JAMA | Preliminary Communication

Active Monitoring With or Without Endocrine Therapy for Low-Risk Ductal Carcinoma In Situ
The COMET Randomized Clinical Trial

E. Shelley Hwang, MD, MPH; Terry Hyslop, PhD; Thomas Lynch, PhD; Marc D. Ryser, PhD; Anna Weiss, MD; Anna Wolf, BA; Kelsey Norris, MPH; Meredith Witten, MD; Lars Grimm, MD; Stuart Schnitt, MD; Sunil Badve, MD; Rachel Factor, MD; Elizabeth Frank, MA; Deborah Collyar, BSc; Desiree Basila, MSc; Donna Pinto, BA; Mark A. Watson, MD, PhD; Robert West, MD, PhD; Louise Davies, MD, MS; Jenny L. Donovan, PhD; Ayako Shimada, MS; Yutong Li, MS; Yan Li, PhD; Antonia V. Bennett, PhD; Shoshana Rosenberg, ScD; Jeffrey Marks, PhD; Eric Winer, MD; Marc Boisvert, MD; Armando Giuliano, MD; Kelsey E. Larson, MD; Kathleen Yost, MD; Priscilla F. McAuliffe, MD; Amy Krie, MD; Nina Tamirisa, MD; Lisa A. Carey, MD; Alastair M. Thompson, MBChB, MD; Ann H. Partridge, MD, MPH; for the COMET Study Investigators

IMPORTANCE Active monitoring for low-risk ductal carcinoma in situ (DCIS) of the breast has been proposed as an alternative to guideline-concordant care, but the safety of this approach is unknown.

OBJECTIVE To compare rates of invasive cancer in patients with low-risk DCIS receiving active monitoring vs guideline-concordant care.

DESIGN, SETTING, AND PARTICIPANTS Prospective, randomized noninferiority trial enrolling 995 women aged 40 years or older with a new diagnosis of hormone receptor–positive grade 1 or grade 2 DCIS without invasive cancer at 100 US Alliance Cancer Cooperative Group clinical trial sites from 2017 to 2023.

INTERVENTIONS Participants were randomized to receive active monitoring (follow-up every 6 months with breast imaging and physical examination; n = 484) or guideline-concordant care (surgery with or without radiation therapy; n = 473).

MAIN OUTCOMES AND MEASURES The primary outcome was 2-year cumulative risk of ipsilateral invasive cancer diagnosis, according to planned intention-to-treat and per-protocol analyses, with a noninferiority bound of 5%.

RESULTS The median age of the 957 participants analyzed was 63.6 (95% CI, 55.5-70.5) years in the guideline-concordant care group and 63.7 (95% CI, 60.0-71.6) years in the active monitoring group. Overall, 15.7% of participants were Black and 75.0% were White. In this prespecified primary analysis, median follow-up was 36.9 months; 346 patients had surgery for DCIS, 264 in the guideline-concordant care group and 82 in the active monitoring group. Forty-six women were diagnosed with invasive cancer, 19 in the active monitoring group and 27 in the guideline-concordant care group. The 2-year Kaplan-Meier cumulative rate of ipsilateral invasive cancer was 4.2% in the active monitoring group vs 5.9% in the guideline-concordant care group, a difference of −1.7% (upper limit of the 95% CI, 0.95%), indicating that active monitoring is not inferior to guideline-concordant care. Invasive tumor characteristics did not differ significantly between groups.

CONCLUSIONS AND RELEVANCE Women with low-risk DCIS randomized to active monitoring did not have a higher rate of invasive cancer in the same breast at 2 years compared with those randomized to guideline-concordant care.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02926911

Visual Abstract
Editorial
Supplemental content
Related article at jamaoncology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The COMET Study Investigators appear in Supplement 3.

Corresponding Author: E. Shelley Hwang, MD, MPH, Duke University, 465 Seeley G. Mudd Bldg, DUMC Box 3513, Durham, NC 27710 (shelley.hwang@duke.edu).

JAMA. doi:10.1001/jama.2024.26698
Published online December 12, 2024. Corrected on January 16, 2025.

Annually, approximately 65 million women undergo mammographic screening in the US at a cost of more than $13 billion.[1] Although mammography has been associated with a reduction in breast cancer mortality rates,[2,3] there is increasing concern that this benefit has been accompanied by overdiagnosis and overtreatment.[4] Overdiagnosis occurs when cancer screening detects conditions that may never cause harm if left untreated; treatment for these conditions provides no survival benefit and can result in harm.

For breast cancer, much of the burden of overdiagnosis is thought to derive from the detection of ductal carcinoma in situ (DCIS), a diagnosis faced by more than 50 000 women in the US annually.[5,6] DCIS is a preinvasive neoplasia that lacks the potential to spread and cause symptoms unless it undergoes progression to invasive cancer. When diagnosed, DCIS is conventionally treated with surgery, often combined with adjuvant radiation, and/or endocrine therapy.[7,8] These treatments are the same as those recommended for women with low- to intermediate-risk invasive cancer. Adverse effects of these therapies can include long-term pain, altered body image, sexual dysfunction, menopausal symptoms, or, rarely, secondary cancers.[9] Because not all DCIS progresses to invasive cancer,[10-13] there is a potential opportunity to deescalate surgery in the management of DCIS.

We performed a prospective, randomized, pragmatic noninferiority trial for women with newly diagnosed low-risk DCIS comparing guideline-concordant care, including surgery, with active monitoring, with surgery reserved only for disease progression to invasive cancer. The primary objective was to assess whether active monitoring was noninferior to guideline-concordant care as defined by the invasive cancer rate in affected breasts at 2 years.

Key Points

Question What is the short-term safety of an active monitoring approach vs guideline-concordant care (surgery with or without radiation therapy) for hormone receptor–positive, grade 1 or grade 2 breast ductal carcinoma in situ?

Findings In this prospective randomized clinical trial of 957 participants, the 2-year Kaplan-Meier cumulative rate of ipsilateral invasive cancer was 5.9% in the guideline-concordant care group vs 4.2% in the active monitoring group, a difference of −1.7% (upper limit of the 95% CI, 0.95%), indicating that active monitoring is not inferior to guideline-concordant care.

