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The COMET (Comparison of Operative to Monitoring and Endocrine Therapy) Trial: A phase III randomized trial for low-risk ductal carcinoma in situ (DCIS)

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ABSTRACT

INTRODUCTION: Ductal carcinoma in situ (DCIS) is a non-invasive non-obligate precursor of invasive breast cancer. With guideline concordant care (GCC), DCIS outcomes are at least as favorable as some other early stage cancer types such as prostate cancer, for which active surveillance (AS) is a standard of care option. However, AS has not yet been tested in relation to DCIS**.** The goal of the COMET (Comparison of Operative to Monitoring and Endocrine Therapy) trial for Low-Risk DCIS is to gather evidence to help future patients consider the range of treatment choices for low-risk DCIS, from standard therapies to active surveillance. The trial will determine whether there may be some women who do not substantially benefit from current GCC and who could thus be safely managed with AS. This protocol is version 5 (July 11th 2018). Any future protocol amendments will be submitted to Quorum IRB/local IRBs for approval via the sponsor of the study (Alliance Foundation Trials).

METHODS AND ANALYSIS: COMET is a phase III, randomized-controlled clinical trial (RCT) for patients with low-risk DCIS. The primary outcome is ipsilateral invasive cancer rate in women undergoing GCC compared to AS. Secondary objectives will be to compare surgical, oncological and patient-reported outcomes. Patients randomized to the GCC group will undergo surgery as well as radiotherapy when appropriate; those in the AS group will be monitored closely with surgery only upon identification of invasive cancer. Patients in both the GCC and AS groups will have the option of endocrine therapy. The total planned accrual goal is 1200 patients.

ETHICS AND DISSEMINATION: The COMET trial will be subject to bi-annual formal review at the Alliance Foundation Data Safety Monitoring Board (DSMB) meetings. Interim analyses for futility/safety will be completed annually, with reporting following Consolidated Standards of Reporting Trials (CONSORT) guidelines extension for non-inferiority trials.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- COMET is a phase III randomized-controlled clinical trial (strength)
- The comparator arms are very different from each other (limitation)
- Ongoing data collected from women who decline randomization will provide valuable information about the potential for selection bias/enable the study to be made more generalizable (strength)
- There exists considerable variation between pathologists in the diagnosis of DCIS (limitation)

INTRODUCTION

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] with more than 50,000 women in the United States diagnosed with DCIS each year. Almost all diagnoses are made in completely asymptomatic individuals.[2] Without treatment, it is estimated that only 20-30% of DCIS will progress to invasive cancer.[3,4] However, once diagnosed, over 97% are treated according to current guidelines with a combination of surgery, radiation and endocrine therapy—treatments similar to those recommended for patients with invasive breast cancer.

The term "overdiagnosis" has been used to define conditions that look like early cancer, but are not destined to cause symptoms or death.[5] In 2013, an independent review commissioned by the Department of Health in the UK established that screening saves lives but also that overdiagnosis exists.[6] There is a general consensus that much of the overdiagnosis and overtreatment burden in breast cancer derives from the treatment of DCIS. Currently, almost all DCIS is treated according to guideline-concordant care (GCC); of those treated for low-risk DCIS, some patients will not benefit if they never develop invasive breast cancer. One possible approach to GCC for low-risk lesions is active surveillance (AS). Currently, only 3% of women in the United States with DCIS opt for AS. Given that much of the treatment for low-risk DCIS may represent overtreatment there has been global interest to address whether AS, with intervention only for invasive cancer, would be sufficient for those women unlikely to have a future DCIS or invasive breast cancer.

Current gaps in evidence. Current treatment options routinely offered for DCIS include surgery (lumpectomy or mastectomy), radiation, and endocrine therapy. These options constitute GCC according to National Comprehensive Cancer Network (NCCN) treatment recommendations.[7] Between 1991 and 2010, 23.8% of women diagnosed with DCIS in the United States underwent unilateral mastectomy (4.5% bilateral mastectomy), 43% lumpectomy with radiation, and 26.5% lumpectomy without radiation.[8]

Published UK screening data suggest that in some cases, major surgical 'cancer' treatment of low-risk DCIS is unnecessary, inappropriate and misleading for the recipient.[9] In those women who undergo surgical treatment for DCIS, there may be both short- and long-term morbidities, including poor cosmesis and the risk of developing persistent pain at the surgical site, with estimates ranging from 25-68%.[10-13] In addition, patients may experience complications from radiation (cardiac or pulmonary symptoms, secondary malignancies) or reconstruction (infection, loss of implant, need for multiple surgeries). To date, among the 97% of women with DCIS treated with GCC, neither randomized trials nor observational studies have shown a survival advantage of any one treatment option over another.[14] Moreover, none of the treatments has ever been compared in a rigorous fashion to AS. The COMET (Comparison of Operative to Monitoring and Endocrine Therapy for Low-Risk DCIS) is a 5-year phase III, randomized-controlled clinical trial (RCT) that commenced on July 1st 2016. The study was designed with a specific objective: to determine the risks and benefits of GCC compared to those of AS for low-risk DCIS. This protocol is based on version 5 (dated July 11th 2018). Any future protocol amendments will be submitted to Quorum central institutional review board (IRB) or local IRBs, in accordance with institutional requirements, via the sponsor of the study (Alliance Foundation Trials).

METHODS AND ANALYSIS

Trial Design and Setting. COMET is a phase III randomized clinical trial for low-risk DCIS (Figure 1) with two comparator arms, GCC and AS. The study, funded by the Patient-Centered Outcomes Research Institute (PCORI), is conducted through the Alliance for Clinical Trials in Oncology cooperative group network with plans to open at up to 100 sites in the United States (a list of currently activated sites can be found at clinicaltrials.gov - NCT02926911). Patients with a new diagnosis of DCIS are identified at participating Alliance study sites and screened for eligibility. Written informed consent is obtained prior to randomization by site staff, including consent for the potential use of biological specimens in future studies (Appendix 1). Alliance has obtained a Certificate of Confidentiality from the Department of Health and Human services (DHSS) in order to protect the privacy of individuals who are subjects of research by

withholding their names and other identifying characteristics from all persons not connected with the conduct of Alliance research.

Data collection activities are embedded within the Alliance Statistics and Data Center (SDC) infrastructure. Resource and data management for the trial follow the established Alliance standard operating processes for the collection, storage, and analysis of on-line case report forms and other data. These procedures have been established for Alliance clinical trials. This includes all quality assurance processes that are in place for Alliance clinical trials as well as the use of Medidata RAVE as the electronic data capture tool.

Eligibility Criteria. Inclusion criteria for COMET were designed to select a group of English- and Spanish-speaking patients at low risk for invasive progression based upon retrospective epidemiologic data. Low-risk criteria were identified for clinical, radiologic, and pathologic features. As a pragmatic trial, central review of imaging and pathology is not performed in real time, but reviewed post hoc. However, given the known limited inter-reviewer correlation between pathologists in the diagnosis of DCIS, the inclusion criteria require that at least two pathologists deem that the histological features meet COMET pathology eligibility criteria. A complete list of COMET inclusion and exclusion criteria are presented in Table 1.

Table 1. Eligibility Criteria for the COMET trial

Inclusion Criteria	Exclusion Criteria
✓ New diagnosis of DCIS without invasive cancer	× All Grade III DCIS
✓ Unilateral, bilateral, unifocal, or multifocal DCIS	× Male DCIS
✓ A patient who has had a lumpectomy with positive margins as part of their treatment for a current DCIS diagnosis is eligible	× Concurrent diagnosis of invasive or microinvasive breast cancer in either breast prior to randomization
✓ No previous history of breast cancer (DCIS or invasive cancer) in either breast prior to current DCIS diagnosis	× Documented mass on examination or imaging at site of DCIS prior to biopsy yielding diagnosis of DCIS
✓ 40 years of age or older at time of DCIS diagnosis	× Bloody nipple discharge or skin changes associated with DCIS
✓ ECOG performance status 0 or 1	× Mammographic finding of BIRADS 4 or greater within 6 months of registration at site other than that of known DCIS, without pathologic assessment
✓ No contraindication for surgery	× Use of investigational cancer agents within 6 weeks
✓ Baseline imaging: ▪ Unilateral DCIS: contralateral normal mammogram ≤ 6 months of registration and	

ipsilateral breast imaging ≤ 120 days of registration ▪ Bilateral DCIS: bilateral breast imaging ≤ 120 days of registration ✓ Pathologic criteria: ▪ ADH suspicious for DCIS ▪ Any grade I or grade II DCIS ▪ Absence of invasion or microinvasion ▪ Diagnosis confirmed on core needle, vacuum-assisted or surgery ≤ 120 days of registration ▪ ER(+) and/or PR(+) by IHC (≥ 10% staining or Allred score ≥ 4) ▪ HER2 0, 1+, or 2+ by IHC if HER2 testing is performed ✓ Histology slides reviewed and agreement between two clinical pathologists that pathology fulfils COMET eligibility criteria. ✓ At least two sites of biopsy for those cases where mammographic extent of calcifications exceeds 4 cm, with second biopsy benign or both sites fulfilling pathology eligibility criteria ✓ Amenable to follow up examinations ✓ Ability to read, understand and evaluate study materials and willingness to sign a written informed consent document in Spanish or English	prior to diagnosis × Any serious and/or unstable pre-existing medical, psychiatric, or other existing condition that would prevent compliance with the trial or consent process × Pregnancy × Documented history of prior tamoxifen, aromatase inhibitor, or raloxifene in last 6 months

Allocation and Randomization. Allocation and randomization is conducted by Alliance site staff. Randomization is computer-generated via Medidata RAVE and stratified based on the following factors: age at diagnosis: *<55, 55-65, >65;* maximum diameter of microcalcifications: *<2cms, 2-5cms, >5cms;* and DCIS nuclear grade: I or II. We record whether the patient has had prior surgical excision for the index diagnosis; this variable will be used for subset analysis but will not be a stratification factor.

Use of endocrine therapy is permitted in both arms with adherence and duration of therapy recorded. Although women are not recruited to the COMET trial if they do not agree to randomization, those women who are consented but then decline randomization (or their allocated arm) are still eligible to continue participation in the study if they agree to provide follow up and survey data. The demographics of the cohort declining their allocated arm will be compared with those of women who adhere to the

randomization. It is anticipated that these data will provide valuable information about the potential for selection bias and will ultimately enable the study to be made more generalizable.

Both intent-to-treat and per protocol analyses can be biased in the presence of drop-out, non-compliance [15, 16]. Thus, we intend to complete both of these analyses as sensitivity analyses, but the primary analysis approach will be based upon an estimate of the treatment effect among those who comply with arm allocation [17].

STUDY ARMS

Guideline-concordant care. *Surgery:* Patients randomized to the GCC 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. If a patient randomized to the GCC arm opts for AS, they will be considered as a "cross-over" and will continue to participate in completion of Patient Reported Outcome surveys.

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

Active Surveillance. Patients in the Active Surveillance arm will not undergo surgery unless a biopsy during surveillance documents invasive disease which requires surgical intervention. If the patient opts for surgery in the absence of invasive cancer, they will be considered as a "cross-over" and will continue to participate in completion of Patient Reported Outcome surveys. Figure 2 presents the surveillance protocol for patients on the AS arm of the study.

Endocrine Therapy. The use of endocrine therapy is not mandatory but patients are encouraged to discuss this with their providers in both arms of the trial. Selection of endocrine therapy will be determined

based on provider recommendations and patient preferences, and administered for a maximum duration of five years. If applicable, data regarding the use of endocrine therapy (type, duration, adherence, and side effects) will be captured at each visit and patient-reported adherence will be measured in follow-up surveys.

All additional follow-up and monitoring beyond that required per protocol (described below), will be conducted according to the standard of care from each provider and institution. 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. breast MRI, DXA scanning).

SURVEILLANCE PROTOCOL

For both the GCC and AS groups, required surveillance consists of clinical examination, including history and physical examination, every six months for a minimum of five years and every 12 months thereafter, up to ten years from the time of registration. Patients on the GCC arm who have not had a mastectomy will have bilateral mammography annually; those on the AS arm will have ipsilateral mammography every six months and contralateral mammography every 12 months (Table 2).

TABLE 2. Schedule of Eligibility Screening and Clinical Follow up

		Eligibility Screening		Day 1-180	Every 6 months through year 5	Every 12 months through year 5	Every 12 months year 5-7
Tests & Observations	History and physical	X	Registration		X		X
	Weight, height	X					
	Pulse, Blood Pressure	X					
	Randomization			X			
Imaging studies[β]	Contralateral MMG					X	
	Ipsilateral breast imaging	X[γ]			X (AS only)	X (GCC only)	
	Bilateral MMG	X[γ]					X
tic pr	Surgery			X (GCC only)			

	Radiation			X (GCC only)			
	Discussion regarding endocrine therapy. Initiation if patient opts for treatment			X			

Clinical criteria requiring further investigation include: new breast signs and symptoms such as new breast mass; nipple/skin retraction; nipple discharge; and breast edema/erythema on clinical examination in either breast. Radiographic criteria for biopsy include an increase in extent of calcifications ≥ 5mm in at least one dimension compared to the most recent prior MMG in the index breast as well as new suspicious findings on other radiologic studies (US, MRI) in either breast (Table 3).

