ALLIANCE FOUNDATION TRIALS (AFT)

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COMPARING AN OPERATION TO MONITORING, WITH OR WITHOUT ENDOCRINE THERAPY (COMET) FOR LOW-RISK DCIS: A PHASE III PROSPECTIVE RANDOMIZED TRIAL

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Study Resources

Systems used for this study		Access website link
AFT portal gives access to: **-Rave/EDC (Medidata Rave)** **-BioMS** **-Site Zone**	**-Rave**: Data collection/submission **-BioMS**: AFT Biorepository at Washington University for specimen collection, shipping, tracking and banking **-Site Zone**: Upload and submit required documents for site activation Find the most up-to-date study documents, such as protocol, model informed consent form, etc For Site Zone help: [redacted]	https://alliancefoundationtrials.org
PRO Core	Patient-reported outcomes (PRO) data collection system	https://pro.unc.edu

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Synopsis and schema

Study Title	**COMPARING AN OPERATION TO MONITORING, WITH OR WITHOUT ENDOCRINE THERAPY (COMET) FOR LOW-RISK DCIS: A PHASE III PROSPECTIVE RANDOMIZED TRIAL**
Study Number	AFT-25
Study Type/Phase	Interventional Phase III Randomized Clinical Trial
Clinical Indication	Low-risk ductal carcinoma in situ (DCIS)
ClinicalTrials.gov Identifier	NCT02926911
IND Number	Not applicable
Number of Trial Patients	1,080
Estimated Duration of Trial	Accrual: 78 months (07/01/16- 12/31/22) Follow up: 2-, 5- 7- and 10-years
Rationale	To study the risks and benefits of active monitoring (AM) compared to surgery in the setting of a pragmatic prospective randomized trial for low-risk DCIS. Our overarching hypothesis is that management of low-risk DCIS using an AM approach does not yield inferior invasive breast cancer or quality of life outcomes compared to surgery.

Primary Objective	To assess whether 2-year ipsilateral invasive breast cancer rate for AM is non-inferior to that for surgery.
Secondary Objectives	To determine whether AM is non-inferior to surgery for the following outcomes: 2-, 5-, 7- and 10-year mastectomy rate, breast conservation rate, contralateral invasive breast cancer rate, overall survival and invasive breast cancer specific survival; health-related QOL, anxiety and depression at baseline, 6 months, 1 year, annually year 2-6, biannually thereafter; coping at baseline; intolerance of uncertainty at baseline and 2 years.
Trial Design and Schema	Multicenter Phase III Prospective Randomized Trial comparing surgery to active monitoring with option of endocrine therapy (in both arms) for low-risk ductal carcinoma in situ (DCIS) (see Study Schema below)

Inclusion Criteria	• Diagnosis of unilateral, bilateral, unifocal, multifocal, or multicentric DCIS without invasive breast cancer (date of diagnosis defined as the date of the first pathology report that diagnosed the patient with DCIS) **OR:** atypia verging on DCIS **OR:** DCIS + LCIS (mix and/or separate locations in the same breast)
	• A patient who has had a lumpectomy or partial mastectomy with margins positive for DCIS (i.e. <2mm/ink on tumor) as part of their treatment for a current DCIS diagnosis is also eligible (post-excision bilateral mammogram required at enrollment to establish a new baseline)
	• No previous DCIS or invasive breast cancer in ipsilateral breast 5 years prior to current DCIS diagnosis
	• 40 years of age or older at time of DCIS diagnosis
	• ECOG performance status 0 or 1
	• No contraindication for surgery
	• Baseline imaging (must include dimensions):
	  ○ unilateral DCIS: contralateral normal mammogram ≤ 6 months of registration and ipsilateral breast imaging ≤ 120 days of registration (must include ipsilateral mammogram; can also include ultrasound or breast MRI)
	  ○ bilateral DCIS: bilateral breast imaging ≤ 120 days of registration (must include bilateral mammogram; can also include ultrasound or breast MRI)
	  ○ DCIS s/p lumpectomy: post excision mammogram on side of excision ≤60 days of registration
	• Pathologic criteria:
	  ○ All grade I DCIS (irrespective of necrosis/comedonecrosis)

	○ All grade II DCIS (irrespective of necrosis/comedonecrosis) ○ Absence of invasion or microinvasion ○ Diagnosis of DCIS confirmed on core needle biopsy, vacuum-assisted biopsy, or surgery ≤ 120 days of registration ○ ER(+) and/or PR(+) by IHC (≥ 10% staining or Allred score ≥ 4) unless atypia verging on DCIS in which case biomarker criterion does not apply ○ HER2 0, 1+, or 2+ by IHC if HER2 testing is performed • Histology slides reviewed and agreement between **two** clinical pathologists (not required to be at same institution) that pathology fulfils COMET eligibility criteria. In cases of disagreement between the two pathology reviews about whether or not a case fulfils the eligibility criteria, a third pathology review will be required. • At least two sites of biopsy for those cases where individual mammographic extent of calcifications exceeds 4 cm, with second biopsy benign or both sites fulfilling pathology eligibility criteria (ER/PR testing required for second biopsy) • Amenable to follow up examinations • Ability to read, understand and evaluate study materials and willingness to sign a written informed consent document • Reads and speaks Spanish or English
Exclusion Criteria	• All grade III DCIS • Male DCIS • Concurrent diagnosis of invasive or microinvasive breast cancer in either breast • Documented mass on examination or mass/hypoechoic area on imaging at site of DCIS **prior to** biopsy yielding diagnosis of DCIS, with exception of: subsequent lumpectomy or partial mastectomy (with positive DCIS margins i.e. <2mm/ink on tumor) followed by a post-surgery MMG; fibroadenoma at a distinct/separate site from site of DCIS; or diagnosis of mass/hypoechoic area as a cyst or a papilloma. In cases of uncertainty about whether the mass was present on physical examination prior to biopsy, the following criteria should be applied: if mammogram noting abnormal findings is diagnostic MMG = symptomatic/if mammogram noting abnormal findings is screening MMG = asymptomatic. If a patient has a mass on imaging that is biopsied (worked-up) and does not show invasive breast cancer, they are eligible. If a patient has a mass on initial MMG that is not seen on

	subsequent MMG, they are eligible (if initial mass occurred due to additional work-up). • Any color/bloody nipple discharge (ipsilateral breast) • Mammographic finding of BIRADS 4 or greater within 6 months prior to registration at site of breast other than that of known DCIS, without pathologic assessment • Use of investigational cancer agents within 6 weeks prior to diagnosis of DCIS • Any serious and/or unstable pre-existing medical, psychiatric, or other existing condition that would prevent compliance with the trial or consent process. • Pregnancy. If a woman has been confirmed as pregnant, she will not be eligible to take part in the trial. If she suspects there is a chance that she may be pregnant, a pregnancy test should be undertaken, although a pregnancy test for all women of child-bearing potential is not mandatory. In addition, if a woman becomes pregnant once registered to the trial, she can continue to be followed (endocrine therapy is not a mandatory requirement of the study). • Documented history of prior tamoxifen, aromatase inhibitor, or raloxifene use in the 6 months prior to registration • Current use of exogenous hormones (i.e. oral progesterone)

Study Schema (Years 1-10)

NOTE: the use of endocrine therapy in either arm (years 1-5) is non-obligatory – women can choose endocrine therapy (based on provider recommendation and personal preference), but this choice is optional and not a mandatory requirement of the trial. The study does not recommend the use of endocrine therapy after the 5-year timepoint. However, the decision about whether to continue ET should be at the discretion of the patient in consultation with their treating physician.

Alliance Foundation Trials

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1. BACKGROUND INFORMATION

1.1 Overview of Ductal Carcinoma in Situ and Patient Population

1.1.1 Overview of Ductal Carcinoma in Situ

Ductal Carcinoma in Situ (DCIS): potential risks and burdens. Annually, approximately 65 million women undergo mammographic screening in the United States at a cost of over 13 billion dollars. Almost one in 1300 mammograms will detect ductal carcinoma *in situ*, or DCIS,[1] considered the earliest detectable form of pre-breast cancer. Approximately 51,000 women in the United States will be diagnosed with DCIS this year alone, almost all of these diagnoses made in completely asymptomatic individuals.[2] DCIS is characterized by a proliferation of malignant cells confined to the milk ducts of the breast.[3] Unlike invasive breast cancer, DCIS cells remain trapped within the breast duct and therefore have little potential to spread to distant organ sites and cause symptoms or death. Without treatment, it is estimated that only 20-30% of DCIS will progress to invasive breast cancer.[4,5] However, once diagnosed, over 97% of women are treated according to current guidelines with a combination of surgery, radiation and hormonal therapy—treatments similar to those recommended to patients with invasive breast cancer.

DCIS was rarely diagnosed prior to widespread use of screening mammography. Although mammography has been shown to reduce overall breast cancer mortality by over 20%,[6] there is growing concern that for some patients, particularly those with DCIS, breast cancer screening may unintentionally cause harm by introducing additional procedures, promoting anxiety, and detecting pre-cancerous conditions that may never cause illness. Advances in epidemiology and cancer biology have shown that the group of diseases currently deemed "cancers" are actually many conditions with enormous variation in biologic behavior, and that screening uncovers some conditions that may never impact a person's overall health if left undetected.[7-11] The term "**overdiagnosis**" has been used to define these conditions including DCIS, that look like early cancer, but are not destined to cause symptoms or death during a patient's lifetime.[12] Attempts to resolve the controversy that has grown around the best management of these overdiagnosed conditions, including calls to remove the word "cancer" from their description,[13,14] have garnered intense interest, anxiety, and scrutiny from patients, their families, and other health care stakeholders.

There is a general consensus that much of this burden derives from the treatment of DCIS. Currently, almost all DCIS is treated aggressively with surgery despite the fact that other similar conditions (such as Lobular Carcinoma in Situ and Atypical Ductal Hyperplasia) are not; of those treated, the majority may not benefit if they would not have developed invasive breast cancer. An alternative to surgery is active monitoring (AM). Currently, only 3% of women in the United States with DCIS opt for AM. Thus, there has been global interest to address the issue of whether AM would be sufficient for women at low risk of progression to invasive breast disease.

1.1.2 Current Treatment Approach Indication

Current gaps in evidence. Current treatment options routinely offered for DCIS include surgery (lumpectomy or mastectomy), radiation (radiation or none) and/or hormonal therapy according to National Comprehensive Cancer Network (NCCN) treatment recommendations.[15] Between 1991 and 2010, 23.8% of women diagnosed with DCIS in the United States underwent mastectomy, 43% lumpectomy with radiation, and 26.5% lumpectomy without radiation, based on data from the Surveillance, Epidemiology, and End Points Registry.[16] Among the 97% of women with DCIS treated with

surgery, neither randomized trials or retrospective studies to date have shown a survival advantage of any treatment option over another.[16] To date, none of the treatment options has ever been compared in a rigorous fashion to AM.

