imaging (MRI based breast density or MRD) within individuals and between treatment arms at 12 months.

Secondary and Exploratory Outcome Variables (if applicable)

4.3 Secondary Objectives

The secondary objective of this study is to determine if sulindac at a dose of 150 mg BID for 6 months decreases breast tissue collagen straightness in postmenopausal women at elevated risk of breast cancer when compared to a placebo control.

Secondary Endpoints

1. Change in MRD within individuals and between treatment arms at 6 months.
2. Change in breast density within and between treatment arms at 12 months and stratified on use of aromatase inhibitors.

4.4 Exploratory Endpoints

1. Change in MRI-acquired R2* in breast adipose tissue and percentage of CD68+, CD163+, CD80+, CD203+ macrophages in breast tissue biopsies within individuals and between treatment arms.
2. Test if MRI-acquired R2* correlates with increased percent and number of CD68+, CD163+, CD80+, CD203+ M2 macrophages in breast tissue biopsies.
3. Effect of sulindac on measures of pain and quality of life for all and separately for women on AIs and those who are not.
4. Change in breast tissue collagen type expression measured by whole tissue matrix assisted laser desorption ionization (MALDI) mass spectrometry within individuals and between treatment arms at 12 months.

5. Change in breast tissue collagen alignment and collagen type expression measured by second resonance generated harmonics within individuals and between treatment arms at 12 months.

5 - Study Design

5.1 General Design Description

The trial design is a randomized, placebo controlled, double blind 2-arm clinical trial of sulindac 150 mg BID vs. placebo BID where all study endpoints are analyzed blinded to assignment. Sulindac is an FDA approved drug being investigated off label in this study as a breast cancer chemoprevention agent. The design, sample size and the statistical plan are specified to test the primary hypotheses that sulindac at 150 mg BID will decrease breast density measured by magnetic resonance imaging of fat and water in the breast compared to placebo. Secondary analyses are included to assess effects of sulindac on breast tissue extracellular matrix proteins and specifically, collagen, and their relationship to breast density and breast density changes compared to the control arm. In addition, exploratory aims are included that seek to confirm our preliminary findings of effects of sulindac on the breast adipose tissue using magnetic resonance imaging and tissue-based biomarker analysis of breast tissue and breast adipose macrophages.

In addition to these primary and secondary study endpoints, we have designed the study and target population to allow us to explore an alternative hypothesis that the effect of sulindac on breast density in postmenopausal women taking aromatase inhibitors observed in the interim analysis of our prior, completed study may in fact have resulted or been potentiated from an interaction between sulindac with aromatase inhibitors on breast density. This hypothesis is based on evidence for effects of cyclooxygenase derived prostaglandin E2 to increase aromatase expression in mammary adipose tissue. We will intentionally enroll postmenopausal women on aromatase inhibitors for prevention or treatment of premalignant or early-stage breast cancers to allow us to explore if the effects of sulindac is greater in women who are also taking an aromatase inhibitor.

5.1.1 Study Date Range and Duration

It is anticipated that this study will open to enrollment in March of 2020 with a targeted completion i.e., the last participant to complete the study in December 2024.

5.1.2 Number of Study Sites

This clinical portion of the study will be conducted at multiple study sites:

- Stony Brook University, Stony Brook, NY
- Cedars Sinai Medical Center, Los Angeles, CA
- University of Arizona, Tucson, AZ

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

Change in breast density as measured by magnetic resonance imaging (MRI based breast density or MRD) within individuals and between treatment arms at 12 months.

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Secondary Outcomes

1. Change in MRD within individuals and between treatment arms at 6 months.
2. Change in breast density within and between treatment arms at 12 months in the subset of women on AIs compared to those who are not on AI therapy.

Exploratory Outcomes

1. Change in MRI-acquired R2* in breast adipose tissue and number and subtype of macrophages in breast tissue biopsies within individuals and between treatment arms.
2. Test if MRI-acquired R2* correlates with increased number and subtype of macrophages in breast tissue biopsies.
3. Effect of sulindac on measures of pain and quality of life for all and separately for women on AIs and those who are not.
4. Change in breast tissue collagen alignment and collagen type expression measured by second harmonic generation (SHG) microscopy and whole tissue matrix assisted laser desorption ionization (MALDI) mass spectrometry within individuals and between treatment arms at 6 months.

5.3 Study Population

The clinical trial will randomize postmenopausal women with either high risk [e.g., family history, genetic predisposition, or personal history of high-risk breast lesions (i.e. atypical hyperplasia or in situ cancer)] or early stage breast cancer to one of two study arms: placebo PO BID or sulindac 150 mg PO BID. We estimate that ~150 subjects will need to be consented and randomized to obtain 60 subjects per arm with complete data at 6 months and 55 subjects per arm at 12 months. This includes a conservative estimate of dropout rates of 10% in washout, 10% from 0-6 months on intervention and an additional 10% from 6 to 12 months. When we reach 120 complete at the 6-month measure, we will suspend recruitment to the study. Women on aromatase inhibitors (AIs) will be enrolled up to 1/2 the study population (n=75) to explore a potential interaction between nonsteroidal anti-inflammatory (NSAIDs) and aromatase inhibitors. Women will be screened for the study based on mammographically determined breast density. Women with density described as *heterogeneously dense* or (ie. *mostly*, or *extremely*) dense within 12 months of randomization and women with percent breast density of 10% or greater at their baseline measure will be eligible for the study based on evidence that postmenopausal women with elevated density scores have more than a doubling in their risk of breast cancer compared to women with predominantly fatty breasts or breasts with only scattered fibroglandular tissue. Specifically, subjects (50% on aromatase inhibitors) that meet study eligibility will be randomized 1:1 to each intervention, sulindac or no treatment control arms, using stratified permuted block randomization with aromatase inhibitor treatment (yes vs no) and study sites as a stratification factors and block sizes 4, 6, 8 and start intervention.

5.3.1 Number of Participants

The total number of participants expected is 150 with ~50% on aromatase inhibitors. The total number to screen to achieve the 150 is estimated at 340 based on the recently completed study of the same dose and duration of sulindac in a similar target population.

5.3.2 Eligibility Criteria

To be eligible for the study, all the following inclusion criteria must be met:

- 1) Age ≤ 70 years
- 2) Subject must be postmenopausal.

Note: Postmenopausal is defined according to the National Comprehensive Cancer Network (NCCN) guidelines:

- Prior bilateral oophorectomy
- ≥ 60 years
- if age < 60 years, must be amenorrheic for 12 or more months in the absence of any ovarian suppression therapies or have follicle-stimulating hormone (FSH) and/or plasma estradiol in the postmenopausal range or be receiving ovarian suppression therapy with an LHRH agonist and have a plasma estradiol in the postmenopausal range.

- 3) Must have at least one unaffected normal appearing breast that is free of any malignancy determined by mammogram or MRI within the past 12 months. Unaffected breast is defined as no prior diagnosis of invasive cancer, radiation, or prosthetics. Prior (excisional) biopsies with no diagnosis of invasive cancer are acceptable.
- 4) Must have breast density defined as *heterogeneously dense* or *dense* (incl. *extremely* or *mostly dense*) within 12 months of randomization. Women with density described as *scattered fibroglandular density* are eligible if they have a minimum percent breast density of 10% measured within 12 months prior to randomization. See section 6.3.3 Screening for instructions on how to determine % breast density.
- 5) Must be at elevated risk for developing breast cancer.

Definition for being at elevated risk for developing breast cancer includes any ONE or more of the following:

- a. Prior biopsy w/ atypical hyperplasia, lobular cancer in situ (LCIS), ductal carcinoma in situ (DCIS), or invasive cancer. For patients who have received therapy for early-stage disease, at least 1 months must have elapsed since prior surgery, chemotherapy, and/or radiotherapy to affected breast.
- b. Known genetic predisposition to breast cancer (e.g., BRCA1, BRCA2, TP53, PTEN, CHEK2, PALB2 or other gene mutation) with at least one intact breast and not considering prophylactic mastectomy within the next 12 months
- c. A 5-year risk of developing breast cancer is 1.7% or greater based on either:

- (i) the Gail Model (<https://bcrisktool.cancer.gov/>), OR

- (ii) 5-year BC Surveillance Consortium Risk V2 (<https://tools.bccsc-scc.org/BC5yearRisk/calculator.htm>) (considers breast density), AND
- (iii) she has a life expectancy of at least 10 years. (This meets the criteria established NCCN Guidelines Version 1.2019 for breast cancer risk reduction in the woman that desires risk-reducing therapy that includes but is not limited to considering chemoprevention or participating in a clinical trial.)
- d. Family history consistent with hereditary breast cancer. This is defined using the NCCN Guidelines Version 2.2015 and includes both moderate and high-risk breast cancer gene carriers. Patients are eligible for being at elevated risk if the answer to any one or more of the following is yes:
- I. Two or more breast cancer diagnoses in a single-family member at any age
 - II. Two or more family members on the same side of the family with breast cancer (maternal or paternal) at any age and either gender
 - III. One or more family members with a history of invasive ovarian cancer
 - IV. First- or second-degree relative with breast cancer ≤ 50 years.
 - V. Personal and/or family history of three or more of the following diagnosed at 50 or younger: pancreatic cancer, breast cancer, prostate cancer (Gleason > 7 or metastatic), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer.
- 6) (Recommended but optional) A negative fecal occult blood test, if the participant completed one at screening.
 - 7) Serum creatinine $<$ upper limit of normal (ULN) or creatinine clearance > 60 mL/min.
 - 8) Serum ALT and AST $\leq 2 \times$ ULN
 - 9) A willingness to follow the study protocol, as indicated by provision of informed consent to participate.
 - 10) A willingness to avoid taking NSAIDs outside of the trial (rare NSAID use for musculoskeletal symptoms, flu, fever acceptable).
 - 11) Use of aromatase inhibitors is allowed. Participants taking aromatase inhibitors must plan to continue taking them for the duration of the study.

Participants will be **excluded** for participating for the following reasons.

- 1) Daily aspirin or other daily NSAID use (any dose) for any reason.
- 2) Known intolerance to NSAIDs.
- 3) Use of any selective estrogen receptor modulator therapy (e.g., tamoxifen, raloxifene) within past 3 months

- 4) Chronic uncontrolled GERD (reflux disease or heartburn) or any history of gastrointestinal (GI) bleeding and/or peptic ulcer disease (PUD) in the last 5 years.
- 5) History of bleeding disorder or current use of anti-coagulation or anti-platelet medication including aspirin 81 mg.
- 6) History of cardiovascular disease including myocardial infarction, angina, transient ischemic attack, or stroke.
- 7) Diabetes requiring insulin therapy.
- 8) Current regular tobacco smoker.
- 9) History of severe claustrophobia or inability to undergo imaging in a closed MRI.
- 10) Presence of electrically, magnetically, or mechanically activated implants including cardiac pacemaker, cochlear implants, magnetic surgical clips or prostheses that would preclude MRI.
- 11) Uncontrolled hypertension. See section 6.3.3 Screening for definitions and blood pressure requirements. Blood pressure values at screening will be documented in the Vital Signs log.
- 12) Participant is actively receiving oral and patch hormone replacement therapy and/or anti-cancer treatment (including but not limited to abemaciclib, ribociclib, olaparib, niraparib, rucaparib, trastuzumab, etc.), except for aromatase inhibitors and bone targeted therapy.

6 - Methods

6.1 Treatment - Drug

6.1.1 Identity of Investigational Product/New Drug

The active study agent to be investigated is the FDA approved drug sulindac (also marketed as ClinorilTM). Sulindac and its matching placebo will be given orally at 150 mg twice a day. Sulindac and its matching placebo will be provided by Catalent. The active agent sulindac will be commercially sourced as generic (NDC#42806-018-05) from an approved manufacturer and packaged in bottles. The matching placebo (not identical as per FDA requirements) will be manufactured and packaged by Catalent in bottles to match the active study agent.

Physical and Chemical Characteristics

Active Agent.

Sulindac is a non-steroidal, anti-inflammatory indene derivative designated chemically as (Z)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl] methylene]-1H-indene-3-acetic acid. It is not a salicylate, pyrazolone or propionic acid derivative (Figure 2). It has a molecular weight of 356.42 and is a yellow crystalline compound which is a weak organic acid practically insoluble in water below pH 4.5 but very soluble as the sodium salt or in buffers of pH 6 or higher. Sulindac is available in 150 mg and 200 mg tablets for oral administration.

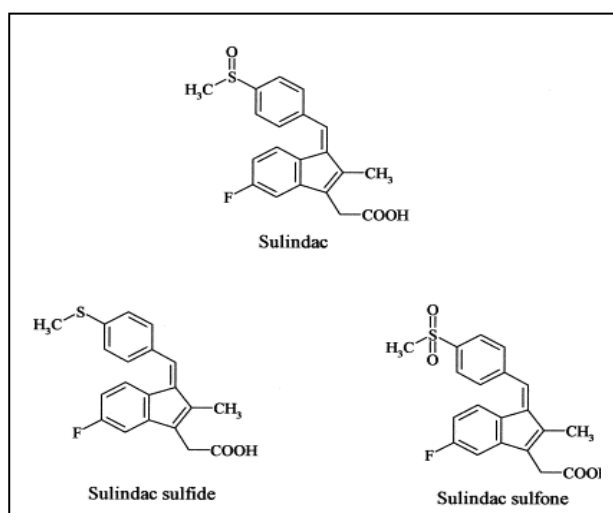


Figure 2. Structural Formulas for sulindac and its metabolites in man

Pharmacokinetics

Absorption: Immediate, rapid and ~90% absorbed from gastrointestinal tract. With the twice-a-day dosage regimen, plasma concentrations of sulindac and its two metabolites accumulate: mean concentration over a dosage interval at steady state relative to the first dose averages 1.5 and 2.5 times higher, respectively, for sulindac and its active sulfide metabolite.