Table 3. Criteria for Potential DCIS Progression and Indications for Biopsy

Clinical criteria
• 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
• New mass* /architectural distortion*/ density* on surveillance mammogram in either breast according to *ACR Breast Imaging Reporting and Data System (BI-RADS) for mammography in assessment of masses and calcifications[18] • 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

Duration of Follow-Up. Progression, recurrence, new primary disease, residual DCIS (or an additional DCIS lesion) and mortality status will be collected up to ten years from randomization.

OUTCOMES

Endpoints were selected in two broad categories: 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* which include an array of relevant quality of life and psychosocial outcomes collected from patient surveys (Table 4).

Table 4. COMET Trial Primary and Secondary Endpoints

	Clinical Outcomes	QOL and Psychosocial Patient Reported Outcomes
Primary Endpoints	**2-year:** Ipsilateral invasive cancer rate **5, 7-year:** Ipsilateral invasive cancer rate	
Secondary Endpoints	**2-year:** Mastectomy/breast conservation rate Contralateral invasive cancer rate Overall survival and disease-specific survival **5, 7-year:** Overall survival and disease-specific survival	**Baseline, 6 months, years 1-5:** Health-related QOL Anxiety and depression **Baseline, 2 years:** Intolerance of uncertainty **Baseline:** Coping
Other Endpoints	**6-12 month:** Number of radiologic studies Number of biopsies Number of procedures Rate of crossover and dropout **2-year:** Breast MRI rate Breast biopsy rate Radiation rate Chemotherapy rate **5, 7-year:** Radiation rate Chemotherapy rate	**Baseline, 6 months, years 1-5:** Pain and other symptoms Body image and sexual function Employment status Self-reported co-morbidity **6 months, years 1-5:** Adherence to hormonal therapy **6 months, 2 years:** Health behavior/lifestyle factors Use of complementary therapies **Years 1-5:** Decisional regret **Baseline, 2 years:** Quality of decision-making Knowledge and risk perception **6 months:** Financial burden **Baseline:** Decisional conflict

Primary Clinical Outcomes. *Ipsilateral Breast Events.* Investigational biopsies will be performed in both study arms for suspicion of a new DCIS or invasive breast cancer in the ipsilateral breast as deemed clinically appropriate by the patient's treatment team. The resulting pathology slides from the biopsy will be reviewed by two pathologists and disease management recommended according to the histologic diagnosis. In the GCC arm, any diagnosis will be managed according to standard of care for local breast event or benign biopsy. In the AS arm, only an invasive cancer diagnosis will prompt intervention, according to standard management of invasive breast cancer.

Contralateral Breast Events. For both AS and GCC arms**,** contralateral findings for suspicion of new DCIS or invasive breast cancer will also be managed as deemed clinically appropriate by the patient's treatment team. The resulting diagnosis will be managed according to best standard practice as determined by provider recommendation and patient preference. If the new contralateral diagnosis is a DCIS that fulfills criteria for the COMET study, the patient can be offered AS or GCC for this diagnosis.

Secondary outcomes: Additional clinical outcomes which are also relevant to the differences between the GCC and AS groups include further surgical procedures and regional or distant metastatic breast cancer events. Since DCIS cells remain trapped within the breast duct and therefore have little potential to spread to distant organ sites and cause symptoms or death, few metastatic events are anticipated.

Patient Reported Outcomes. Patient Reported Outcomes (PROs) that are potentially important and relevant to women with DCIS will be elicited longitudinally at pre-specified time points during the study (Table 5).

Table 5: Schedule of PRO surveys

	Baseline	Month 6	Month 12	Month 24	Month 36, 48 and 60
Socio-demographics					
ALLIANCE Patient Questionnaire, adapted with employment items[19-22]	X	X - Employment	X ▪ Marital status ▪ Health insurance ▪ Household size/income	X ▪ Marital status ▪ Health insurance ▪ Household size/income	X ▪ Marital status ▪ Health insurance ▪ Household size/income

			▪ Employment	▪ Employment	▪ Employment
Medical and Family History					
Family history	X				
Self-Administered Co-Morbidity Questionnaire[23]	X	X	X	X	X
Genetics			X		
Complementary Therapies					
CAM Measure[24]		X		X	
Adherence to hormonal therapy					
Medication Adherence measure[25]		X	X	X	X
Health behaviors/lifestyle factors					
ALLIANCE Patient Questionnaire[26-38] Smoking Alcohol Physical activity Diet		X		X	
Psychological/Emotional					
STAI Trait Y2[39]	X				
STAI State Y1[39]	X	X	X	X	X
CES-D-10[40]	X	X	X	X	X
Brief COPE[41]	X				
Intolerance of uncertainty- Short form[42-44]	X			X	
Quality of life					
SF-36[45]	X	X	X	X	X
EQ-5D-5L[46,47]	X	X	X	X	X
QLACS[48]	X			X	
Breast-Q (arm, breast side effects, body image, sexuality)[49]	X	X	X	X	X
Modified BCPT symptom scale (menopausal symptoms)[50]	X	X	X	X	X
Breast Cancer Pain Questionnaire – Neuropathic symptoms[51,52.53]	X	X	X	X	X
Brief Pain Inventory[54]	X	X	X	X	X
BC/DCIS knowledge and perceptions					
BCS-DQI[55,56]	X			X	
True/False questions[57]	X			X	
Risk perceptions[58]	X			X	
Decision-making					
Decisional regret[59]			X	X	X
SURE scale[60,61]	X				
Sources of information[62]	X				
Costs					
Financial burden (adapted from CanCors, NHIS)[63,64]		X			
COMET website questions					
How participant learned about COMET Use of website	X	X			

Domains identified as potentially salient to women with DCIS, including validated measures specific to arm and breast symptoms, body image, and decision-making will be collected. To ensure that there is no

excessive burden to patients, and to test content flow and clarity, all surveys were piloted by the Patient Leadership Team (PLT) prior to trial initiation. The surveys are provided in print, online, or phone interview versions according to patient preference, and are also available in Spanish. All PRO data is entered into PRO-CORE, a study-specific survey data collection platform for web-based assessment of PROs, built and managed by the University of North Carolina Patient-Reported Outcomes Core Facility (UNC PRO-Core).

Collaborating sites send mammogram files consisting of the last screening and diagnostic mammogram studies that immediately predates the diagnostic core/vacuum-assisted biopsy or surgical excision; submission of biospecimens is also a required component of COMET and an integrated part of the consent process (Appendix 2).

STATISTICAL CONSIDERATIONS

Sample size. Sample size for this study was estimated using a 2-group test of non-inferiority of proportions, with the 2-year invasive cancer rate in the GCC group assumed to be 0.10 based on published studies.[65,66] The non-inferiority margin assumed was 0.05 as this was thought to be a clinically meaningful difference between the two arms, beyond which AS could not be reasonably considered to be equivalent to GCC. 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 [67] to detect the specified non-inferiority margin. A secondary time-to-event analysis will also be performed.

Planned analysis for clinical outcome data. The primary analysis will not simply follow the intent-to-treat principle but will analyze as randomized all patients with outcomes measured. However, we believe that this trial, as in other studies which randomize to operative versus non-operative arms, will have both non-compliers and contamination, due to patients who will have a desire to avoid surgery as well as patients who, conversely, will have a desire to have any pre-cancerous lesion removed. Thus, the final study design will include a per-protocol component as well as a pragmatic component for those patients who are randomized and decline participation in the assigned arm. We will define a cross-over as any switch from

AS to GCC as any breast surgery on the affected breast in the absence of invasive cancer when randomized to AS. Similarly, a cross-over from GCC to AS occurs if the patient refuses surgery when randomized to GCC.

Planned subgroup analyses. Although endocrine therapy is not required on either study arm, we will collect data on its use to determine whether it impacts rates of invasive breast cancer either group.[68] Thus, a planned subset analysis of endocrine therapy use will be completed using multivariable logistic regression, with similar adjustments for drop-out and non-adherence. Additionally, factors that may impact the selection of endocrine therapy in both arms such as age and pathological features will also be included. Similarly, we are interested in understanding how imaging modality used may impact assessment of invasive breast cancer during AS, i.e. whether magnetic resonance imaging (MRI) detects higher rates of invasive cancer than mammogram (MMG) for those patients whose providers opt to include MRI for surveillance. This will also be assessed in the AS group with logistic regression, controlling for factors that could impact selection of MMG versus MRI, such as patient age or breast density. We will also consider menopausal status and baseline risk of breast cancer, and whether these factors influence rate of invasive breast cancer at two years. While the study is not powered on these endpoints, these factors are likely to impact outcomes, and thus will be evaluated in planned subset analyses.

PATIENT AND PUBLIC INVOLVEMENT

Patients, patient advocates and other stakeholders have been actively engaged in the conception and development of this proposal, including the preliminary studies conducted to inform the work. In order to facilitate advocate engagement, we established the Patient Leadership Team (PLT). The input and activities of the PLT and advocacy networks guide direction of the trial throughout its entirety.

The PLT have been heavily engaged in the conception and development of the study (including the original research question) and partnered in all phases of planning and development. The PLT collaborate with investigators in the definition of study comparators and outcomes, key constructs to be measured, and choice of validated measures to assess those key constructs. The identification of outcomes *that the DCIS*

population of interest notice and care about is particularly relevant in order to provide practical information that can help patients make informed decisions about their health and health care. The appropriateness/relevance of survey measures has been reviewed by patient advocates and survey questions have been piloted with them for usability testing.

Patient advocates on the study have diverse involvement or leadership in DCIS and breast cancer patient advocacy organizations. They been strong leaders in the DCIS advocacy community for decades, and have deep ties to their constituencies; this will enable them to mentor members of these constituencies who lack this background in order to facilitate their full participation. This active engagement with key stakeholders will be crucial in the compilation of future dissemination strategies/translation of study findings to both professional and patient/public constituencies.

In sum, the PLT: 1) provides input to create effective protocols and survey designs that answer relevant questions for patients, clinicians and research; 2) contributes to the development of educational and implementation tools for clinical sites and DCIS patients; 3) recruits patient advocates to “beta” test surveys and patient tools; 4) develops and implements strategies to measure the impact of patient involvement on the advancement of engagement science; and 5) monitors accrual and participates in the overall implementation of the study.

ETHICS AND DISSEMINATION

The COMET trial will be subject to bi-annual formal review at the Alliance Foundation Data Safety Monitoring Board (DSMB) meetings. At each meeting, the DSMB will review a report of primary and secondary objectives, study schema, definition of primary endpoint, a summary of target accrual goals, a brief administration summary of current study status, accrual goals versus actual accrual, a summary of patient characteristics to date, a summary of drop-out or cross-over from allocated arm, an assessment of data completeness for the various types of data collected, a summary of primary and secondary outcomes by study arm, and finally, a summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) that will be reported from study entry until 7 years after registration.

Data safety monitoring at interim analysis. Interim analyses for futility/safety will be completed annually, with reporting following Consolidated Standards of Reporting Trials (CONSORT) guidelines extension for non-inferiority trials.[69] We consider stopping under two scenarios: if there is sufficient indication of 1) lack of efficacy or 2) potential harm.

First, we will determine if the deviation of the point estimate of the invasive cancer event rate difference for AS versus GCC exceeds 0 by more than 4 SD or 3 SD at either of the interim analyses completed when 1⁄2 and 3⁄4 of the expected number of total events has accumulated, respectively. The SD will be computed from the Kaplan-Meier estimates at two years. In the case that SD exceeds the predetermined bounds, the probability that AS is non-inferior is minimal, and the trial will be halted due to lack of efficacy.

Second, the trial was developed based on the premise that the up-staging rate to invasive breast cancer is approximately 10%.[70] If this rate is substantially higher than 10%, then we would potentially be exposing AS patients to harm. Thus, if the estimate for the up-staging rate in the GCC arm is significantly greater than 10% based on the Kaplan Meier estimate at two years, the trial will be halted due to potential patient harm.

DISCUSSION

Overdiagnosis and overtreatment may be unintended consequences of mammographic screening.[71] Given that DCIS is a non-obligate precursor of invasive breast cancer, for those women whose DCIS might never progress even without treatment or whose treatment and outcomes may not differ even if invasion occurs, there is a pressing need to study more selective clinical strategies than the current, non-risk-based therapies for DCIS originally intended for invasive breast cancer. For DCIS at low-risk of progression such as low-grade, small, non-palpable lesions, there may be no significant benefit to surgery or radiation and a de-escalation approach should be tested as it has been in other cancers (for example, prostate cancer).[72,73] There is recognition that high-grade DCIS is more likely to progress to an invasive breast cancer and these patients are excluded from the study. Given the lead-time between the development of

DCIS and appearance of invasive breast cancer, [74] there may also be a case for tailoring intervention by age and presence of competing comorbidities.