Meaning These data support the short-term safety of active monitoring compared with guideline-concordant care in patients with low-risk ductal carcinoma in situ.

Methods

Study Design, Setting, and Patients

The COMET (Comparing an Operation to Monitoring, With or Without Endocrine Therapy for Low-Risk DCIS; AFT-25) study is a large, pragmatic, randomized noninferiority trial that compares clinical and patient-reported outcomes between patients randomized with guideline-concordant care (surgery with or without radiation therapy) or active monitoring. The study has been described previously (see the eAppendix in Supplement 1).[14] End points were selected with the input of the COMET Study Patient Leadership Team, which consisted of 4 patient advocate investigators who were involved in all phases of the study. This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials.

The trial was coordinated across 100 Alliance for Clinical Trials in Oncology Foundation Trials (AFT) member sites between June 2017 and January 2023; 83 sites accrued at least 1 patient to the study. Institutional review board (IRB) approval of the study protocol was obtained at each site or through the Advarra central IRB, and all patients provided written informed consent to participate in the study. The study protocol and statistical analysis plan are available in Supplement 2.

The study population included women with newly diagnosed DCIS who were aged 40 years or older and had screen-detected, nuclear grade 1 or 2 estrogen and/or progesterone receptor–positive (≥10% staining for Allred Score ≥40), *ERBB2*-receptor negative (immunohistochemistry scores of 0, 1+, or 2+ if tested) disease, without evidence of invasive cancer. Concurrence of 2 pathologists' reviews of diagnostic specimens was required to confirm eligibility. Patients with breast symptoms or mass on baseline breast imaging were excluded.

Data Collection and Study Oversight

The AFT data and safety monitoring board (DSMB) provided ongoing oversight for the conduct of the study and allowed for data release on March 31, 2024. The dataset was locked on June 30, 2024, for the primary analysis. Eligible participants were randomized 1:1 to guideline-concordant care or active monitoring. Randomization was stratified by age at diagnosis (<55, 55-65, or >65 years), maximum diameter of microcalcifications (<2 cm, 2-5 cm, or >5 cm), and DCIS nuclear grade (1 or 2). Race and ethnicity classifications were based on investigator observation for this analysis.

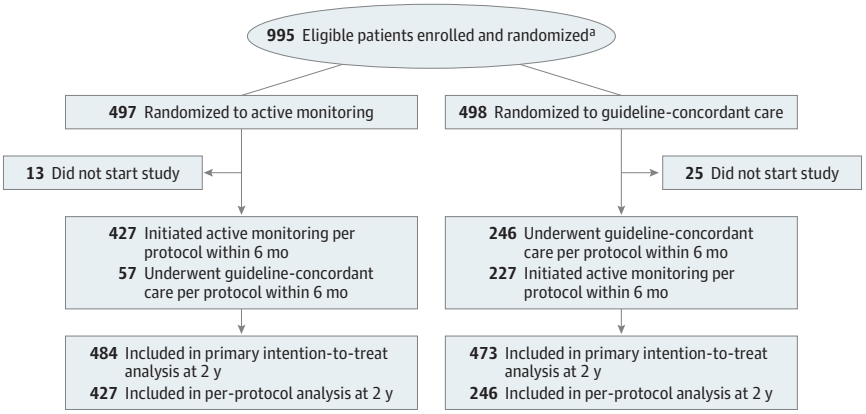
Guideline-Concordant Care

Patients randomized to guideline-concordant care had usual-care treatment for their diagnosis, including surgery. The choice of mastectomy or breast-conserving surgery was made by patients together with their surgeons. Patients undergoing breast-conserving surgery were offered adjuvant radiation treatment in accordance with standard practice. Diagnostic mammograms were required every 12 months for both the affected (if not treated with mastectomy) and unaffected breast.

Active Monitoring

Patients in the active monitoring group were regularly monitored with imaging and physical examination. Diagnostic mammograms were required every 6 months for the affected breast

Figure 1. Flow of Participants Through the COMET Trial



Patient acceptance of randomized intervention was defined at 6 months, but the primary outcome was cumulative during the 2-year follow-up period. COMET indicates Comparing an Operation to Monitoring, With or Without Endocrine Therapy for Low-Risk DCIS.

[a]Data on the number of potential participants approached at each site were not collected prospectively.

as part of active monitoring and every 12 months for the unaffected breast. Patients with a new breast mass, nipple/skin changes on physical examination, or imaging findings concerning for disease progression (eg, a new mass, new architectural distortion, and/or increase in extent of calcifications ≥5 mm in ≥1 dimension) were recommended to undergo core needle biopsy. Surgical intervention was required if the needle biopsy identified invasive cancer. For benign breast changes, atypia, or DCIS, continued active monitoring was recommended. Patients who wished to have surgery at any time, for any reason, proceeded to surgery in consultation with their treating surgeon, with the reason for surgery and pathology diagnosis at surgical excision recorded.

Endocrine Therapy

Patients in both groups could elect to take endocrine therapy in consultation with their treating physician; any use was recorded at each study visit.

Primary Outcome

The primary outcome of the study was the 2-year cumulative rate of ipsilateral invasive cancer diagnosis, inclusive of all invasive cancers detected at any time after enrollment. Secondary outcomes included overall survival as well as 2-year rates of mastectomy, radiation, and chemotherapy treatment, as well as patient-reported outcomes.[15] These end points were collected prospectively at prespecified study time points in both groups.[14]

Statistical Analysis

Sample Size Considerations and Noninferiority Bound

The general analytic approach is a prospective randomized trial design wherein the hypothesis is based on a noninferiority end point, namely that the 2-year invasive breast cancer detection rate is not inferior for active monitoring compared with guideline-concordant care. The noninferiority margin was designated at 5% based on published data, expert consensus opinion, and patient advocate input, as the maximum difference that could be deemed to have negligible clinical impact. Sample size for this study was estimated using a 2-group test of noninferiority of proportions, with the 2-year ipsilateral invasive breast cancer rate in the surgery group assumed to be 10% based on published data that showed that for women undergoing surgery for DCIS, the "upstaging" rate (ie, the rate at which invasive cancer is identified in patients diagnosed with DCIS only prior to surgery) for low-risk DCIS is approximately 5% to 16%.[16-18] Based on a 1-sided unpooled z test with $\alpha = .05$, a sample size of n = 446 per group had 80% power[19,20] to detect the specified noninferiority margin. The protocol included a stopping rule that if the upstaging rate for women who had surgery exceeded 10% at any time during the study, the DSMB would recommend trial discontinuation. Interim analysis was based on point estimates and the overall standard deviation. Only 1 formal interim analysis was completed, when half of the events had occurred. Other analyses done at the request of the DSMB used pooled data only.