Distribution: Widely distributed to all tissues and fluids in the body including the central nervous system (CNS) and breast milk and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart and lungs.

Metabolism: Hepatic metabolism is an important elimination pathway. Sulindac undergoes two major biotransformations of its sulfoxide moiety: oxidation to the inactive sulfone and reduction to the pharmacologically active sulfide. The latter is readily reversible in man. These metabolites are present as unchanged compounds in plasma and principally as glucuronide conjugates in human urine and bile.

Excretion: Approximately 50% of the administered dose of sulindac is excreted in the urine with the conjugated sulfone metabolite accounting for the major portion. Approximately 25% is found in the feces, primarily as the sulfone and sulfide metabolites.

T_{1/2}: The mean effective half-life (T_{1/2}) is 7.8 and 16.4 hours, respectively, for sulindac and its active sulfide metabolite.

Placebo

The placebo is formulated as lactose (48%), microcrystalline cellulose (48%), sodium crosscarmellose (3%) and magnesium stearate (1%), plus colorant (< 1%).

6.1.2 Dosage, Admin, Schedule (if applicable)

For the planned study, sulindac and a matching placebo tablet will be formulated as the 150 mg dose of sulindac per tablet for oral dosing. Study participants will be instructed to take one tablet in the morning with a meal and one tablet in the evening with a meal. Participants may also choose to start the study drug/placebo at once-a-day dose (150 mg QD), and increase to twice a day (150 mg BID), if tolerated, after 1-2 weeks. All study participants will be instructed to avoid reclining for one hour after taking study medication to reduce the incidence of gastrointestinal upset.

Dose reductions from two pills per day (150 mg BID) to one pill per day (150 mg QD), and vice versa dose increases from QD to BID, will be allowed for suspected toxicity and/or initial ramp-up. If dose reduction below 150 mg QD is required, protocol therapy will be permanently discontinued and the participant will remain on study for the duration of the follow-up and complete the remainder of the assessment, as intent-to-treat. All changes to daily dosage must be recorded in the research records regardless of the reason. When possible, the original dose, date of dosage change, final dosage, and any other pertinent information must be documented.

If a participant's blood pressure rises above 160/90, either self-reported, or recorded at study visits, they will be provided an in-home blood pressure monitors and asked to record her blood pressure at three times points each day over the subsequent 2 days. If a study participant exhibits persistent elevation in blood pressure with in-home measures during the treatment phase, study drug will be stopped, and the subject asked to see her primary care or study physician prior to study continuation. Study drug can be restarted at full or dose-reduced after blood pressure control is achieved on recommendation of the treating physician.

6.1.3 Method of Assignment/Randomization

Dr. Jie Yang, Lead Study Biostatistician, or her designees will be responsible for subject randomization. Subjects will be randomized 1:1 to each arm using stratified permuted block randomization with AI treatment (yes vs no) and study site as stratification factors and block sizes 4, 6, 8. Following randomization, the blinded assignment (Arm A or B) for each individual participant will be sent to the research pharmacists at both study sites, the protocol manager at the lead site, and the delegated biostatistician(s).

6.1.4 Blinding and Procedures for Unblinding (if applicable)

Blinding Procedures.

This is a double-blinded study. For this study, sulindac and its matching placebo (formulated and tooled to resemble the active agent) will be blinded in the labeling process of the pill bottles as study agent A or B by the manufacturer on direction from the study Biostatistician. The code for unblinding will be held by Drs. Jie Yang and her deputies (data analyst). *Note: The matching placebo tablet is not 'identical' to the active agent as per FDA requirements.* The study biostatistician and data analyst will be aware of tablet level tooling differences between active agent and placebo.

Unblinding Procedures. For this document, "unblinding" means revealing the arm to which an individual participant has been assigned. This is divided into full and individual unblinding procedures.

Full Unblinding

It is expected that all participants will be unblinded simultaneously at the completion of the study when the data are complete. As there are no preplanned interim analyses with stopping rules, there is no preplanned full unblinding triggered by findings of an interim analysis.

Note: For Data Safety and Monitoring Committees, all data prepared by the study biostatistician and data analyst for the Cancer Center Data and Safety Monitoring Board (DSMB) will be unblinded for their review in a closed session for which study investigators and staff are excluded. As such, full unblinding may occur if either the DSMB recommend stopping the study for safety concerns.

Individual Participant Unblinding

Unblinding at the individual patient level may occur during the conduct of the trial to:

- a) make clinical treatment decisions
- b) due to an unexpected serious adverse event (i.e., urgent unblinding due to medical emergency)
- c) At the request of the Data Safety Monitoring Board

Most medical emergencies and events attributed to sulindac therapy can be adequately managed without knowledge of the treatment arm. However, in the event that the need arises to unblind for a medical emergency (e.g., life-threatening, unexpected adverse event

that is at least possibly related to sulindac and for which unblinding would influence treatment decisions, medication error such as an accidental overdose), the study participant, family member or treating physician should contact the unblinded individuals listed above at the site at which they were recruited. To insure rapid access to study assignment for urgent unblinding, study Biostatistician and data analyst will hold the blind information and be assigned as emergency contacts for blind information to the study staff and study investigators. The Data and Safety Monitoring Committees will be notified in the event of any individual participant unblinding as to cause, result and event outcome.

6.1.5 Packaging/Labelling

Study agent (sulindac and matching placebo) will be packaged in a light resistant container (100 pills per bottle) with a child-resistant closure. Study agent will be labeled with study blind as A or B designated by the study statistician Dr. Jie Yang.

6.1.6 Storage Conditions

Study agent will be stored between 20 and 25°C (68 to 77°F) as per manufacturer recommendation in a locked cabinet located in Research Pharmacy. Sulindac as the active agent is stable at these conditions for 3 years. Any drug remaining after expiration date will be destroyed.

6.1.7 Concomitant therapy

1. **Non-protocol use of aspirin or other NSAIDs is discouraged throughout the duration of the study.** Use of acetaminophen for treatment of aches, pains, and fevers will be permitted.

During the washout period, occasional use of NSAID or aspirin is allowable for up to a total of 5 days but not within the last week of the washout period. Use of more than 5 days during the washout period and use within the last week will result in removal from the study.

During the intervention period, in the event that a study subject needs to take an NSAID or aspirin temporarily for a medical reason (e.g., flu, fever, muscle strain), the subject will be allowed to stop study agent and take an NSAID or aspirin for up to 14 consecutive days and not to exceed a total of 30 days during the entire study period. Non-protocol use of these medications during the intervention period will not result in removal from study unless they exceed 30 days but must be noted on concomitant medication form.

2. **Proton pump inhibitors (PPIs) may be used at the discretion of the treating study physician.**
3. **Only aromatase inhibitor therapy is allowed as endocrine therapy on study with the agent determined by the treating physician.** The length of use and type of aromatase inhibitor will be recorded. For participants on aromatase inhibitor therapy, it is expected that participants will remain on an aromatase inhibitor throughout the duration of the study as medically indicated. However, stopping of the

aromatase inhibitor will not result in removal from the study. Aromatase inhibitor therapy will be documented on the concomitant medication form.

4. **Patients should receive full supportive care while on study.** Any concomitant medications received from the first day of study treatment administered until 30 days after the final dose will be recorded.

6.1.8 Restrictions

Drug Interactions

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Concomitant administration of NSAIDs and aspirin may lead to increased bleeding or decreased renal function and will be avoided.

ACE-inhibitors or angiotensin II antagonists. NSAIDs, including sulindac, may decrease the effectiveness of ACE-inhibitors or angiotensin II antagonists. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy. NSAIDs, including sulindac should not be given in patients **with compromised renal function** as use in combination with ACE-inhibitor or angiotensin II antagonists may lead to further deterioration of renal function even acute renal failure that is usually reversible on cessation of drug.

Oral anti-coagulants. Sulindac at a dose of 400 mg daily (higher than the planned 300 mg daily) have shown no clinically significant interaction with oral anticoagulants. However, the effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. If participants on study require initiation of an oral anticoagulation therapy, they will be removed from study.

Holding study drug for surgical procedures. Since sulindac can be associated with an increased risk of post-operative bleeding, some surgical procedures require stopping all NSAID use before and after a procedure. If the treating physician or surgeon determines that NSAIDs would be held for a procedure as standard practice, then the study drug should be held for the same period of time. For the purpose of the research breast biopsy, participants may start the study drug 2 days after the first baseline biopsy and stop it 5 days prior to their on-treatment biopsy and restart 2 days later. The total period that the study drug can be held due to surgical procedures, or other medically-related reason, should not exceed 45 consecutive days.

6.2 Assessments

6.2.1 Efficacy

This is a biomarker based clinical study. The primary measure of efficacy in this study is defined as a decrease in breast density in the sulindac arm compared to the placebo arm. Breast density and change in breast density in this study is determined using a non-contrast magnetic resonance imaging method designated MRD that has been developed and validated by our group (55).

All subjects will undergo breast imaging by noncontrast MRI to obtain MRD and R2* maps (used in exploratory analyses of sulindac effect on breast adipose tissue) at 0, 6, and 12 months. All imaging procedures will adhere to FDA and OSHA guidelines.

The MRI pulse sequences used in this study are all FDA-cleared and operating under FDA limits.

6.2.2 Safety/Pregnancy-related policy

All participants in the planned study will be postmenopausal and not childbearing.

6.2.2.1 Adverse Events, Serious Adverse Events: Definitions and Reporting

An adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product irrespective of a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether related to the medicinal (investigational) product.

Any and all adverse events will be recorded on adverse events record form and reviewed by the Principal Investigator.

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf) and will address:

1. Grade
2. Relationship to study drug (not related, unlikely, possible, probable, definitely)
3. Causality other than study drug (disease related, concomitant medication related, inter-current illness, other)
4. Date of onset, date of resolution
5. Frequency of event (single, intermittent, continuous)
6. Event outcome (resolved, ongoing, death)
7. Action taken (none, held, dose reduced, discontinued, medication given)

All adverse events will be documented beginning on the start date of study treatment and continue up to one month following the last dose of study agent.

All adverse events will be documented in the electronic study database provided in REDCap. Access to REDCap can be requested at the link below, entering the email of the Protocol Manager indicated on the cover page of this protocol as *Account Sponsor at SBM*.

<https://redcap.stonybrookmedicine.edu/surveys/?s=WWKDRXWTXX>

Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

1. Results in death.
2. Is life-threatening.
3. Requires in-patient hospitalization for >24h, or prolongation of an existing hospital stay;
4. Results in persistent disability or significant disability/incapacity, or:
5. Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events will be documented beginning on the start date of study treatment and continue up to one month following the last dose of study agent.

All serious adverse events, regardless of attribution, and any deaths will be reported to the lead site within 24 hours of the study team becoming aware of the event, as follows:

- 1) Complete “*Appendix 1. UAPs and SAEs*” and email it to both the lead site PI and Protocol Manager, AND
- 2) Enter the SAE details in the Subject Console in Oncore.

Any updates will be promptly provided to the lead site in the same way.

SAEs will be reported to sites’ IRBs as applicable per local requirements.

6.2.3 Pharmacokinetics (if applicable)

Not applicable

6.2.4 Biomarkers (if applicable)

Methods for tissue biomarker measurement for planned secondary study endpoints for effects of sulindac on breast tissue biomarkers.

We estimated that 60% of subjects (n = 45 per arm) will consent to serial core biopsy procedures of the contralateral, unaffected breast at baseline and 6 months, allowing us to explore the effect of sulindac on molecular and cellular biomarkers in normal tissue. These estimates are based on the participation rates in our previous study.

Second Harmonic Generation Microscopy of breast tissue from core biopsy

Breast Density (BD) is an image feature that correlates with tissue stroma, which is comprised of extracellular matrix (ECM) proteins including a predominant contribution from fibrillary collagens. (57)(54) While still a relatively new area of investigation and to date studied near exclusively in relation to tumors and risk of relapse, second harmonic generation (SHG) microscopy have enabled advanced image analysis of collagen 'architecture' ex vivo using tissue sections. (51)(52) SHG occurs when the laser field undergoes a nonlinear, second-order polarization on passing through noncentrosymmetric ordered structures like fibrillary collagen. SHG is currently being applied to breast, ovarian, prostate and other cancer tissues where fiber orientation, including more aligned collagen orientation or 'straightness', is emerging as a feature of the invasive phenotype. Using this technique, bundles of straightened and aligned collagen oriented perpendicular to the breast

tumor boundary has emerged as a poor prognostic factor. (53)(52) COX2 has been shown to promote collagen deposition, a denser appearing tissue and mammary tumor development in mouse models. (44)

Using this approach, we will obtain a distribution (histogram) of 'straight' fibers in 5 randomly selected areas of the tissue with ≥ 100 fibers per area. Random areas of the tissue will be imaged blinded to pre/post intervention and BD status on a Zeiss LSM 510 META NLO Two-Photon laser scanning confocal microscope system and processed using the computer-assisted image feature extraction software, CT-FIRE.(52) CT-FIRE allows us to extract tissue fiber information from an image using an automated tracking algorithm that enables collagen fibers to be characterized as wavy or straight on fiber length, angle and position. Using this approach, we will analyze the distribution (i.e., histogram) of collagen features including straightness, width, length and angel. Straightness of individual fibers are calculated as the linear length of a fiber divided by the distance along the fiber and ranges from 0 to 1 (1 being linear across the entire fiber length versus no linear features or 0).