Moreover, the impact of surgery and AM for DCIS on quality of life have not been carefully evaluated. Although research suggests that over 40% of women who are provided risk/benefit information regarding DCIS treatment would consider non-surgical management,[17] the clinical outcomes and patient reported outcomes (PRO) of active monitoring have never been studied. Thus women face a tremendous burden of uncertainty when considering the tradeoffs of surgery or AM for DCIS.[18,19]

1.2 Study Rationale

Overdiagnosis and overtreatment resulting from mammographic screening have been estimated to be as high as 1 in 4 patients diagnosed with breast cancer,[20-23] although the absence of standard definitions for measuring overdiagnosis has led to much uncertainty around this estimate.[24] The national health care expenditure resulting from false positive mammograms and breast cancer overdiagnosis has been estimated to approach $4 billion annually.[25] There is general consensus that much of this burden derives from the treatment of DCIS; for those estimated 40,000 women per year whose DCIS may never have progressed even without treatment, medical intervention can only harm. In those women who undergo surgical management of DCIS, there is risk of developing persistent pain at the surgical site, with estimates ranging from 25-68%.[26-29] Importantly, persistent pain after lumpectomy may be as prevalent as that after total mastectomy.[26,27,30] Persistent postsurgical pain is rated by patients as the most troubling symptom,[31] leading to disability and psychological distress, and is often resistant to management;[32] Although prospective population-based data have demonstrated significant patient and surgical focus on pain with remarkably high levels of chronic pain 4 and 9 months after breast surgery, much of these data have been collected in women with invasive breast cancer, with little data directly relevant to patients with DCIS.

1.2.1 Omitting Surgery for Ductal Carcinoma in situ

There are minimal data on the natural history of patients diagnosed with DCIS, with most published studies presenting retrospective reviews of missed diagnoses. They relate to an era of very different qualities of imaging and biopsy and do not include active monitoring by mammography. Many of the patients described in these series would not be eligible for the COMET trial and almost all presented symptomatically.

There has been interest in recent years in active monitoring for low risk DCIS, in part based upon the recognition of the tremendous biological heterogeneity in the group of conditions defined as “DCIS.” Clearly, the most controversial approach to the management of DCIS is “active monitoring,” based on the philosophy that the goal of DCIS treatment should be directed towards prevention or early detection of invasion rather than “treatment” of the DCIS lesion. The approach is based on the contention that current treatment for DCIS and early stage invasive breast cancer are not significantly different for hormone receptor-positive DCIS, and that the morbidity of treatment could be reserved for those patients who show a rapid tempo of DCIS. Much along the lines of active monitoring for early stage prostate cancer, intervention would only be undertaken with clinical progression, in the form of increased extent of DCIS or clinical evidence of invasion.

In a small retrospective study of a cohort of patients who elected to delay surgery for DCIS, 9 of 14 patients either had clinical stability without intervention or had surgery which revealed DCIS without invasion.[33] In Europe, this strategy has culminated in a recently initiated randomized clinical trial which offers active

monitoring for women with low risk DCIS. Critical to such an approach is a physician-patient relationship which includes a well-informed patient, clear communication of treatment options and risks, and mutual commitment to close and regular monitoring.

The first prospective clinical trial randomizing patients with low risk DCIS (age >45, grade 1 or 2 DCIS) to active monitoring with or without endocrine therapy was initiated in the UK in 2014. Named the "LORIS" study, the trial is aimed to determine how invasive breast cancer incidence, and overall/invasive breast cancer-specific survival are impacted with monitoring alone.[34] In the United States, the COMET study will aim to address this question in a cohort of low risk, ER-positive HER2-negative DCIS.

1.2.2 Role of endocrine therapy for DCIS

Most of the published literature on endocrine therapy for DCIS relates to the effect of endocrine therapy in the adjuvant setting. There is evidence from one placebo-controlled trial, NSABP B-24[35], that in pre- and post-menopausal patients treated for DCIS with lumpectomy and adjuvant radiotherapy, tamoxifen reduces the risk of ipsilateral local recurrence by 30% and of contralateral breast cancer by 50%.[36] The absolute risk at 5 years of any (invasive or non-invasive) breast cancer event is small (tamoxifen arm 8% and placebo arm 13%). Survival was not influenced by treatment.

A subsequent randomized controlled trial with a more complex design[37] examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS in the absence or presence of radiotherapy. In the absence of radiotherapy, tamoxifen was again associated with a 30% overall reduction in breast events through reduction in DCIS recurrence and contralateral DCIS and invasive breast cancer. Tamoxifen was however ineffective in preventing ipsilateral invasive recurrence. In the presence of radiotherapy, tamoxifen appeared ineffective. Survival was not impacted by radiotherapy or tamoxifen in this trial, with breast cancer accounting for only 20% of all deaths (2% breast deaths and 11% overall deaths).

Recently, anastrozole, an aromatase inhibitor, has been compared to tamoxifen in two large randomized trials enrolling post-menopausal women with DCIS. In NSABP B-35 which enrolled 3104 post-menopausal women who had undergone lumpectomy to clear margins and adjuvant radiation for DCIS, anastrozole treatment was associated with a small but statistically significant improvement in breast cancer free interval compared to tamoxifen (HR 0.73 [95% CI 0.56-0.96]. p=0.023), although disease-free survival was the same at 120 months (HR 0.89 [95% CI 0.75-1.07], p=0.21).[38] Among women <60 in this study (n=1447), anastrozole was associated with significant improvements in breast cancer-free interval (BCFI) and disease-free survival (DFS) compared to tamoxifen, HR 0.53 (95%CI 0.35-.080) and HR 0.69 (95% CI 0.51-0.93), respectively. However, IBIS II, which enrolled 2980 post-menopausal women with DCIS who had undergone lumpectomy to clear margins +/- radiation, failed to demonstrate an improvement with the AI compared with tamoxifen (HR 0.89 [95% CI 0.64-1.23], p=0.49).[39]

Two studies have reported the effect of preoperative endocrine therapy in DCIS. Boland and colleagues evaluated women who discontinued exogenous hormonal therapy between the time of DCIS diagnosis and surgery (14-41 days). A reduction in Ki67, ER and PR was observed in this group.[40] In a 3-month neaodjuvant trial of endocrine therapy for DCIS, postmenopausal women on letrozole had significant reduction of PR, and Ki67 as well as increase in CD68-positive cells.[41] Combined evidence from adjuvant, preoperative trials supports the suggestion that endocrine therapy may have a primary role in this setting.

1.3 Study Design

The proposed study is a Phase III large pragmatic randomized trial **c**omparing an **o**peration to **m**onitoring, with or without **e**ndocrine **t**herapy for low risk DCI**S.**

The two treatment arms are patients undergoing surgery or AM. The use of radiotherapy following surgery will be also recorded**.**

1.4 Study Design Rationale

The overarching hypothesis of the study is that management of low-risk DCIS using an active monitoring (AM) approach does not yield inferior invasive breast cancer or quality of life outcomes compared to surgery. The two arms of the trial were initially referred to as "active surveillance" and "guideline-concordant care". However, the study team decided that "active monitoring" was a more proactive and appropriate term than "active surveillance", and that "surgery" better described the primary treatment that patients would receive - as opposed to "guideline-concordant care", a term that many patients found difficult to understand.

The **primary comparator groups** are **"surgery"** and **"active monitoring (AM)"** groups for biopsy confirmed diagnosis of low-risk DCIS (see Eligibility Criteria) (date of diagnosis is defined as the date of the first pathology report that diagnosed the patient with DCIS). As a pragmatic study, patients randomized to the surgery group will choose any of the NCCN standard treatment options for DCIS[15] (with or without endocrine therapy), as they have all been shown to yield comparable breast cancer-specific survival.[16,42] Patients randomized to the AM group choose either AM without endocrine therapy, or AM with endocrine therapy, and adherence/duration of therapy noted. Randomization will be stratified based on the following factors: **age at diagnosis:** *<55, 55-65, >65;* **maximum diameter of microcalcifications**: *<2cms, 2-5cms, >5cms;* DCIS nuclear **grade**: I or II. We will collect whether the patient has had prior surgical excision for the index diagnosis; this variable will be used for subset analysis and not stratification.

Given the numerous variables for which stratification is not planned, selection biases may occur. Thus, key covariates will be collected and included in the analysis to help overcome and adjust for inherent treatment biases expected within study arms. All eligible patients must be willing to undergo either surgery or AM prior to randomization, and must not have contraindication for surgery.

Selection of patient-centered outcomes. For this proposal, patient-centered outcomes have been divided into two broad categories: **clinical outcomes** and **patient-reported outcomes**. We selected the endpoints based on the following criteria abstracted from data in response to the following questions posed to stakeholders during the grant preparation process: 1) is this endpoint important for patients and stakeholders? 2) is this endpoint evaluable during the study period? 3) will this endpoint lead to improved understanding of whether and for which patients AM has a favorable risk/benefit assessment?

We will test the association of PRO data with all breast events, including invasive or recurrent breast disease in the surgery arm, tumor progression in the AM arm, and decision to undergo surgery in the AM arm despite absence of clinical change.

PRO surveys composed of validated measures will be administered at pre-specified time points during the study; a brief overview is provided below (**see Appendix for full description of scales and survey administration schedule).** We will collect PROs identified as salient issues to women with DCIS in our prior survey (see **Appendix**), including items specific to arm and breast symptoms, body image, and decision-making.

We have carefully considered the burdens and barriers of the survey in conjunction with our patient advocate stakeholders. In so doing, we selected the number of survey items to reduce survey burden while not detracting substantially from the scientific goals. We anticipate that patients will be able to complete the full survey in approximately 30 minutes. To ensure that there is no excessive burden to patients as well as to test content flow and clarity, all surveys will be piloted with patient advocates prior to trial initiation. The surveys will be provided in print and online versions and will include the following measures (available in both English and Spanish versions):

Socio-demographics: Women will be asked about their race, education, employment and financial status using items selected from the **Alliance Patient Questionnaire** that is currently being piloted (Alliance A191401), adapted to include an item on employment status that has been tested previously in a breast cancer population and is going to be added to the next version of the Alliance Patient Questionnaire.[96-98]

Medical and Family history: We will survey women about their family history of breast/ovarian history. We will assess co-morbidities using the **Self-Administered Co-morbidity Questionnaire** (based on Charlson Co-morbidity Index and other comorbidity indices).[44]

Adherence to hormonal therapy: We will measure adherence to hormonal therapy using a Medication Adherence measure based on work from Voil et al. Specifically, we will adapt Part 1 of the two-part measure of medication adherence, which includes 3 items that evaluate the extent of non-adherence over the past week.[45,46]

Quality of Life (QOL): We will use the **SF-36**[43] **t**o measure health-related QOL. A modified 19-item version of the **Breast Cancer Prevention Trial (BCPT) Symptom Checklist** will evaluate commonly reported menopausal symptoms.[47] The **Breast-Q**, a validated instrument to evaluate outcomes following surgery, will be used to evaluate satisfaction with appearance, body and self-image, and sexual functioning.[48] Four items from the **Quality of Life in Adult Cancer Survivors** (QLACS) scale will be adapted to evaluate frequency (1=never; 7=always) of worries about DCIS, including concerns about future breast events and death from DCIS.[76] The presence, severity, and functional impact of pain will also be evaluated. Neurosensory symptoms will be assessed using 7 items from the **Breast Cancer Pain Questionnaire (BCPQ);**.[27,49,50]. We will also use the **Brief Pain Inventory**, a well-validated general measure of pain and disability worst pain, least pain, and interference.[95]

Utility: The **EQ-5D-5L** will be used to generate and evaluate QALYs. The EQ-5D-5L is a summary measure of health status for use in evaluating health and healthcare and includes five functional dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) plus a visual analog scale (EQ-VAS) that asks participants to assess how good or bad their health is today on a 0 (worst health imaginable) -100 (best health imaginable) scale.[78, 81]

Complementary therapies: We will utilize a revised form of the **CAM Questionnaire** used by Burstein et al. to assess women's use of complementary therapies. [80]

Health behaviors/lifestyle factors: Health behaviors, including physical activity, [81-85] smoking,[86-88] alcohol use,[87, 90] and diet, [91-94-] will be evaluated using items selected from the **Alliance Patient Questionnaire** that is currently being piloted (Alliance A191401).