Primary Outcome Analysis

Kaplan-Meier cumulative incidence curves were used to estimate the rate of invasive cancer, with the difference in 2-year cumulative rates estimated and a 1-sided upper confidence limit of (active monitoring − guideline-concordant care) computed. We would conclude that active monitoring is not inferior to guideline-concordant care if the upper confidence limit on the risk difference was less than 5%. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 4.4.2 (R Foundation).

Results

Study Population

The COMET study enrolled 995 participants, of which 957 were randomized between June 2017 and January 2023 to either guideline-concordant care (n = 473) or active monitoring (n = 484) (**Figure 1**). Patient and disease characteristics were comparable between the 2 groups (**Table 1**; eTable 1A in Supplement 1). Overall, 15.7% of participants were Black and 75.0% were White. DCIS nuclear grade was reported as grade 1 in 26.3% of patients (n = 252), with the remainder grade 2. The

Table 1. Baseline Participant Characteristics

Characteristics	No. (%)	
	Active monitoring (n = 484)	Guideline-concordant care (n = 473)
Age, y		
<55	112 (23.1)	114 (24.1)
55-65	164 (33.9)	164 (34.7)
>65	208 (43)	195 (41.2)
Race	n = 466	n = 458
American Indian or Alaska Native	1 (0.2)	1 (0.2)
Asian	23 (4.8)	23 (4.9)
Black or African American/African heritage	80 (16.5)	70 (14.8)
Native Hawaiian or Other Pacific Islander	0	3 (0.6)
White	359 (74.2)	359 (75.9)
More than 1 race	3 (0.6)	2 (0.4)
Ethnicity	n = 472	n = 457
Hispanic	34 (7)	17 (3.6)
Non-Hispanic	438 (90.5)	440 (93)
DCIS laterality at diagnosis		
Left	247 (51)	235 (49.7)
Right	233 (48.1)	236 (49.9)
Bilateral	4 (0.8)	2 (0.4)
DCIS grade at diagnosis		
1	125 (25.8)	127 (26.8)
2	359 (74.2)	346 (73.2)
DCIS estrogen receptor positive at diagnosis	473 (97.7)	467 (98.7)
DCIS progesterone receptor status at diagnosis	n = 405	n = 411
Positive	364 (75.2)	359 (75.9)
Negative	41 (8.5)	52 (11)
DCIS *ERBB2* status at diagnosis	n = 4	n = 8
0	1 (0.2)	3 (0.6)
1+	3 (0.6)	5 (1.1)
Premenopausal/perimenopausal	90 (18.6)	92 (19.5)
ECOG performance status score[a]		
0	431 (89)	410 (86.7)
1	53 (11)	63 (13.3)
Comorbidities[b]	n = 432	n = 431
Any comorbidity	284 (58.7)	256 (54.1)
Total No. of comorbidities		
0	148 (30.6)	175 (37)
1	137 (28.3)	124 (26.2)
2	58 (12)	55 (11.6)
3	34 (7)	27 (5.7)
4	14 (2.9)	11 (2.3)
≥5	41 (8.4)	39 (8.2)

Abbreviations: DCIS, ductal carcinoma in situ; ECOG, Eastern Cooperative Oncology Group.

[a] ECOG performance status scores range from 0 to 5 (higher scores indicate greater disability).

[b] Comorbidities reported include hypertension, diabetes, chronic obstructive pulmonary disease, kidney failure/insufficiency, stroke, myocardial infarction, and other as specified on the report.

median age was 63.6 years (95% CI, 55.5-70.5 years) for the guideline-concordant care group and 63.7 years (95% CI, 60.0-71.6 years) for the active monitoring group.

Primary and Secondary Clinical Outcomes

Primary Outcome: 2-Year Rate of Ipsilateral Invasive Cancer

There were 46 ipsilateral invasive cancers diagnosed, 27 in the guideline-concordant care group and 19 in the active monitoring group (**Table 2**). In the intention-to-treat analysis, we observed a 2-year cumulative rate of invasive cancer of 5.9% with guideline-concordant care (95% CI, 3.71%-8.04%) and 4.2% with active monitoring (95% CI, 2.31%-6.00%), a difference of −1.7% (upper limit of the 95% CI, 0.95%), supporting the conclusion that active monitoring is not inferior to guideline-concordant care (**Figure 2**A; eFigure 1A in Supplement 1).