Global Collaboration: Adoption of significant practice changes in breast cancer treatment has often required consideration of multiple sources of information. Thus, compatibility of COMET with other trials is an important goal for implementation of findings from the COMET study. The LOw Risk dcIS study (LORIS trial; ISRCTN 27544579)[75,76] is a randomized-controlled trial of AS versus GCC in the UK, which opened to accrual in 2015. The patient populations, health care environments and the clinical trials organization of the COMET and LORIS studies represent an exceptional opportunity to combine resources and strategies, compare outcomes, and to identify similarities and differences in DCIS diagnosis, treatment and surveillance policies both from a patient population and a health care systems perspective. To that end, LORIS principal investigators have worked with the COMET team in order to closely align the two studies and allow future meta-analysis of both clinical and PRO endpoints. Specifically, we have prospectively designed the eligibility criteria, outcomes, and surveillance protocol which, while not identical in every instance, will nevertheless allow for a planned meta-analysis at completion of both studies. In addition there is a randomized, international, multicenter, phase III non-inferiority trial being conducted in the Netherlands (The LORD - LOw Risk DCIS study)[77] as well as other global efforts to identify biological components of DCIS 'risk'; for example, the Prevent Ductal Carcinoma in Situ Invasive Overtreatment Now – (PRECISION) study.[78]

The broad, long-term objective of this proposal is to provide high quality evidence regarding outcomes of treatment versus surveillance for DCIS and to determine whether data support the inclusion of AS in treatment guidelines for DCIS. It is anticipated that the evidence provided by the COMET study, together with data collected from the other low-risk DCIS studies, will enable patients and stakeholders to make better informed decisions about management options for low risk DCIS.

The COMET study represents an important opportunity to address a highly relevant health care issue with broad-reaching health, social, and economic implications. Moreover, we hope that this study may provide a

framework for evidence development in other low-risk conditions where overtreatment is an emerging concern.

AUTHOR CONTRIBUTIONS

The PI and first author of this paper (E. Shelley Hwang) was instrumental in the compilation of this study protocol. Each co-author (Terry Hyslop; Thomas Lynch; Elizabeth Frank; Donna Pinto; Desiree Basila; Deborah Collyar; Antonia Bennett; Celia Kaplan; Shoshana Rosenberg; Alastair Thompson; Anna Weiss; Ann Partridge) contributed equally to subsequent development of the protocol. Elizabeth Frank, Donna Pinto, Desiree Basila, and Deborah Collyar form the COMET Study Patient Leadership Team.

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COMPETING INTEREST STATEMENT

None of the authors involved in the publication of this paper have a competing interest (financial or otherwise).

DATA SHARING STATEMENT

Technical appendix, statistical code, and current dataset are available from the Alliance Statistics and Data Center (SDC) who will also have access to the final trial dataset.

SPIRIT CHECKLIST

We used the SPIRIT checklist when writing this protocol report [79].

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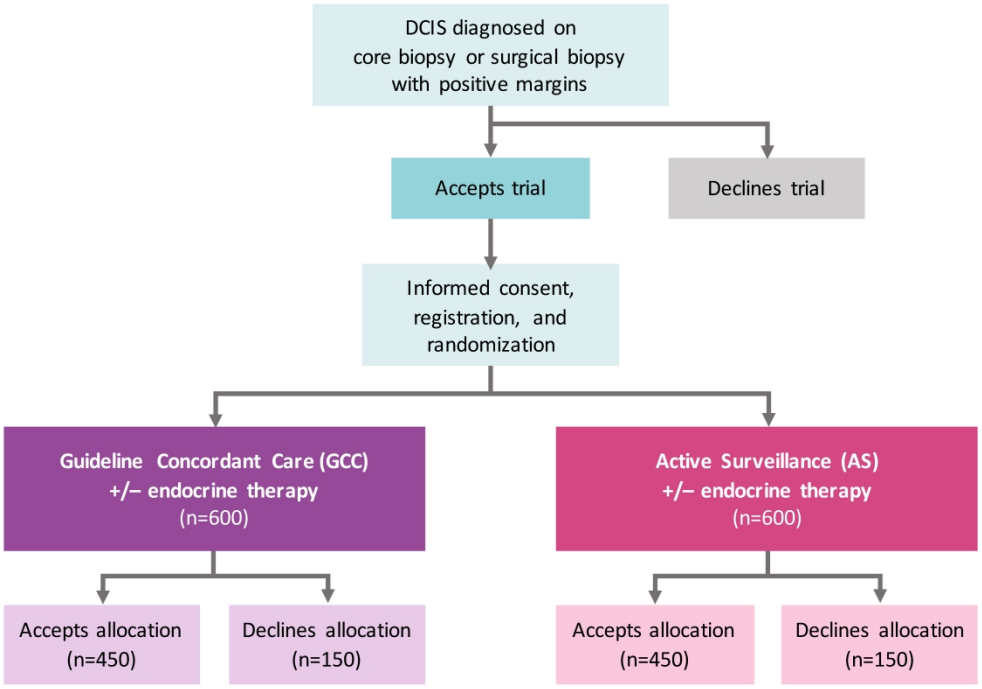
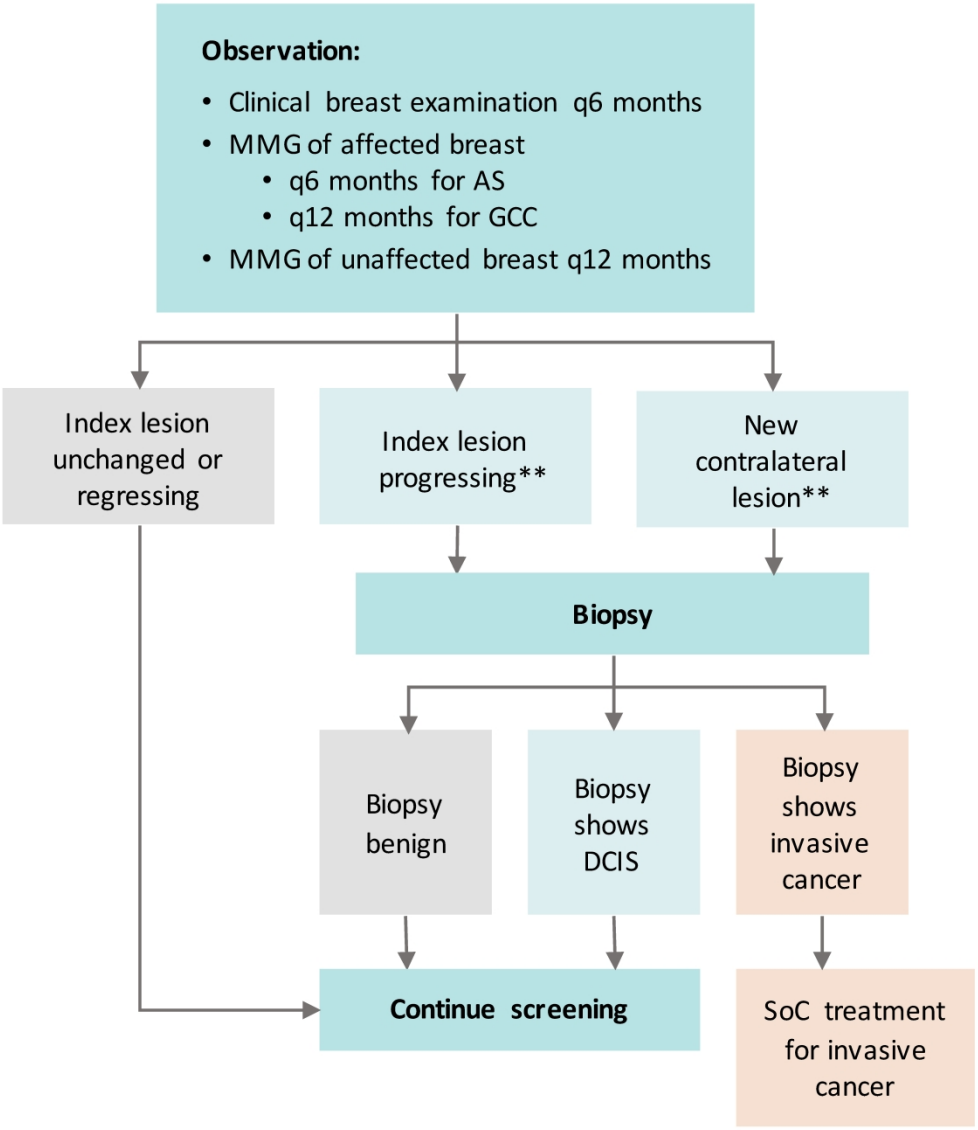
Figure Legends

Figure 1. COMET Trial Schema. Patient flow for accrual and registration. Eligibility criteria for **Low Risk** DCIS include 40 years of age or older, grade I/II DCIS without invasive cancer diagnosed on core, vacuum-assisted, or surgical biopsy, ER(+) and/or PR(+), HER2(-), and no mass on PE or imaging with exception of fibroadenoma at a distinct/separate site from site of DCIS. The primary study endpoint upon which the sample size is based is **rate of 2-year invasive cancer diagnosis among patients randomized to GCC compared to AS**. ITT analyses adjusted for dropout, non-compliance and contamination will be performed on all randomized patients including those who do and do not accept the arm to which they are randomized. Patient Reported Outcome surveys will be collected from all patients who are registered for the study, including those who cross over. Mammograms will be performed q6 months for the index breast and q12 months for the contralateral breast in the active surveillance arm and q12 months in both the index and contralateral breast in the guideline concordant care arm. No chest wall imaging will be performed if mastectomy has been performed.

Figure 2. Surveillance protocol for COMET Trial. MMG not required if mastectomy performed. **Criteria for progression: a) New **mas**s/architectural **distortion**/ **density** on surveillance 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.


DCIS diagnosed on
core biopsy or surgical biopsy
with positive margins
Accepts trial
Declines trial
Informed consent,
registration, and
randomization
Guideline Concordant Care (GCC)
+/– endocrine therapy
(n=600)
Active Surveillance (AS)
+/– endocrine therapy
(n=600)
Accepts allocation
(n=450)
Declines allocation
(n=150)
Accepts allocation
(n=450)
Declines allocation
(n=150)


Observation:
• Clinical breast examination q6 months
• MMG of affected breast
• q6 months for AS
• q12 months for GCC
• MMG of unaffected breast q12 months
Index lesion unchanged or regressing
Index lesion progressing**
New contralateral lesion**
Biopsy
Biopsy benign
Biopsy shows DCIS
Biopsy shows invasive cancer
Continue screening
SoC treatment for invasive cancer

COMET INFORMED CONSENT FORM

Study Title:	Comparison of Operative to Monitoring and Endocrine Therapy (COMET) Trial For Low Risk DCIS: A Phase III Prospective Randomized Trial
Study #:	<<protocol number>>
Sponsor:	<<sponsor>>
Study Doctor:	<<investigator>>
	<<firm name>>
	<<street address>>, <<city>>, <<state>> <<zip>>
Telephone Number:	<<000-000-0000>>
After Office Hours:	<<000-000-0000>>

For California participants: Before you read this consent form, you should read and sign a copy of the California Experimental Subject's Bill of Rights. Ask the study staff for a copy of this document if you haven't already received one.

This study is conducted and paid for by the Sponsor, Alliance Foundation Trials, LLC, a national clinical research group made up of cancer study doctors, other professionals, and laboratory researchers whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of people with cancer.

<<Quorum may add site-specific conflict-of-interest language to the form based on information the site reports to Quorum.>>

Introduction

You are being asked to take part in this study because you have been diagnosed with ductal carcinoma in situ (DCIS) in the cells lining the breast milk gland ducts. This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for further explanation.

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you must sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

How is DCIS usually treated?

Women diagnosed with DCIS most commonly receive a combination of surgery, radiation and/or endocrine (hormone-blocking) therapy (the "usual treatment" approach).

A small number of women choose to have close monitoring over a period of time. Close monitoring means a condition is watched with follow-up exams and tests such as mammograms, breast ultrasounds, and breast MRI. This study is being conducted because researchers wish to know whether, after 2 years, clinical and quality of life outcomes for women with low risk DCIS who receive usual treatment are the same as those for women with low risk DCIS who receive close monitoring.

What are my choices if I do not take part in this study?

If you decide to not take part in this study, you have a number of choices:

- You may still choose usual treatment for DCIS;
- You may still choose close monitoring for DCIS;
- You may choose not to be treated for DCIS;
- You may choose to take part in a different study, if one is available.

You can decide upon which alternative you would like to choose with the study doctor or study staff. In addition, you may discuss your options with your regular health care provider.

Why is this study being done?

The purpose of this study is to compare the risks and benefits of the usual treatment approach for DCIS compared to the close monitoring approach. There will be about 1200 women taking part in the study.

What are the study groups?

In this research study, you will be randomly assigned to one of two study groups:

- Group 1 will be assigned to **usual treatment** (surgery, radiation and/or endocrine (hormone-blocking) therapy);
- Group 2 will be assigned to **close monitoring** (alone or with endocrine (hormone-blocking) therapy)

A computer will assign you to one of the study groups. This is called randomization (it is like flipping a coin) and it is done by chance. Neither you nor the study doctor or study staff will be able to pick which study group you are in. If you agree to be randomized, you will have an equal chance of being assigned to either study group. Both you and your study doctor will be informed of your study group assignment.

After randomization, you can decline your study group assignment at any time. However, we will ask you whether you would still like to contribute to the study by completing surveys and allowing us to collect your medical records.

How long will I be in this study?

You will be in the study for a minimum of 5 years from time of registration. During the course of the study you will have a physical examination about every six months, a mammogram (or possibly an MRI if you are in the close monitoring group) about every six or twelve months (depending on the study group you are assigned to) and you will be asked to complete a number of surveys. After 5 years, you will undergo a physical examination and mammogram every 12 months. We may wish to continue to follow your progress for up to 10 years.