Whole slide matrix assisted laser desorption mass spectrometry of breast tissue

To gain further insight on the proteins or group of proteins that may change in breast tissue in response to sulindac, we established a collaboration with Drs. Peggi Angel and Rick Drake at the Medical University of South Carolina (Co-Investigators) for whole slide MALDI-based proteomics for studies of the collagenome and glycoproteome. We believe a proteomic approach is critical to gaining insights on the biological effects of sulindac on breast ECM proteins. Drs. Angel and Drake study stromal proteins of BC with evidence that specific stromal peptides cluster according to pre-cancer progression and distinguish between stages of BC (*unpublished data*).

MALDI-IMS is a mature technology with applications to understanding pathological changes in clinical specimens. (58) (59) The state-of-the-art MALDI IMS utilizes robotic sprayers to reproducibly apply thin molecular films of enzymes and matrix onto tissue sections for MS analyses. After imaging, tissues will be stained by H&E for co-registration of peptides to tissue architecture. MALDI-IMS has several advantages: *a priori* information on the distinct protein *is not required*, it is high throughput and it allows a high level of multiplexing with several hundred analyte peaks per pixel. (60) This is highly **useful for discovery efforts of drug effects in rare tissues as is the case with our core biopsy specimens**.

In collaboration with Drs. Drake and Angel, MALDI IMS will map the N-glycome and ECM proteome from our study biopsies. (61) (62) (60) The 2D imaging is done using a MALDI source coupled to a Fourier transform ion cyclotron resonance (FT-ICR) imaging mass spectrometer (7 Tesla Solarix Legacy, Bruker) with high resolution/high mass accuracy peak reporting. The instrument is equipped with a Gaussian shaped beam Nd:YAG laser capable of probing the tissue at a $<15 \mu\text{m}$ spot size (~ 1.5 cells, assuming a cellular diameter of an activated fibroblast of $10 \mu\text{m}$). Typically, one imaging experiment reports >150 N-glycan distributions and $>4,500$ ECM peptide distributions from a single tissue section.

Multiplex Immunofluorescence and histochemistry (IHC) for measures of breast tissue associated macrophages. Inflammation in breast adipose, including upregulation of

aromatase expression, has emerged in recent years as a contributing factor in BC and is hypothesized as an explanation for the link between obesity and BC post menopause when BD declines. (63)(64) In addition to the promising findings for sulindac effects on ECM, we recently observed an effect of sulindac on breast adipose by MRI that is independent of its effects on BD. Our interest in investigating MR methods to assess sulindac effects on breast adipose were motivated by the report that repression and knockout of CD36, a transmembrane receptor important in adipocyte function promoted a stromal matrix that mimics mammographically dense tissue and desmoplastic changes in vitro and in mouse studies. (65) CD36 is downregulated by PGE₂ and upregulated by PPAR- γ for which modulating effects of ASA (66) and other NSAIDs are known. In a pilot study, we found that sulindac in the MMTV mouse model of BC significantly increases the proportion of adipocytes staining 2+ and 3+ on CD36 immunohistochemistry in mammary gland compared to untreated controls ($p < 0.05$). In pursuing this line of thinking for application to our clinical trial, we discovered a significant increase in MR derived R2* signal in breast adipose in the sulindac group (mean change_{0 to 12 months} = 1.209 [sd 1.175], $p = 0.007$) not present in observation group (mean change_{0 to 12 months} = 0.273 [sd=1.672], $p = 0.414$). Most striking was 10 of the 11 available sulindac subjects in our feasibility study for this measure showed an increase whereas 26 subjects in observation showed changes equally in both directions (up and down). R2* is a reciprocal measure of the relaxation time MR technique T2* and has been most correlated with iron content in liver though the tissue features that give rise to the signal are not entirely understood.(67) (68) (69) (70) Currently, our results are highly phenomenological and preliminary. The cause and relevance of sulindac associated increases in R2* in breast adipose are not known but the near uniform increase in the sulindac participants is intriguing. Among the most plausible explanations for the signal is a change in iron levels. Iron levels in adipose tissue and adipocyte-associated macrophages are important for adipocyte function and health. (Hill, Bolus et al. 2014) Deregulated iron handling in fat mass is suspected to causally contribute to inflammation including increase in PGE₂ in adipose. Recent work demonstrating that the polarization status of adipose-associated macrophages is a critical determinant of iron handling in tissues. M2 macrophages (CD68+, CD206+, CD163+) have been shown to express iron binding receptors (e.g., transferrin receptor) and recycle 10-fold greater iron loads than absorbed from the duodenum. (71) Iron-handling M2 macrophages in adipose tissue are postulated to play a critical role in iron homeostasis in adipose tissue that include anti-inflammatory and pro-metabolic effects. Importantly, M2 macrophages decrease in adipose tissue in the obese concurrent with increases in M1 pro-inflammatory macrophages. (72)

Based on this current knowledge with evidence for adipose inflammation as a potential pro-tumor factor in BC, we propose to explore the novel hypothesis that the increased R2* signal with sulindac correlates with an increase in numbers of the M2 type macrophage in breast adipose tissue. This mechanism is consistent with known immune modulating effect of sulindac on M2 macrophages including those discussed earlier as preventing 4T1 tumor metastasis in immune intact mice. Specifically, in addition to obtaining MRI derived R2* (sequence described above in *Methods for Breast Imaging*), we will conduct multiplex immunofluorescence characterization of breast tissue macrophages (whole and adipose) to

enumerate change in the number of triple positive CD68+, CD163+, CD206+ macrophages in breast biopsy samples to All CD68+ macrophages, within and between treatment arms and in relation to R2* pre and post intervention. We will also investigate sulindac effects on CD36+ in the biopsy. Briefly (*exploratory aims*), for these studies we will validate antibodies against human CD36, CD68, CD163 and CD206 on negative and positive controls and then quantify their expression in pre and post intervention breast biopsy samples processed specifically to retain adipocytes (modified, less harsh antigen retrieval) using Perkin Elmers 3 Plex OPAL kit and multispectral microscopy imaging and whole slide scanning or equivalent imaging technology. Analyses will be blinded to intervention with a minimum of 10% replicates using specimens with greater amounts of tissue. Image analysis and quantification will be conducted using ImageJ64 software or equivalent. (73)

Urine and blood biomarkers measures of sulindac action. NSAIDs are highly efficacious for the management of musculoskeletal pain associated with prostaglandin (PG)-mediated inflammation. NSAIDs act by blocking cyclooxygenase (COX)-1 and -2 enzymes metabolism of arachidonic acid (AA) to the PGs. In addition to the well-known COX-mediated metabolism, AA and other unsaturated fatty acids (Ω -6 and Ω -3) are also metabolized by two other enzyme families: the lipoxygenases (LOX) and members of the cytochrome P450 (CYP450) enzyme family. Collectively, these Ω -6 and Ω -3 can be metabolized to over 100 metabolites known as 'oxylipins'. Oxylipins exhibit a wide spectrum of biological activity including pro- and anti-inflammatory effects as well as anti-tumor activity and acting as inducers and inhibitors of pain depending on the enzymes activated and availability of substrates.

For all participants, blood and urine will be collected for research purposes at Baseline (or screening for subjects who do not regularly use NSAIDs) and at 6- and 12-month visits. Serum and plasma for study related biomarkers that include sulindac metabolites, prostaglandins and other eicosanoids related to the mechanism of sulindac activity will be collected in a Red top Vacutainer (serum) and a Lavender top EDTA Vacutainer (plasma). Vacutainer tubes are centrifuged in the clinic the same day as collection. All blood specimens are labeled and tracked with a unique sample ID distinct from the study participant ID. Blood and urine samples will be processed to serum and plasma within 2 hours from collection, then aliquoted and stored at -80°C in the Cancer Center Biobank. Aliquots collected at either research site may be batch shipped for analysis to the laboratory of Dr. Patricia Thompson at University of Arizona, Tucson, AZ, under a material transfer agreement.

Optional banking of specimens for future use. For all participants, blood and urine will be collected for research purposes at Baseline and at 6- and 12-month visits. Serum and plasma for study related biomarkers that include sulindac metabolites, prostaglandins and other eicosanoids related to the mechanism of sulindac activity will be collected in a Red top Vacutainer (serum) and a Lavender top EDTA Vacutainer (plasma). Vacutainer tubes are centrifuged in the clinic the same day as collection. All blood specimens are labeled and tracked with a unique sample ID distinct from the study participant ID. The code linking the sample ID to the participant IDs is stored with the samples managers. Corresponding

specimen IDs for each participant's samples will be entered in the database. Blood samples will be processed to serum and plasma by the Cancer Center Biobank and batch for storage in aliquots at -80oC for future analysis. Aliquots collected at either research site (Stony Brook University and/or Cedars Sinai) may be batch shipped for analysis to the laboratory of Dr. Patricia Thompson at University of Arizona, Tucson, AZ, under a material transfer agreement.

In addition to the prespecified biomarker measures, patients will be asking whether they wish to consent to the use of their leftover blood, urine and breast tissue samples for banking for future studies. It is anticipated that over the course of the study new findings related to circulating biomarkers may arise that if measured would provide additional insights on the effect of sulindac on not only breast density but also on pain and physical function of relevance to the study population. Patients will be consented for the use of serum, plasma and urine for future studies specific to the effect of sulindac on circulating biomarkers of inflammation modulation. All participants will be informed that participation in the banking of any sample for future studies is optional and that they may withdraw their samples at any time.

6.3 Study Procedures

6.3.1 Study Schedule and Procedures

A total of 150 postmenopausal participants will be consented with an expectation that a minimum of 135 participants will be randomized to receive study agent for a period of 6 months and 120 for a period of 12 months.

Following consent, potential participants will be screened for eligibility at a screening visit (Visit 1). Eligible participants who were regularly taking NSAIDs for any reason (except for low dose aspirin) in the 30 days prior to the consent date, will complete a 30 day (not to exceed 60 day) run in period that includes abstaining from any use of aspirin or other non-aspirin NSAIDs. Eligible participants who were not taking NSAIDs prior to consent do not need to complete a washout. Newly consented participants in screening can be instructed to commence study procedures, including a washout period at a later time, in agreement with the study doctor. After completing washout, participants will undergo a baseline visit (Visit 2) with baseline procedures detailed below. After completing their baseline visit, all participants will start study agent with on agent clinic visits at 6 months (Visit 3) and 12 months (Visit 4) with procedures detailed below. After completing the 12-month intervention phase, all study participants will receive a follow-up phone call approximately 30 days after stopping the study agent. Subjects can request optional unscheduled visits more frequently during the first 6 months of the study.

Visit 1 - Screening for Eligibility Visit

The following events will occur at screening:

1. **Medical history** including demographics (race, ethnicity, age, etc.)
2. Review **concomitant medication** and supplement use in the past 30 days

3. **Vital signs** (blood pressure, temperature, pulse). To account for white coat syndrome, any subject observed to have a BP > 160/90 will be provided an in-home blood pressure monitor and asked to record her blood pressure at three times points over the subsequent 2 days. The study nurse will contact the subject and record the readings. If the study subject has persistently elevated blood pressure during screening for enrollment with in-home monitoring, the subject will not be eligible.
4. **Height and weight**
5. **Hematology** (CBC/differential) (results obtained up to 6 months prior to study initiation are valid for eligibility)
6. **Chemistry** panel (to include urea nitrogen, creatinine, ALT, AST) (results obtained up to 6 months prior to study initiation are valid for eligibility)
7. **Fecal sample for occult blood test** (optional, results obtained up to 6 months prior to study initiation are valid for eligibility, if participant completed this test during screening)
8. **Urine and Blood Sample Collection for Research** (Biomarker Measures): blood (one tube for serum and one for plasma) and as much as 100 ml of urine will be collected at the beginning of the study. To minimize phlebotomy events, samples may be collected at screening when prospective subjects do not regularly use NSAIDs (*i.e.*, NSAID use not to exceed one day per week in the preceding 4 weeks). For all other subjects, and in case it was not possible to collect them at screening, these samples can be collected at baseline, after the initial washout. See section 6.2.4 Biomarkers for details on blood and urine samples collection, processing, and submission.

Visit 2 - Baseline Visit (Occurs after at least 30 days of NSAID washout, + 30 days for participants who were taking NSAIDs regularly before consent)

The following events will occur at the baseline visit:

1. **Breast Imaging by MRI (required)** Subjects will be asked to undergo Magnetic Resonance breast imaging at baseline, 6 and 12 months. The procedure will last up to 45' in a closed MRI machine in prone position and does not require contrast agent or exposure to radiation.
2. **Breast Biopsy (Optional).** All participants will be asked to provide an optional core biopsy sample at their baseline visit. For participants who consent to breast biopsy at baseline, the breast specialist at each research site (radiologist or surgeon), as a fee for service, will use any radiologic method (including, but not limited to, mammography or MRI images, ultrasound etc.) to identify two areas of increased density, located at least 2 cm apart, in the upper, outer quadrant of the contralateral (uninvolved) breast. If no imaging is available or conclusive, the radiologist should biopsy the upper outer quadrant. Dense areas will be co-localized with ultrasound guidance, with their relative positions recorded by clock-face and linear distance away from the nipple. Under ultrasound guidance, a 14-gauge cutting needle will be used to obtain up to 8 tissue cores from one of the two identified high-density areas.

Since 5-10 tissue cores are typically obtained during clinically indicated biopsy procedures, our tissue sampling protocol should not impose undue participant burden or risk. Representative FFPE (formalin fixed and paraffin embedded) specimens will be reviewed at Stony Brook University by pathology under the direction of Dr. Ken Shroyer, a board-certified anatomical pathologist who specializes in breast pathology. Additional cores will be processed by Dr. Thompson's laboratory at University of Arizona, Tuscon, AZ, for evaluation of apoptotic, proliferation, and additional biomarkers.