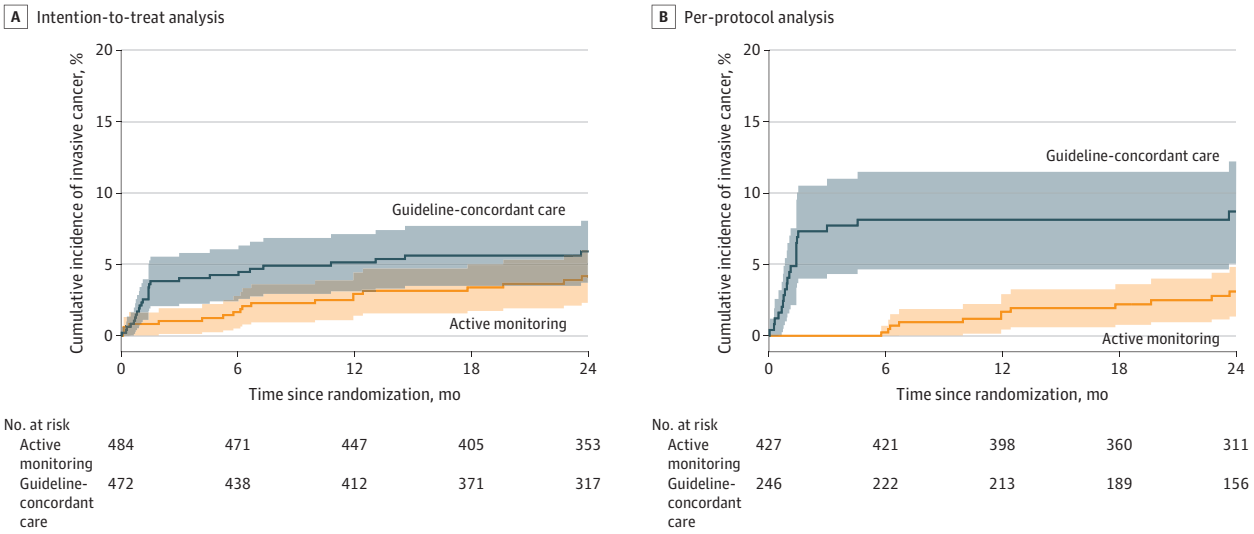
The planned per-protocol analysis included a subset of 673 patients (eTable 1B in Supplement 1) whose overall characteristics were comparable with the intention-to-treat cohort. Among patients randomized to guideline-concordant care, 246

Table 2. Pathology Characteristics of Invasive Cancers Detected[a]

Characteristics	Active monitoring (n = 19)	Guideline-concordant care (n = 27)	*P* value
Invasive cancer largest target lesion, cm	n = 16	n = 24	
Mean (SD)	0.94 (0.77)	0.78 (1.08)	.33
Median (IQR)	0.85 (0.2-1.63)	0.4 (0.28-0.9)	
Invasive cancer largest target lesion, cm, No. (%)	n = 16	n = 24	
0-1	10 (52.6)	20 (74.1)	
1.1-2	5 (26.3)	2 (7.4)	.29
2.1-5	1 (5.3)	2 (7.4)	
Invasive cancer estrogen receptor status, No. (%)	n = 18	n = 26	
Negative	0	2 (7.4)	.51
Positive	18 (94.7)	24 (88.9)	
Invasive cancer progesterone receptor status, No. (%)	n = 17	n = 25	
Negative	7 (36.8)	4 (14.8)	.09
Positive	10 (52.6)	21 (77.8)	
Invasive cancer *ERBB2* status, No. (%)	n = 18	n = 20	
0	6 (31.6)	9 (33.3)	
1+	8 (42.1)	6 (22.2)	.67
2+	4 (21.1)	4 (14.8)	
3+	0	1 (3.7)	
No. of positive nodes removed in sentinel lymph node biopsy, No. (%)	n = 10	n = 13	
0	8 (42.1)	8 (29.6)	.41
≥1	2 (10.5)	5 (18.5)	
Highest invasive cancer grade, No. (%)	n = 13	n = 22	
High	3 (15.8)	1 (3.7)	
Intermediate	6 (31.6)	11 (40.7)	.34
Low	4 (21.1)	10 (37)	

[a] Comparisons of patient characteristics were performed using the χ^2 test or Fisher exact test for categorical variables and analysis of variance or the Wilcoxon rank sum test for continuous variables.

Figure 2. Kaplan-Meier Estimates of the 2-Year Cumulative Probability of Invasive Cancer Diagnosis, by Treatment Group



Shaded areas indicate 95% CIs. A, In the intention-to-treat analysis, the 2-year cumulative rates of invasive cancer were 5.9% (95% CI, 3.71%-8.04%) in the guideline-concordant care group and 4.2% (95% CI, 2.31%-6.00%) in the active monitoring group, for a difference of −1.7%. B, In the per-protocol analysis, the 2-year cumulative rates of invasive cancer were 8.7% (95% CI, 5.06%-12.21%) in the guideline-concordant care group and 3.1% (95% CI, 2.31%-6.00%) in the active monitoring group, for a difference of −5.6%.

Table 3. Treatment Received Within 24 Months

Treatment within 24 mo	No. (%)	
	Active monitoring (n = 484)	Guideline-concordant care (n = 473)
Any endocrine therapy	345 (71.3)	310 (65.5)
Any radiotherapy	36 (7.4)	126 (26.6)
Any chemotherapy	6 (1.2)	5 (1.1)
Type of surgery	n = 82	n = 264
Lumpectomy	64 (13.2)	228 (48.2)
Mastectomy	18 (3.7)	26 (5.5)
Reexcision	0	10 (2.1)

(52%) had received surgery by 6 months; among patients randomized to active monitoring, 427 (85.9%) had initiated the active monitoring protocol at 6 months (Figure 1). In the per-protocol analysis, we observed a 2-year cumulative rate of invasive cancer of 8.7% for guideline-concordant care (95% CI, 5.06%-12.21%) and 3.1% for active monitoring (95% CI, 2.31%-6.00%), a difference of −5.6% (upper limit of the 95% CI, −2.07%), supporting the conclusion that active monitoring is superior to guideline-concordant care (Figure 2B; eFigure 1 in Supplement 1).

Recognizing the unexpectedly high rate of nonadherence to allocated intervention with potential for bias due to self-selection of treatment, we evaluated patient characteristics in 4 subgroups: those who were randomized to guideline-concordant care and received guideline-concordant care; those who were randomized to guideline-concordant care but received active monitoring; those who were randomized to active monitoring and received active monitoring; and those who were randomized to active monitoring but received guideline-concordant care. We found no obvious imbalance between groups (eTable 1C in Supplement 1).

Characteristics of Ipsilateral Invasive Cancer Diagnosed, by Treatment Group

Tumor size of invasive cancers did not differ between groups; in the guideline-concordant care group, 81.5% of invasive cancers were T1, compared with 78.9% in the active monitoring group. A higher proportion of invasive cancers were low grade and node positive in the guideline-concordant care group compared with the active monitoring group, although these differences failed to achieve statistical significance. There were no marked differences in invasive cancer characteristics among the 4 subgroups based on randomization group/treatment received, although some of the comparisons were compromised by small sample sizes (Table 2; eTable 2 in Supplement 1).