Emotional/Psychological: To assess generalized anxiety, we will use the **State Trait Anxiety Inventory (STAI)** scale.[51] Depressive symptoms will be evaluated with the **Center for Epidemiologic Studies Depression Scale (CES-D-10).**[77] The CES-D-10 will be scored automatically by PRO Core when it is completed online by the patient or when it is data entered by study staff at DFCI. If a participant scores

10 or greater, indicative of potential depression, the PRO Core system will automatically send an email to the site principal investigator, so that symptoms can be addressed as needed. In addition, site study personnel who log in to PRO Core will be able to see the flagged survey alert. Site study personnel must complete a brief form in Pro Core indicating that the flagged survey alert has been seen and triaged as appropriate. We will assess feelings of uncertainty using the **Intolerance of Uncertainty Scale** (Short-form), which has been used in studies of active monitoring in the prostate cancer setting.[72-74] Coping will be evaluated using the **Brief COPE**, a shortened form of the COPE Inventory, inclusive of 28 items (14 subscales).[75]

Decision-making: Four items (**The SURE scale**) adapted from the **Decisional Conflict Scale** will be used to measure patients' uncertainty about participating in the COMET trial.[78, 79] The **Decision Regret Scale** will measure how women perceived their DCIS treatment/management decision including decision to participate in the trial.[52] **Sources of information** about DCIS management options will be assessed using items adapted from a prior study of surgical decision-making.[53]

Knowledge and Risk Perceptions: DCIS and breast cancer knowledge will be measured with items adapted from the **Breast Cancer Surgery Decision Quality Instrument (BCS-DQI)** as well as questions developed specifically for a study that assessed DCIS knowledge and risk perceptions.[54,55,100] We will assess risk perceptions in women with DCIS using questions developed by Lerman and Croyle[56] that were used in a prior study of psychosocial outcomes in women with DCIS.[18]

Financial burden: We will adapt items from the **National Health Interview Survey**[57] and the **Cancer Outcomes Research and Surveillance** (CanCORS) Caregiver Study[58] to assess financial burden and to estimate out of pocket expenses attributed to their DCIS diagnosis.

1.5 Study Agents

There are no drugs included within the arms of the trial as experimental agents, although the use of endocrine agents (tamoxifen or aromatase inhibitors) as adjuvant therapy within both arms of the trial are encouraged to be considered and adherence be recorded. Such endocrine agents have many decades of use in standard clinical practice and have extensive safety profiles. In the setting of DCIS, tamoxifen in both pre- and post-menopausal women is associated with reduction in the risk of ipsilateral and contralateral breast cancer events. Recent studies comparing the aromatase inhibitor anastrozole to tamoxifen in post-menopausal women have revealed that the aromatase inhibitor is similarly to slightly more effective with regard to efficacy.

Side effects and adverse events do vary between the two agents and this factor may be the rationale for choosing one agent over the other in post-menopausal women (for premenopausal women, tamoxifen is the primary hormonal therapy option).[38,59] Risks of tamoxifen include but are not limited to hot flashes, night sweats, vaginal discharge, premature cataracts as well as more serious but rare risks of uterine cancer and thrombosis. Risks of anastrozole include but are not limited to hot flashes, night sweats, vaginal dryness, musculoskeletal symptoms as well as increased risk of osteoporosis and fractures. Recent patients reported outcomes data from the NSABP B-35 trial comparing adjuvant tamoxifen to anastrozole in post-menopausal women with DCIS suggested that women treated with tamoxifen had increased severity of vasomotor symptoms, bladder control and gynecologic symptoms compared to women treated with anastrozole who reported increased severity of musculoskeletal and vaginal symptoms.[38,59] Of note, benefits were greatest in women under 60, particularly for women receiving anastrozole, but in

both arms these younger women reported had significantly worse vasomotor, vaginal and gynecologic symptoms as well as more weight gain.

1.6 Risks and Benefits

Surgery is, by definition, the prevailing standard of care for DCIS. The risks associated with surgical management of a breast lesion are well documented and include, but are not limited to, surgical and anesthetic side effects and/or complications; side effects and complications of subsequent radiotherapy following breast conservation therapy, if utilized; side effects and complications of endocrine therapy, if prescribed and taken. All local treatments may also be associated with a negative impact on cosmesis.

For surgery, the potential benefits (while uncertain on an individual patient basis) include reduced incidence of invasive breast cancer and reduced recurrence of DCIS or invasive breast disease. For endocrine therapy the impact on ipsilateral DCIS or recurrence/invasive breast cancer is uncertain, although there is a clear population-based reduction in contralateral DCIS and invasive breast cancer.

For AM, the risk of progression of DCIS to more extensive involvement of the breast or to developing invasive breast cancer is a key clinical outcome of the trial. The greatest potential risk to patients is posed by the delay in diagnosis of invasive breast cancer as a result of understaging on core biopsy. Among women who are diagnosed with low or intermediate grade DCIS without invasive breast cancer on core biopsy, the estimate of upstaging to invasive cancer upon surgical excision ranges from 0-20% in published literature.[60-62] One recent study,[62] reported a 0% upstaging among women who would have fulfilled criteria for the LORIS trial, indicating that a low risk subgroup could be identified. The impact of a delay in diagnosis of invasive breast cancer or the development of invasive breast cancer while undergoing monitoring is thought to pose a low risk to patients if detected at an early stage, although this has not been definitively shown.

Additional risks to study participation include potential distress and loss of privacy when answering questions when filling out the surveys. While the direct responses to the survey will not be shared with the participants' medical team directly, we will alert the study team (registering physician and study coordinator at site) if a participant scores 10 or greater indicative of substantial depressive symptoms on the CES-D-10.

2 OBJECTIVES AND ENDPOINTS

This trial will compare both clinical outcomes and PRO between patients treated with surgery versus AM for biopsy-proven DCIS

Primary study outcomes. Endpoints were selected in two broad categories of 1) *Clinical Outcomes* defined as those disease- and treatment-related outcomes to be collected by research staff from primary source documentation, and 2) *Patient Reported Outcomes (PRO)* which will include comprehensive domains of QOL and psychosocial outcomes collected from patient surveys.

2.1 Primary Objectives

The hypothesis is based upon a non-inferiority endpoint that ***2-year rate of invasive breast cancer diagnosis is not inferior in the AM group compared to the surgery group.*** The estimate of invasive breast cancer upstaging (i.e. identified at the time of surgery) is 10% in the surgery group. Non-inferiority will be

declared if the 2-year detection of invasive breast cancer in the AM group does not exceed 15% (based on statistical estimates).

2.2 Secondary Objectives

2.2.1 Quality of life and psychosocial outcomes:
The secondary hypothesis is based upon a non-inferiority endpoint that ***2-, 5-, 6, 8, 10 health-related quality of life, rate of anxiety, and rate of depression are not inferior in the AM group compared to the surgery group.***

2.2.2 Clinical outcomes:
The secondary hypothesis is based upon a non-inferiority endpoint that ***2-, 5-, 7- and 10-year rates of mastectomy, contralateral invasive breast cancer, and survival (both overall survival and invasive breast cancer-specific survival) are not inferior in the AM group compared to the surgery group.***

2.3 Endpoints

2.3.1 Primary endpoint: Proportion of new diagnoses of ipsilateral invasive breast cancer in surgery and AM arms at follow up of 2-years.

2.3.2 Secondary endpoints:

- Quality of life and psychosocial outcomes;
    - Health related QOL at baseline, 6 months, 1 year, annually year 2-6, biannually thereafter.
    - Anxiety/depression at baseline, 6 months, 1 year, annually year 2-6, biannually thereafter.
    - Coping at baseline
    - Intolerance of uncertainty at baseline and 2 years
- Clinical outcomes
    - Mastectomy rate at 2, 5, 7 and 10 years
    - Breast conservation rate at 2, 5, 7 and 10 years
    - Contralateral invasive breast cancer rate at 2, 5, 7 and 10 years
    - Overall survival and invasive breast cancer-specific survival at 2, 5, 7, and 10 years
    - Ipsilateral invasive breast cancer rate in surgery and AM arms at 5, 7 and 10 years

2.3.3 Exploratory endpoints:

- Breast MRI utilization at 2, 5, 7 and 10 years
- Breast biopsy rate at 2, 5, 7 and 10 years
- Radiation rate at 2, 5, 7 and 10 years
- Chemotherapy rate at 2, 5, 7 and 10 years
- Self-reported co-morbidity at baseline, 6 months, 1 year, annually year 2-6, biannually thereafter.
- Adherence to hormonal therapy at 6 months, 1 year, annually year 2-6, biannually thereafter.
- Health behavior/lifestyle factors at 6 months and 2 years
- Symptoms, pain, body image, sexual function at baseline, 6 months, 1 year, annually year 2-6, biannually thereafter.

- Quality of decision making at baseline and 2 years
- Decisional regret at 1 year, annually year 2-6, biannually thereafter.
- Knowledge and risk perceptions at baseline and 2 years
- Decisional conflict at baseline
- Financial burden at 6 months
- Employment status at baseline, 6 months, 1 year, annually year 2-6, biannually thereafter.
- Use of complementary therapies at 6 and 24 months

3 PATIENT SELECTION/POPULATION

The trial population will reflect that of patients undergoing treatment for DCIS at participating ALLIANCE sites that have representation from all race/ethnicities and socioeconomic classes; the study population will reflect this diversity and thus improve generalizability to the overall population of women diagnosed with DCIS. Study participants will be patients at participating ALLIANCE sites who present for a treatment consultation for a new DCIS diagnosis and who are considered at low risk. Patients for randomization will be required to meet the inclusion criteria outlined at 3.1.