3. **Study Medication.** Study medications will be distributed in bottles of 100 pills per bottle and each participant will receive a 6-month supply at two distributions (baseline and 6 months). Participants may also choose to start the study drug/placebo at once-a-day dose (150 mg QD), and increase to twice a day (150 mg BID), if tolerated, after 1-2 weeks. Changes in study drug dosage will be documented in the research records.
4. **Measures of pain and quality of life in clinical trials.** Results from our recently completed single arm study of sulindac in breast cancer patients on adjuvant aromatase inhibitor therapy support a positive effect of sulindac on more significant pain, physical function, and overall quality of life. As such, all participants will be asked to complete the Brief Pain Inventory Short Form (BPI-SF), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Functional Assessment of Cancer Therapy: General (FACT-G) questionnaires at baseline, 6 and 12 months (copy of instruments provided in Appendix).
5. **FACT-G.** The FACT-G is a validated general quality of life instrument intended for use with a variety of chronic illness conditions. Originally validated in a general cancer population. The core instrument is based on the validated Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, a system which has multiple disease-, treatment-, and condition-specific subscales to complement the FACT-G. The FACT-G contains 4 domains (physical, social/family, emotional and functional well-being) with 27 items. The time to complete is approximately 5 minutes.
6. **BPI-SF.** The Brief Pain Inventory (BPI) was designed and validated to rapidly assess the severity of pain and its impact on functioning in the individual (Cleeland and Ryan 1994, Keller, Bann et al. 2004, Mendoza, Mayne et al. 2006, Dworkin, Turk et al. 2010). The Short Form is the most widely used in clinical trials. The BPI-SF is a one-page form that provides patients with simple language with which to communicate about their pain using a simple numeric rating system. The BPI-SF asks patients to rate their pain at its worst, least, and average during the past 24 hours with each item rated on a 0-10 scale, with 0 indicating 'no pain' and 10 indicating 'pain as bad as you can imagine' (copy of instrument is provided in Appendix 1). The BPI-SF also rates, for exploratory analyses, how much the pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a scale of 0 to 10, with 0 indicating 'does not interfere' and 10 indicating 'completely

interferes'. The primary pain-related endpoint for our study will be 12-month change in the past 24 hours' worst pain score. Past 24 hours' average and past 24 hours' least pain scores will be included as secondary pain-related study endpoints.

7. **WOMAC Questionnaire based measures of pain, stiffness and physical function.** The WOMAC, a 24-item instrument developed to assess pain, stiffness, and physical function in participants with hip and/or knee osteoarthritis (Wolfe and Kong 1999). This instrument is well validated (Wolfe and Kong 1999) and has been modified from its original form and used extensively to examine specific joint pain changes following treatment, including drug-based interventions for back pain, rheumatoid arthritis, and fibromyalgia (Rothenfluh, Reedwisch et al. 2008). For our study, we will use the 5-point Likert-type format.
8. If not collected at screening, **Urine and Blood Sample Collection for Research (Biomarker Measures):** blood (one tube for serum and one for plasma) and as much as 100 ml of urine will be collected at this time point from all other subjects (i.e. those who were regular NSAID users at the time of screening (i.e. NSAID use exceeded one day per week in the preceding 4 weeks), or in case samples were not collected at screening for any reason). See section 6.2.4 Biomarkers for details on blood and urine samples collection, processing and submission.

Visits 3 and 4 - On study agent Visits

The following events will occur at 6 and 12 months on study:

1. **Breast Imaging by MRI (6- and 12-month mandatory)** See baseline measures
2. **Breast Biopsy (On treatment biopsy between 6 and 12 months - Optional).** See baseline measures
3. **Review of Adverse Events.** The research nurse will review adverse events with study participants in person at baseline, 6 and 12 months and during phone calls planned at month 1, 2 and 3 and at the end of study (see below). Study participants will also be asked to record any adverse events in a diary and these will be review at each contact time with the research nurse and recorded.
4. **Review concomitant medication and supplement** use for past 6 months. The research nurse will review all concomitant medications at each visit and record any changes.
5. **Vital signs** (blood pressure, temperature, pulse). To account for white coat syndrome, any subject observed to have a blood pressure > 160/90 will be provided an in-home blood pressure monitor and asked to record her blood pressure at three times points over the subsequent 2 days. The study nurse will contact the subject and record the readings. If a study participant exhibits persistent elevation in blood pressure with in-home measures, study drug will be stopped, and the subject asked to see her primary care or study physician prior to study continuation. Study drug can be restarted at full or dose-reduced after blood pressure control is achieved on recommendation of the treating physician.

6. **Height and weight**
7. **Hematology (CBC/differential)**
8. **Chemistry panel** (to include urea nitrogen, creatinine, ALT, and AST)
9. **Study Medication.** At 6 month visit only, new study medications will be distributed in bottles of 90 pills per bottle and each participant will receive a 6 month supply
10. **Unused study medication.** Return any unused or empty pill bottles. Remaining pills will be counted and numbers recorded.
11. **Urine and Blood Sample Collection for Biomarker Measures.** Same as baseline measure at 6 and 12 months.
12. **Measures of pain and quality of life in clinical trials (6 and 12 months).** Same as baseline measure to include the Brief Pain Inventory Short Form (BPI-SF), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Functional Assessment of Cancer Therapy: General (FACT-G) questionnaires at 6 and 12 months.

End of Study Procedures (Phone Call)

End of study procedures will be performed within 28 days of the end of study period. For participants who stop study agent early, they will be encouraged to stay on study for up to 12 months and continue to complete their study visits and study procedures. For those participants who withdraw early from the study, their end of study procedures will be performed within 28 days of study withdrawal.

Following discontinuation of study agent at any point, participants experiencing adverse events will be contacted weekly by telephone or clinic visit until resolution or stabilization of condition. Abnormal laboratory values will be followed until resolution or one month post last dose of study agent(s) whichever occurs first.

Follow up for AE or SAE. All participants will have a follow-up visit or telephone contact scheduled one month after the last dose of study medication/end-of-treatment to follow-up for AEs and SAEs that may have occurred during or after discontinuation from the study. AEs and SAEs that are still ongoing at the time of discontinuation will continue to be followed weekly until resolution or stabilization of condition, or one month post last dose of study drug(s) whichever occurs first. Abnormal laboratory values will be followed every 14 days until resolution or one month post last dose of study drug(s) whichever occurs first.

6.3.2 Informed Consent

Patients referred to the study team at each research site will be consented in a quiet private room. A trained and authorized study team member will explain all aspects of the study in lay language to the potential eligible participants, answer all questions regarding the study, and assess the capacity of potential participants to demonstrate understanding that the activity is research, not standard treatment; the risks and benefits of the study; The alternatives that are available if s/he does not participate; and the decision not to participate will be accepted without jeopardizing clinical care.

If the participant decides to participate in the study, she will be asked to review, sign and date the IRB-approved Informed Consent Form (ICF) and HIPAA authorization form, as applicable for each site. The ICF has to be completed prior to initiating any study related procedures.

6.3.3 Recruitment, Enrollment and Retention

Recruitment and referral sources

Advertisement material: a study-wide tri-fold brochure and a one-page flyer are available for this study. Each site can further develop advertisement or patient-facing material as needed. See section 8.4 for IRB submission procedures of site-specific patients facing material.

Stony Brook University

Stony Brook Cancer Center staff will be responsible for identifying and recruiting candidate participants, evaluating their suitability for participation in the study, following participants during the treatment phase of the trial, monitoring participants for possible toxicity, and continuing to follow participants for subsequent toxicity during the post-treatment follow-up period.

Recruitment will proceed under the auspices of the Cancer Center Clinical Trials Office. Working in accordance with HIPAA regulations, study coordinators or treating medical staff will identify potential participants and they will be screened for eligibility to the study. Recruitment will occur through physician referral at the time of a regular screening, initial consultation or follow up visit at the Carol M. Breast Center, Stony Brook Advanced Imaging or Stony Brook University Cancer Center.

The Breast Team at SBCC is a high performing disease management team that currently provides over 60% of the clinical trial accruals for the cancer center. The Carol M. Baldwin Breast Center sees over 600 new cases of breast cancer per year with the majority being in situ or stage I and thus likely eligible for this study.

In addition, the Carol M Baldwin Center performs over 12,000 screening mammograms a year with the modified Gail score calculated for every patient. Any patient with a >20% lifetime increased risk (double the risk of our target population) is considered high risk and is referred for MRI screening at the center. This is approximately 700 patients per year and will be a target population for accrual to the study in collaboration with our radiology center. In addition, patients receiving screening mammograms at the Baldwin Breast Center may receive a study brochure if their mammogram is negative for a suspicious lesion and shows a density score defined as *heterogeneously dense* or (i.e., *mostly*, or *extremely*) *dense* within 12 months of randomization. Women with percent breast density of 10% or greater at their baseline measure are also eligible regardless of the density score.

Cedars Sinai Medical Center

Staff at the Saul and Joyce Brandman Breast Center and the CTRC staff at the CS site will be responsible for identifying and recruiting candidate participants, evaluating their suitability for participation in the study, following participants during the treatment phase of the trial,

monitoring participants for possible toxicity, and continuing to follow participants for subsequent toxicity during the post-treatment follow-up period.

Recruitment will proceed under the auspices of the Saul and Joyce Brandman Breast Center and CTRC at the CS site. Working in accordance with HIPAA regulations, study coordinators or treating medical staff will identify potential participants and they will be screened for eligibility to the study. Recruitment will occur through physician referral at the time of a regular screening, initial consultation or follow up visit at the respective Breast Center, Advanced Imaging facility or Cancer Center.

The Breast Teams at CS is a high performing disease management team that currently provides the majority of the clinical trial accruals to the respective cancer centers. The Saul and Joyce Brandman Breast Center at Cedars Sinai Medical Center sees over 1000 new cases of breast cancer each year similarly with a majority early stage eligible for this study.

In addition, the S. Mark Taper Foundation Imaging Center performs over 20,000 screening mammograms a year with the modified Gail score calculated for every patient. Any patient with a >20% lifetime increased risk (double the risk of our target population) is considered high risk and is referred for MRI screening at the center. In addition, all patients receiving screening mammograms at the S Mark Taper Foundation Imaging Center will receive a study brochure and short questionnaire in which they may opt in to be contacted by our staff for participation on the study if their mammogram is negative for a suspicious lesion but shows density score defined as *heterogeneously dense* or (ie. *mostly*, or *extremely*) *dense* within 12 months of randomization. Women with percent breast density of 10% or greater at their baseline measure are also eligible regardless of the density score.

- o Enrollment rate (e.g., number of participants meeting eligibility criteria for enrollment per month).

To complete recruitment in year 4, 4 to 5 subjects must be recruited per month. To achieve this, we will need to screen an average of 4-5 subjects/week.

- o Discussion of potential recruitment delays or challenges and alternative strategies that can be implemented if there are enrollment delays or shortfalls.

The study team and the breast multidisciplinary team at the lead site may also review accruals to open clinical trials and issues of slow or low accrual addressed. The study team meets regularly to review accrual and safety. Clinical leads are encouraged to regularly address the study at weekly surgery and oncology breast tumor board. These strategies have been employed successfully and ensure study team personnel (e.g. coordinator) is familiar with clinicians, encourage clinicians to always consider eligibility in a trial of all their patients, and to conduct pre-screening of patient lists by the clinicians. In the event that these are insufficient, eligibility criteria may be reviewed to expand eligible population.

- o Procedures to monitor enrollment and track/retain participants for follow-up assessments.

All consented individuals will be added to the Clinical Trial Management System, using Oncore – PC/CRA console. Participants' details will include medical record numbers, referring physician(s), whether eligibility criteria are met, and the type of contact made with

the patient (e.g. on the phone, in person, via mail etc.) and whether the patient was interested in the study. The coordinator will contact new referrals and potential candidates who have expressed interest in the study and are evaluating the opportunity to enroll. If a patient agrees, the coordinator will also record the reason why an eligible patient may decline participating in the study. Referral rate, accrual numbers and reasons not to enroll (if available) will be discussed during study team meetings. The Cancer Center Clinical Trial Office - Protocol Review and Monitoring Committee (PRMC) also reviews actual vs. expected accrual of each study every six months and issues a warning letter to the PI.

The coordinator furnishes each new enrolled patient with a folder with a copy of the consent, a study schedule, an IRB-stamped "STOP-BC fact-sheet", and his/her phone number. In this way the subject will be able to follow the study duration at a glance. Three weeks ahead of each follow up visit, the coordinator calls the patient and schedules the next appointment. Participants will receive a reminder and any forms needed for the subject to fill out (e.g. MRI safety checklist, questionnaires etc.). At each visit the coordinator explains the study procedures for the next visit and its duration.

To enhance retention on study, a preliminary determination of eligibility will be made through review of medical records and contact with the participating physicians/patients. The research nurse/coordinator and/or treating physician will discuss the study with potential subjects, confirm eligibility, and obtain informed consent from those interested. Eligible subjects who were regularly taking NSAIDs in the 30 days prior to consent (except for low dose aspirin) will enter a 30 days (max. 60 days) washout period during which they will abstain from any aspirin or non-aspirin NSAID use. Immediately before or at baseline, subjects will be randomized to the sulindac or placebo arms. All randomized subjects will receive tablets that are blinded as to their identity.

Our experience with breast cancer trials is that the vast majority of subjects adhere to therapy and cooperate with study procedures if they are appropriately chosen and carefully instructed and motivated. An important first step will be to recruit only subjects who show a strong potential for following the prescribed drug regimen. This assessment will be made by the clinical PI (Dr. Stopeck) and research nurse or study coordinator at the initial patient visit. The NSAID washout phase will permit study staff to judge likely adherence to study agents before randomization. To defray the time, expense, and inconvenience to participants, in-person visits for women being followed for history of breast cancer will be coordinated to occur with their scheduled oncology visits for their breast cancer care or minimally impact the schedules of our high-risk women. Subjects will be asked to report any new symptoms, indicate new or change in concomitant medications, and have their vital signs assessed at each visit. In particular, patients will be evaluated for gastrointestinal symptoms, signs or symptoms of GI bleeding, and elevated blood pressure values.

o Evidence to support the feasibility of enrollment, including prior experience and yield from research efforts using similar referral sources and/or strategies.