Treatment Received, by Study Group

At the time of the intention-to-treat analysis, 36% of patients (n = 346) had undergone any surgery, 264 (55.8%) in the guideline-concordant care group and 82 (16.9%) in the active monitoring group (**Table 3**; eFigure 2 in Supplement 1). Adjuvant radiation was received by 26.6% of women (n = 126) in the guideline-concordant care group compared with 7.4% (n = 36) in the active monitoring group. Chemotherapy was received by 5 women (1.1%) in the guideline-concordant care group and 6 (1.2%) in the active monitoring group. The mastectomy rate was similar between intention-to-treat groups, with 5.5% of women (n = 26) in the guideline-concordant care group and 3.7% (n = 18) in the active monitoring group undergoing mastectomy. Among the 4 subgroups base on randomization group/treatment received, the rate of mastectomy performed was 32 (10.5%) of 303 patients opting for guideline-concordant care (ie, those randomized to guideline-concordant care and undergoing guideline-concordant care and those randomized to active monitoring but undergoing guideline-concordant care) and 12 (1.8%) of 654 patients opting for active monitoring (ie, those randomized to active monitoring and undergoing active monitoring and those randomized to guideline-concordant care but undergoing active monitoring) (eTables 3A and 3B in Supplement 1).

Overall Survival

At the time of analysis, 6 patients had died, 2 in the guideline-concordant care group and 4 in the active monitoring group, none with a cause of death attributed to breast cancer (eTable 4 in Supplement 1).

Subgroup Analysis by Endocrine Therapy

Overall, 68.4% of the cohort (n = 665) reported initiation of endocrine therapy, 65.5% (n = 310) in the guideline-concordant care group and 71.3% (n = 345) in the active monitoring group (Table 3; eTables 3A and 3B in Supplement 1). In the endocrine therapy subgroup, the ipsilateral invasive cancer rate was 7.15% for guideline-concordant care and 3.21% for active monitoring, for a difference of−3.94% (95% CI, −5.72% to −2.16%) (eFigure 3 and eTables 5A, 5B, 6A, and 6B in Supplement 1).

Discussion

COMET is the first randomized clinical trial, to our knowledge, to report outcomes comparing guideline-concordant care with active monitoring for management of low-risk DCIS. In an intention-to-treat analysis, we found that the 2-year cumulative rate of invasive cancer was 5.9% for women randomized to guideline-concordant care and 4.2% for active monitoring. These results show that at 2 years, patients randomized to active monitoring have noninferior invasive breast cancer risk in the affected breast compared with those randomized to guideline-concordant care. The findings are novel, as all current treatments for DCIS require surgical excision, despite a growing body of evidence that supports that not all DCIS is destined to progress to invasive cancer.[11,21]

For women with a low risk of invasive progression, guideline-concordant care may offer little clinical benefit, resulting in potential for overtreatment. Deescalation trials in DCIS have aimed to optimize oncologic outcomes and minimize toxicity by selective omission of radiation or endocrine therapy.[22,23] However, omission of surgery for DCIS remains a highly controversial challenge to dogma, with both patients and clinicians fearing that the absence of excision might result in an unacceptably high rate of invasive cancer. Thus, virtually all

patients with DCIS currently undergo surgery, with up to a third of women undergoing mastectomy in some published series.[8,24] In the COMET study, more than 10% of patients who had guideline-concordant care underwent mastectomy, compared with 1.8% in the active monitoring group, suggesting that the active monitoring approach does not increase likelihood of eventual need for more extensive surgery.

We note that in the COMET trial, more than 70% of women in the active monitoring group reported use of endocrine therapy, which may have resulted in a reduced rate of invasive cancer in the active monitoring group. Previous studies have shown that both selective estrogen receptor modulators and aromatase inhibitors reduce the incidence of invasive cancer by approximately 50%, with plausible mechanisms being either the deterrence of DCIS progression in the context of prevention[25-28] or the reversal of invasive cancer as demonstrated in neoadjuvant endocrine therapy trials as treatment response.[29-31] COMET was not designed to address important questions regarding the magnitude of benefit conferred from endocrine therapy or the optimal duration of treatment, and these questions remain to be answered. Future deescalation studies should be designed with inclusion of patient-reported outcome measures to determine whether some patients may prefer surgery and possible radiation to prolonged endocrine therapy with its attendant adverse effects.

Trials such as COMET that compare surgical and medical treatments are confronted with unique challenges. In such trials, neither patients nor clinicians are blinded to the 2 treatment groups. Thus, the processes of recruitment, randomization, and protocol adherence lead to unpredictable and variable adherence to study protocol between groups. Indeed, in other randomized clinical trials that have compared surgical and medical treatments, the published rates of patients who elect surgery when randomized to the surgical group range broadly, from less than 20% to more than 90%.[32-35] In an evidence synthesis that assessed factors specifically relevant to trials comparing surgical and nonsurgical treatments,[36] several main themes emerged, including (1) the extreme and evident differences between study treatments; (2) patient reluctance to be randomized to a surgical intervention; and (3) the lack of equipoise between groups for both patients and clinicians.[37-41] Such issues contribute to early trial discontinuation for 1 in 5 surgical randomized trials, with a third of completed trials never resulting in publication, and were likely important factors at play in the COMET trial.[42]

Accordingly, we found an imbalance of patient adherence to allocated protocol between study groups, with 44% of the guideline-concordant care group electing to decline surgery and 14% of the active monitoring group declining monitoring. The COMET trial was designed as a pragmatic trial, and a 30% nonacceptance of allocation was anticipated and accommodated in the study design, with a prespecified per-protocol analysis included in the statistical analysis plan. However, we did not anticipate the strong preference for monitoring over surgery among study participants. We compared participants by randomization group and treatment received and did not identify an obvious imbalance between patients who did and did not adhere to the allocated protocol. Nevertheless, we cannot exclude the introduction of important unmeasured differences between groups, leading to selection and participation biases despite the prospective randomized design.