3.1 Inclusion Criteria

- Diagnosis of unilateral, bilateral, unifocal, multifocal or multicentric DCIS without invasive breast cancer (date of diagnosis defined as the date of the first pathology report that diagnosed the patient with DCIS) **OR:** atypia verging on DCIS **OR:** DCIS + LCIS (mix and/or separate locations in the same breast)
- A patient who has also had a lumpectomy or partial mastectomy with margins positive for DCIS (i.e. <2mm/ink on tumor) as part of their treatment for a current DCIS diagnosis is eligible (post-excision mammogram required at enrollment to establish a new baseline)
- No previous DCIS or invasive breast cancer in ipsilateral breast 5 years prior to current DCIS diagnosis
- 40 years of age or older at time of DCIS diagnosis
- ECOG performance status 0 or 1
- No contraindication for surgery
- Baseline imaging (must include dimensions):
    - unilateral DCIS: contralateral normal mammogram ≤ 6 months of registration and ipsilateral breast imaging ≤ 120 days of registration (must include ipsilateral mammogram; can also include ultrasound or breast MRI)
    - bilateral DCIS: bilateral breast imaging ≤ 120 days of registration (must include bilateral mammogram; can also include ultrasound or breast MRI)
    - DCIS s/p lumpectomy: post excision mammogram on side of excision ≤60 days of registration
- Pathologic criteria:
    - All grade I DCIS (irrespective of necrosis/comedonecrosis)
    - All grade II DCIS (irrespective of necrosis/comedonecrosis)
    - Absence of invasion or microinvasion
    - Diagnosis of DCIS confirmed on core needle biopsy, vacuum-assisted biopsy or surgery ≤ 120 days of registration

- ER(+) and/or PR(+) by IHC (≥ 10% staining or Allred score ≥ 4) unless atypia verging on DCIS in which case biomarker criterion does not apply
- HER2 0, 1+, or 2+ by IHC if HER2 testing is performed

- Histology slides reviewed and agreement between **two** clinical pathologists (not required to be at same institution) that pathology fulfils COMET eligibility criteria. In cases of disagreement between the two pathology reviews about whether the case fulfils the eligibility criteria, a third pathology review will be required.
- At least two sites of biopsy for those cases where individual mammographic extent of calcifications exceeds 4 cm, with second biopsy benign or both sites fulfilling pathology eligibility criteria (ER/PR testing required for second biopsy)
- Amenable to follow up examinations
- Ability to read, understand and evaluate study materials and willingness to sign a written informed consent document
- Reads and speaks Spanish or English

3.2 Exclusion Criteria

- All grade III DCIS
- Male DCIS
- Concurrent diagnosis of invasive or microinvasive breast cancer in either breast
- Documented mass on examination or mass/hypoechoic area on imaging at site of DCIS **prior to** biopsy yielding diagnosis of DCIS, with exception of: subsequent lumpectomy or partial mastectomy (with positive DCIS margins i.e. <2mm/ink on tumor) followed by a post-surgery MMG; fibroadenoma at a distinct/separate site from site of DCIS; or diagnosis of mass/hypoechoic area as a cyst or a papilloma. In cases of uncertainty about whether the mass was present on physical examination prior to biopsy, the following criteria should be applied: if mammogram noting abnormal findings is diagnostic MMG = symptomatic/if mammogram noting abnormal findings is screening MMG = asymptomatic. If a patient has a mass on imaging that is biopsied (worked-up) and does not show invasive breast cancer, they are eligible. If a patient has a mass on initial MMG that is not seen on subsequent MMG, they are eligible (if initial mass occurred due to additional work-up).
- Any color/bloody nipple discharge (ipsilateral breast)
- Mammographic finding of BIRADS 4 or greater within 6 months prior to registration at site of breast other than that of known DCIS, without pathologic assessment
- Use of investigational cancer agents within 6 weeks prior to diagnosis of DCIS
- Any serious and/or unstable pre-existing medical, psychiatric, or other existing condition that would prevent compliance with the trial or consent process
- Pregnancy. If a woman has been confirmed as pregnant, she will not be eligible to take part in the trial. If she suspects there is a chance that she may be pregnant, a pregnancy test should be undertaken, although a pregnancy test for all women of child-bearing potential is not mandatory. In addition, if a woman becomes pregnant once registered to the trial, she can continue to be followed (endocrine therapy is not a mandatory requirement of the study).
- Documented history of prior tamoxifen, aromatase inhibitor, or raloxifene use in the 6 months prior to registration.
- Current use of exogenous hormones (i.e. oral progesterone)

3.3 Inclusion of Women and Minorities

Technically, women of all races and ethnic groups are eligible for this trial. However, the trial is currently limited to English- and Spanish-speaking patients only.

4 METHOD OF TREATMENT ASSIGNMENT

4.1 Stratification Factors

Randomization will be stratified based on the following factors: **age at diagnosis:** *<55, 55-65, >65;* **maximum diameter of microcalcifications**: *<2cms, 2-5cms, >5cms;* DCIS nuclear **grade**: I or II. We will collect whether the patient has had prior surgical excision for the index diagnosis; this variable will be used for subset analysis and not stratification.

4.2 Treatment Assignment

The study is designed to provide a 1:1 randomization of all patients to surgery or AM.

4.3 Treatment Blinding

Given the nature of the two study arms, there will be no treatment blinding.

5 TREATMENT PLAN

5.1 Surgery Arm

5.1.1 Baseline

Baseline data will be collected, to include details of medical history, and details of recommended surgical therapy, including whether patient would be a candidate for lumpectomy.

5.1.2 Treatment

5.1.2.1 Surgery

Patients randomized to the surgery arm will undergo appropriate surgery for DCIS according to local guidelines. It is expected that patients will complete definitive surgery within 60 days of randomization. Data on all related surgical procedures, including data on immediate or delayed breast reconstruction, will be collected.

5.1.2.2 Radiotherapy

The recommendation for post-surgical radiotherapy should be decided following surgery and prescribed according to standard local protocols. The use of post-surgical radiotherapy is not mandated within the trial. However, data on the use of radiotherapy will be collected.

5.1.2.3 Endocrine Therapy

The use of endocrine therapy is not mandatory within the trial but will be discussed with each patient on the surgery arm. Selection of endocrine therapy will be determined based on provider recommendations and patient preferences and administered for a maximal duration of 5 years. If applicable, data on the use of endocrine therapy (type, duration, adherence, and side effects) will be captured at each visit.

Participants in the surgery arm of the study will meet with a provider to discuss the option of endocrine therapy following surgery, including side effects of treatment. The provider can be either a surgical oncologist or medical oncologist who is informed regarding endocrine systemic treatment options for DCIS. If the patient elects endocrine therapy, it will be prescribed by the treating physician following surgery according to standard dosing and schedule used for routine breast cancer chemoprevention. Prescriptions will be provided directly to the patient or to the pharmacy of patient's choice and will not be provided by the study.

All follow up and monitoring will be conducted according to the standard of care of each provider and institution, dependent on whether the patient elects or declines endocrine therapy. The provider will also exercise their best clinical judgment regarding the necessity for baseline laboratory testing (e.g. liver function tests, triglycerides) and imaging (e.g. bone scan) as determined by the institution's and individual provider's routine standard of care.

5.1.2.4 Use of Genomic Health DCIS Score

The use of the Genomic Health DCIS Score is allowed within both arms of the trial if requested by the patient or her clinician but will not be used to determine eligibility for the trial.

5.2 Active Monitoring (AM) Arm

5.2.1 Baseline

Baseline data will be collected, to include details of medical history and medication use.

5.2.2 Treatment

5.2.2.1 Surgery

Patients in the Active Monitoring arm will not undergo primary surgery and will only undergo surgery if there is documentation of invasive breast progression requiring surgical intervention. If the patient opts for surgery in the absence of invasive breast progression, they will be considered as having declined the arm to which they were specifically randomized (see Section 11.2); in this case they will be offered an option to continue to complete follow-up.

5.2.2.2 Endocrine Therapy

The use of endocrine therapy is not mandatory within the trial but will be discussed with each patient on the AM arm. Selection of endocrine therapy will be determined based on provider recommendations and patient preferences and administered for a maximal duration of 5 years. If applicable, data on the use of endocrine therapy (type, duration, adherence, and side effects) will be captured at each visit.

Participants in the AM arm of the study will meet with a provider to discuss the option of endocrine therapy, including side effects of treatment. The provider can be either a surgical oncologist or medical oncologist who is informed regarding endocrine systemic treatment options for DCIS. If the patient elects endocrine therapy, it will be prescribed by the treating physician according to standard dosing and schedule used for routine breast cancer chemoprevention. Prescriptions will be provided directly to the patient or to the pharmacy of patient's choice and will not be provided by the study.

All follow up and monitoring will be conducted according to the standard of care of each provider and institution, dependent on whether the patient elects or declines endocrine therapy. The provider will also exercise their best clinical judgment regarding the necessity for baseline laboratory testing (e.g. liver function tests, triglycerides) and imaging (e.g. bone scan) as determined by institution and individual provider routine standard of care.

5.2.2.3 Use of Genomic Health DCIS Score

The use of the Genomic Health DCIS Score is allowed within both arms of the trial if requested by the patient or her clinician but is not used to determine eligibility for the trial.

5.3 Follow-up protocol in Surgery and AM Arms

5.3.1 Pre-Treatment Criteria

There are no specific pre-treatment laboratory criteria for participation in this trial. However, it is anticipated that at minimum, patients will undergo routine blood tests prior to surgery or initiation of endocrine therapy according to standard of care, consisting of CBC, electrolytes, BUN, creatinine, and glucose. Additional lab tests may be obtained at the discretion of the care team subject to standard procedure at each site.

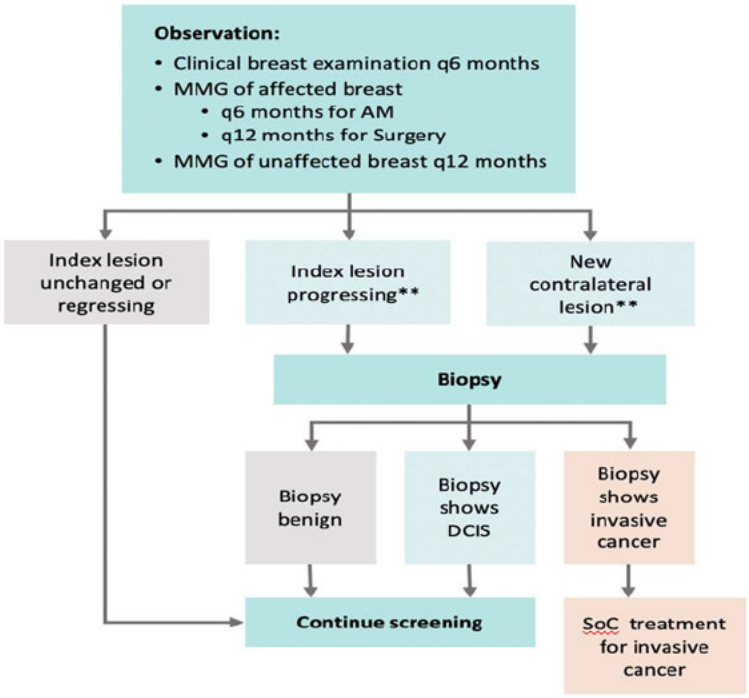

Figure 1. Follow-up protocol in AM arm for COMET Trial. **Criteria for progression: a) New **mass**/architectural **distortion**/ **density** on mammogram in either breast according to ACR Breast Imaging Reporting and Data System (BI-RADS); b) Increase in extent of calcifications ≥ 5mm in at least one dimension compared to the most recent prior MMG of the index breast; c) New **suspicious** findings on other radiologic studies (US, MRI) in either breast (i.e. hypoechoic area).