Both Drs. Stopeck (Stony Brook University) and Thompson (Cedars Sinai Hospital) have demonstrated experience in recruiting to clinical trials. This is evidenced by the current

clinical study of sulindac in patients on AIs and their prior accomplishments in cancer treatment and chemoprevention clinical trials. While their relocation to Stony Brook University significantly impacted the accrual rate to the current sulindac trial as they restarted the trial and established a new research team, these issues have been resolved and a strong clinical trials-oriented research team is now in place and recruitment has increased steadily over the past several months with the new infrastructure. Important for this study, there is a high level of enthusiasm for the study from our radiology and surgery colleagues who see high-risk patients. This with the expansion of the target population and interest from women in Long Island in breast cancer prevention should facilitate a high recruitment success.

- Strategies to ensure the study population has scientifically appropriate diversity and representativeness.

Stony Brook University

The racial and ethnic breakdown of Long Island by County. Stony Brook University Cancer Center and School of Medicine are located in Northwestern Suffolk approximately 20 miles from Nassau County.

- White: 85.8% Suffolk County, 77.3% Nassau County (New York: 71.2%)
- Black: 8.2% Suffolk, 12.2% Nassau (New York: 17.5%)
- American Indian: 0.6% Suffolk, 0.5% Nassau (New York: 1%)
- Pacific Islander: 0.1% Suffolk, 0.1% Nassau (New York: 0.1%)
- Asian: 3.7% Suffolk, 8.4% Nassau (New York: 8%)
- Hispanic or Latino of any race: 17.3% Suffolk, 15.3% Nassau (New York: 8%)

Long Island is ethnically very diverse with 1 in 5 persons new migrants to the U.S. Individuals of Hispanic ethnicity comprise the largest minority population (~17%) followed by African American (~10%) Population. While breast cancer risk factors are generally lower in new immigrant and Hispanic populations, Stony Brook Breast Cancer Clinics and Clinical Trial Office employ Spanish-speaking nurses and coordinators, which assist with recruitment of eligible patients who are Spanish-speaking to clinical research. All our consenting procedures are offered in English and Spanish, using an IRB-approved Spanish consent form. Use of a Short Form is not allowed for this study. The consenting process for non-English speakers must follow institutional procedures.

Other research sites

Each site will enroll participants consistently with their respective demographics representation. Sites will create study documents in the languages their expected population to be fluent in, including but not limited to English and Spanish.

6.3.4 Removal and withdrawal of subjects from treatment or study

Off Intervention

Participants will be withdrawn from intervention with sulindac/placebo, and will not be replaced, under the following circumstances:

1. Completed the protocol-prescribed intervention
2. Unacceptable adverse event(s), as judged by the study physician, which may be related or unrelated to study drug
3. Inadequate agent supply
4. Initiation of protocol-prohibited medications (e.g., selective estrogen receptor modulators, etc.)
5. Medical contraindication
6. The participant is noncompliant with intervention procedures

Participants who express the intention to start a (new) course of either prohibited medication will be encouraged to complete their participation in the study before starting the medication. See Section 6.1.2 paragraph on dose modification for additional off-treatment criteria.

As described in section 6.3.1, a study team member will follow-up with the participant approximately 30 days after the last day of the intervention with sulindac/placebo to assess symptoms and adverse events, and document concomitant medications and supplements. All other study procedures (MRI, QOL questionnaires, vitals, concomitant medications, research samples and optional biopsy) will continue to be performed at the time points specified in the Schedule of Events, unless study procedures pose a risk to the study participant in the opinion of the investigator.

Off Study

1. Study closure,
2. Participant decision to withdraw from the study or, in the judgment of the investigator, further participation would not be in the best interest of the participant,
3. The participant is noncompliant with study procedures

Patients who decide to prematurely withdraw from the study will be asked to visit the clinic one more time for an optional end of treatment visit and will not be replaced. Procedures to be conducted at this visit will be at the discretion of the principal investigator but should include at a minimum review of all concomitant medications and supplements within the last 30 days, adverse events, and vital signs.

6.4 Statistical Method

6.4.1 Statistical Design

This is an intent-to-treat randomized, placebo controlled and blinded 2-arm phase II biomarker trial to test if sulindac will significantly decrease BD compared to placebo. BD will be measured at baseline, 6 and 12 months.

6.4.2 Sample Size Considerations

Using a linear mixed effect model to analyze our preliminary data for subjects with higher baseline MRD, the estimated percentage change of BD from baseline to month 6 were -7.5% (95% CI: -14.8%, -0.1%) and -1.2% (-8.2%, 5.7%) for sulindac and control groups,

respectively. At month 12, the percent changes are -19.2% (-28.9%, -9.6%) and -5.4% (-14.9%, 4.2%), respectively. The 2-by-2 covariance structure from the fitted model was unstructured with $\sigma_1^2 = 0.0309$, $\sigma_{1,2} = 0.0229$, and $\sigma_2^2 = 0.0538$. The estimated statistical power for testing one primary hypothesis using linear mixed effect model with different sample sizes (N per group=50, 55, 60, 65) are provided in Table 3. Each is estimated based on 2000 simulations. In these simulations, the dependence structure of BD changes were based on those estimated from our interim analysis of our current Trial and the type I error was controlled at 0.05 for testing each primary hypothesis (See *PHS Human Subjects/Clinical Trials Information Section 4.2 Study Design Narrative*). Note, as above, the use of log-transformed baseline BD, should improve the efficiency and thus power for modeling % change in BD directly.

Based on evidence of no significant effect of AI in our study and in previous studies as discussed above, (McTiernan, Wang et al. 2009) the percentage change in BD at month 12 is estimated to decrease between 0% and 7% (conservative). Detection power for comparisons between sulindac and placebo are > 90% with 50 patients per group if the placebo arm has a BD drop < 5% at month 12 and > 80% with more subjects if the drop in the placebo arm is greater. With a starting target enrollment of 150 subjects, we anticipate (conservatively) that 60 and 55 subjects in each group will complete 6 and 12-month measures, respectively. A target of 55 for 12-month completers thus provides a robust sample size target for detecting a similar level of effect in our completed single arm study in the planned placebo-controlled study.

Table 3. Estimate of Power to Detect Effect of Sulindac on MRD by % change in placebo arm for four target sample sizes.				
	# of samples in each group assuming no dropout			
% change at 12 months in the placebo group	50	55	60	65
0	98.6	99	99.65	99.85
1	97.1	97.75	99.1	99.2
2	95.8	97.2	98.6	98.4
3	94	95.55	97.75	98
4	90.3	92.6	95.6	95.95

5	86.3	89	91.6	93.55
6	79.65	84.9	85.65	90.35
7	72.55	76.55	81.35	85.05

In estimation of power, we did not consider BD change in the absence of AIs nor do we have information about the effect of sulindac in the absence of AIs. More importantly, most studies show no or small effects of AIs on BD. Whether the 5% decrease in all women in the observation arm of our current study reflect effects of AIs is not known but we suspect this reflects a small effect of AI. Thus, while only half of subjects in this study will be concurrently on AIs, BD change in the placebo arm in this trial is likely to be smaller than what we have based our sample size on our current data. As a result, if the decrease in the placebo arm is indeed smaller, we will have more power to detect a difference between sulindac and placebo. Note, for simplicity, these simulations discarded participants with missing data. Thus, our actual power is likely to be greater since the final data analysis will include all available data.

6.4.3 Planned Analyses

6.4.3.1 Primary Analyses

We will employ an intent- to-treat design. All randomized subjects in the groups to which they are randomly assigned, regardless of the intervention they actually receive and regardless of subsequent withdrawal from treatment or deviation from the protocol for any cause will be included in the final analysis. Our trial has two follow-up time points (6 and 12 months). Subjects who are unable to tolerate sulindac (~5%) will remain on study to complete their 6- and 12-month MRI and biopsy endpoints. Based on our experience, continued participation on study is expected to be high across all arms. As such we expect missing data will be minimal and not imbalanced across the arms, especially for the primary endpoint. Causes of missing data in the previous study have been largely image quality issues that have been minimized.

The linear mixed effect model accounts for missing data by implicitly assuming data is missing at random (MAR). Missing data in this RCT is highly likely to be intermittent and random. We have excluded subjects with a history of more aggressive disease; as such deaths are not expected during the study. Nonetheless, as a sensitivity analysis, we will use multiple imputations by chained equation to impute missing primary endpoints, use complete cases only for analysis and pattern mixture approach, which is useful in the case of informative dropout or missing data mechanism as missing not at random (MNAR). We will also use a "tipping point" approach as a sensitivity analysis under the MNAR assumption. All data analysis will be performed using SAS 9.4 (SAS institute Inc., Cary, NC).

In general, baseline characteristics will be summarized with appropriate descriptive statistics. Continuous characteristics will be compared between two study arms using t-test or

Wilcoxon's rank sum test when appropriate. Skewed continuous variables will be transformed appropriately (e.g., with log transformation). Categorical variables will be compared using Chi-square test and exact p-values based on simulations may be reported if there is data sparsity. All model assumptions will be diagnosed, and data transformation will be applied as needed to meet model assumptions. All data analysis will be performed using SAS 9.4 (SAS institute Inc., Cary, NC).

Linear mixed effects model for longitudinal data will be used for testing these hypotheses. A two-sided test at the significance level of 0.05 will be used to test if BD decreased more at month 12 in the sulindac group compared with placebo. The fixed effects of the model will include group (sulindac and placebo), visit (month 6 and month 12) and an interaction between group and visit. Baseline BD, AI use, study sites, as well as important prognostic variables such as history of breast cancer, BMI and age will be used as covariates. The model will include a random intercept at the subject level to account for correlations due to the repeated measurements from the same subjects. The dependence structure for longitudinal data from the same subject will be selected with the Akaike Information Criterion. For this trial another linear mixed effect model with log-transformed BD at each time point used as the outcome with adjustment for log-transformed baseline BD will be constructed to improve efficiency and hence, power for modeling % change in BD directly (see letter). This type of linear mixed effect model allows us to estimate the BD% changes at month 6 and month 12 within each of two arms and test if any significant difference exists among arms at either month 6 or month 12. As a secondary analysis for primary hypothesis, per-study analysis for primary hypothesis will also be performed by only using subjects who are compliant with study protocols (compliance is defined as having taken at least 70% of study agent).

6.4.3.2 Secondary Objectives Analyses

Analysis plan for secondary aims. One of our secondary hypotheses is that sulindac will decrease collagen straightness, change collagen type expression levels at 6 months, and demonstrate greater change than control. Similar to the primary endpoint analysis, a linear mixed effect model for longitudinal data will be used to model collagen straightness or collagen expression level from all subjects over time. The interaction between time (baseline and month 6) and group (sulindac and control) will allow us to test if there is a decrease in collagen straightness or collagen type expression level at 6 months and compare change between sulindac and control.

For the secondary aim of examining the change in breast density within and between treatment arms at 12 months in the subset of women on AIs compared to those who are not on AI therapy, a linear mixed model similar to the one for the primary data analysis with a three-way interaction term among AI use (yes vs no), group (SUL vs. placebo) and time (6 vs 12 month) will be fitted. This will allow us to estimate and to report BD change at each time point stratified on AI use in the control and separately in the SUL arm and to explore BD change differences between arms at each time and stratified on AI use.

Analysis plan for exploratory aims. The exploratory outcomes can be found in Table 1. Since breast adipose MRI-acquired $R2^*$ and absolute number and percent of CD68+/CD163+/CD206+ MACs are longitudinal continuous data, linear mixed effect modeling will be used to estimate the difference between baseline and month 6 and to compare differences between two arms. The correlation between $R2^*$ and CD68+/CD163+/CD206+ expression levels at baseline and month 6 will be examined through Pearson's correlation coefficients using all subjects and within each treatment arm, separately. Differences in correlation between two will be explored through linear mixed effect models for longitudinal data with appropriate interaction terms.

To explore the effect of sulindac on measures of pain and quality of life for all and separately for women on AIs and those who are not, descriptive analysis will be performed first. Linear mixed effect modelling for longitudinal data will be used to report the difference in pain or quality of life between two study arms at 6 month and 12 months first. A three-way interaction term among AI use (yes vs no), group (SUL vs. placebo) and time (6 vs 12 month) will be further fitted to report such differences stratified by AI use.

6.4.3.3 Safety/Pregnancy-related policy

All participants in the planned study will be postmenopausal and not childbearing.

6.4.3.4 Analysis of Subject Characteristics

The clinical trial will randomize postmenopausal women with either high risk [e.g., family history, genetic predisposition, or personal history of high-risk breast lesions (i.e. atypical hyperplasia or lobular and ductal in situ cancer)] or early stage BC to one of 2 arms: sulindac 150mg BID or matching placebo. The trial is limited to postmenopausal women to reduce recognized heterogeneity between pre and postmenopausal breast biology and to allow us to examine AI/sulindac interaction. Recruitment will include 75 subjects on AI therapy to explore further possible interaction between NSAID and AI. All eligible women will have breast density deemed BiRADs 3 or 4 or have a baseline BD $\geq 10\%$ in at least one unaffected breast by mammography.

In general, baseline subject characteristics will be summarized with appropriate descriptive statistics. Continuous characteristics will be compared between two study arms using t-test or Wilcoxon's rank sum test when appropriate. Skewed continuous variables will be transformed appropriately (e.g., with log transformation). Categorical variables will be compared using Chi-square test and exact p-values based on simulations may be reported if there is data sparsity. All model assumptions will be diagnosed, and data transformation will be applied as needed to meet model assumptions. All data analysis will be performed using SAS 9.4 (SAS institute Inc., Cary, NC).