Limitations

Several additional limitations of the study should be noted. The noninferiority margin was selected based on published data and stakeholder input, including perspectives from patient advocates. However, it may be perceived as generous relative to the actual observed cumulative incidence of invasive cancers, which was lower than projected. We performed a more stringent analysis using a 1-sided 97.5% CI, which resulted in the same conclusion but does not abrogate this concern. In addition, although patients have interest in deescalation of DCIS treatment, it is unclear whether the COMET results can be generalized to a broad cohort. It should also be emphasized that the clinical outcomes reported herein must be considered within the context of the lived experience of patients in the study[15] to gain a richer understanding of the quality-of-life trade-offs for patients undergoing active monitoring. Perhaps most importantly, we underscore that these results are reported at a median follow-up of 37 months, with a primary outcome that may be highly sensitive to the follow-up duration. We expect that with longer follow-up, there will be more invasive events, particularly in the active monitoring group, and it is possible that the results reported in this analysis may be reversed when applied to a later time point. Thus, although these findings are provocative, it remains uncertain whether the noninferiority of active monitoring compared with guideline-concordant care will be maintained with longer follow-up. To that end, additional analyses of the COMET cohort are crucial and are planned at 5, 7, and 10 years.

Our findings have important implications for future inclusion of active monitoring as an option for low-risk DCIS, particularly in patients who may consider endocrine therapy as part of active monitoring or who have multiple competing comorbidities. Other ongoing trials in low-risk DCIS will also contribute to knowledge in this area. Recruitment for the LORD patient preference trial (EORTC-BCG 1401)[43] is anticipated to be completed by 2026. The LORETTA study (JCOG 1505) completed recruitment in January 2024 as a single-group study of 360 estrogen receptor–positive DCIS patients treated with tamoxifen for 5 years as an alternative to surgery. The LORIS prospective randomized trial conducted in the UK closed early with 188 patients, and we await the 10-year results.[44]

Conclusions

This primary analysis of the COMET trial found that women with low-risk DCIS randomized to active monitoring did not have a higher rate of invasive cancer at 2 years compared with those randomized to guideline-concordant care. Longer follow-up will help determine whether active monitoring offers durable safety and acceptability for patients in the management of this low-risk disease.

ARTICLE INFORMATION

Accepted for Publication: November 28, 2024.

Published Online: December 12, 2024. doi:10.1001/jama.2024.26698

Correction: This article was corrected on January 16, 2025, to fix typos in the reporting of the noninferiority margin.

Author Affiliations: Department of Surgery, Duke University, Durham, North Carolina (Hwang, Lynch, Marks); Department of Pharmacology, Physiology, and Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania (Hyslop); Departments of Population Health Sciences and Mathematics, Duke University, Durham, North Carolina (Ryser); Department of Surgery/Oncology, University of Rochester, Rochester, New York (Weiss); Alliance Foundation Trials, Boston, Massachusetts (Wolf, Norris); Aurora Health Care, Milwaukee, Wisconsin (Witten); Department of Radiology, Duke University, Durham, North Carolina (Grimm); Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts (Schnitt); Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia (Badve); Department of Pathology, Duke University, Durham, North Carolina (Factor); COMET Study Patient Leadership Team, Alliance Foundation Trials, Boston, Massachusetts (Frank, Collyar, Basila, Pinto); Department of Pathology and Immunology, Washington University in St Louis, St Louis, Missouri (Watson); Department of Pathology, Stanford University, Stanford, California (West); The VA Outcomes Group, Department of Veterans Affairs Medical Center, White River Junction Vermont and Geisel School of Medicine at Dartmouth, Hanover, New Hampshire (Davies); Population Health Sciences, University of Bristol, Bristol, United Kingdom (Donovan); Division of Biostatistics/Bioinformatics, Thomas Jefferson University, Philadelphia, Pennsylvania (Shimada, Yutong Li); Duke Cancer Institute Biostatistics Shared Resource, Duke University, Durham, North Carolina (Yan Li); Department of Health Policy and Management, University of North Carolina at Chapel Hill (Bennett); Division of Epidemiology, Weill Cornell University, New York, New York (Rosenberg); School of Medicine, Yale University, New Haven, Connecticut (Winer); Division of Breast Surgery, Medstar Washington Hospital Center, Washington, DC (Boisvert); Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California (Giuliano); Department of Surgery, The University of Kansas Health System, Kansas City (Larson); Cancer Research Consortium of West Michigan NCORP, Grand Rapids (Yost); Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania (McAuliffe); Metro MN Community Oncology Research Consortium, St Louis Park, Minnesota (Krie); Department of Breast Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston (Tamirisa); Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill (Carey); Department of Surgery, Baylor College of Medicine, Houston, Texas (Thompson); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Partridge).

Author Contributions: Drs Hwang and Hyslop had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Thompson and Partridge are co–senior authors.
Concept and design: Hwang, Hyslop, Lynch, Ryser, Grimm, Badve, Frank, Collyar, Basila, Rosenberg, Winer, Thompson, Partridge.
Acquisition, analysis, or interpretation of data: Hwang, Hyslop, Lynch, Ryser, Weiss, Wolf, Norris, Witten, Grimm, Schnitt, Badve, Factor, Collyar, Basila, Pinto, Watson, West, Davies, Donovan, Shimada, Yutong Li, Yan Li, Bennett, Marks, Boisvert, Giuliano, Larson, Yost, McAuliffe, Krie, Tamirisa, Carey, Thompson, Partridge.
Drafting of the manuscript: Hwang, Hyslop, Lynch, Grimm, Badve, Shimada, Giuliano, Thompson.
Critical review of the manuscript for important intellectual content: Hwang, Hyslop, Lynch, Ryser, Weiss, Wolf, Norris, Witten, Grimm, Schnitt, Badve, Factor, Frank, Collyar, Basila, Pinto, Watson, West, Davies, Donovan, Shimada, Yutong Li, Yan Li, Bennett, Rosenberg, Marks, Winer, Boisvert, Larson, Yost, McAuliffe, Krie, Tamirisa, Carey, Thompson, Partridge.
Statistical analysis: Hwang, Hyslop, Shimada, Yutong Li, Yan Li.
Obtained funding: Hwang, Weiss, Wolf, Basila, Carey, Thompson, Partridge.
Administrative, technical, or material support: Hwang, Lynch, Weiss, Wolf, Norris, Grimm, Schnitt, Badve, Frank, Basila, Pinto, Watson, Donovan, Bennett, Carey, Thompson, Partridge.
Supervision: Hwang, Weiss, Wolf, Witten, Grimm, Badve, Bennett, Carey, Thompson, Partridge.