5.3.2 Diagnosis of Ipsilateral Breast Events

Investigational biopsies will be performed in both study arms, as deemed clinically appropriate by the patient's treatment team for suspicion of a new breast event (DCIS or invasive) in the ipsilateral breast. The resulting pathology slides from the biopsy will be reviewed by two pathologists and managed according to the following diagnoses:

Histologic diagnosis	Surgery arm	AM arm
Invasive breast cancer	Proceed to standard surgery for invasive breast cancer	Proceed to standard surgery for invasive breast cancer
DCIS	Proceed to standard surgery for DCIS	Return to routine follow up
Benign breast disease	Return to routine follow up	Return to routine follow up

5.3.3 Diagnosis of Contralateral Breast Events

Investigational biopsies will be performed in both study arms, as deemed clinically appropriate by the patient's treatment team for suspicion of new DCIS (high grade) or invasive cancer in the contralateral breast. The resulting diagnosis will be managed according to best standard practice according to provider recommendations and patient preferences. If the new contralateral diagnosis is a DCIS that fulfills criteria for the COMET study, the patient will be offered AM or surgery for this diagnosis. Treatment information will be collected and recorded.

5.3.4 Survival

If the patient is in clinical follow up years 0-5, sites must report patient deaths by completing the Patient Status form and Adverse Event forms immediately upon being made aware of the event. If the patient is in clinical follow up years 6-10 or survival follow up only, the patient status form needs to be completed annually.

6. STUDY ASSESSMENTS AND PROCEDURES

Close follow up of outcomes in each group is critical to the validity of the proposed comparisons. Following registration and consent at the initial clinic visit, baseline demographic information and data regarding clinical presentation will be collected. All clinical outcome data will be collected by a trained clinical research assistant who has received GCP and HIPAA training. All registered patients will be asked to complete the **baseline survey** on paper after they have been registered (but prior to being randomized), with the follow-up surveys completed at specified time-points (either on-line or on paper) (see Section 7.1.3 Patient-Reported Outcomes describing the procedures for survey data collection.) Once registered to the trial, patients will be randomized to one of the treatment arms within four weeks; the monitoring period will start on the date of registration.

6.1. Assessment Types

6.1.1 Clinical Examination Assessment Plan

For both the surgery and AM groups, required clinical follow-up **years 1-5** will consist of:

- Clinical examination including history and physical examination every 6 months.
- Unilateral mammography (MMG) of the affected breast every 12 months in the surgery arm; not required if patient has had mastectomy of the affected breast.
- Unilateral mammography (MMG) of the affected breast every 6 months in the AM arm.
- MMG of the unaffected breast every 12 months in both arms; not required if patient has had mastectomy of the unaffected breast.
- All mammograms should be performed within 4 weeks of each clinic visit.

For the surgery and AM groups, required clinical follow-up **years 6-10** consists of:

- Clinical examination including history and physical examination every 12 months (both arms).
- Bilateral mammogram every 12 months (both arms) (*mammogram not required if patient has had mastectomy of both the index and the unaffected breast).*
- For patients on the AM arm, the study does not require 6-monthly MMG after the 5-year timepoint. However, *the decision about whether to continue 6-monthly MMG should be at the discretion of the patient in consultation with their treating physician.*
- The study does not recommend the use of endocrine therapy after the 5-year timepoint. However, *the decision about whether to continue ET should be at the discretion of the patient in consultation with their treating physician.*

Standardized case report forms will be completed for each scheduled study visit. In the surgery group, treatment data, including surgery and radiation if received, will be collected. For both groups, the use of endocrine therapy will be recorded. We will also collect clinical outcomes, including procedures, interventions, and recurrence history since the last visit. More frequent clinic visits or additional imaging studies other than those required by the study protocol will be accommodated and recorded. All radiology

and pathology reports as well as the primary source image data will be uploaded to the ALLIANCE central imaging data submission portal.

6.1.2 Imaging Assessment Plan

Clinical criteria for DCIS progression and indications for biopsy or treatment will be left to the best clinical judgment of the treating provider, together with the patient. ***Pragmatic clinical criteria requiring additional work up include the following:***

- New breast mass on clinical examination in either breast
- Other new breast signs including nipple/skin retraction, nipple discharge, breast edema/erythema in either breast.

Radiographic criteria for DCIS progression and indications for biopsy or treatment will be left to the best clinical judgment of the treating provider, together with the patient and breast imagers at each site. ***Pragmatic radiographic criteria for biopsy recommendation during follow up are the following:***

- New **mass**/architectural **distortion***/**density*** on mammogram in either breast according to *ACR Breast Imaging Reporting and Data System (BI-RADS) for mammography in assessment of masses and calcifications.[63]
- Increase in extent of calcifications ≥ 5mm in at least one dimension compared to the most recent prior MMG in the index breast.
- New **suspicious** findings on other radiologic studies (US, MRI) in either breast (i.e. hypoechoic area).

For all routine mammograms, patients will be informed of the result of the mammogram within 1 week of the date of the mammogram. If a patient fails to schedule or keep a mammogram appointment, a second appointment will be scheduled. If the patient fails to keep the second appointment, the patient will be contacted by telephone. The site research team must make every effort to ensure that patient contact details are up to date.

Diagnostic or surgical procedures other than those required by the protocol, as well as any change in management (e.g. participant in AM arm wishes to proceed with surgery in the absence of clinical and/or radiographic progression or participant in surgery arm decides not to proceed with surgery) and reason for change will be recorded, along with the findings prompting the recommendation or decision. In addition, any recommendations for management declined by the patient will also be recorded.

6.1.3 Patient Reported Outcomes

Survey instruments for the project have been carefully selected to provide the most relevant patient centered outcomes (see Section 1.3). Questionnaire packets will be completed at baseline, 6, 12, 24, 36, 48, 60, 72, 96, and 120 months; a gap year letter will be sent to participants at months 84 and 108 (the years when a survey packet is not being sent) from UNC PRO Core in the same way that they receive the survey packets (either by email or by mail). This patient-reported outcome data collection will be conducted using the PRO Core survey platform, which enables web-based questionnaire completion, automated email reminders, data entry of paper forms, and tracking of participant survey completion. Surveys will be available in English or in Spanish. Language preference for each participant will be noted in PRO Core at baseline and can be changed throughout the study. Detailed information (screenshots, etc.) about how to use PRO Core for this study is provided in the training slide deck. The baseline questionnaire will be completed on paper after the patient has registered for the study (but prior to randomization). It will be data-entered into PRO Core by the site study staff and a copy will be kept on file at the site. The baseline questionnaires should be uploaded to Pro-Core.

The 6-, 12-, 24-, 36-, 48-, and 60-month follow-up questionnaires must be completed within an 8-week survey window, which begins on the scheduled survey date and ends 8 weeks later on the survey expiration date; the 72-month follow-up questionnaire must be completed within a 52-week survey window, which begins on the scheduled survey date and ends 52 weeks later on the survey expiration date; the 96-, and 120-month follow-up questionnaires must be completed within a 16-week survey window, which begins on the scheduled survey date and ends 16 weeks later on the survey expiration date. All these dates are indicated in PRO Core. The follow-up questionnaires will be completed online if the participant has an email address and regular internet access (i.e., checking email at least once a week). It will be completed on paper if the participant does not have email and regular internet access, or if the participant prefers to complete it on paper. However, all follow-up questionnaires should be completed using the electronic version if possible. Alternatively, the site study coordinator may call the participant and collect the data via phone interview (i.e. reading the questionnaire to the participant and marking their answers on the paper questionnaire form).

The participant's preferred method of contact for the follow-up surveys (e.g., mailed paper survey or emailed survey link) and their contact information (e.g., mailing address or email address, respectively) must be noted in PRO Core at baseline and can be changed throughout the study. Participants who are completing the follow-up questionnaires online will be emailed a unique link to the web-based questionnaire. For the 6-, 12-, 24-, 36-, 48-, and 60-month follow-up questionnaires, the email will be sent automatically by the PRO Core system on the scheduled survey date, and again at 2, 4, and 6 weeks thereafter if the questionnaire has not been completed; for the 72-month follow-up questionnaire, the email will be sent automatically by the PRO Core system when the survey becomes available (e.g., on the scheduled survey date), and again every 2 weeks thereafter up to 7 times if the questionnaire has not been completed; for the 96-, and 120-month follow-up questionnaires, the email will be sent automatically by the PRO Core system on the scheduled survey date, and again at 2, 4, 6, 8, 10, 12, and 14 weeks thereafter if the questionnaire has not been completed.

Participants who are completing the follow-up questionnaires on paper will be mailed a questionnaire packet within the first week of the scheduled survey date. The packet will contain the questionnaire and a stamped envelope addressed to the data entry staff at DFCI who will scan and upload a copy of the questionnaire into PRO Core, and subsequently enter the data into PRO Core. Sites that have tablet or desktop computers in their clinic available for patients to use privately and securely may have patients complete the baseline and follow-up questionnaires online during their clinic visit. If the site is going to have the participant complete the questionnaire on paper in clinic, a copy of the questionnaire can be printed from the website of AFT. If a participant needs to complete a follow-up questionnaire at a clinic visit, site staff should update the participant's survey mode in PRO Core prior to the scheduled survey date.

Each participant's survey completion must be monitored by the site study staff through the tracking and reporting functionality of PRO Core. For the 6-, 12-, 24-, 36-, 48-, and 60-month follow-up questionnaires, site study staff will call participants who have not completed an online survey or returned a paper survey by week four, to provide a reminder and to answer any questions; for the 72-month follow-up questionnaire, site study staff will call participants who have not completed an online survey or returned a paper survey every 4 weeks for up to 12 weeks from when the survey became available to provide a reminder and to answer any questions; for the 96-, and 120-month follow-up questionnaires, site study staff will call participants who have not completed an online survey or returned a paper survey by week

four, week eight, and week twelve, to provide a reminder and to answer any questions. Survey completion rates will be reviewed on a monthly basis by the investigative team for the duration of the study. Participants who have opted to complete the questionnaires online will be emailed a reminder about their upcoming annual/bi-annual follow-up questionnaire approximately 2 months before that time as a reminder, engagement and retention strategy. In this correspondence, we will also remind participants about the website and thank them for their continued contributions to the study. Participants who have opted to complete the questionnaire on paper will not be mailed a reminder because the paper questionnaire packet itself is substantial and includes text thanking them for their continued contribution to the study.

Engagement with the DCIS Website: We will assess engagement with the website associated with this study (cometstudy.org) by asking participants on the baseline survey to tell us how they heard about the study, whether they knew about the cometstudy.org website, whether they have visited the website, and if so, whether they found the content useful. We will also have detailed data on use of the website that will be used to assess rate of engagement with the website. Although these variables are not key outcomes, these data will provide some indication of the role of the website component of this research and help to inform future research, care and communication efforts surrounding both DCIS and clinical trials in general.

7. STUDY ASSESSMENT TABLE

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. There are no mandatory lab tests required for this study; if no labs are drawn per physician discretion (based on routine site practice), that is acceptable. It is expected that patients on this study will cared for by physicians experienced in the treatment and supportive care of patients on this trial. Date of registration is Day 1 on study.