6.4.3.5 Interim Analysis

An interim analysis for futility will be conducted when 40 patients complete their 6-month visit with MRI endpoints.

To continue the study, the p value for the difference of breast density change at 6 months between the treatment and placebo group must be ≤ 0.4 . A p value above 0.4 will be used as

an indicator of futility and the study will stop accruing. Based on our earlier, non-randomized findings for change in breast density at 6 months with sulindac and no change in the non-randomized, observation-only group, this yields a 28% possibility that we will not continue the study. If the study passes through the futility analysis, the sample size and power to detect a difference between the arms of the study will be re-estimated based on data from the current randomized, placebo-controlled study and evaluated for feasibility. Findings will be reported to the Data Safety and Monitoring Committee and the NCI for recommendations regarding study continuation.

6.4.3.6 Health economic evaluation

Not applicable

6.4.3.7 Other

Images from standard of care breast mammograms obtained between 3 years prior and after participation at either research site (Stony Brook and Cedars Sinai) may be used in validation of findings identified on investigational breast MRI. DICOM images available within each research centers PACS systems will be collected. Comparing imaging modalities (standard of care mammograms and investigational MRIs) will allow for a more accurate assessment of concordance or discrepancy between MRI and mammographic features, which is essential for the study's aims.

6.4.4 Handling of Missing Data

As our study has only two follow-up time points and subjects with early withdrawal before month 6 will be replaced, we expect missing data will be minimal, especially for the primary endpoint. Causes of missing data that were largely image quality issues in our preliminary study have been minimized. The linear mixed effect model accounts for missing data by implicitly assuming data is missed randomly. Missing data in this RCT is highly likely to be intermittent and random. As a sensitivity analysis, we will use multiple imputations by chained equation to impute missing primary endpoints, (74) use complete cases only for analysis and pattern mixture approach, (75) (76) which is useful in the case of informative dropout.

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

This protocol is subjected to critical review by the Stony Brook University IRB, which serves as single IRB, before and for the duration of the study. The information presented in this document is consistent with the current knowledge of the risks and benefits of the study drug, as well as with the moral, ethical and scientific principles governing clinical research in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56, and the institutional requirements provided in the Human Stony Brook University IRB "Subjects Standard Operating Procedures". The University applies the International Conference on Harmonization ("ICH") Good Clinical Practices ("GCP") Guidelines (sometimes referred to as "ICH-GCP" or "E6") to research when required by a Supporting Institution(s), and only to the extent that they are compatible with FDA and DHHS regulations. The actions of the University will also conform to all other applicable federal, state, and local laws and regulations.

There will be no payment to study subjects for being in this study. In the unlikely event that a previously unknown condition or genetic disposition is discovered during the study, the treating oncologist will review this new information and discuss with the patient further diagnostic and treatment options. Sensitive data collected as part of this study (i.e. HIV of hepatitis status) will be reviewed and discussed with each patient in person and in a private setting. In case of other people accompanying a prospective participant, verbal assent will be obtained by the provider before disclosing any sensitive information in their presence.

7.2 Institutional Review Board (IRB) Review

Stony Brook University applies the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as "ICH-GCP" or "E6") to research when required by a Supporting Institution(s), and only to the extent that they are compatible with FDA and DHHS regulations. The actions of the University will also conform to all other applicable federal, state, and local laws and regulations.

The IRB prospectively reviews and make decisions concerning all non-exempt human research conducted at its facilities or by its employees or agents, under the auspices of the University. The IRB is responsible for the protection of rights and welfare of human research subjects. It discharges this duty by complying with the requirements of the Common Rule, FDA regulations, other relevant federal regulations, state regulations, the FWA; and University policies.

The Office of Research Compliance (ORC) at Stony Brook University (Ward Melville Library, Stony Brook, NY 11794) is responsible for the oversight of this protocol through a designated Institutional Review Board (IRB), locally referred to as Committees on Research Involving Human Subjects (Stony Brook University IRB). This protocol has been evaluated and initially approved by the Stony Brook University IRB and is subject to annual reviews for the duration of study accrual and analysis in accordance to the published Human Research Standard Operating Procedures (SOPs).

The IRB is responsible for reviewing and approving each protocol version and stamping relevant study documentation (i.e. informed consent form, eligibility checklist), with the date of approval and expiration clearly legible.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated and prior to the shipment of study supplies to participating sites, if applicable. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

7.3 Subject Confidentiality

Subjects' privacy and confidentiality will be protected throughout the study, in full respect of the guidance provided by the Health Insurance Portability and Accountability Act (HIPAA). Study IDs will not contain participants' initials, or any of the 18 identifiers defined by HIPAA (<https://www.hhs.gov/hipaa/for-professionals/privacy/laws-regulations/index.html>).

Information about study subjects will be kept confidential and managed according to the requirement of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to the information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for the use of their PHI

If a participant revokes authorization to collect or use PHI, the investigator retains the ability to use all information collected prior to the revocation of subject authorization.

Physical Case Report Forms for all subjects will be kept on file per institutional guidelines. Any data, specimens, forms, reports, and other records that leave the research site or entered in an EDC will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality.

7.4 Deviations/Unanticipated Problems

All deviations to study procedures will be submitted to the IRB for review. When possible, e.g., in case of planned deviations from study schedule to happen in the future, the PI will seek out IRB acknowledgement of such deviation before it occurs. However, all and any last-minute deviations will be submitted retrospectively. These will include changes in dosage, schedule, inability to collect data relevant to study objectives, e.g. tests, biopsies, etc.

Reportable events must meet all three of the following criteria

- a. Unanticipated or unexpected in nature, frequency or severity, AND
- b. Related or possibly related to participation in the research (there is a reasonable possibility that it is related), AND
- c. The event suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (not already referenced in existing study documents, such as the protocol, consent form or Investigator's Brochure).

7.5 Data Collection and Management Responsibilities

It is the responsibility of PIs at each site to ensure the accuracy, completeness, legibility, and timeliness of all study data that are reported to the Sponsor.

Source data include the medical records, patient facing questionnaires (BPI, WOMAC, FACT-G), case report forms, physician and nurse notes, study-specific MRI-based imaging, standard of care mammograms and MRIs. Data, including PHIs necessary to identify participants, will be entered in a password-protected REDcap electronic database, hosted on the Stony Brook Medicine IT portal.

To ensure remote source data verification (SDV), all sites must enter data in REDCap, the electronic data capture (EDC) system, within two weeks from completion of procedures associated to each time point, and upload selected de-identified source materials when instructed, or as applicable.

Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Access to REDCap can be requested at the link below, entering the email of the Protocol manager indicated on the cover page of this protocol as *Account Sponsor at SBM* to the lead site Protocol Manager indicated on the cover page of this protocol.

<https://redcap.stonybrookmedicine.edu/surveys/?s=WWKDRXWTXX>

Training on how to enter data in REDCap is available at

https://redcap.vanderbilt.edu/consortium/videoplayer.php?video=data_entry_overview_02.mp4&title=An%20Overview%20of%20Basic%20Data%20Entry%20in%20REDCap&referrer=redcap.stonybrookmedicine.edu

Data collected for subjects who screen fail or withdraw from the study for any reason before the start of study treatment, will include consent form, demographic information and screening results.

Study staff, the PIs and the biostatistician office will have access to the database. There is no specified retention end date for such database. All identifiers will be removed/destroyed at the end of the study.

7.6 Monitoring and Data Quality Assurance

The Stony Brook Cancer Center Data and Safety Monitoring Committee (SBCC DSMC) will provide ongoing oversight for this phase 2 multicenter trial for data quality assurance and will monitor adverse events and the overall conduct of the trial at a minimum every 6 months according to the Institutional Clinical Trial Data and Safety Monitoring Plan (DSMP).

SBCC DSMC multicenter oversight will include routine review of subject data and essential documents performed twice a year by the Quality Assurance and Process Improvement Unit (QIU). The QIU has the responsibility of study monitoring to ensure that the investigation is conducted in compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The QIU review includes evaluation of the current accrual relative to the planned total accrual; examination of all reported violations; review of past monitoring visits and correspondence with the PI; review of data accuracy, review of previous correspondence between the PI and the QIU/DSMC. Additional details may be found in the SBCC DSMP.

DSMC will be notified of upcoming monitoring visits and will be expected to provide de-identified source documents for remote monitoring of patients, and/or access to the site EMR. Queries will be issued in the EDC and a detailed monitoring report will be provided to the participating site. The SBCC CCTO will also forward any monitoring and/or auditing reports to the SBCC DSMC.

In addition, the Protocol Manager at the lead site will facilitate conference call meetings with investigators and staff at all participating sites at least monthly (and more often as needed) to discuss study progress. If there are no patients on treatment or in follow-up, email communication may be used in lieu of a teleconference, or in the circumstance where a scheduling conflict does not permit phone attendance.

Sites will ensure that the study monitor or other compliance or quality assurance reviewer obtains access to the electronic medical records, as well as to the pharmacy records for an adequate amount of time, as requested by the monitor. Monitoring visits may include on-site and/or remote monitoring in accordance to current local policies. Documentation of trial monitoring will be distributed to sites and maintained along with other protocol related documents.

The first routine audit visit will include at a minimum, informed consent of 100% of case enrolled; subject eligibility in 100% of cases enrolled, and data review in 100% of cases (up to three subjects). All subsequent QA reviews will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected

cases, as applicable. A QA report will be completed within two weeks of the review; a copy will be maintained in the study file. The study coordinator and research nurse will be given a copy of this form for resolution of queries/findings.

The Principal Investigator is responsible for applying ALCOA principles (Attributable, Legible, Contemporaneous, Original, and Accurate) to all source documents and Case Report Form (CRF) to ensure data integrity, validity, and subject safety.

7.7 Study Records

All study related documents including but not limited to all regulatory documents, the study protocol, the consent forms, case report forms, subject medical record and questionnaires are considered study records.

7.8 Access to Source

Source data are all information, medical records, consultation, and progress notes, clinical or laboratory findings related to diagnoses, adverse events, imaging or biomarker observations, or other activities including patient reported events that occur in the conduct of the clinical trial necessary for the reconstruction and evaluation of the trial. Case report forms and questionnaire data to be collected in this study are included in source documents. Access to study-specific source documents (e.g. shadow charts, CRFs, questionnaires etc.) will be restricted to study team members, the sponsor of this study, and those hired to conduct this study, including quality assurance monitors, IRB or other regulatory body, as needed.

7.9 Data or Specimen Storage/Security

Participant confidentiality is strictly held in trust by the study investigators and study team members. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, biological specimens and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the participants or the IRB. The study participant's contact information will be securely stored for internal use during the study.

Study participant research and specimen data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the study data analyst under the direction of the study biostatistician. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data base (Redcap) and clinical trial management system (Oncore) are password protected and only accessible to study team members. At the end of the study, the study database will be de-identified and archived.

All study related specimens will be labeled and tracked with a unique sample ID distinct from the study participant ID. The code linking the sample ID to the participant IDs is stored with the study biostatistician, Dr. Jie Yang. Study biospecimens will be stored in the Cancer Center Biobank and batch shipped to the laboratory of Dr. Patricia Thompson (University of

Arizona, Tucson, AZ) as required for planned biomarker studies and future unplanned studies. All study research specimens will receive a unique identifier generated by the study biostatistician and provided to the laboratory that is distinct from that of the participant identifier and which does not contain information related to the personal information of the donor. MUSC collaborators will receive de-identified specimens / data, using the described unique sample ID, but no other identifiers.

The study biostatistician and study team members will hold the key for linking the study participant to their specific specimens for the purposes of data analyses and relating specimen derived data to the study participant at the end of the study. This code will not be released outside of Stony Brook.

7.10 Retention of Records

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations. At the end of the study, physical records may be moved to a contracted long storage facility. The PI and study coordinator will be informed should the need to move the records arise.

7.11 Data Safety Monitoring Plan

This trial has been designated as a medium risk study. Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are not designated as high risk per NCI and the IND is not held by the investigator.

The SBCC DSMB will provide ongoing oversight for this trial twice a year.

Routine study activity and safety information will be reported to the DSMB twice a year, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events);
- Deviations
- Unanticipated Problems
- Monitoring and protocol compliance.
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

Authority to suspend or close study

The Data Safety and Monitoring Board (DSMB) have the authority to suspend or close the study on safety or quality concerns. For each adverse event, the DSMB will review causality as reported by the Principal Investigator, outcome and the potential impact the event has on patient safety, the need for informed consent modification and the date the event was reported to the IRB of record (if applicable). This will also include trend analyses for serious adverse events. Any clinical study event that is judged to be an adverse event must be recorded per departmental requirements. The clinical PI (Dr. Stopeck) must evaluate all

adverse events for severity, causal relationship to the test article under study, action taken and outcome. All supportive information is filed in the source documents. SAEs and AEs will be reviewed at team meetings. A summary of this information is made available to the Investigator, Protocol Review and Monitoring Committee, and IRB or any other staff or committees as appropriate.

While there are no predefined stopping rules for well-studied agents like sulindac, the DSMB is charged to monitor increased frequency or appearance of unexpected grade 2 or higher adverse events, as well participants' drop-out rate due to drug intolerances (>10%). Either entity or the PI can recommend stopping the trial on excessive grade 2 events related to study agent and/or a high dropout rate.

7.12 Study Modification

Minor clarifications on the study protocol may be addressed via protocol clarifications letters, submitted to the Stony Brook IRB per institutional requirements.