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

BEFORE YOU BEGIN THE MAIN PART OF THE STUDY

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

- A history and physical exam, including your height, weight, pulse, blood pressure and temperature
- Routine blood tests
- Blood or Urine pregnancy test, if applicable
    - The study doctor or study staff will tell you if the pregnancy test results are positive.
    - The results of the pregnancy testing must be negative in order for you to be in the study.
- Mammogram

BASELINE SURVEY

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be asked to complete a baseline participant survey (paper version or on a tablet computer where available per site) where general information (age, race, general health, family health history, quality of life, etc.) will be collected. Clinical information will also be collected by a trained clinical research assistant. The survey will take about 30 minutes to fill out.

STUDY PROCEDURES

You will be randomly assigned to one of the two study groups:

- Group 1 will be assigned to usual treatment for DCIS (surgery, radiation, or both);
- Group 2 will be assigned to close monitoring for DCIS

If you are assigned to the usual treatment group, you will undergo the appropriate surgery for DCIS within 60 days of randomization.

Participants in both groups will have a discussion with their regular care provider about taking endocrine (hormone-blocking) therapy, a pill that is taken once a day. These drugs are commonly used for DCIS and will not be paid for or administered by the study.

A biopsy (tissue sample taken from the breast) may be performed on either breast if any changes are detected during follow-up.

Your mammograms, breast ultrasounds, and breast MRIs (if any) will be collected for future research on DCIS.

SCHEDULE OF SUBSEQUENT STUDY SURVEYS

The study researchers would like to collect information about your health, quality of life, and other experiences of DCIS.

- About six months after you begin the study, you will be asked to complete a follow-up participant survey;
- About twelve months after you begin the study, you will be asked to complete another follow-up participant survey;
- You will then be asked to complete a follow-up participant survey every 12 months for the remainder of the study.

The surveys are required because your responses to them are a very important part of the study. The surveys will help us (the study doctor and study staff) to compare the benefits, harms, and burdens of usual treatment versus close monitoring in participants diagnosed with DCIS. The surveys will be available to complete online. If you cannot complete the surveys online, you will be provided with a survey packet with a stamped envelope, self-addressed to complete and mail back. Each survey will take approximately 30 minutes to complete.

Will I need time to recover after my participation in the study?

Ask the study doctor or study staff for the estimated recovery time of your participation in this study.

BLOOD AND TISSUE SAMPLES

As part of this study, you are being asked to provide tissue and blood samples (specimens) for future research. Tissue specimens will only be provided from biopsies that you have or will have as part of your care. Blood samples will involve no more than 4-6 tablespoons of extra blood.

After your tissue samples and blood are collected, they will be stored at room temperature (Tissue) or frozen (blood) in the AFT biorepository until they are used by research investigators. The biorepository is a place where biological samples (e.g. blood and/or tissue) are stored and protected from unauthorized use.

Your samples will be used by approved investigators working with AFT, the sponsor of this trial. Future studies may include genetic (DNA) analysis of your tissue and your blood. DNA is like an instruction book for each cell. Specific changes in your DNA may help to explain why some of your cells do not behave like others, or how you might respond to drugs and other treatments. Other types of studies may identify inherited variations in your DNA (which can be passed on and could reveal information about your family members) that are important for explaining why you may or may not respond to therapy. Investigators also plan to use some of your blood to look for DNA or other substances in your blood that may be used to predict how people will respond to therapy.

For all of the samples collected and all of the studies that will be performed on them, you should know:

- Your samples will be labeled only with code numbers. Only certain AFT personnel will have access to the list that links the code number to your name. The sample code number is linked to our study participant identification number in the AFT biorepository database. No study investigator will be able to link the sample code number to your name.
- Information collected during the main research study (research data such as your response to treatment, results of the study tests, and drugs you are given) may be provided to approved researchers along with your sample.
- The samples will be stored in the United States at the Alliance Foundation Biorepository, currently located at Washington University in St. Louis, MO.
- You will never receive any individual results from the research tests performed on your samples. These results will not be placed in your regular medical record.
- If your samples or the information generated from their use in research results in commercial products, you will not be able receive any profits from such products.
- Research data, as well as your genetic (DNA) research data (which contains information about variations in your DNA that can tell us about potential health risks to you and your children) may be shared with other investigators and the FDA, and may be placed in a publicly accessible database for further research use.

Your samples will be kept and used for approved research studies until they are physically used up or until you request that your samples be returned to your hospital or destroyed.

What will happen to my blood and tissue samples?

Your samples might be kept for ten years or even longer. Your specimens will be labeled only with code numbers. If you change your mind later, be aware that your samples may or may not be withdrawn from the research, depending on the sponsor's policies. You can ask the study doctor or study staff about this.

What will happen if I am assigned to close monitoring but my condition changes?

If you are assigned to close monitoring but your condition changes in some way, you may choose to be treated with breast surgery, radiation and/or endocrine (hormone-blocking) therapy.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- The close monitoring approach may not be better, and could possibly be worse, than the usual treatment approach for DCIS. Please ask your study doctor if you have questions about this;
- There may be physical, emotional and psychological side effects of surgical treatment. These may include bruising, bleeding, pain and changes to the look and feel of your breasts. These side effects may have an impact on your daily life;
- Radiation side effects may include burns to the skin and changes in the texture of the breast;
- Potential side effects of endocrine (hormone-blocking) therapy may include hot flashes, joint pain, weight gain, bone changes, blood clots. Rarely new cancers have been reported;
- You may be asked sensitive or private questions which you normally do not discuss;
- Additional risks include potential distress and loss of privacy or confidentiality when answering survey questions. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire. You have the right to refuse to answer any questions. While your direct responses to the survey will not be shared with the entire study team (study doctor and all study staff), we will alert your study team if you report substantial depressive symptoms;
- There is a risk of loss of confidentiality through the transfer of your personal health information (PHI). This includes the information we have stored about you in the database, for example revealing that you carry a genetic disease. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study;
- The information shared in the database may include your DNA results. Because your DNA information is unique to you, there is a chance that someone could trace it back to you. The risk of this happening is small, but may be greater in the future;
- If your tissue is used for research studies, there may be insufficient tissue remaining for other uses, should it be needed in the future for your medical care.

Ask the study doctor if you have questions about the signs or symptoms of any of the risks that you read about in this consent form.

Please tell the study doctor or study staff right away if you have any problems with your health or the way you feel during the study, whether or not you think these problems are related to the study procedures.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the findings of this study will help people who have DCIS currently. Providing samples for the biorepository will not help you. However, we hope that information from the study will help researchers to better understand treatment of DCIS and that this could help people diagnosed with this condition in the future.

Can I stop taking part in this study?

Yes - you can decide to stop at any time. There will be no penalty to you, and you won't lose any benefits. If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely.

If you withdraw from the study, the study doctor or study staff can still use your information that they have already collected.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. You may be taken out of the study:

- If your health changes and the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped by the sponsor, Quorum Review or the U.S. Food and Drug Administration (FDA).

If you stop taking part in your assigned group, but would like to still remain in the study, you will be invited to complete the follow-up surveys so that researchers can learn about the health and quality of life of women with DCIS. However, if you decide that you do not wish to take additional surveys and would like to exit the study completely, you will no longer be asked to complete them and you will no longer be contacted about the study unless you give permission.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty or loss of benefits to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for all of the costs of your care while in this study, including the cost of tests, procedures, or medicines. **Before you decide to take part in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.**

Will I receive payment?

<<Quorum will add site-specific compensation language to the form based on information the site reports to Quorum.>>

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. Medical treatment will be provided as usual. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be billed for any costs.

If you are injured as a result of this study, you keep all your legal rights to receive payment. You do not give up any of your legal rights by signing this form.

Who will see my medical information?

Your identity will be protected as required by law and according to any policies the study center or sponsor may have. Be aware that your study records (which include your medical records, your signed consent form, and other information) will be shared as needed for the study. Your information may be given out if required by law. For example, certain States require doctors to report to health boards if they find a disease like tuberculosis or if the study doctor or study staff suspects that you are going to harm yourself or others. The researchers will do their best to make sure information is not released that could potentially identify you, although there is a risk of loss of confidentiality through the transfer of your personal health information (PHI) which will be kept in a central database for research.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance Foundation Trials, LLC;
- Quorum Review - a group of people who review research studies to protect the rights and welfare of research participants;
- The Food and Drug Administration.

Where can I get more information?

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

Who can answer my questions about this study?

In the event of an emergency, dial 911 immediately.

If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor or study staff as soon as possible.

You can ask questions about the study at any time. You can call the study doctor or study staff at any time if you have any concerns or complaints. You should call the study doctor or study staff at the phone number listed on page 1 of this form if you have questions about the study procedures, study costs (if any), study payment (if any), or if you get hurt or sick during the study.

Quorum Review reviewed this study. Quorum Review is a group of people who review research studies to protect the rights and welfare of research participants. Review by Quorum Review does not mean that the study is without risks. If you have questions about your rights as a research participant, if you are not able to resolve your concerns with the study doctor or study staff, if you have a complaint, or if you have general questions about what it means to be in a research study, you can call Quorum Review or visit the Quorum Review website at www.quorumreview.com.

Quorum Review is located in Seattle, Washington.
Office hours are 8:00 AM to 5:00 PM Pacific Time, Monday through Friday.
Ask to speak with a Research Participant Liaison at 888-776-9115 (toll free).

HOW WILL MY INFORMATION BE USED AND SHARED FOR THIS STUDY?

This section explains who will use and share your health information if you agree to be in this study. You must authorize this use and sharing of your information by signing this form or you cannot be in the study. You can still be in the main part of the study even if you do not authorize the use and sharing of your information for the optional parts of the study (which you will read about below).

The study doctor and study staff will collect, use, and share health information about you, including any information needed to do the study and other identifying information about you, such as your name, address, phone number, or social security number. The information used and shared will include:

- information from your medical records
- information collected about you during the research about study visits, tests, procedures, etc.

Your information may be used and shared with these people for the following purposes:

- The study doctor and study staff to conduct this research.

- The sponsor, Alliance Foundation Trials; people who work with or for the sponsor; and other researchers involved in this study. These people will use your information to review the study, and to check the safety and results of the study.
- Others required by law to review the quality and safety of research, including the FDA, other government agencies in the United States and other countries, and Quorum Review.
- A public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions.

After your information is shared with the people and companies listed above, the law may not require them to protect the privacy of your information. To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally would have access to your health information.

You can cancel your authorization to use and share your information at any time by writing a letter to the study doctor. If you cancel your authorization, you will not be able to continue in the study. You can cancel your authorization for the optional parts of the study and remain in the main study.

If you cancel your authorization, the study doctor and study staff will still be able to use and share your information that they have already collected.

This authorization to use and share your information expires in 50 years.

_____ _____

Signature of Participant Date

<<*Quorum staff: Include the following for Indiana sites:*

In **Indiana,** you must complete the following information:

_____

Participant's Street Address

_____

Participant's City, State, ZIP>>

Comet Informed Consent Form
Alliance Foundation Trials, LLC
AFT – 25

Signature Agreeing to Take Part in the COMET Study

I have read this consent form or had it read to me. I have discussed it with my study doctor and my questions have been answered. I will be given a signed copy of this consent form. I agree to take part in the COMET study and any additional study components below where I circle 'yes'. By signing this form, I do not give up any of my legal rights.

I agree to take part in the COMET Study. I agree to provide tissue and blood samples for future research.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent Date

Comet Informed Consent Form
Alliance Foundation Trials, LLC
AFT – 25

Optional Component of the Study:

This part of the consent form is about an optional component of the study that you can choose to take part in or not. You can still take part in the COMET study even if you say "no" to the optional component. If you sign up for but cannot complete the optional component for any reason, you can still take part in the COMET study.

- Option to be contacted about future clinical trials

Please circle your answer: I agree to be contacted about any future clinical trials.

YES NO Initial: _____

If yes, please provide your telephone number and e-mail address (if you have one) below:

_____ _____
Email Address Telephone Number

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

Comet Informed Consent Form
Alliance Foundation Trials, LLC
AFT – 25

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be contacted about any future clinical trials.

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent Date

CORRELATIVE STUDIES

Image Collection. Collaborating sites send mammogram files consisting of the last screening and diagnostic mammogram studies that immediately predates the diagnostic core/vacuum-assisted biopsy or surgical excision. If breast ultrasound and/or breast MRI are performed as part of surveillance, those images are also requested for submission. If a core/vacuum-assisted biopsy is performed for a finding identified during follow-up on either the AS or GCC arm, the last diagnostic mammogram that immediately predates the diagnostic core/vacuum-assisted biopsy or surgical excision is requested. Four standard screening views as well as all diagnostic views, including all magnification views are also collected.