TABLE 1. Schedule of Eligibility Screening and Clinical Follow up

	Eligibility Screening	REGISTRATION	Day 1-28	Further event (DCIS or IBC)[8]	Day 1-180	Every 6M (years 0-5)	Every 12M (years 1-5)	Every 12M (years 6-10)[9]
Tests & Observations								
History/physical	X					X		X
Weight, height	X							
Pulse, Blood Pressure	X							
Randomization			X					
Biospecimen collection								
Blood sample			X	X			X[1]	X[1]
Tissue sample			X	X				
Imaging studies[2]								
Contralateral MMG							X (both arms)	
Ipsilateral MMG[3]	X			X		X (AM arm)	X (surgery arm)	
Bilateral MMG[4]	X							X (both arms)
Therapeutic procedures								
Surgery[5]					X			
Radiation (optional)[6]					X			
Discuss endocrine therapy (both arms)					X			
#Adverse Events[7]								
Report AEs (both arms)					X	X	X	

[1] For patients registered after August 14, 2020

[2] if routine bilateral MMG performed on an annual basis, it can be used for the contralateral MMG findings also (not required if patient has had mastectomy of the indicated breast)

[3] ipsilateral mammogram ≤ 120 days of registration (can also include ultrasound or breast MRI)

[4] bilateral mammogram ≤ 6 months of registration

[5] for surgery arm only

[6] for surgery arm only (optional)

[7] Record any new AE (or increase of a documented pre-existing condition from screening/history) within 30 days (see also section 9.1.1 - Routine Adverse Event Reporting)

[8] up to four weeks after a further event (DCIS or invasive breast cancer) occurs

[9] if patient cannot attend in person, status update can be collected over the phone (patient does not have to provide blood draw or submit MMG)

All follow up visits (including imaging) will take place at scheduled month +/- 4 weeks. Time points should be based on day 1 (date of registration); however, if there is an out of window visit, all subsequent visits should use that timepoint as the date of reference.

Table 2: Schedule of PRO surveys

	Baseline	Month 6	Month 12	Month 24	Month 36, 48, 60, 72, 96, 120
Socio-demographics					
ALLIANCE Patient Questionnaire, adapted with employment items[94, 95, 96, 97]	X	X - Employment	X - Marital status - Health insurance - Household size/income - Employment	X - Marital status - Health insurance - Household size/income - Employment	X - Marital status - Health insurance - Household size/income - Employment
Medical and Family History					
Family history	X				
Self-Administered Co-Morbidity Questionnaire[44]	X	X	X	X	X
Genetics			X		
Complementary Therapies					
CAM Measure[78]		X		X	
Adherence to hormonal therapy					
Medication Adherence measure[45,45]		X	X	X	X
Health behaviors/lifestyle factors					
ALLIANCE Patient Questionnaire Smoking[84-87] Alcohol[85-88] Physical activity[79-83] Diet[89-92]		X		X	
Psychological/Emotional					
STAI Trait Y2[51]	X				
STAI State Y1[51]	X	X	X	X	X
CES-D-10 [75]	X	X	X	X	X
Brief COPE[73]	X				

Intolerance of uncertainty- Short form[70-72]	X			X	
Quality of life					
SF-36[43]	X	X	X	X	X
EQ-5D-5L[78, 79]	X	X	X	X	X
QLACS[74]	X			X	
Breast-Q (arm, breast side effects, body image, sexuality)[48]	X	X	X	X	X
Modified BCPT symptom scale (menopausal symptoms)[47]	X	X	X	X	X
Breast Cancer Pain Questionnaire – Neuropathic symptoms [27,49,50]	X	X	X	X	X
Brief Pain Inventory[93]	X	X	X	X	X
BC/DCIS knowledge and perceptions					
BCS-DQI[54,98]	X			X	
True/False questions [55]	X			X	
Risk perceptions[56]	X			X	
Decision-making					
Decisional regret[52]			X	X	X
SURE scale[76, 77]	X				
Sources of information[53]	X				
Costs					
Financial burden (adapted from CanCors, NHIS)[57,58]		X			
COMET website questions					
How participant learned about COMET Use of website	X	X			

8. ADVERSE EVENTS

8.1. Adverse Events - General Overview

Per the International Conference of Harmonization (ICH) guidelines, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

8.1.1 Routine Adverse Event Reporting

For the COMET study, patients will receive surgery, radiation therapy, or hormonal therapy. The toxicity profiles of these standard treatments for DCIS have been well described.

Adverse event (AE) data collection and reporting, are done to ensure the safety of patients enrolled in the study. AEs will be reported from study entry until 5 years after registration.

Preexisting conditions will be recorded as part of medical history during Screening. Any new AEs or increase of a documented preexisting condition from screening/history will be recorded from the time of study registration through the end of year 5 on study. AEs are reported in a routine manner at scheduled times according to the study calendar in section 8. All AEs are entered into the eCRFs in Rave.

The following are regarded as expected AEs for the purpose of the study:

- AEs related to image-guided biopsy
- AEs relating to adjuvant treatment for primary breast cancer or recurrence, such as AEs relating to endocrine therapy (examples include tamoxifen, anastrozole)
- AEs relating to radiotherapy such as hematoma, wound infection or seroma
- AEs relating to surgery such as hematoma, wound infection, or seroma.

If an AE occurs that does not meet the criteria above the AE should be reported in RAVE. To report any AEs other than those listed on the *Adverse Events: Solicited form*, answer "Yes, and reportable adverse events occurred" to the question "Were (other) adverse events assessed during this reporting period?" at the bottom of the eCRF. This will roll out the *Adverse Events: Other* form in the same folder in Rave for the reporting of these other AEs.

Some AEs may not be assessed if tests or procedures are not specifically required within the protocol.

AEs should be reported so that they can be monitored and compared between groups, it is unlikely that AEs will be related to active monitoring, due to the minimal nature of this treatment. Therefore, it is expected that AEs will frequently be considered "unrelated to active monitoring". Detection of invasive disease is not an AE, thus this should be recorded elsewhere in the CRF.

8.1.2 Solicited Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical study are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies with similar treatments. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Table 1. For this study, the Forms "Adverse Events: Solicited" and "Adverse Events: Other" are used for routine AE reporting in RAVE. AE reporting is only required during years 1-5 of the study (it is not required years 6-10).

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited and severity graded at each reporting period.

- Allergic Reaction
- Arthralgia
- Fever
- Hot Flashes
- Myalgia
- Acute Coronary Syndrome
- Ischemia Cerebrovascular
- Hypertension
- Nausea
- Fracture
- Osteoporosis
- Cholesterol (High)

8.1.3 Expedited Adverse Event Reporting

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the AFT and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. SAEs must be entered into Rave as applicable within 24 hours of learning of the event. This will allow the safety monitor to review the information and assess the safety of the patient.

8.1.4 Severe Adverse Event Reporting Requirements

Severe Adverse Events (SAEs) will be reported from study entry until 5 years after registration.

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS
NOTE: Investigators **MUST** immediately report to the sponsor (AFT) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
7) Or is a new cancer (that is not a condition of the study).
8) Or is associated with an overdose.

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to AFT via Rave and within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization > 24h	Enter into Rave within 24h of the sites awareness of the event			
Not resulting in Hospitalization ≥ 24h	Not required to enter into Rave		Enter into Rave within 24h of the sites awareness of the event	

9. DATA COLLECTION AND MANAGEMENT

9.1 Data Collection and Submission

Data collection for this study will be conducted through the Medidata Rave electronic data capture (EDC) system, accessible via the AFT website. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System.

PRO data will be collected predominantly through the PRO Core system hosted at the University of North Carolina (UNC). Staff permissions and access to PRO Core will automatically be granted to any site staff who also have access to the Medidata Rave EDC system. PRO Core data are stored in a secure enterprise-level Oracle database; the databases and web servers are hosted by the UNC Center for Bioinformatics. The approaches for submitting PRO data are described for each survey time-point in Section 7.1.3; the approaches include data entry of baseline paper forms into PRO Core by site staff, mailing follow-up paper surveys directly from patient to DFCI for data entry into PRO Core, and patient completion of the questionnaire online.

9.2 Data Confidentiality

Patient medical information is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law.

10 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

10.1 Overview of the Study Design

The general analytic approach is a prospective randomized trial design where the hypothesis is based upon a non-inferiority endpoint, namely that *2-year invasive breast cancer detection rate is not inferior in the AM group compared to the surgery group* (see **Study Schema**).

10.2 Sample Size, Accrual Time and Study Duration

Power and Sample Size Considerations. Sample size for this study was estimated using a 2-group test of non-inferiority of proportions, with the 2-year invasive breast cancer rate in the surgery group assumed to be 0.10 based on published studies.[61,62] The non-inferiority margin assumed was 0.05. Based on a 1-sided un-pooled z-test, with alpha=0.05, a sample size of n=446 per group will have 80% power[64] to detect the specified non-inferiority margin. The proportion of patients who decline the arm to which they are specifically randomized can diminish the estimate of treatment difference, and could also widen the confidence bounds, but the analytical approaches proposed here aim to diminish the impact on bias of the treatment difference. With a 3-year duration of accrual and 2 additional years of follow-up, we anticipate approximately 148 total events.

Analysis of Primary Outcome (See below for outcomes definitions). This trial was designed anticipating non-acceptance of arm allocation, and the proportion of patients that do not accept their arm allocation can lead to bias in estimates of treatment differences. Thus, we plan to complete several analyses of the primary outcome, reporting the primary intent to treat (ITT) analysis as well as sensitivity analyses that are intended to reduce the bias in estimation of treatment difference in this setting.

We assume that a clinically acceptable difference in 2-year invasive cancer diagnosis rate in order to conclude non-inferiority is 5%. Cumulative incidence curves will be used to estimate the invasive cancer diagnosis rates over time, and at the 2-year point, the difference in rates will be estimated and a 1-sided upper confidence bound of (AM-GCC) will be computed, using methods described by Austin.[65] We will conclude that AM is not inferior to Surgery if the upper confidence bound on the risk difference at 2 years is less than 5%.

ITT Analysis. The ITT analysis of 2-year invasive cancer diagnosis rate will be conducted using all patients, as randomized, and will be completed using Kaplan-Meier estimates, stratified by group, combined with the Greenwood's confidence interval. The difference in invasive cancer risks will be computed from the Cox model with treatment at 2 years, with a 1-sided 95% confidence interval of the difference (AM-GCC) computed.

Sensitivity analyses. Several sensitivity analyses are planned, including a per protocol analysis, as treated analysis, an instrumental variable analysis, as well as a principal stratification analysis.[68,69] The sensitivity analysis will account for loss of follow-up, rejection of randomization allocation and withdrawals, and pre-randomization factors influencing rejection of randomization, described in further detail below.

Intent-to-treat (ITT) analysis is typically the standard in reporting results of clinical trials. However, in the presence of rejection of randomization allocation (here defined as selecting surgery when randomized to AM, and choosing AM when randomized to surgery), ITT results can be biased;[66-68] similarly per protocol (PP) and as-treated (AT) analyses could yield biased estimates, especially since these analyses may no longer maintain balance achieved by randomization. Cuzick et al[66] outline an approach to measure treatment effect among compliers, which follows the randomization (e.g. ITT), but assures that the estimates are not diluted by allocation changes. Thus, studies using this approach are similarly powered to ITT analysis, but provide appropriately wider confidence limits, which will be critical in a non-inferiority study. Principal stratification approaches can improve upon the width of confidence intervals and can

allow for covariate adjustment to aid in this improvement. Additionally, the covariates can aid in identifying subgroups with differential clinical response or treatment preference.