Conflict of Interest Disclosures: Dr Hwang reported receipt of grants from the National Cancer Institute, the Department of Defense, and CRUK; personal fees from Merck; and nonfinancial support from Clinetic, Exai Bio, and Havah Therapeutics. Dr Hyslop reported receipt of grants from the National Cancer Institute. Dr Lynch reported receipt of grants from the Department of Defense. Dr Weiss reported receipt of advisory board payments from Merck. Dr Grimm reported receipt of personal fees from Hologic and Medscape Reference. Dr Badve reported receipt of grants from the National Cancer Institute and from Eli Lilly to his institution and personal fees from Agilent, AstraZeneca, Daiichi Sankyo, and BMS. Ms Collyar reported receipt of personal fees from SimBioSys, AstraZeneca, Parexel, Evidera, MaxisHealth, Aster Insights, CRUK, Incyte, Apellis, and Kinnate. Dr Bennett reported receipt of grants from the Rising Tide Foundation. Dr Rosenberg reported receipt of grants from Pfizer/Conquer Cancer. Dr Thompson reported spousal employment by Eli Lilly. No other disclosures were reported.

Funding/Support: The COMET trial was supported by Patient-Centered Outcomes Research Institute award 1505-30497 and Breast Cancer Research Foundation awards BCRF-23-074, SPEC-24-020, and SPEC-22-021. The study was sponsored by Alliance Foundation Trials.

Role of the Funder/Sponsor: Alliance Foundation Trials, the study sponsor, was responsible for the conduct and management of the study. The study supporters otherwise had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Group Information: The COMET Study Investigators appear in Supplement 3.

Disclaimer: The COMET trial writing committee assumes responsibility for the content of this article. The views presented in this work are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its board of governors, or its methodology committee.

Meeting Presentation: This research was presented at the San Antonio Breast Cancer Symposium; December 12, 2024; San Antonio, Texas.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank the Alliance Foundation Trials data and safety monitoring board for trial oversight. Most importantly, we thank the many surgeons, physicians, and research staff members for their ongoing enthusiasm and support for the study and all the COMET trial participants for their courage, generosity, and altruism. For a list of entities that have provided support to Alliance for Clinical Trials in Oncology and Alliance Foundation Trials programs, visit https://acknowledgments.alliancefound.org.

REFERENCES

1. Ong MS, Mandl KD. National expenditure for false-positive mammograms and breast cancer overdiagnoses estimated at $4 billion a year. *Health Aff (Millwood)*. 2015;34(4):576-583. doi:10.1377/hlthaff.2014.1087

2. Hendrick RE, Baker JA, Helvie MA. Breast cancer deaths averted over 3 decades. *Cancer*. 2019;125(9):1482-1488. doi:10.1002/cncr.31954

3. Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative modeling of the benefits and harms associated with different US breast cancer screening strategies. *Ann Intern Med*. 2016;164(4):215-225. doi:10.7326/M15-1536

4. Welch HG. Overdiagnosis and mammography screening. *BMJ*. 2009;339:b1425. doi:10.1136/bmj.b1425

5. American Cancer Society. *Breast Cancer Facts and Figures 2024-2025*. American Cancer Society; 2024. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2024/breast-cancer-facts-and-figures-2024.pdf

6. Ryser MD, Hendrix LH, Worni M, Liu Y, Hyslop T, Hwang ES. Incidence of ductal carcinoma in situ in the United States, 2000-2014. *Cancer Epidemiol Biomarkers Prev*. 2019;28(8):1316-1323. doi:10.1158/1055-9965.EPI-18-1262

7. Virnig BA, Shamliyan T, Tuttle TM, Kane RL, Wilt TJ. Diagnosis and management of ductal carcinoma in situ (DCIS). *Evid Rep Technol Assess (Full Rep)*. 2009;(185):1-549.

8. Worni M, Akushevich I, Greenup R, et al. Trends in treatment patterns and outcomes for ductal carcinoma in situ. *J Natl Cancer Inst*. 2015;107(12):djv263. doi:10.1093/jnci/djv263

9. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*. 2009;302(18):1985-1992. doi:10.1001/jama.2009.1568

10. Ryser MD, Lange J, Inoue LYT, et al. Estimation of breast cancer overdiagnosis in a US breast screening cohort. *Ann Intern Med*. 2022;175(4):471-478. doi:10.7326/M21-3577

11. Ryser MD, Weaver DL, Zhao F, et al. Cancer outcomes in DCIS patients without locoregional treatment. *J Natl Cancer Inst*. 2019;111(9):952-960. doi:10.1093/jnci/djy220

12. Sagara Y, Mallory MA, Wong S, et al. Survival benefit of breast surgery for low-grade ductal carcinoma in situ: a population-based cohort study. *JAMA Surg*. 2015;150(8):739-745. doi:10.1001/jamasurg.2015.0876

13. Maxwell AJ, Hilton B, Clements K, et al. Unresected screen-detected ductal carcinoma in situ: outcomes of 311 women in the Forget-Me-Not 2 study. *Breast*. 2022;61:145-155. doi:10.1016/j.breast.2022.01.001

14. Hwang ES, Hyslop T, Lynch T, et al. The COMET (Comparison of Operative Versus Monitoring and Endocrine Therapy) trial: a phase III randomised controlled clinical trial for low-risk ductal carcinoma in situ (DCIS). *BMJ Open*. 2019;9(3):e026797. doi:10.1136/bmjopen-2018-026797

15. Partridge AH, Hyslop T, Rosenberg SM, et al; COMET Study Consortium. Patient-reported outcomes for low-risk ductal carcinoma in situ: the COMET randomized clinical trial. *JAMA Oncol*. Published online December 12, 2024. doi:10.1001/jamaoncol.2024.6556