Any substantial modification (whether minor or major) to the study or study team members will be submitted to the Stony Brook IRB for review in accordance to institutional requirements. Changes will not be implemented until IRB grants approval to such modification.

7.13 Study Discontinuation

The study may be discontinued for a variety of reasons, including but not limited to:

- unsatisfactory results of the interim futility analysis (see section 6.4.3.5)
- new and unexpected study-related risks for participants or others
- request from funding agencies, regulatory authorities, IRB or DSMC
- lower accrual than expected for any reason

7.14 Study Completion

The trial will be completed when the last subject on study finishes all study related events to include post intervention 30-day phone call follow up. The IRB will be notified when the study is closed to accrual and all subjects have completed the trial. The study will continue receiving IRB oversight for as long as collection of identifiable information continues.

7.15 Conflict of Interest Policy

All conflict-of-interest reporting will be according to institutional policies as required for all study investigators and amended as needed.

7.16 Funding Source

The study is funded by a National Cancer Institute federal grant number RO1CA2357201 (<https://app.protocolbuilderpro.com/overview/48519/985/986>).

7.17 Publication Plan

Primary and secondary findings from the proposed clinical trial will be published in a peer reviewed journal as an expectation of the sponsor, the National Cancer Institute. Drs. Thompson (University of Arizona) and Stopeck (Stony Brook University) hold the primary responsibility for publishing the results of the trial in a timely fashion.

7.17 Record Retention

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location for two years, or longer, in accordance with local dispositions.

8.0 Multi-Site Expansion of Study

8.1 Required Documentation for Site Activation

Prior to implementing this protocol at a participating site, the protocol, site-level informed consent form, HIPAA authorization and any other information pertaining to participants (e.g. advertisement) must be approved by the Stony Brook Institutional Review Board (IRB), which is serving as the single IRB of record. There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to the lead site Protocol Manager in order to create an initial site-level IRB submission:

- Site-specific informed consent form
- Site-level Advertisement
- Curriculum vitae and medical licenses for each investigator and consenting professional
- Documentation of Human Subject Research and Good Clinical Practice Certification for investigators, consenting professionals and key study personnel at the participating site. For interventional studies funded by the NIH, GCP training must be renewed every 3 years.
- Participating site laboratory and pharmacy certifications

Upon approval by the sIRB, the lead site will distribute the approved study documents to the participating site and grant permission to proceed with enrollment.

8.2 Eligibility Verification and Participants Registration

Documentation of current IRB approval must be on file prior to registration of patients on this study for participating institutions.

The study team at each sites will register consented participants using the Stony Brook instance of Oncore - Subject Console, and notify the Protocol Manager by email as soon as a potential subject is consented.

Access to Oncore can be requested at the link below, indicating the lead site Protocol Manager email in the field *Account Sponsor at SBM*.

<https://redcap.stonybrookmedicine.edu/surveys/?s=WWKDRXWTXX>

All consented patients will received a study ID consisting of an alphanumerical string of 8 characters. All IDs will begin with SBC, to identify the STOP-BC study, followed by 5 digits. IDs starting with a digit between 0 and 4 will be assigned to participants enrolled at Stony Brook. IDs with a digit beginning with a 5 will be assigned to participants enrolled at Cedars Sinai. IDs with a digit beginning with a 6 will be assigned to participants enrolled University of Arizona.

The following documentation must be uploaded not-redacted under Documents/Attachments of the respective participant's Oncore - Subjects Console section:

- Copy of the ICF, signed by the participant and by the person obtaining consent
- Completed and signed Eligibility Checklist. For screen failures, the failed criterion must be clearly indicated, and the subjects marked as ineligible in Oncore
- Only for fully eligible subjects: supporting documentation of all eligibility criteria (eg. copies of lab tests, vital signs, imaging reports, consultation notes, concomitant medications, pathology reports, medical history etc.) must be uploaded in Oncore Subject Console, under Documents – Attachments within 30 days of consent.

Study teams at each site will verify eligibility and notify the lead site once participants can begin the NSAID washout step or are exempted from this step. Research sites will request to the lead site protocol coordinator, or their delegate, to randomize the participants ahead of the baseline visit.

Participants are considered enrolled in the study once they are randomized to sulindac/placebo.

Institution's specific patient registration will follow the process for each institution and will be handled by each site.

8.3 Sponsor-initiated Amendments/Modifications

Each change to the protocol document must be organized and documented by SBU and approved first by the sIRB (SB IRB). All protocol amendments will be promptly distributed to participating sites upon receipt of the sIRB approval.

If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continuing enrolling new participants until the sIRB approval of the revised protocol and ICF documents is granted.

8.4 Site-Initiated Amendments/Modifications

Each participating site must obtain sIRB approval for site-initiated changes to all documents other than the protocol (e.g informed consent, advertisement and site-specific patient facing material).

Study teams will notify the lead-site of site-specific amendments and changes by

- 1) completing "*Appendix 3. Amendment to site-specific documents*", AND
- 2) preparing redline and clean versions for all documents included in the amendment, AND

3) emailing all documents to be submitted (including a certificate of accuracy for any translated material) and the completed *Appendix 3* to the lead PI and Protocol Manager indicated on the cover page of this protocol.

The lead site will submit the documentation to the sIRB on behalf of each site and provide approved documents back to the study team.

8.5 Additional Sponsor and sIRB Reporting and Correspondence

8.5.1 Continuing Review Approval

Documentation required to obtain annual sIRB approval must be submitted to the lead-site at least 60 days prior to the study's expiration date, by emailing the lead-site PI and Protocol Manager indicated on the cover page of this protocol. Information required annually at the time of continuing review include whether:

- subjects experienced unexpected harm
- anticipated adverse events have taken place with greater frequency or severity than expected
- subjects withdrew from the study
- unanticipated problems involving risks to subjects or others have occurred
- there were complaints about the study
- there are publications in the literature relevant to risks or potential benefits
- there are interim findings
- multi-center trial reports are available
- data safety monitoring reports are available
- regulatory actions have been taken that could affect safety and risk assessments
- other relevant information regarding this study are available, especially information about risks
- in the opinion of the PI, the risks and potential benefits are unchanged
- all modifications to the protocol have been submitted to the IRB
- all problems that require prompt reporting to the IRB have been submitted

Failure to provide information needed for re-approval will result in suspension of new participant enrollment.

8.5.2 Additional Sponsor and sIRB Reporting Requirements for participating sites

Unanticipated problems (UAPs): Definitions and Reporting

1. Serious adverse events which in the opinion of the principal investigator are both unexpected and related to the research activity (a type of UAP).
2. Adverse events (other than SAEs) which in the opinion of the principal investigator meet the criteria for an unanticipated problem involving risk to subjects or others (unanticipated, related to the research and increase risk to subjects).
3. An unanticipated event related to the research that exposes subjects to potential risk

4. An unanticipated event related to the research that exposes individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk.
5. Information that indicates a change to the risks or potential benefits of the research. For example:
 - 5.1 A safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
 - 5.2 A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
6. A breach of confidentiality.
7. Incarceration of a subject in a protocol not approved to enroll prisoners.
8. Changes increasing the risk to subjects and/or significantly affecting the conduct of the trial.
9. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research subject.
10. Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.
11. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed subjects or others or that indicates subjects or others may be at increased risk of harm.
12. Event that requires prompt reporting to the sponsor.
13. Sponsor imposed suspension for risk.
14. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
15. Unanticipated adverse device effect - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.150(a)).
16. Any other event that indicates subject or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

Reportable events must meet all three of the following criteria

1. Unanticipated or unexpected in nature, frequency or severity, AND
2. Related or possibly related to participation in the research (there is a reasonable possibility that it is related), AND

3. The event suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (not already referenced in existing study documents, such as the protocol, consent form or package insert).

UAPS will be reported to the lead site within 24 hours of the study team becoming aware of the event, by completing “*Appendix 1. UAPs and SAEs*”, and emailing it to both the lead site PI and Protocol Manager indicated on the cover page of this protocol.

Participating sites are responsible for reporting UAPs to their institution’s IRB per local guidelines.

Deviations / Exceptions: Definitions and Reporting

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the sIRB, the study shall be conducted exactly as described in the approved protocol.

Protocol deviations: Circumstances that are unanticipated and happen without any prior sponsor or IRB approval. (e.g., protocol visit scheduled outside protocol window, blood work drawn outside protocol window, etc.). Minor scheduling deviations of study visits that are unavoidable and do not impact subject safety do not constitute a deviation.

Protocol exceptions: Circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific subject (e.g., subject is allergic to one of the medications provided as supportive care). Exceptions are planned, and the investigator gets approval from the sponsor and the sIRB ahead of time. In order to be approved by the IRB, exceptions must not increase risk or decrease benefit, affect the subject’s rights, safety, welfare, or affect the integrity of the resulting data. The only time a protocol exception would not require prior sponsor and IRB approval is when it is done to avoid an immediate hazard to the subject.

Protocol deviations and exceptions must be reported to the lead site as soon as possible, by:

- 1) completing “*Appendix 2. Request for Deviations Exception*” and email it to both the lead site PI and Protocol Manager indicated on the cover page of this protocol, AND
- 2) Enter Deviation / Exception details in the PC Console in Oncore under either protocol, or subject deviation, as appropriate.

Participating sites are responsible for reporting all deviations to their institution’s IRB per local guidelines.

Appendices

Appendix #	Title	Section	Topic
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1	UAPs and SAEs	6.2 Assessments	sIRB submission form
2	Request for Deviations Exceptions	8.5.2 Additional Sponsor and sIRB reporting	sIRB submission form
3	Amendment to site-specific documents	8.4 Site-initiated Amemdments/Modifications	sIRB submission form
4	WOMAC Questionnaire	6 Methods	6.3.1 Study Schedule
5	Brief Pain Inventory (BPI)	6 Methods	6.3.1 Study Schedule
6	FACT-G	6 Methods	6.3.1 Study Schedule
7	Study Schedule	6 Methods	6.3.1 Study Schedule

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RESEARCH CONSENT FORM

Project Title: Double-blind, randomized phase II clinical trial of sulindac for reducing breast density in postmenopausal women at risk of developing breast cancer

Principal Investigator: Alison Stopeck, MD

Department: Stony Brook University Cancer Center

(1) The information in this form is being used to seek your consent for a research study. Being in the study is voluntary; it is up to you.

(2) This research is being done to find out if the drug sulindac decreases breast density. Participation will last up to 14 months. Study procedures for this research are:

- Take a study medicine twice a day by mouth
- Have three breast MRI without contrast
- Complete questionnaires three times about your quality of life
- Have blood drawn three times by inserting a needle into a vein
- Give a urine sample three times
- Let the research team record information from your medical record related to your health and medications you are taking
- Optional: have a piece of breast tissue removed through a needle

(3) The most likely risks to you of the research are:

- Upset stomach

Please see the RISKS AND DISCOMFORTS section for a complete list of expected side effects

(4) The most likely benefits to you of the research are: less joint pain if you have arthritis or joint pains. You may not benefit from taking part in this study otherwise.

(5) If you decide not to be in the research, your choices are to continue the care proposed by your doctor, be in another research study or do nothing.

You are being asked to be a volunteer in a research study.

PURPOSE

You are eligible for this study if you have increased breast density and are either taking an aromatase inhibitor for breast cancer *or* at increased risk of developing breast cancer.

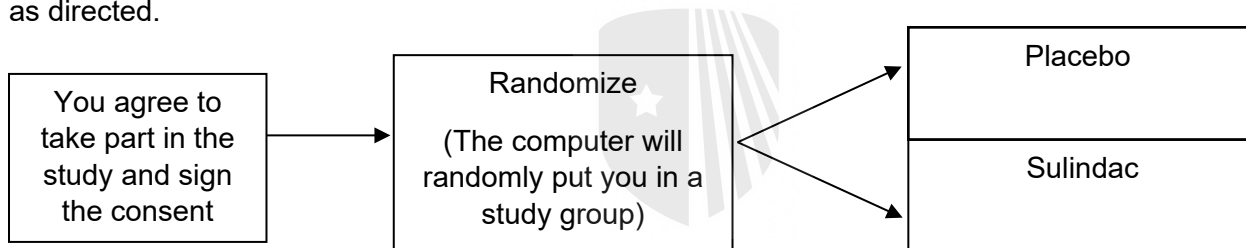
The purpose of this study is to find out if sulindac, an anti-inflammatory drug similar to aspirin (nonsteroidal anti-inflammatory drug, or NSAID), can decrease breast density in post-menopausal women when taken by mouth twice a day for twelve months, compared to a placebo.

This study has two study groups. Neither you nor your physician will know to which group you will be assigned. One group will receive the study drug, sulindac at 150 mg per tablet. The other group will receive a placebo, an inactive substance that looks like the study drug, but contains no medication. All subjects will take study drug (sulindac or placebo) twice a day. In some cases, your study doctor may tell you to take the sulindac/placebo tablet once a day for the first few days, and then switch to twice a day, in order to adjust to the full dose. People who are currently taking aromatase inhibitors will continue as directed by their physician.

A computer will by chance assign you to one of the treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other. Neither you nor your doctor can choose the group that you will be in. You will have a 50% chance of being placed in the group receiving sulindac. Neither you nor your doctor will know which group you are assigned to. Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.

If you decide to participate in this study you should not take any aspirin or any nonsteroidal anti-inflammatory medications while you are in this study without first discussing with the study team. Your study doctor or study staff will talk to you about other medications you should not take while you are on study medications.

If you choose to take part in the study, you will need to come to the research clinic every six months, or more often if necessary, to review any side effects and also to see if you are taking the study drug as directed.



Approximately 150 women will participate in this study between Stony Brook University Cancer Center, Cedars Sinai Medical Center, and University of Arizona.