We recognize the potential to lose patients to follow-up; yet, we consider approaches that could still provide some level of information for all patients who were randomized. Dunn et al[67] describe instrumental variable methods with inverse probability weighting for missing data and latent class models as two approaches to deal with loss to follow-up. Each approach makes assumptions, most of which are feasible for this trial, but we will report the assumptions as well as the comparative analyses in the literature and disseminate findings. We will also assess sensitivity to departures from these assumptions through simulation studies.

At interim time-points as the study is enrolling, we plan to assess the level of withdrawal from the study completely, as well as the level of rejection of allocation or later changes in treatment (can only occur in Active Monitoring arm). We will utilize these levels to carry out simulation studies, but with parameters based upon ranges around our observations during the trial enrollment in order to assess our ability to maintain unbiased results of the treatment differences, particularly in the context of a non-inferiority setting. We will also implement sensitivity to the assumptions made in these simulations, including missing data mechanism (MD-5). If all of the approaches are generally equal in reducing bias, we will report on the approach that maintains alpha level and appropriate non-inferiority conclusion as our primary focus, but will also report the other approaches as comparators. The simulation results will be reported as evidence supporting conclusions, when applicable.

***Participant subgroups and planned subgroup analyses*.** We hypothesize that both clinical outcomes and PRO measures may be dependent upon treatment arm and patient characteristics. Pre-specified subgroups for assessment of heterogeneity of treatment effect will include (1) **endocrine therapy** (yes/no as well as duration of therapy); (2) **choice of surgery** (lumpectomy or mastectomy); (3) **receipt of radiation** (yes/no); (4) **mode of monitoring** (q 6 month MMG versus additional imaging, i.e. ultrasound or MRI); (5) **race** (African-American women compared to white women; other minorities will also be assessed for HTE, but precision is likely to be low); (6) **menopausal status (**pre-or post-menopausal, as reported by the patient); (7) **baseline risk of invasive breast cancer** based on modified Gail Score; (8) **burden of co-morbidities** at diagnosis which will impact the magnitude of clinical benefit derived from surgery for DCIS. These subgroup analyses will be completed using methods described by Austin[65] to estimate the average treatment effect (ATE) and the average treatment effect for the treated (ATT), using adjusted Cox models. The ATE would answer the question about how outcomes would change if a policy was instituted that all patients eligible for either therapy were only offered the "experimental therapy", which here is Active Monitoring. We also consider the use of time-dependent methods for endocrine therapy and receipt of radiation therapy, using the Austin approaches as well, with time-dependent covariates in the Cox models.

Definitions of outcomes

Subsequent local breast events (SLBE) events are coded as one of the following types:

- ***iINV:*** Ipsilateral invasive in-breast cancer (includes chest wall recurrence)
- ***iCIS:*** Ipsilateral in situ in-breast cancer
- ***cINV:*** Contralateral invasive in-breast cancer (includes chest wall recurrence)
- ***cCIS:*** Contralateral in situ in-breast event cancer
- ***iLX:*** Ipsilateral lymph node cancer
- ***cLX:*** Contralateral lymph node cancer

Distant breast cancer metastasis (DistMet) is the only non-SLBE breast event considered

Ipsilateral invasive breast event is defined as first occurrence of either of the following:

(i) *ipsilateral invasive breast cancer*,

(ii) ipsilateral lymph node cancer *in the absence* of a preceding ipsilateral invasive breast cancer event,

(iii) distant breast cancer metastasis *if none* of the following events have occurred previously: ipsilateral invasive breast cancer, contralateral invasive breast cancer, ipsilateral lymph node cancer, contralateral lymph node cancer.

(iv) breast cancer death *if none* of the following events have occurred previously: ipsilateral invasive breast cancer, contralateral invasive breast cancer, ipsilateral lymph node cancer, contralateral lymph node cancer, distant breast cancer metastasis.

Ipsilateral breast event (in situ or invasive) is defined as first occurrence of either of the following:

(i) *ipsilateral invasive breast cancer* (see definition above)

(ii) ipsilateral in situ breast cancer

Censoring vs Ignoring of events

For all time to event analysis (Kaplan-Meier, Cox models), we have to assign to each occurrence one of the following actions (Table 3):

Time to event outcome	Ipsilateral invasive breast event	Ipsilateral breast event	Disease-specific survival	Overall survival
Ipsilateral invasive in-breast cancer	Event	Event	Ignore	Ignore
Ipsilateral in situ in-breast cancer	Ignore	Event	Ignore	Ignore
Contralateral invasive in-breast cancer	Ignore	Ignore	Ignore	Ignore
Contralateral in situ in-breast event cancer	Ignore	Ignore	Ignore	Ignore
Ipsilateral lymph node cancer	Event if no prior iINV	Event if no prior iINV	Ignore	Ignore
Contralateral lymph node cancer	Ignore	Ignore	Ignore	Ignore
Distant breast cancer metastasis	Event if no prior iINV or cINV or cLX or iLX	Event if no prior iINV or cINV or cLX or iLX	Ignore	Ignore
Death from breast cancer	Event if no prior iINV or cINV or cLX or iLX or DistMet	Event if no prior iINV or cINV or cLX or iLX or DistMet	Event	Event
Death from breast-cancer unrelated cause	Censor	Censor	Censor	Event
Loss to follow-up	Censor	Censor	Censor	Censor

Table 3. See SLBE coding section for abbreviations of iINV, cINV, iLX, cLX and DistMet

Planned subgroup analyses (NCDB Special Study). The large DCIS registry developed through collaboration with the National Cancer Database (NCDB) will allow for the continued collection of long-term outcomes for patients as well as for the comparison of primary and secondary outcomes (when measurable in NCDB) for **AM versus surgery** amongst those patients who are randomized and accept their arm allocation versus those patients who are randomized but do not accept their arm allocation versus patients not registered or randomized to COMET, but who generally meet our broad inclusion criteria for the trial. Patients will be identified from all study sites during the time interval of COMET accrual. These analyses will be from predominantly non-randomized patients, so we plan to utilize observational study approaches for analyses. We will use full regression models (logistic or Cox model, dependent upon outcome measure) to control for potential confounders, including pathology, age, race, academic versus community setting, among others. As in other analyses, we will utilize inverse-probability weighting to handle missing data.[70]

Analyses of long-term outcomes. Analyses of long-term outcomes will follow the approaches outlined above, modifying the year of rate calculations, accordingly. PRO data will utilize longitudinal linear mixed models over time, following appropriate scoring and transformation, if needed.

10.3 Stratification Factors

Randomization will be stratified based on the following factors:

- **Age at diagnosis:** *<55, 55-65, >65*
- **Maximum diameter of microcalcifications**: *<2cms, 2-5cms, >5cms*
- DCIS nuclear **grade**: I or II

We will collect whether the patient has had prior surgical excision for the index diagnosis; this variable will be used for subset analysis and not stratification.

10.4 Data Safety Monitoring Board (DSMB) Reporting

The COMET trial will be subject to bi-annual formal review at the Alliance Foundation DSMB meetings. At each meeting we will utilize a template report formulated for use in Alliance trials, with appropriate modifications for the COMET follow-up study.

10.5 Supplementary/Secondary Analysis Plans

***Planned Analysis for PRO data*:** For analyses of PRO endpoints, we will use t-tests and ANOVA to compare unadjusted mean scores for health-related PRO measures at baseline. We will use linear mixed-effects models to assess change in these domains over time. Among women who are allocated to surgery, we will examine differences by surgery type (e.g., lumpectomy followed by radiation vs. unilateral mastectomy vs. bilateral mastectomy) and compare changes between these groups over time. In addition to baseline disease and socio-demographic data, information relating to other treatment (e.g., endocrine treatment, radiation) as well as co-morbidities will allow us to control for potential confounding by these factors. We will also analyze the decision-making, DCIS knowledge, and risk perception data at baseline and compare these domains between the surgery and AM groups. We plan to measure risk perceptions and knowledge again at 2 years and will assess change between the two time points in each group using t-tests (e.g., for continuous scores) and McNemar's test (e.g., proportion correctly perceiving their risk).

10.6 Duration of Follow-Up

Participants in both arms of the study will be followed for 10 years from time of registration. For the surgery and AM groups, required monitoring **years 1-5** consists of the following:

- Clinical examination including history and physical examination every 6 months.
- Unilateral mammography (MMG) of the affected breast every 12 months in the surgery arm; not required if patient has had mastectomy of the index breast.
- Unilateral mammography (MMG) of the affected breast every 6 months in the AM arm.
- MMG of the unaffected breast every 12 months; not required if patient has had mastectomy of the unaffected breast

After 5 years, participants in both arms will undergo physical examination and bilateral mammogram every 12 months; mammogram is not required if patient has had mastectomy of both the index and the unaffected breast (for additional information on required clinical follow-up (years 6-10), see Section 7.1.1.).

10.7 Survival Follow up

Any study participant can choose to withdraw from the study at any time for any reason, including no specified reason. Patients in the surgery arm cannot opt for the AM arm after surgery, but in the event that a patient withdraws from the study, the date of withdrawal and reason for withdrawal will be recorded. The patient will be censored in time-to-event analyses at the date of withdrawal from the study

Patients in the AM arm may choose to either withdraw from the study or opt to proceed with surgery at any time. In the event that a patient in the AM arm opts to proceed with surgery in the absence of invasive progression, the date of withdrawal and reason for withdrawal will be recorded. As for the surgery arm, in the event that a patient withdraws from the study, the patient will be censored at the date of withdrawal from the study.

Patients in the AM arm with progression to invasive breast cancer are required by the study protocol to proceed with surgery for their invasive breast cancer. Patients who have invasive breast progression and do not wish to have surgery will continue to remain in follow up with their invasive cancer event recorded, at the time of invasive breast progression for the primary analysis. For further exploratory analyses, the lack of surgery for these patients will be recorded.

For patients who choose to no longer be followed per the protocol schedule, the patient can choose to enter the Survival Follow-up Phase. Survival data, ongoing adjuvant therapies and subsequent disease progression data will be collected during this phase of the study every 12 months for 10 years from registration. Telephone contact is acceptable as well as medical record review.

Follow-up will be discontinued early due to:

- Patient Death
- Patient Withdrawal of consent for all follow-up
- Patient deemed lost to follow-up

10.8 Criteria for Taking a Patient Off Study

Patients will be recorded at the time of death from any cause, and depending upon cause, may contribute to an invasive cancer event. Date and cause of death will be recorded. Patients lost to follow up will be defined as those patients for whom clinical data is not available for ≥ 24 months. Those patients will be censored at 24 months from last contact.

10.9 Study Monitoring (Reports, Summaries)

Enrollment and AE/SAE reports will be completed every 6 months from study initiation and submitted to the AFT office and the DSMB.

10.10 Data and Safety Monitoring

Interim Reports from the statistical team will be generated for the Data and Safety Monitoring Board (DSMB), as per the safety monitoring plan.

11 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING (ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES)

11.1. Compliance with Trial Enrollment and Results Posting Requirements

The trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their health-related conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2. Regulatory and Ethical Compliance

By signing the protocol, the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his/her personnel as well as the IRB. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

11.3. Informed Consent

If potential participants wish to speak with a patient advocate about the trial or any other aspect of the study, they will be provided with the contact details of a member of the COMET Patient Leadership Team (PLT). All participants (both potential and registered) will be provided with access to educational materials specifically designed by the PLT to inform them about the study, as well as to support decision making between options allowed in each arm following randomization.