16. Grimm LJ, Ryser MD, Partridge AH, et al. Surgical upstaging rates for vacuum assisted biopsy proven DCIS: implications for active surveillance trials. *Ann Surg Oncol*. 2017;24(12):3534-3540. doi:10.1245/s10434-017-6018-9

17. Iwamoto N, Nara M, Horiguchi SI, Aruga T. Surgical upstaging rates in patients meeting the eligibility for active surveillance trials. *Jpn J Clin Oncol*. 2021;51(8):1219-1224. doi:10.1093/jjco/hyab082

18. Soumian S, Verghese ET, Booth M, et al. Concordance between vacuum assisted biopsy and postoperative histology: implications for the proposed Low Risk DCIS Trial (LORIS). *Eur J Surg Oncol*. 2013;39(12):1337-1340. doi:10.1016/j.ejso.2013.09.028

19. Chow S, Shao J, Wang H. *Sample Size Calculations in Clinical Research*. 2nd ed. Chapman & Hall; 2008:90. CRC Biostatistics Series.

20. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594-2604. doi:10.1001/jama.2012.87802

21. Poelhekken K, Lin Y, Greuter MJW, van der Vegt B, Dorrius M, de Bock GH. The natural history of ductal carcinoma in situ (DCIS) in simulation models: a systematic review. *Breast*. 2023;71:74-81. doi:10.1016/j.breast.2023.07.012

22. Allred DC, Anderson SJ, Paik S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol*. 2012;30(12):1268-1273. doi:10.1200/JCO.2010.34.0141

23. Wright JL, Gray R, Rahbar H, et al. Lumpectomy without radiation for ductal carcinoma in situ of the breast: 20-year results from the ECOG-ACRIN E5194 study. *NPJ Breast Cancer*. 2024;10(1):16. doi:10.1038/s41523-024-00622-w

24. Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. *JAMA Oncol*. 2015;1(7):888-896. doi:10.1001/jamaoncol.2015.2510

25. Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet*. 2014;383(9922):1041-1048. doi:10.1016/S0140-6736(13)62292-8

26. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol*. 2011;12(1):21-29. doi:10.1016/S1470-2045(10)70266-7

27. Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295(23):2727-2741. doi:10.1001/jama.295.23.joc60074

28. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol*. 2001;28(4):400-418. doi:10.1016/S0093-7754(01)90133-2

29. Cataliotti L, Buzdar AU, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. *Cancer*. 2006;106(10):2095-2103. doi:10.1002/cncr.21872

30. Eiermann W, Paepke S, Appfelstaedt J, et al; Letrozole Neo-Adjuvant Breast Cancer Study Group. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol*. 2001;12(11):1527-1532. doi:10.1023/A:1013128213451

31. Smith IE, Dowsett M, Ebbs SR, et al; IMPACT Trialists Group. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol*. 2005;23(22):5108-5116. doi:10.1200/JCO.2005.04.005

32. Bailey CS, Rasoulinejad P, Taylor D, et al. Surgery versus conservative care for persistent sciatica lasting 4 to 12 months. *N Engl J Med*. 2020;382(12):1093-1102. doi:10.1056/NEJMoa1912658

33. Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424. doi:10.1056/NEJMoa1606220

34. Weinstein JN, Tosteson TD, Lurie JD, et al; SPORT Investigators. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *N Engl J Med*. 2008;358(8):794-810. doi:10.1056/NEJMoa0707136

35. Courcoulas AP, Goodpaster BH, Eagleton JK, et al. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg*. 2014;149(7):707-715. doi:10.1001/jamasurg.2014.467

36. Davies L, Beard D, Cook JA, Price A, Osbeck I, Toye F. The challenge of equipoise in trials with a surgical and non-surgical comparison: a qualitative synthesis using meta-ethnography. *Trials*. 2021;22(1):678. doi:10.1186/s13063-021-05403-5

37. McSweeney LA, Rousseau NS, Wilson JA, Wilkes S, Haighton CA. Stakeholders' views of recurrent sore throat, tonsillitis and their management: a qualitative interview study for the National Trial of Tonsillectomy in Adults (NATTINA Part 1). *Clin Otolaryngol*. 2017;42(2):301-306. doi:10.1111/coa.12720

38. Mills N, Donovan JL, Smith M, Jacoby A, Neal DE, Hamdy FC. Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. *Control Clin Trials*. 2003;24(3):272-282. doi:10.1016/S0197-2456(03)00020-5

39. Mills N, Donovan JL, Wade J, Hamdy FC, Neal DE, Lane JA. Exploring treatment preferences facilitated recruitment to randomized controlled trials. *J Clin Epidemiol*. 2011;64(10):1127-1136. doi:10.1016/j.jclinepi.2010.12.017

40. Minns Lowe CJ, Moser J, Barker KL. Why participants in the United Kingdom Rotator Cuff Tear (UKUFF) trial did not remain in their allocated treatment arm: a qualitative study. *Physiotherapy*. 2018;104(2):224-231. doi:10.1016/j.physio.2017.09.002

41. Thorstensson CA, Lohmander LS, Frobell RB, Roos EM, Gooberman-Hill R. Choosing surgery: patients' preferences within a trial of treatments for anterior cruciate ligament injury: a qualitative study. *BMC Musculoskelet Disord*. 2009;10:100. doi:10.1186/1471-2474-10-100

42. Chapman SJ, Shelton B, Mahmood H, Fitzgerald JE, Harrison EM, Bhangu A. Discontinuation and non-publication of surgical randomised controlled trials: observational study. *BMJ*. 2014;349:g6870. doi:10.1136/bmj.g6870

43. Elshof LE, Tryfonidis K, Slaets L, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ—the LORD study. *Eur J Cancer*. 2015;51(12):1497-1510. doi:10.1016/j.ejca.2015.05.008

44. Francis A, Fallowfield L, Rea D. The LORIS trial: addressing overtreatment of ductal carcinoma in situ. *Clin Oncol (R Coll Radiol)*. 2015;27(1):6-8. doi:10.1016/j.clon.2014.09.015