Biospecimen Collection. Submission of biospecimens is a required component of COMET and an integrated part of the consent process. In the event that it is physically impossible to submit required biospecimens, patients may still be enrolled to the trial without biospecimen submission. Core biopsy tissue and blood are collected at baseline and any core biopsy tissue obtained during follow-up will also be requested. 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 are stored in a CAP-accredited biorepository 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 the time of analysis.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See note 1
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	20
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	20

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See note 2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17-18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17-18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See note 3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	7-8

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	15-16

		imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	See note 4
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5
Declaration of	#28	Financial and other competing interests for principal	20

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17-18
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	See note 5
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

Author notes

1. N/A - registered in clinicaltrials.gov
2. 20 (Anna Weiss)
3. Table 2/Figure 2
4. N/A - IRB approval obtained
5. NA - no authorship eligibility guidelines or intended use of professional writers

BMJ Open

The COMET (Comparison of Operative to Monitoring and Endocrine Therapy) Trial: A phase III randomized trial for low-risk ductal carcinoma in situ (DCIS)

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The COMET (Comparison of Operative to Monitoring and Endocrine Therapy) Trial: A phase III randomized trial for low-risk ductal carcinoma in situ (DCIS)

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Subtitle: COMET study for Low Risk DCIS

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ABSTRACT

INTRODUCTION: Ductal carcinoma in situ (DCIS) is a non-invasive non-obligate precursor of invasive breast cancer. With guideline concordant care (GCC), DCIS outcomes are at least as favorable as some other early stage cancer types such as prostate cancer, for which active surveillance (AS) is a standard of care option. However, AS has not yet been tested in relation to DCIS**.** The goal of the COMET (Comparison of Operative to Monitoring and Endocrine Therapy) trial for Low-Risk DCIS is to gather evidence to help future patients consider the range of treatment choices for low-risk DCIS, from standard therapies to active surveillance. The trial will determine whether there may be some women who do not substantially benefit from current GCC and who could thus be safely managed with AS. This protocol is version 5 (July 11th 2018). Any future protocol amendments will be submitted to Quorum CIRB/local IRBs for approval via the sponsor of the study (Alliance Foundation Trials).

METHODS AND ANALYSIS: COMET is a phase III, randomized-controlled clinical trial (RCT) for patients with low-risk DCIS. The primary outcome is ipsilateral invasive cancer rate in women undergoing GCC compared to AS. Secondary objectives will be to compare surgical, oncological and patient-reported outcomes. Patients randomized to the GCC group will undergo surgery as well as radiotherapy when appropriate; those in the AS group will be monitored closely with surgery only upon identification of invasive cancer. Patients in both the GCC and AS groups will have the option of endocrine therapy. The total planned accrual goal is 1200 patients.

ETHICS AND DISSEMINATION: The COMET trial will be subject to bi-annual formal review at the Alliance Foundation Data Safety Monitoring Board (DSMB) meetings. Interim analyses for futility/safety will be completed annually, with reporting following Consolidated Standards of Reporting Trials (CONSORT) guidelines extension for non-inferiority trials.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- COMET is a phase III randomized-controlled clinical trial (strength)
- The comparator arms are very different from each other (limitation)
- Ongoing data collected from women who decline randomization will provide valuable information about the potential for selection bias/enable the study to be made more generalizable (strength)
- There exists considerable variation between pathologists in the diagnosis of DCIS (limitation)

INTRODUCTION

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] with more than 50,000 women in the United States diagnosed with DCIS each year. Almost all diagnoses are made in completely asymptomatic individuals.[2] Without treatment, it is estimated that only 20-30% of DCIS will progress to invasive cancer.[3,4] However, once diagnosed, over 97% are treated according to current guidelines with a combination of surgery, radiation and endocrine therapy—treatments similar to those recommended for patients with invasive breast cancer.

The term "overdiagnosis" has been used to define conditions that look like early cancer, but are not destined to cause symptoms or death.[5] In 2013, an independent review commissioned by the Department of Health in the UK established that screening saves lives but also that overdiagnosis exists.[6] There is a general consensus that much of the overdiagnosis and overtreatment burden in breast cancer derives from the treatment of DCIS. Currently, almost all DCIS is treated according to guideline-concordant care (GCC); of those treated for low-risk DCIS, some patients will not benefit if they never develop invasive breast cancer. One possible approach to GCC for low-risk lesions is active surveillance (AS). Currently, only 3% of women in the United States with DCIS opt for AS. Given that much of the treatment for low-risk DCIS may represent overtreatment there has been global interest to address whether AS, with intervention only for invasive cancer, would be sufficient for those women unlikely to have a future DCIS or invasive breast cancer.

Current gaps in evidence. Current treatment options routinely offered for DCIS include surgery (lumpectomy or mastectomy), radiation, and endocrine therapy. These options constitute GCC according to National Comprehensive Cancer Network (NCCN) treatment recommendations.[7] Between 1991 and 2010, 23.8% of women diagnosed with DCIS in the United States underwent unilateral mastectomy (4.5% bilateral mastectomy), 43% lumpectomy with radiation, and 26.5% lumpectomy without radiation.[8]

Published UK screening data suggest that in some cases, major surgical 'cancer' treatment of low-risk DCIS is unnecessary, inappropriate and misleading for the recipient.[9] In those women who undergo surgical treatment for DCIS, there may be both short- and long-term morbidities, including poor cosmesis and the risk of developing persistent pain at the surgical site, with estimates ranging from 25-68%.[10-13] In addition, patients may experience complications from radiation (cardiac or pulmonary symptoms, secondary malignancies) or reconstruction (infection, loss of implant, need for multiple surgeries). To date, among the 97% of women with DCIS treated with GCC, neither randomized trials nor observational studies have shown a survival advantage of any one treatment option over another.[14] Moreover, none of the treatments has ever been compared in a rigorous fashion to AS. The COMET (Comparison of Operative to Monitoring and Endocrine Therapy for Low-Risk DCIS) is a 5-year phase III, randomized-controlled clinical trial (RCT) that commenced on July 1st 2016. The study was designed with a specific objective: to determine the risks and benefits of GCC compared to those of AS for low-risk DCIS. This protocol is based on version 5 (dated July 11th 2018), approved by QUORUM Centralized Institutional Review Board (CIRB) and all local institutional review boards (IRBs) where relevant. Any future protocol amendments will be submitted to Quorum CIRB or local IRBs, in accordance with institutional requirements, via the sponsor of the study (Alliance Foundation Trials).

METHODS AND ANALYSIS

Trial Design and Setting. COMET is a phase III randomized clinical trial for low-risk DCIS (Figure 1) with two comparator arms, GCC and AS. The study, funded by the Patient-Centered Outcomes Research Institute (PCORI), is conducted through the Alliance for Clinical Trials in Oncology cooperative group network with plans to open at up to 100 sites in the United States (a list of currently activated sites can be found at clinicaltrials.gov - NCT02926911). Patients with a new diagnosis of DCIS are identified at participating Alliance study sites and screened for eligibility. Written informed consent is obtained prior to randomization by site staff, including consent for the potential use of biological specimens in future studies (Appendix 1). Alliance has obtained a Certificate of Confidentiality from the Department of Health and Human services (DHSS) in order to protect the privacy of individuals who are subjects of research by

withholding their names and other identifying characteristics from all persons not connected with the conduct of Alliance research.

Data collection activities are embedded within the Alliance Statistics and Data Center (SDC) infrastructure. Resource and data management for the trial follow the established Alliance standard operating processes for the collection, storage, and analysis of on-line case report forms and other data. These procedures have been established for Alliance clinical trials. This includes all quality assurance processes that are in place for Alliance clinical trials as well as the use of Medidata RAVE as the electronic data capture tool.

Eligibility Criteria. Inclusion criteria for COMET were designed to select a group of English- and Spanish-speaking patients at low risk for invasive progression based upon retrospective epidemiologic data. Low-risk criteria were identified for clinical, radiologic, and pathologic features. As a pragmatic trial, central review of imaging and pathology is not performed in real time, but reviewed post hoc. However, given the known limited inter-reviewer correlation between pathologists in the diagnosis of DCIS, the inclusion criteria require that at least two pathologists deem that the histological features meet COMET pathology eligibility criteria. A complete list of COMET inclusion and exclusion criteria are presented in Table 1.

Table 1. Eligibility Criteria for the COMET trial

Inclusion Criteria	Exclusion Criteria
✓ New diagnosis of DCIS without invasive cancer	× All Grade III DCIS
✓ Unilateral, bilateral, unifocal, or multifocal DCIS	× Male DCIS
✓ A patient who has had a lumpectomy with positive margins as part of their treatment for a current DCIS diagnosis is eligible	× Concurrent diagnosis of invasive or microinvasive breast cancer in either breast prior to randomization
✓ No previous history of breast cancer (DCIS or invasive cancer) in either breast prior to current DCIS diagnosis	× Documented mass on examination or imaging at site of DCIS prior to biopsy yielding diagnosis of DCIS
✓ 40 years of age or older at time of DCIS diagnosis	× Bloody nipple discharge or skin changes associated with DCIS
✓ ECOG performance status 0 or 1	× Mammographic finding of BIRADS 4 or greater within 6 months of registration at site other than that of known DCIS, without pathologic assessment
✓ No contraindication for surgery	
✓ Baseline imaging: ▪ Unilateral DCIS: contralateral normal mammogram ≤ 6 months of registration and	

ipsilateral breast imaging ≤ 120 days of registration ▪ Bilateral DCIS: bilateral breast imaging ≤ 120 days of registration ✓ Pathologic criteria: ▪ ADH suspicious for DCIS ▪ Any grade I or grade II DCIS ▪ Absence of invasion or microinvasion ▪ Diagnosis confirmed on core needle, vacuum-assisted or surgery ≤ 120 days of registration ▪ ER(+) and/or PR(+) by IHC (≥ 10% staining or Allred score ≥ 4) ▪ HER2 0, 1+, or 2+ by IHC if HER2 testing is performed ✓ Histology slides reviewed and agreement between two clinical pathologists that pathology fulfils COMET eligibility criteria. ✓ At least two sites of biopsy for those cases where mammographic extent of calcifications exceeds 4 cm, with second biopsy benign or both sites fulfilling pathology eligibility criteria ✓ Amenable to follow up examinations ✓ Ability to read, understand and evaluate study materials and willingness to sign a written informed consent document in Spanish or English	× Use of investigational cancer agents within 6 weeks prior to diagnosis × Any serious and/or unstable pre-existing medical, psychiatric, or other existing condition that would prevent compliance with the trial or consent process × Pregnancy × Documented history of prior tamoxifen, aromatase inhibitor, or raloxifene in last 6 months

Allocation and Randomization. Allocation and randomization is conducted by Alliance site staff. Randomization is computer-generated via Medidata RAVE and stratified based on the following factors: age at diagnosis: *<55, 55-65, >65;* maximum diameter of microcalcifications: *<2cms, 2-5cms, >5cms;* and DCIS nuclear grade: I or II. We record whether the patient has had prior surgical excision for the index diagnosis; this variable will be used for subset analysis but will not be a stratification factor.

Use of endocrine therapy is permitted in both arms with adherence and duration of therapy recorded. Although women are not recruited to the COMET trial if they do not agree to randomization, those women who are consented but then decline randomization (or their allocated arm) are still eligible to continue participation in the study if they agree to provide follow up and survey data. The demographics of the cohort declining their allocated arm will be compared with those of women who adhere to the

randomization. It is anticipated that these data will provide valuable information about the potential for selection bias and will ultimately enable the study to be made more generalizable.

Both intent-to-treat and per protocol analyses can be biased in the presence of drop-out, non-compliance [15, 16]. Thus, we intend to complete both of these analyses as sensitivity analyses, but the primary analysis approach will be based upon an estimate of the treatment effect among those who comply with arm allocation [17].

STUDY ARMS

Guideline-concordant care. *Surgery:* Patients randomized to the GCC 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. If a patient randomized to the GCC arm opts for AS, they will be considered as a "cross-over" and will continue to participate in completion of Patient Reported Outcome surveys.

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

Active Surveillance. Patients in the Active Surveillance arm will not undergo surgery unless a biopsy during surveillance documents invasive disease which requires surgical intervention. If the patient opts for surgery in the absence of invasive cancer, they will be considered as a "cross-over" and will continue to participate in completion of Patient Reported Outcome surveys. Figure 2 presents the surveillance protocol for patients on the AS arm of the study.

Endocrine Therapy. The use of endocrine therapy is not mandatory but patients are encouraged to discuss this with their providers in both arms of the trial. Selection of endocrine therapy will be determined

based on provider recommendations and patient preferences, and administered for a maximum duration of five years. If applicable, data regarding the use of endocrine therapy (type, duration, adherence, and side effects) will be captured at each visit and patient-reported adherence will be measured in follow-up surveys.

All additional follow-up and monitoring beyond that required per protocol (described below), will be conducted according to the standard of care from each provider and institution. 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. breast MRI, DXA scanning).

SURVEILLANCE PROTOCOL

For both the GCC and AS groups, required surveillance consists of clinical examination, including history and physical examination, every six months for a minimum of five years and every 12 months thereafter, up to ten years from the time of registration. Patients on the GCC arm who have not had a mastectomy will have bilateral mammography annually; those on the AS arm will have ipsilateral mammography every six months and contralateral mammography every 12 months (Table 2).

TABLE 2. Schedule of Eligibility Screening and Clinical Follow up

		Eligibility Screening		Day 1-180	Every 6 months through year 5	Every 12 months through year 5	Every 12 months year 5-7
Tests & Observations	History and physical	X	Registration		X		X
	Weight, height	X					
	Pulse, Blood Pressure	X					
	Randomization			X			
Imaging studies[β]	Contralateral MMG					X	
	Ipsilateral breast imaging	X[∀]			X (AS only)	X (GCC only)	
	Bilateral MMG	X[∀]					X
Th er	Surgery			X (GCC only)			

a p	Radiation			X (GCC only)			
	Discussion regarding endocrine therapy. Initiation if patient opts for treatment			X			

Clinical criteria requiring further investigation include: new breast signs and symptoms such as new breast mass; nipple/skin retraction; nipple discharge; and breast edema/erythema on clinical examination in either breast. Radiographic criteria for biopsy include an increase in extent of calcifications ≥ 5mm in at least one dimension compared to the most recent prior MMG in the index breast as well as new suspicious findings on other radiologic studies (US, MRI) in either breast (Table 3).