PROCEDURES

If you decide to be in this study, your part will involve:

- **Screening visit (approximately 1.5 hour):**
 - sign the consent form,
 - give a blood sample (up to 1.5 tablespoons) for clinical laboratory testing for liver and kidney function and have your vital signs measured (blood pressure, heart rate, height and weight),
 - *If you did not use aspirin or other NSAIDs (e.g. ibuprofen, etc.) more than one day per week in the prior 4 weeks*, give a urine sample and additional blood (up to 1.5 tablespoons) for research studies
 - fill out questionnaires about your quality of life,
 - tell the study staff about all medications and supplements you are taking

- If your blood pressure is high, you will continue measuring your blood pressure at home for two days
- *Optional, highly recommended:* Fecal occult blood testing (FOBT). This is a non-invasive test that you can do at home, and is done to make sure you do not have internal bleeding.
- **Visit 1 – Study Starts (approximately 2 hours):**
 - *If you used aspirin or other NSAIDs (e.g. ibuprofen, etc.) more than one day per week for the prior 4 weeks before your screening visit, you will give a blood sample (up to 1.5 tablespoons) and a urine sample for research studies at this visit,*
 - have your vital signs measured,
 - fill out questionnaires about your quality of life,
 - tell the study staff about all medications and supplements you are taking,
 - have an MRI of your breast without contrast,
 - OPTIONAL: undergo a breast biopsy with ultrasound,
 - receive study medication (either sulindac or placebo)
- **Visit 2 – 6 months after study start (approximately 2 hours):**
 - bring back any unused study medication and bottles,
 - give blood samples (up to 3 tablespoons) and a urine sample
 - have your vital signs measured,
 - fill out questionnaires about your quality of life,
 - tell the study staff about all medications and supplements you are taking
 - have an MRI of your breast without contrast,
 - OPTIONAL: undergo a breast biopsy with ultrasound anytime between Visit 2 through Visit 3
 - receive study medication (either sulindac or placebo)
- **Visit 3 – 12 months after study start (approximately 2 hours):**
 - bring back any unused study medication and bottles,
 - give blood samples (up to 3 tablespoons) and a urine sample
 - have your vital signs measured,
 - fill out questionnaires about your quality of life,
 - tell the study staff about all medications and supplements you are taking,
 - have an MRI of your breast without contrast
 - OPTIONAL: undergo a breast biopsy with ultrasound anytime between Visit 2 through Visit 3

The study staff will call you at regular intervals during the study and one month after the end of the study treatment. They will ask about your health, and medications or supplements that you are taking. If your blood pressure is high, you will be asked to measure your blood pressure at home. You may request to visit the research center more often during the first 6 months of the study treatment, however this is optional and may or may not be allowed depending on hospital guidelines.

Time in the study	Screening (4 weeks before treatment starts)	Treatment starts	Once a month	After 6 months	After 9 months	After 12 months treatment ends	1 month after treatment ends
Informed Consent	X						
Visit the research center	X	X	X (if needed at 3 months)	X		X	
Answer Questionnaires	X	X		X		X	
Give blood and/or urine	X	X		X		X	
Breast MRI		X		X		X	
Breast Biopsy		X (optional)		X (optional)			
Receive sulindac or placebo bottles		X		X			
Phone Call			X		X		X

INFORMATION ABOUT DATA AND/OR SPECIMENS

Research samples and banking for future research:

- The purpose of the biopsy and blood studies is to learn more about how sulindac works in the body. Scientists may look at certain substances in your blood, urine or breast tissue samples and learn about the effects of sulindac on breast density and inflammation.
- If you agree to the optional biopsy and banking of leftover samples described in this section, identifiers (such as your name or date of birth) will be removed from your identifiable private information or identifiable leftover blood, urine and breast samples. After such removal, the information or biospecimens may be used or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.
- You have the right to withdraw this permission by calling your study doctor, or Alison Stopeck, at 631-638-1000, or writing a letter to Alison Stopeck, 101 Nicolls Road, Stony Brook, NY 11794, who will inform the researcher to destroy your samples. However, researchers will continue to use data derived from samples that were already used up before you withdraw this authorization.
- Leftover blood, urine and breast samples will be banked in the department of pathology at Stony Brook University (NY) or University of Arizona (AZ).
- You will not be informed of the details or results of such future studies.
- There is no additional physical risk from collecting additional samples from a procedure that is being done as part of this study, such as blood or urine tests.

- There are additional physical risks from collecting breast tissue samples via the optional biopsy, which are described in the next section.
- There is a risk that someone could get access to the stored information or samples. In spite of the security measures and safeguards we will use, we cannot guarantee that your identity will never become known.
- There may be risks that at this time are unknown. As technology advances, there may be new ways of linking information back to you that we cannot foresee now.
- The information and samples that you provide will no longer belong to you. The research may lead to new medical knowledge, tests, treatments, or products. These products could have some financial value. There are no plans to provide financial payment to you or your relatives should this occur.
- This authorization does not expire.
- (Circle your response) I agree to give additional breast tissue samples via breast biopsies for the purpose of this study.

YES

NO

Participant Initials: _____

- (Circle your response) Any leftover samples (blood, urine and breast tissue) and related information may be kept in a biobank for use in future unspecified health research.

YES

NO

Participant Initials: _____

This is the end of the section about optional tissue, blood and urine studies.

RESULTS OF RESEARCH TESTS

- **The results of the following research tests will be shared with you and your doctor and added to your medical records:**
 - Blood and fecal occult blood tests used to assess your health
- **The results of the following research tests will NOT be shared with you and your doctor:**
 - Blood and urine tests for research purposes
 - Results from the research MRI or histology results from the optional biopsy. These tests are experimental and should not be used by your doctor to make medical decisions.

RISKS / DISCOMFORTS

The following risks/discomforts may occur as a result of you being in this study:

COMMON, RARELY SERIOUS	
In 100 people receiving sulindac, from 10 to 20 may have	
• Upset stomach	
OCCASIONAL, SOME MAY BE SERIOUS	
In 100 people receiving sulindac, from 1 to 10 may have	
• Ulcer of stomach or intestines	
• Bleeding from the stomach or intestines	
• Bleeding under the skin or more bleeding than usual from minor cuts can be expected	

- Excess stomach acid
- Feel like throwing up
- Heartburn
- Decreased blood cells
- Headache
- Rash
- Indigestion
- Decreased appetite
- Elevations in blood pressure

RARE, AND SERIOUS

In 100 people receiving sulindac, 2 or fewer may have:

- Reaction due to allergy
- Inflammation of liver or kidney
- Liver function abnormalities
- Severe skin reaction
- Ringing in ear
- Serious bleeding
- Inflammation of the pancreas
- Ulcers of gastrointestinal system that may perforate
- Worsening of heart failure in patients with pre-existing heart disease
- Cardiac events such as blockage of blood vessels, heart attack and even stroke. These risks are greatest in individuals with preexisting heart disease, or who are already at high risk for developing heart disease or stroke

Let your study doctor know of any question you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Risk of the breast MRI: This procedure does not involve radiation or contrast agents. For individuals with no contraindications to non-contrast MRI imaging, there are no known long term side effects from this procedure. The physical confinement, noise and isolation produced by the MRI scanner could cause mild to moderate distress or anxiety.

Risks of the OPTIONAL breast biopsy:

Very Common Risks (1 or more per 10 people):

- Bleeding and/or bruising at the biopsy site which resolves by itself
- Pain
- A small scar may remain at the site of the biopsy

Rare side effects (less than 1 per 100 people)

- Bleeding complications requiring surgery or hospitalization
- Infection following biopsy

Risk associated with Blood Sample Collection

Very common side effects (1 or more per 10 people)

- temporary pain and bruising where the needle enters the skin, and sometimes, fainting and/or infection

BENEFITS

There is no direct benefit to you expected as a result of you being in this study. However, if you have arthritis or joint pain you may feel less pain. This study will help researchers learn things that may help people at risk of breast cancer in the future.

PAYMENT TO YOU

You will not be paid or reimbursed for being in this study.

PAYMENT TO THE INSTITUTION

This project is funded, in part, by a grant from the National Cancer Institute to the Research Foundation of Stony Brook University, in support of the Investigators' work on this study. The amount of payment from this sponsor is dependent upon timely enrollment that includes protecting the safety and privacy of study participants.

CONFIDENTIALITY

We will take steps to help make sure that all the information we get about you is kept confidential. Your name will not be used wherever possible. We will use a code instead. All the study data that we get from you will be kept locked up. The code will be locked up too. If any papers and talks are given about this research, your name will not be used. The code, and not your name or initials, will be used when sharing research samples with our collaborators at the University of South Carolina (SC), Emory University (GA), Cedars Sinai Hospital (CA), and University of Arizona (AZ). Stony Brook University will keep the master list that links your code number to your identifying information and only certain Stony Brook University research staff members will ever have access to this master list.

We want to make sure that this study is being done correctly and that your rights and welfare are being protected. For this reason, we will share the data we get from you in this study with the study team, the sponsor of the study (and those who work for them), Stony Brook University's Institutional Review Board, applicable Institutional officials, and certain federal offices, including the Office for Human Research Protections (OHRP), and, where applicable, the Food and Drug Administration (FDA). However, if you tell us you are going to hurt yourself, hurt someone else, or if we believe the safety of a child is at risk, we will have to report this.

This study requires that we collect very personal information about you. Therefore, we had the National Institutes of Health give us a Certificate of Confidentiality (COC). This piece of paper says that nobody can force the researchers to give out your information, even if a court of law asks for it. This will give you more protection. The only time information about you can be given out is:

- If you are going to hurt yourself,
- If you are going to hurt someone else
- If we believe the safety of a child is at risk.
- If the Department of Health and Human Services, who pays for this study, wants to look over the study.
- If the data are required by other federal, state or local laws, such as for reporting of communicable diseases.

You should know that the Certificate of Confidentiality does not apply to information about your participation in research, including a consent form that is placed in your medical record (though HIPAA protection does apply). This information may be disclosed to individuals requesting your medical record.

This Certificate doesn't mean you can't talk about this study. If you give written permission, your insurance company, your boss, or your medical doctor can be given the research information too.

While you are in this study we will get data about your health from your medical record. We will also get health data from the results of the tests you will have done in this study. You have a right to privacy but the data we get about your health in this study can be shared with the people referenced above (the study team, the sponsor of this study, those who work for the sponsor, Stony Brook University's Institutional Review Board, applicable institutional officials, and federal offices such as OHRP, FDA) as well as:

- your insurance company
- your medical doctor
- A board that reviews the safety of the study on an on-going basis.

Your health data are shared to make sure the study is being done correctly, costs are charged correctly, and to make sure your rights and safety are protected. Not all of these people are required by law to protect your health data. They might share it with others without your permission. For example, the sponsor or collaborators of this study do not have to make the same promise under the law to protect your health data, however, we will not share your name or identifiers with them, only a code.

Some of the health information we get from you in this study cannot be shared with you until the end of the study.

This authorization for use and reporting of your health data will remain in effect unless and until you tell us otherwise. You have the right to stop allowing us to use or give out your health data. You can do this at any time by writing to or calling Dr. Alison Stopeck at alison.stopeck@stonybrookmedicine.edu, or (631) 638-1000. If you do this, we will stop collecting any new health data from you, except if we need to keep an eye on a bad side effect you were having in the study. We will use any data we collected before you wrote your letter. When you sign the consent form at the end, it means:

- That you have read this section.

- That you will allow the use and reporting of your health data as described above.
- You have received a form from the University Hospital. It is called the Notice of Privacy Practices form.

CLINICAL TRIAL REGISTRY

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

COSTS TO YOU

There are no costs to you for being in this study.

ALTERNATIVES

Your alternative to being in this study is to simply not participate. Sulindac can also be prescribed by your regular doctor.

IN CASE OF INJURY

If you are injured as a result of being in this study, please contact your study doctor or Dr. Alison Stopeck, at telephone # 631-638-1000. The services of Stony Brook University Hospital will be open to you in case of such injury.

However, you and/or your insurance company will be responsible for payment of any resulting treatment and/or hospital stay.

CONSEQUENCES OF WITHDRAWING

You are free to withdraw from the study at any time. However we request that you inform study staff and return any unused medication as well as any study material you may have received. You will also be required to visit the research center one last time to do blood tests to ensure you are in good health.

REMOVAL FROM STUDY

Your study doctor may remove you from the study for the following reasons:

- You decide to stop being in the study,
- Your study doctor feels being in the study is not in your best interest
- The study is closed,
- You are unable or unwilling to do the study procedures

YOUR RIGHTS AS A RESEARCH SUBJECT

- Your participation in this study is voluntary. You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a signed and dated copy of this consent form to keep.
- You do not lose any of your legal rights by signing this consent form.

QUESTIONS ABOUT THE STUDY OR YOUR RIGHTS AS A RESEARCH SUBJECT

- If you have any questions, concerns, or complaints about the study, you may contact your study doctor, or Dr. Alison Stopeck, at telephone # (631-638-1000).
- If you have any questions about your rights as a research subject or if you would like to obtain information or offer input, you may contact the Stony Brook University Research Subject Advocate, Ms. Lu-Ann Kozlowski, BSN, RN, (631) 632-9036, OR by e-mail, lu-ann.kozlowski@stonybrook.edu
- Visit Stony Brook University's Community Outreach page, <http://research.stonybrook.edu/orc/community.shtml#overview-of-volunteering-in-research> for more information about participating in research, frequently asked questions, and an opportunity to provide feedback, comments, or ask questions related to your experience as a research subject.

If you sign below, it means that you have read (or have had read to you) the information given in this consent form, and you would like to be a volunteer in this study.

Subject Name (Printed)

Subject Signature

Date

Time

Name of Person Obtaining Consent (Printed)	Signature of Person Obtaining Consent	Date	Time
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