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

It is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed Informed Consent Form must comply with the ICH GCP guideline and regulatory requirements

11.4. Responsibilities of the Investigator/IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312(21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.
Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The Investigator is responsible for ensuring all patients are informed about the study and that written consent is obtained prior to the conduct of any study related procedures. In addition, the Investigator is responsible for reviewing all health-related information collected for each study patient in order to identify any safety related issues/adverse events (AE).

As specified in 21CFR 312.62 (Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, medical records that are applicable for this study and source documents, the protocol, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) (see Appendix 1) in a timely manner. Due to the limited nature of the study protocol signature pages, medical licenses, IRB member lists and regulatory documents including GCP and CVs for the Sub-Investigators will not be collected.

11.5. Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff.

11.6. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB.

11.7. Retention of Records (Study Documentation, record keeping, and retention of records)

Any records and documents relating to the conduct of this study and the distribution of ICFs, eCRFs, PRO data, must be retained by the study chair until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

11.8. Data Confidentiality

Patient medical information, both associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will in general not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

11.9. Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

Rave EDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to AFT within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

The Clinical Research Coordinator (CRC) or designated study site personnel will complete the eCRF within 5 days following a subject visit and queries are to be addressed within 5 days from the date issued. Subjects will not be identified by name in the study database or on any study documents to be collected by the AFT (or designee), but will be identified by a site number, subject number.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto ergs. Each eCRF must be reviewed for accuracy by the Investigator, corrected as necessary, and then approved.

At study completion, when the database has been declared to be complete and accurate, the database will be locked.

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself. The Investigator must obtain AFT's written permission before disposing of any records, even if retention requirements have been met.

11.10. Site Auditing

The Investigator grants permission to AFT (or designee), and appropriate regulatory authorities to conduct auditing of all appropriate study documentation. Investigator sites may be audited by AFT under the AFT site audit program.

11.11. Data and Safety Monitoring Board (DSMB)

The Alliance Foundation Trials Data Safety Monitoring Board (DSMB) will be monitoring this study to ensure objectivity and the safety of participants. The DSMB will meet twice each year either by face-to-face meeting or by teleconference. At each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DSMB will also review formal interim analyses of the outcome data. If necessary, the DSMB will recommend study closure or modifications. Any DSMB

recommendations for changes to the study will be circulated to investigators in the form of addenda to this protocol document.

Reports provided to the DSMB will include accrual data, adverse events, and results of interim analyses when available. In determining whether the trial should be continued, the DSMB will consider the results of each interim analysis, as described above. The DSMB will also consider the evidence regarding safety, i.e. adverse events, and the feasibility of completing the trial, i.e. the accrual rate. Weighing the adverse events and the feasibility of study completion is complex and therefore no particular cut-offs of these measurements are provided in advance. The DSMB will use its discretion in weighing these measurements.

11.12. Regulatory Reporting

It is the responsibility of the investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy. As this is an IND exempt study, some regulations do not apply.

11.13. Audits and Inspections

To enable evaluations and/or audits from regulatory authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of AFT-25.

11.14. Publication of Study Protocol and Results

Initial results of the study will be published following analysis performed once a follow up time of 2 years has been achieved. Additional planned analyses at 5-, 7- and 10-year follow up will be conducted and reported. Publication in the instance of early termination will depend upon the number of patients accrued at the time of termination. A plain-language study result summary will also be produced and distributed to trial participants and public venues, including clinicaltrials.gov.

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this trial. No investigator may present or publish any portion of this trial without written approval from AFT.

12. BIOSPECIMEN COLLECTION

Biospecimen collection is a required component of this protocol, in order to perform future correlative science objectives. Please see the COMET (AFT-25) Correlative Science Manual for additional details with regard to sample processing, labeling, and shipping.

12.1 Sample Collection

Consent for biospecimen collection will be required of all study participants. Once consent is obtained, the study site will request the FFPE tissue samples from: 1) the diagnostic core or vacuum-assisted biopsy of the primary DCIS or surgical excision specimen of the DCIS from those patients who entered the study after initial excision; and 2) diagnostic core or vacuum-assisted biopsy or surgical excision specimen of the invasive breast cancer, if diagnosed.

Each site will submit a representative paraffin block up to four weeks after registration and also up to four weeks after a further event (DCIS or invasive breast cancer) occurs; sites will also submit a block up to four weeks after a biopsy where benign breast disease is diagnosed. If a block cannot be submitted, 20 unstained tissue slides will be requested. If it is not deemed possible to submit 20 slides in the pathologist's or histologist's best judgement, as many slides as possible will be sent without compromising the diagnostic integrity of the block.

In addition, for patients registered before August 14, 2020, 24 ml peripheral blood (or as much as can reasonably be drawn) will be collected for cell-free tumor DNA analysis and constitutional DNA from white blood cells (1 x 8ml Whole Blood/2 x 8ml Plasma for cfDNA in three separate tubes), up to four weeks after registration and will be collected up to four weeks after a further event (DCIS or invasive breast cancer) occurs and up to four weeks after a biopsy where benign breast disease is diagnosed. For patients registered after August 14, 2020, 32 ml peripheral blood (or as much as can reasonably be drawn) will be collected for cell-free tumor DNA analysis and constitutional DNA from white blood cells (1 x 8ml Whole Blood/3 x 8ml Plasma for cfDNA in four separate tubes), up to four weeks after registration and annually thereafter. This amount of blood will also be collected up to four weeks after a further event (DCIS or invasive breast cancer) occurs and up to four weeks after a biopsy where benign breast disease is diagnosed. Specialized blood collection and shipping materials will be provided to enrolling sites.

12.2 Specimen Tracking System Specimen Submission Instructions

Specimens for patients registered on this study must be logged and shipped using the online Alliance Foundation Trials Specimen Tracking System (AFT.BioMS). All institutions may access this system via the Alliance Foundation Trials Web site (https://alliancefoundationtrials.org).

A copy of the Shipment Packing Slip produced by the AFT.BioMS System must be printed and placed in the shipment with the specimens. USE OF THE SPECIMEN TRACKING SYSTEM IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM. For procedural help in logging and shipping specimens, please refer to the AFT.BioMS User Guide, which can be accessed via the Help link on the AFT.BioMS web site. To report technical problems with the AFT.BioMS, such as login issues or application errors, and/or for further assistance using the application, please email the AFT.BioMS helpdesk at [redacted].

12.3 Sample Shipping

The AFT Biorepository at Washington University will be the lead correlative study center for this retrospective tissue-based study. Collaborating sites will send FFPE tissue slides and peripheral blood samples (as described above) for central archiving and storage.

A method of shipping that is secure and traceable will be used. Extreme heat precautions will be taken when necessary.

Collaborating sites will send FFPE samples for analysis to the following address:

AFT Biorepository at Washington University
c/o Siteman Cancer Center Tissue Procurement Core
425 S. Euclid Avenue
BJCIH Building, Room 5120
St. Louis, MO 63110-1005
[redacted]

13. Future Biomedical Research

Submission of biospecimens is a required component of this trial and an integrated part of the consent process. In the event that it is physically impossible to submit required biospecimens, however, patients may still be enrolled to the trial without biospecimen submission. Biospecimens will be used to address future biomarker correlative science questions that are relevant to this treatment trial. This may include genomic and epigenomic analysis, central histopathology review, immunohistochemical studies, and other molecular biomarker studies. All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), a CAP-accredited biorepository at Washington University in St. Louis, until biospecimen accrual and clinical follow-up is sufficiently complete to allow for the design and execution of specific correlative analyses using 'state-of-the-art' analytical platforms that will be available at that time.

Such biomarker research will address emergent questions not described elsewhere in this protocol. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments in the context of this trial. Proposals for future correlative research will undergo rigorous scientific, programmatic, and statistical review by AFT, and biospecimens will only be released to those investigators who have obtained appropriate regulatory approval and demonstrate adequate funding to successful complete proposed research aims. AFT will ensure that all collected specimens are used only for approved research protocols.

Anonymized (de-identified) data generated from biospecimens used for future correlative research, including somatic and constitutional (germline) genomic data, may be shared with other researchers or deposited in a publicly accessible or controlled-access data repositories. Correlative study results and data will not be returned to individual patients.

14. IMAGING REPOSITORY

14.1 Image Collection

Image collection is a required component of this protocol, in order to perform future correlative science objectives.

From the date of this protocol revision, collaborating sites will submit ALL mammograms to the Imaging and Radiation Oncology Core (IROC) Quality Assurance Review Center (QARC). If breast ultrasound, breast MRI, contrast-enhanced mammography, and/or image guided breast biopsies is performed during the surveillance or study period, those images with corresponding reports are also requested for submission.

In addition, a request will be made to submit ALL retrospective imaging previously undertaken at each site for AFT-25 that *has not been required for QARC submission under previous versions of the protocol.*

If a core/vacuum-assisted biopsy or surgical procedure is performed for a finding identified during follow up on either the AM or surgery arm, the last diagnostic mammogram that immediately predates the core/vacuum-assisted biopsy or surgical excision (with positive DCIS margins) will be requested for each event. Four standard screening views as well as all diagnostic views, including all magnification views are requested.

Image Type	Status	Required	Ship To
Mammography	Screening and diagnostic mammogram immediately predating diagnostic core/vacuum-assisted biopsy or surgical biopsy (with positive DCIS margins)	Four standard screening views plus all diagnostic and magnification views	Quality Assurance Review Center
Mammography	Diagnostic mammogram immediately predating core/vacuum-assisted biopsy or surgical biopsy (with positive DCIS margins) performed for a finding identified during follow up	Four standard screening views plus all diagnostic and magnification views	Quality Assurance Review Center

Diagnostic imaging data may be submitted in digital/electronic format on CD-ROM to QARC, although **submission via sFTP is preferred**; duplicate films or printouts will not be collected. De-identified digital mammograms will be in DICOM format with PHI redacted. Screen-film mammograms will be digitized using mammography grade scanners, with PHI blocked during scanning or digitally cropped out after scanning. De-identification will be performed with procedures approved by each institution's IRB and/or information security office. It will be emphasized that the software used to de-identify images does not remove the date of the scan. Other PHI will be replaced with the protocol number and Patient Study ID.

Collaborating sites will also provide a copy of mammography reports for the images, with PHI redacted except for exam date in month/year. This will be provided electronically in each subject's image folder. These files may also be submitted in digital/electronic format on CD-ROM to QARC, although **submission via sFTP is preferred**. Multiple studies for the same patient may be submitted on one CD/DVD; however, only one patient will be submitted per CD/DVD. QARC will be available for questions or more information.

Digital data submission instructions including instructions for obtaining a sFTP account, can be found at www.QARC.org, following the link labeled digital data. Alternatively, if submission via sFTP is not feasible, the imaging may be burned to a CD and mailed to QARC at the address below, as explained in the prior paragraphs.

All images and reports should to be shipped to the address below:

IROC Rhode Island QA Center - QARC
UMass Chan Medical School
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
[redacted]

NOTE: If protocol therapy is discontinued early then QARC must be notified of the reason(s) and the date the patient stopped therapy. The notification must be submitted in writing via email to: [redacted] or [redacted].

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