Table 3. Criteria for Potential DCIS Progression and Indications for Biopsy

Clinical criteria
• 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
• New mass* /architectural distortion*/ density* on surveillance mammogram in either breast according to *ACR Breast Imaging Reporting and Data System (BI-RADS) for mammography in assessment of masses and calcifications[18] • 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

Duration of Follow-Up. Progression, recurrence, new primary disease, residual DCIS (or an additional DCIS lesion) and mortality status will be collected up to ten years from randomization.

OUTCOMES

Endpoints were selected in two broad categories: 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* which include an array of relevant quality of life and psychosocial outcomes collected from patient surveys (Table 4).

Table 4. COMET Trial Primary and Secondary Endpoints

	Clinical Outcomes	QOL and Psychosocial Patient Reported Outcomes
Primary Endpoints	**2-year:** Ipsilateral invasive cancer rate **5, 7-year:** Ipsilateral invasive cancer rate	
Secondary Endpoints	**2-year:** Mastectomy/breast conservation rate Contralateral invasive cancer rate Overall survival and disease-specific survival **5, 7-year:** Overall survival and disease-specific survival	**Baseline, 6 months, years 1-5:** Health-related QOL Anxiety and depression **Baseline, 2 years:** Intolerance of uncertainty **Baseline:** Coping
Other Endpoints	**6-12 month:** Number of radiologic studies Number of biopsies Number of procedures Rate of crossover and dropout **2-year:** Breast MRI rate Breast biopsy rate Radiation rate Chemotherapy rate **5, 7-year:** Radiation rate Chemotherapy rate	**Baseline, 6 months, years 1-5:** Pain and other symptoms Body image and sexual function Employment status Self-reported co-morbidity **6 months, years 1-5:** Adherence to hormonal therapy **6 months, 2 years:** Health behavior/lifestyle factors Use of complementary therapies **Years 1-5:** Decisional regret **Baseline, 2 years:** Quality of decision-making Knowledge and risk perception **6 months:** Financial burden **Baseline:** Decisional conflict

Primary Clinical Outcomes. *Ipsilateral Breast Events.* Investigational biopsies will be performed in both study arms for suspicion of a new DCIS or invasive breast cancer in the ipsilateral breast as deemed clinically appropriate by the patient's treatment team. The resulting pathology slides from the biopsy will be reviewed by two pathologists and disease management recommended according to the histologic diagnosis. In the GCC arm, any diagnosis will be managed according to standard of care for local breast event or benign biopsy. In the AS arm, only an invasive cancer diagnosis will prompt intervention, according to standard management of invasive breast cancer.

Contralateral Breast Events. For both AS and GCC arms**,** contralateral findings for suspicion of new DCIS or invasive breast cancer will also be managed as deemed clinically appropriate by the patient's treatment team. The resulting diagnosis will be managed according to best standard practice as determined by provider recommendation and patient preference. If the new contralateral diagnosis is a DCIS that fulfills criteria for the COMET study, the patient can be offered AS or GCC for this diagnosis.

Secondary outcomes: Additional clinical outcomes which are also relevant to the differences between the GCC and AS groups include further surgical procedures and regional or distant metastatic breast cancer events. Since DCIS cells remain trapped within the breast duct and therefore have little potential to spread to distant organ sites and cause symptoms or death, few metastatic events are anticipated.

Patient Reported Outcomes. Patient Reported Outcomes (PROs) that are potentially important and relevant to women with DCIS will be elicited longitudinally at pre-specified time points during the study (Table 5).

Table 5: Schedule of PRO surveys

	Baseline	Month 6	Month 12	Month 24	Month 36, 48 and 60
Socio-demographics					
ALLIANCE Patient Questionnaire, adapted with employment items[19-22]	X	X - Employment	X ▪ Marital status ▪ Health insurance ▪ Household size/income	X ▪ Marital status ▪ Health insurance ▪ Household size/income	X ▪ Marital status ▪ Health insurance ▪ Household size/income

			▪ Employment	▪ Employment	▪ Employment
Medical and Family History					
Family history	X				
Self-Administered Co-Morbidity Questionnaire[23]	X	X	X	X	X
Genetics			X		
Complementary Therapies					
CAM Measure[24]		X		X	
Adherence to hormonal therapy					
Medication Adherence measure[25]		X	X	X	X
Health behaviors/lifestyle factors					
ALLIANCE Patient Questionnaire[26-38] Smoking Alcohol Physical activity Diet		X		X	
Psychological/Emotional					
STAI Trait Y2[39]	X				
STAI State Y1[39]	X	X	X	X	X
CES-D-10[40]	X	X	X	X	X
Brief COPE[41]	X				
Intolerance of uncertainty- Short form[42-44]	X			X	
Quality of life					
SF-36[45]	X	X	X	X	X
EQ-5D-5L[46,47]	X	X	X	X	X
QLACS[48]	X			X	
Breast-Q (arm, breast side effects, body image, sexuality)[49]	X	X	X	X	X
Modified BCPT symptom scale (menopausal symptoms)[50]	X	X	X	X	X
Breast Cancer Pain Questionnaire – Neuropathic symptoms[51,52.53]	X	X	X	X	X
Brief Pain Inventory[54]	X	X	X	X	X
BC/DCIS knowledge and perceptions					
BCS-DQI[55,56]	X			X	
True/False questions[57]	X			X	
Risk perceptions[58]	X			X	
Decision-making					
Decisional regret[59]			X	X	X
SURE scale[60,61]	X				
Sources of information[62]	X				
Costs					
Financial burden (adapted from CanCors, NHIS)[63,64]		X			
COMET website questions					
How participant learned about COMET Use of website	X	X			

Domains identified as potentially salient to women with DCIS, including validated measures specific to arm and breast symptoms, body image, and decision-making will be collected. To ensure that there is no

excessive burden to patients, and to test content flow and clarity, all surveys were piloted by the Patient Leadership Team (PLT) prior to trial initiation. The surveys are provided in print, online, or phone interview versions according to patient preference, and are also available in Spanish. All PRO data is entered into PRO-CORE, a study-specific survey data collection platform for web-based assessment of PROs, built and managed by the University of North Carolina Patient-Reported Outcomes Core Facility (UNC PRO-Core).

Collaborating sites send mammogram files consisting of the last screening and diagnostic mammogram studies that immediately predates the diagnostic core/vacuum-assisted biopsy or surgical excision; submission of biospecimens is also a required component of COMET and an integrated part of the consent process (Appendix 2).

STATISTICAL CONSIDERATIONS

Sample size. Sample size for this study was estimated using a 2-group test of non-inferiority of proportions, with the 2-year invasive cancer rate in the GCC group assumed to be 0.10 based on published studies.[65,66] The non-inferiority margin assumed was 0.05 as this was thought to be a clinically meaningful difference between the two arms, beyond which AS could not be reasonably considered to be equivalent to GCC. 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 [67] to detect the specified non-inferiority margin. A secondary time-to-event analysis will also be performed.

Planned analysis for clinical outcome data. The primary analysis will not simply follow the intent-to-treat principle but will analyze as randomized all patients with outcomes measured. However, we believe that this trial, as in other studies which randomize to operative versus non-operative arms, will have both non-compliers and contamination, due to patients who will have a desire to avoid surgery as well as patients who, conversely, will have a desire to have any pre-cancerous lesion removed. Thus, the final study design will include a per-protocol component as well as a pragmatic component for those patients who are randomized and decline participation in the assigned arm. We will define a cross-over as any switch from

AS to GCC as any breast surgery on the affected breast in the absence of invasive cancer when randomized to AS. Similarly, a cross-over from GCC to AS occurs if the patient refuses surgery when randomized to GCC.

Planned subgroup analyses. Although endocrine therapy is not required on either study arm, we will collect data on its use to determine whether it impacts rates of invasive breast cancer either group.[68] Thus, a planned subset analysis of endocrine therapy use will be completed using multivariable logistic regression, with similar adjustments for drop-out and non-adherence. Additionally, factors that may impact the selection of endocrine therapy in both arms such as age and pathological features will also be included. Similarly, we are interested in understanding how imaging modality used may impact assessment of invasive breast cancer during AS, i.e. whether magnetic resonance imaging (MRI) detects higher rates of invasive cancer than mammogram (MMG) for those patients whose providers opt to include MRI for surveillance. This will also be assessed in the AS group with logistic regression, controlling for factors that could impact selection of MMG versus MRI, such as patient age or breast density. We will also consider menopausal status and baseline risk of breast cancer, and whether these factors influence rate of invasive breast cancer at two years. While the study is not powered on these endpoints, these factors are likely to impact outcomes, and thus will be evaluated in planned subset analyses.

PATIENT AND PUBLIC INVOLVEMENT

Patients, patient advocates and other stakeholders have been actively engaged in the conception and development of this proposal, including the preliminary studies conducted to inform the work. In order to facilitate advocate engagement, we established the Patient Leadership Team (PLT). The input and activities of the PLT and advocacy networks guide direction of the trial throughout its entirety.

The PLT have been heavily engaged in the conception and development of the study (including the original research question) and partnered in all phases of planning and development. The PLT collaborate with investigators in the definition of study comparators and outcomes, key constructs to be measured, and choice of validated measures to assess those key constructs. The identification of outcomes *that the DCIS*

population of interest notice and care about is particularly relevant in order to provide practical information that can help patients make informed decisions about their health and health care. The appropriateness/relevance of survey measures has been reviewed by patient advocates and survey questions have been piloted with them for usability testing.

Patient advocates on the study have diverse involvement or leadership in DCIS and breast cancer patient advocacy organizations. They been strong leaders in the DCIS advocacy community for decades, and have deep ties to their constituencies; this will enable them to mentor members of these constituencies who lack this background in order to facilitate their full participation. This active engagement with key stakeholders will be crucial in the compilation of future dissemination strategies/translation of study findings to both professional and patient/public constituencies.

In sum, the PLT: 1) provides input to create effective protocols and survey designs that answer relevant questions for patients, clinicians and research; 2) contributes to the development of educational and implementation tools for clinical sites and DCIS patients; 3) recruits patient advocates to “beta” test surveys and patient tools; 4) develops and implements strategies to measure the impact of patient involvement on the advancement of engagement science; and 5) monitors accrual and participates in the overall implementation of the study.

ETHICS AND DISSEMINATION

The COMET trial will be subject to bi-annual formal review at the Alliance Foundation Data Safety Monitoring Board (DSMB) meetings. At each meeting, the DSMB will review a report of primary and secondary objectives, study schema, definition of primary endpoint, a summary of target accrual goals, a brief administration summary of current study status, accrual goals versus actual accrual, a summary of patient characteristics to date, a summary of drop-out or cross-over from allocated arm, an assessment of data completeness for the various types of data collected, a summary of primary and secondary outcomes by study arm, and finally, a summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) that will be reported from study entry until 7 years after registration.

Data safety monitoring at interim analysis. Interim analyses for futility/safety will be completed annually, with reporting following Consolidated Standards of Reporting Trials (CONSORT) guidelines extension for non-inferiority trials.[69] We consider stopping under two scenarios: if there is sufficient indication of 1) lack of efficacy or 2) potential harm.

First, we will determine if the deviation of the point estimate of the invasive cancer event rate difference for AS versus GCC exceeds 0 by more than 4 SD or 3 SD at either of the interim analyses completed when 1⁄2 and 3⁄4 of the expected number of total events has accumulated, respectively. The SD will be computed from the Kaplan-Meier estimates at two years. In the case that SD exceeds the predetermined bounds, the probability that AS is non-inferior is minimal, and the trial will be halted due to lack of efficacy.

Second, the trial was developed based on the premise that the up-staging rate to invasive breast cancer is approximately 10%.[70] If this rate is substantially higher than 10%, then we would potentially be exposing AS patients to harm. Thus, if the estimate for the up-staging rate in the GCC arm is significantly greater than 10% based on the Kaplan Meier estimate at two years, the trial will be halted due to potential patient harm.

DISCUSSION

Overdiagnosis and overtreatment may be unintended consequences of mammographic screening.[71] Given that DCIS is a non-obligate precursor of invasive breast cancer, for those women whose DCIS might never progress even without treatment or whose treatment and outcomes may not differ even if invasion occurs, there is a pressing need to study more selective clinical strategies than the current, non-risk-based therapies for DCIS originally intended for invasive breast cancer. For DCIS at low-risk of progression such as low-grade, small, non-palpable lesions, there may be no significant benefit to surgery or radiation and a de-escalation approach should be tested as it has been in other cancers (for example, prostate cancer).[72,73] There is recognition that high-grade DCIS is more likely to progress to an invasive breast cancer and these patients are excluded from the study. Given the lead-time between the development of

DCIS and appearance of invasive breast cancer, [74] there may also be a case for tailoring intervention by age and presence of competing comorbidities.

Global Collaboration: Adoption of significant practice changes in breast cancer treatment has often required consideration of multiple sources of information. Thus, compatibility of COMET with other trials is an important goal for implementation of findings from the COMET study. The LOw Risk dcIS study (LORIS trial; ISRCTN 27544579)[75,76] is a randomized-controlled trial of AS versus GCC in the UK, which opened to accrual in 2015. The patient populations, health care environments and the clinical trials organization of the COMET and LORIS studies represent an exceptional opportunity to combine resources and strategies, compare outcomes, and to identify similarities and differences in DCIS diagnosis, treatment and surveillance policies both from a patient population and a health care systems perspective. To that end, LORIS principal investigators have worked with the COMET team in order to closely align the two studies and allow future meta-analysis of both clinical and PRO endpoints. Specifically, we have prospectively designed the eligibility criteria, outcomes, and surveillance protocol which, while not identical in every instance, will nevertheless allow for a planned meta-analysis at completion of both studies. In addition there is a randomized, international, multicenter, phase III non-inferiority trial being conducted in the Netherlands (The LORD - LOw Risk DCIS study)[77] as well as other global efforts to identify biological components of DCIS 'risk'; for example, the Prevent Ductal Carcinoma in Situ Invasive Overtreatment Now – (PRECISION) study.[78]

The broad, long-term objective of this proposal is to provide high quality evidence regarding outcomes of treatment versus surveillance for DCIS and to determine whether data support the inclusion of AS in treatment guidelines for DCIS. It is anticipated that the evidence provided by the COMET study, together with data collected from the other low-risk DCIS studies, will enable patients and stakeholders to make better informed decisions about management options for low risk DCIS.

The COMET study represents an important opportunity to address a highly relevant health care issue with broad-reaching health, social, and economic implications. Moreover, we hope that this study may provide a

framework for evidence development in other low-risk conditions where overtreatment is an emerging concern.

AUTHOR CONTRIBUTIONS

The PI and first author of this paper (E. Shelley Hwang) was instrumental in the compilation of this study protocol. Each co-author (Terry Hyslop; Thomas Lynch; Elizabeth Frank; Donna Pinto; Desiree Basila; Deborah Collyar; Antonia Bennett; Celia Kaplan; Shoshana Rosenberg; Alastair Thompson; Anna Weiss; Ann Partridge) contributed equally to subsequent development of the protocol. Elizabeth Frank, Donna Pinto, Desiree Basila, and Deborah Collyar form the COMET Study Patient Leadership Team.

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COMPETING INTEREST STATEMENT

None of the authors involved in the publication of this paper have a competing interest (financial or otherwise).

DATA SHARING STATEMENT

Technical appendix, statistical code, and current dataset are available from the Alliance Statistics and Data Center (SDC) who will also have access to the final trial dataset.

SPIRIT CHECKLIST

We used the SPIRIT checklist when writing this protocol report.

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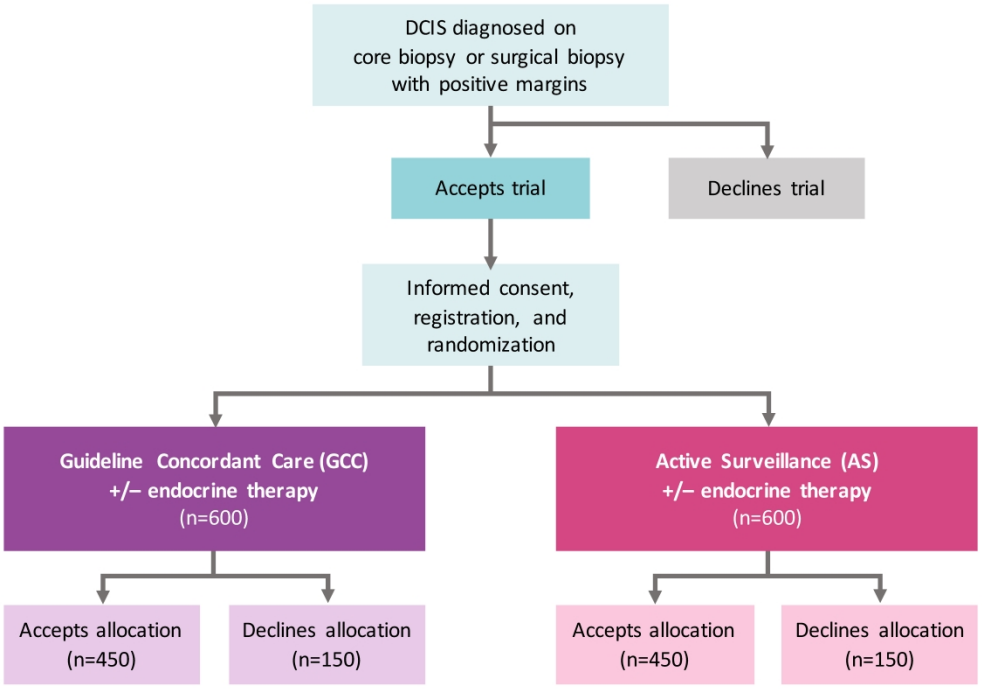
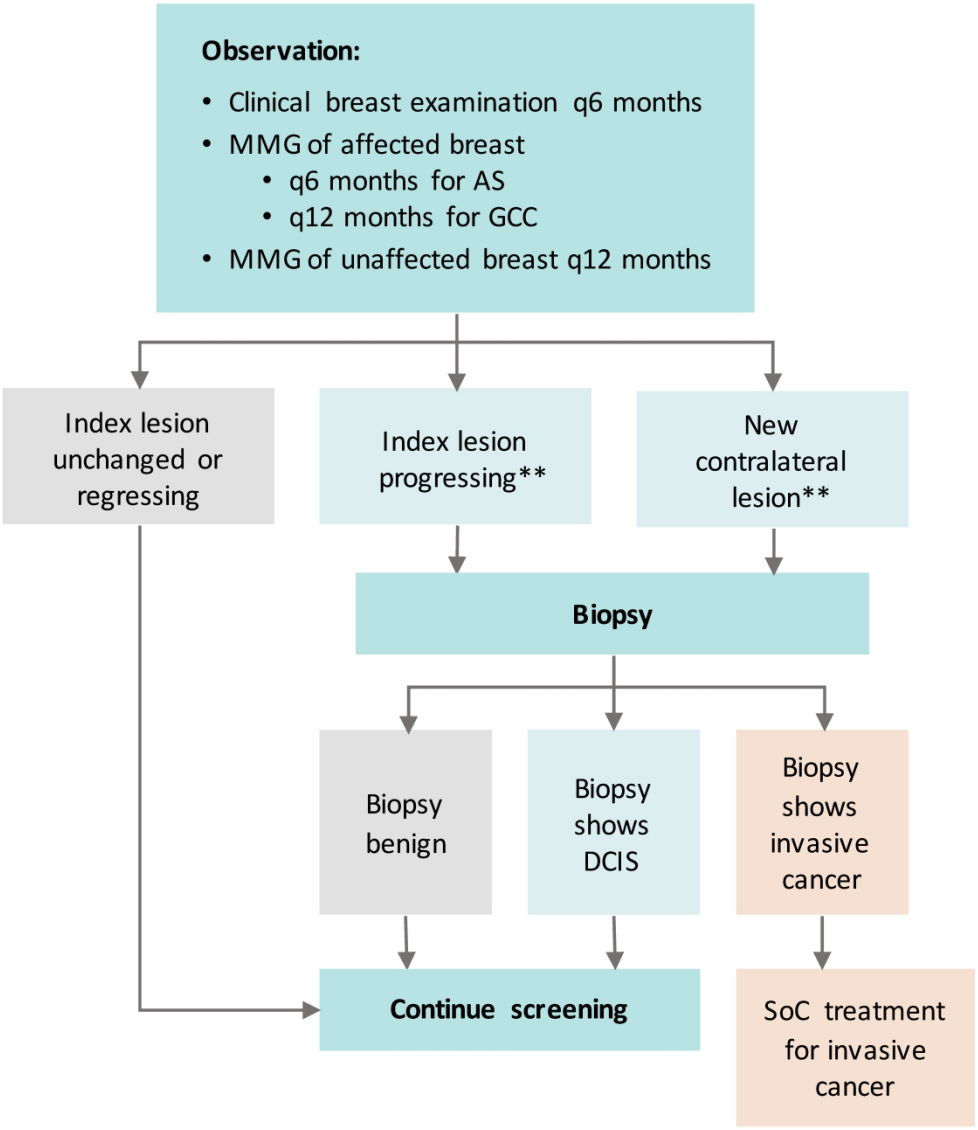
78. https://www.dcisprecision.org Date accessed 05/15/18

Figure Legends

Figure 1. COMET Trial Schema. Patient flow for accrual and registration. Eligibility criteria for **Low Risk** DCIS include 40 years of age or older, grade I/II DCIS without invasive cancer diagnosed on core, vacuum-assisted, or surgical biopsy, ER(+) and/or PR(+), HER2(-), and no mass on PE or imaging with exception of fibroadenoma at a distinct/separate site from site of DCIS. The primary study endpoint upon which the sample size is based is **rate of 2-year invasive cancer diagnosis among patients randomized to GCC compared to AS**. ITT analyses adjusted for dropout, non-compliance and contamination will be performed on all randomized patients including those who do and do not accept the arm to which they are randomized. Patient Reported Outcome surveys will be collected from all patients who are registered for the study, including those who cross over. Mammograms will be performed q6 months for the index breast and q12 months for the contralateral breast in the active surveillance arm and q12 months in both the index and contralateral breast in the guideline concordant care arm. No chest wall imaging will be performed if mastectomy has been performed.

Figure 2. Surveillance protocol for COMET Trial. MMG not required if mastectomy performed. **Criteria for progression: a) New **mas**s/architectural **distortion**/ **density** on surveillance 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.


DCIS diagnosed on
core biopsy or surgical biopsy
with positive margins
Accepts trial
Declines trial
Informed consent,
registration, and
randomization
Guideline Concordant Care (GCC)
+/– endocrine therapy
(n=600)
Active Surveillance (AS)
+/– endocrine therapy
(n=600)
Accepts allocation
(n=450)
Declines allocation
(n=150)
Accepts allocation
(n=450)
Declines allocation
(n=150)


Observation:
• Clinical breast examination q6 months
• MMG of affected breast
• q6 months for AS
• q12 months for GCC
• MMG of unaffected breast q12 months
Index lesion unchanged or regressing
Index lesion progressing**
New contralateral lesion**
Biopsy
Biopsy benign
Biopsy shows DCIS
Biopsy shows invasive cancer
Continue screening
SoC treatment for invasive cancer

COMET INFORMED CONSENT FORM

Study Title: Comparison of Operative to Monitoring and Endocrine Therapy (COMET) Trial For Low Risk DCIS: A Phase III Prospective Randomized Trial

Study #: <<protocol number>>

Sponsor: <<sponsor>>

Study Doctor: <<investigator>>

<<firm name>>

<<street address>>, <<city>>, <<state>> <<zip>>

Telephone Number: <<000-000-0000>>

After Office Hours: <<000-000-0000>>

For California participants: Before you read this consent form, you should read and sign a copy of the California Experimental Subject's Bill of Rights. Ask the study staff for a copy of this document if you haven't already received one.

This study is conducted and paid for by the Sponsor, Alliance Foundation Trials, LLC, a national clinical research group made up of cancer study doctors, other professionals, and laboratory researchers whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of people with cancer.

<<Quorum may add site-specific conflict-of-interest language to the form based on information the site reports to Quorum.>>

Introduction

You are being asked to take part in this study because you have been diagnosed with ductal carcinoma in situ (DCIS) in the cells lining the breast milk gland ducts. This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for further explanation.

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you must sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

How is DCIS usually treated?

Women diagnosed with DCIS most commonly receive a combination of surgery, radiation and/or endocrine (hormone-blocking) therapy (the "usual treatment" approach).

A small number of women choose to have close monitoring over a period of time. Close monitoring means a condition is watched with follow-up exams and tests such as mammograms, breast ultrasounds, and breast MRI. This study is being conducted because researchers wish to know whether, after 2 years, clinical and quality of life outcomes for women with low risk DCIS who receive usual treatment are the same as those for women with low risk DCIS who receive close monitoring.

What are my choices if I do not take part in this study?

If you decide to not take part in this study, you have a number of choices:

- You may still choose usual treatment for DCIS;
- You may still choose close monitoring for DCIS;
- You may choose not to be treated for DCIS;
- You may choose to take part in a different study, if one is available.

You can decide upon which alternative you would like to choose with the study doctor or study staff. In addition, you may discuss your options with your regular health care provider.

Why is this study being done?

The purpose of this study is to compare the risks and benefits of the usual treatment approach for DCIS compared to the close monitoring approach. There will be about 1200 women taking part in the study.

What are the study groups?

In this research study, you will be randomly assigned to one of two study groups:

- Group 1 will be assigned to **usual treatment** (surgery, radiation and/or endocrine (hormone-blocking) therapy);
- Group 2 will be assigned to **close monitoring** (alone or with endocrine (hormone-blocking) therapy)

A computer will assign you to one of the study groups. This is called randomization (it is like flipping a coin) and it is done by chance. Neither you nor the study doctor or study staff will be able to pick which study group you are in. If you agree to be randomized, you will have an equal chance of being assigned to either study group. Both you and your study doctor will be informed of your study group assignment.

After randomization, you can decline your study group assignment at any time. However, we will ask you whether you would still like to contribute to the study by completing surveys and allowing us to collect your medical records.

How long will I be in this study?

You will be in the study for a minimum of 5 years from time of registration. During the course of the study you will have a physical examination about every six months, a mammogram (or possibly an MRI if you are in the close monitoring group) about every six or twelve months (depending on the study group you are assigned to) and you will be asked to complete a number of surveys. After 5 years, you will undergo a physical examination and mammogram every 12 months. We may wish to continue to follow your progress for up to 10 years.

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

BEFORE YOU BEGIN THE MAIN PART OF THE STUDY

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

- A history and physical exam, including your height, weight, pulse, blood pressure and temperature
- Routine blood tests
- Blood or Urine pregnancy test, if applicable
    - The study doctor or study staff will tell you if the pregnancy test results are positive.
    - The results of the pregnancy testing must be negative in order for you to be in the study.
- Mammogram

BASELINE SURVEY

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be asked to complete a baseline participant survey (paper version or on a tablet computer where available per site) where general information (age, race, general health, family health history, quality of life, etc.) will be collected. Clinical information will also be collected by a trained clinical research assistant. The survey will take about 30 minutes to fill out.

STUDY PROCEDURES

You will be randomly assigned to one of the two study groups:

- Group 1 will be assigned to usual treatment for DCIS (surgery, radiation, or both);
- Group 2 will be assigned to close monitoring for DCIS

If you are assigned to the usual treatment group, you will undergo the appropriate surgery for DCIS within 60 days of randomization.

Participants in both groups will have a discussion with their regular care provider about taking endocrine (hormone-blocking) therapy, a pill that is taken once a day. These drugs are commonly used for DCIS and will not be paid for or administered by the study.

A biopsy (tissue sample taken from the breast) may be performed on either breast if any changes are detected during follow-up.

Your mammograms, breast ultrasounds, and breast MRIs (if any) will be collected for future research on DCIS.

SCHEDULE OF SUBSEQUENT STUDY SURVEYS

The study researchers would like to collect information about your health, quality of life, and other experiences of DCIS.

- About six months after you begin the study, you will be asked to complete a follow-up participant survey;
- About twelve months after you begin the study, you will be asked to complete another follow-up participant survey;
- You will then be asked to complete a follow-up participant survey every 12 months for the remainder of the study.

The surveys are required because your responses to them are a very important part of the study. The surveys will help us (the study doctor and study staff) to compare the benefits, harms, and burdens of usual treatment versus close monitoring in participants diagnosed with DCIS. The surveys will be available to complete online. If you cannot complete the surveys online, you will be provided with a survey packet with a stamped envelope, self-addressed to complete and mail back. Each survey will take approximately 30 minutes to complete.

Will I need time to recover after my participation in the study?

Ask the study doctor or study staff for the estimated recovery time of your participation in this study.

BLOOD AND TISSUE SAMPLES

As part of this study, you are being asked to provide tissue and blood samples (specimens) for future research. Tissue specimens will only be provided from biopsies that you have or will have as part of your care. Blood samples will involve no more than 4-6 tablespoons of extra blood.

After your tissue samples and blood are collected, they will be stored at room temperature (Tissue) or frozen (blood) in the AFT biorepository until they are used by research investigators. The biorepository is a place where biological samples (e.g. blood and/or tissue) are stored and protected from unauthorized use.

Your samples will be used by approved investigators working with AFT, the sponsor of this trial. Future studies may include genetic (DNA) analysis of your tissue and your blood. DNA is like an instruction book for each cell. Specific changes in your DNA may help to explain why some of your cells do not behave like others, or how you might respond to drugs and other treatments. Other types of studies may identify inherited variations in your DNA (which can be passed on and could reveal information about your family members) that are important for explaining why you may or may not respond to therapy. Investigators also plan to use some of your blood to look for DNA or other substances in your blood that may be used to predict how people will respond to therapy.

For all of the samples collected and all of the studies that will be performed on them, you should know:

- Your samples will be labeled only with code numbers. Only certain AFT personnel will have access to the list that links the code number to your name. The sample code number is linked to our study participant identification number in the AFT biorepository database. No study investigator will be able to link the sample code number to your name.
- Information collected during the main research study (research data such as your response to treatment, results of the study tests, and drugs you are given) may be provided to approved researchers along with your sample.
- The samples will be stored in the United States at the Alliance Foundation Biorepository, currently located at Washington University in St. Louis, MO.
- You will never receive any individual results from the research tests performed on your samples. These results will not be placed in your regular medical record.
- If your samples or the information generated from their use in research results in commercial products, you will not be able receive any profits from such products.
- Research data, as well as your genetic (DNA) research data (which contains information about variations in your DNA that can tell us about potential health risks to you and your children) may be shared with other investigators and the FDA, and may be placed in a publicly accessible database for further research use.

Your samples will be kept and used for approved research studies until they are physically used up or until you request that your samples be returned to your hospital or destroyed.

What will happen to my blood and tissue samples?

Your samples might be kept for ten years or even longer. Your specimens will be labeled only with code numbers. If you change your mind later, be aware that your samples may or may not be withdrawn from the research, depending on the sponsor's policies. You can ask the study doctor or study staff about this.

What will happen if I am assigned to close monitoring but my condition changes?

If you are assigned to close monitoring but your condition changes in some way, you may choose to be treated with breast surgery, radiation and/or endocrine (hormone-blocking) therapy.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- The close monitoring approach may not be better, and could possibly be worse, than the usual treatment approach for DCIS. Please ask your study doctor if you have questions about this;
- There may be physical, emotional and psychological side effects of surgical treatment. These may include bruising, bleeding, pain and changes to the look and feel of your breasts. These side effects may have an impact on your daily life;
- Radiation side effects may include burns to the skin and changes in the texture of the breast;
- Potential side effects of endocrine (hormone-blocking) therapy may include hot flashes, joint pain, weight gain, bone changes, blood clots. Rarely new cancers have been reported;
- You may be asked sensitive or private questions which you normally do not discuss;
- Additional risks include potential distress and loss of privacy or confidentiality when answering survey questions. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire. You have the right to refuse to answer any questions. While your direct responses to the survey will not be shared with the entire study team (study doctor and all study staff), we will alert your study team if you report substantial depressive symptoms;
- There is a risk of loss of confidentiality through the transfer of your personal health information (PHI). This includes the information we have stored about you in the database, for example revealing that you carry a genetic disease. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study;
- The information shared in the database may include your DNA results. Because your DNA information is unique to you, there is a chance that someone could trace it back to you. The risk of this happening is small, but may be greater in the future;
- If your tissue is used for research studies, there may be insufficient tissue remaining for other uses, should it be needed in the future for your medical care.

Ask the study doctor if you have questions about the signs or symptoms of any of the risks that you read about in this consent form.

Please tell the study doctor or study staff right away if you have any problems with your health or the way you feel during the study, whether or not you think these problems are related to the study procedures.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the findings of this study will help people who have DCIS currently. Providing samples for the biorepository will not help you. However, we hope that information from the study will help researchers to better understand treatment of DCIS and that this could help people diagnosed with this condition in the future.

Can I stop taking part in this study?

Yes - you can decide to stop at any time. There will be no penalty to you, and you won't lose any benefits. If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely.

If you withdraw from the study, the study doctor or study staff can still use your information that they have already collected.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. You may be taken out of the study:

- If your health changes and the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped by the sponsor, Quorum Review or the U.S. Food and Drug Administration (FDA).

If you stop taking part in your assigned group, but would like to still remain in the study, you will be invited to complete the follow-up surveys so that researchers can learn about the health and quality of life of women with DCIS. However, if you decide that you do not wish to take additional surveys and would like to exit the study completely, you will no longer be asked to complete them and you will no longer be contacted about the study unless you give permission.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty or loss of benefits to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for all of the costs of your care while in this study, including the cost of tests, procedures, or medicines. **Before you decide to take part in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.**

Will I receive payment?

<<Quorum will add site-specific compensation language to the form based on information the site reports to Quorum.>>

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. Medical treatment will be provided as usual. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be billed for any costs.

If you are injured as a result of this study, you keep all your legal rights to receive payment. You do not give up any of your legal rights by signing this form.

Who will see my medical information?

Your identity will be protected as required by law and according to any policies the study center or sponsor may have. Be aware that your study records (which include your medical records, your signed consent form, and other information) will be shared as needed for the study. Your information may be given out if required by law. For example, certain States require doctors to report to health boards if they find a disease like tuberculosis or if the study doctor or study staff suspects that you are going to harm yourself or others. The researchers will do their best to make sure information is not released that could potentially identify you, although there is a risk of loss of confidentiality through the transfer of your personal health information (PHI) which will be kept in a central database for research.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance Foundation Trials, LLC;
- Quorum Review - a group of people who review research studies to protect the rights and welfare of research participants;
- The Food and Drug Administration.

Where can I get more information?

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

Who can answer my questions about this study?

In the event of an emergency, dial 911 immediately.

If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor or study staff as soon as possible.

You can ask questions about the study at any time. You can call the study doctor or study staff at any time if you have any concerns or complaints. You should call the study doctor or study staff at the phone number listed on page 1 of this form if you have questions about the study procedures, study costs (if any), study payment (if any), or if you get hurt or sick during the study.

Quorum Review reviewed this study. Quorum Review is a group of people who review research studies to protect the rights and welfare of research participants. Review by Quorum Review does not mean that the study is without risks. If you have questions about your rights as a research participant, if you are not able to resolve your concerns with the study doctor or study staff, if you have a complaint, or if you have general questions about what it means to be in a research study, you can call Quorum Review or visit the Quorum Review website at www.quorumreview.com.

Quorum Review is located in Seattle, Washington.
Office hours are 8:00 AM to 5:00 PM Pacific Time, Monday through Friday.
Ask to speak with a Research Participant Liaison at 888-776-9115 (toll free).

HOW WILL MY INFORMATION BE USED AND SHARED FOR THIS STUDY?

This section explains who will use and share your health information if you agree to be in this study. You must authorize this use and sharing of your information by signing this form or you cannot be in the study. You can still be in the main part of the study even if you do not authorize the use and sharing of your information for the optional parts of the study (which you will read about below).

The study doctor and study staff will collect, use, and share health information about you, including any information needed to do the study and other identifying information about you, such as your name, address, phone number, or social security number. The information used and shared will include:

- information from your medical records
- information collected about you during the research about study visits, tests, procedures, etc.

Your information may be used and shared with these people for the following purposes:

- The study doctor and study staff to conduct this research.

- The sponsor, Alliance Foundation Trials; people who work with or for the sponsor; and other researchers involved in this study. These people will use your information to review the study, and to check the safety and results of the study.
- Others required by law to review the quality and safety of research, including the FDA, other government agencies in the United States and other countries, and Quorum Review.
- A public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions.

After your information is shared with the people and companies listed above, the law may not require them to protect the privacy of your information. To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally would have access to your health information.

You can cancel your authorization to use and share your information at any time by writing a letter to the study doctor. If you cancel your authorization, you will not be able to continue in the study. You can cancel your authorization for the optional parts of the study and remain in the main study.

If you cancel your authorization, the study doctor and study staff will still be able to use and share your information that they have already collected.

This authorization to use and share your information expires in 50 years.

_____ _____

Signature of Participant Date

<<*Quorum staff: Include the following for Indiana sites:*

In **Indiana,** you must complete the following information:

_____

Participant's Street Address

_____

Participant's City, State, ZIP>>

Comet Informed Consent Form
Alliance Foundation Trials, LLC
AFT – 25

Signature Agreeing to Take Part in the COMET Study

I have read this consent form or had it read to me. I have discussed it with my study doctor and my questions have been answered. I will be given a signed copy of this consent form. I agree to take part in the COMET study and any additional study components below where I circle 'yes'. By signing this form, I do not give up any of my legal rights.

I agree to take part in the COMET Study. I agree to provide tissue and blood samples for future research.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent Date

Comet Informed Consent Form
Alliance Foundation Trials, LLC
AFT – 25

Optional Component of the Study:

This part of the consent form is about an optional component of the study that you can choose to take part in or not. You can still take part in the COMET study even if you say "no" to the optional component. If you sign up for but cannot complete the optional component for any reason, you can still take part in the COMET study.

- Option to be contacted about future clinical trials

Please circle your answer: I agree to be contacted about any future clinical trials.

YES NO Initial: _____

If yes, please provide your telephone number and e-mail address (if you have one) below:

_____ _____
Email Address Telephone Number

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

Comet Informed Consent Form
Alliance Foundation Trials, LLC
AFT – 25

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be contacted about any future clinical trials.

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent Date

CORRELATIVE STUDIES

Image Collection. Collaborating sites send mammogram files consisting of the last screening and diagnostic mammogram studies that immediately predates the diagnostic core/vacuum-assisted biopsy or surgical excision. If breast ultrasound and/or breast MRI are performed as part of surveillance, those images are also requested for submission. If a core/vacuum-assisted biopsy is performed for a finding identified during follow-up on either the AS or GCC arm, the last diagnostic mammogram that immediately predates the diagnostic core/vacuum-assisted biopsy or surgical excision is requested. Four standard screening views as well as all diagnostic views, including all magnification views are also collected.

Biospecimen Collection. Submission of biospecimens is a required component of COMET and an integrated part of the consent process. In the event that it is physically impossible to submit required biospecimens, patients may still be enrolled to the trial without biospecimen submission. Core biopsy tissue and blood are collected at baseline and any core biopsy tissue obtained during follow-up will also be requested. 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 are stored in a CAP-accredited biorepository 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 the time of analysis.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See note 1
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	20
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	20

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See note 2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17-18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17-18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See note 3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	7-8

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	15-16

		imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	See note 4
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5
Declaration of	#28	Financial and other competing interests for principal	20

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17-18
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	See note 5
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

Author notes

1. N/A - registered in clinicaltrials.gov
2. 20 (Anna Weiss)
3. Table 2/Figure 2
4. N/A - IRB approval obtained
5. NA - no authorship eligibility guidelines or intended use of professional writers