DR. SOFIA F. GARCIA (Orcid ID : 0000-0003-3300-385X)

DR. AMYE J. TEVAARWERK (Orcid ID : 0000-0002-8087-5119)

DR. RUTH C. CARLOS (Orcid ID : 0000-0001-7055-7662)

DR. BETINA YANEZ (Orcid ID : 0000-0003-1503-0600)

DR. LYNNE I. WAGNER (Orcid ID : 0000-0001-9685-4796)

Article type : Original Article

Fatigue and Endocrine Symptoms among Women with Early Breast Cancer Randomized to Endocrine versus Chemoendocrine Therapy: Results from the TAILORx Patient-reported Outcomes Substudy

Running title: **TAILORx: Fatigue & endocrine symptoms**

Sofia F. Garcia[1], PhD, Robert J. Gray[2,3], PhD, Joseph A. Sparano[4], MD, Amye J. Tevaarwerk[5], MD, Ruth C. Carlos[6], MD, Betina Yanez[1], PhD, Ilana F. Gareen[7,8], PhD, Timothy J. Whelan[9], MD, George W. Sledge[10], MD, David Cella[1],PhD ,Lynne I. Wagner[11] PhD

[1]Northwestern University; [2]Dana Farber Cancer Institute; [3]ECOG-ACRIN Biostatistics Center; [4]Montefiore Medical Center; [5]University of Wisconsin; [6]University of Michigan Comprehensive Cancer Center; [7-8]Center for Statistical Sciences & Department of Epidemiology, Brown

University School of Public Health; [9]Juravinski Cancer Center at Hamilton Health Sciences; [10]Stanford Cancer Institute Palo Alto; [11] Wake Forest University Health Sciences

Sofia F. Garcia, Ph.D.
Northwestern University
625 N. Michigan Ave.
Chicago, IL 60611
312-503-3449; sofia-garcia@northwestern.edu

This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD & Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute under award numbers U10CA180820, U10CA180794, UG1CA189828, UG1CA189859, UG1CA233160, UG1CA233320, U10CA180863, and UG1CA233277, and the Canadian Cancer Society grant #704970. Additional support was provided by the Breast Cancer Research Foundation, the Komen Foundation, the Breast Cancer Research Stamp issued by the U.S. Postal Service, and Genomic Health.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Gray reports funding from Genomic Health, Inc. for data collection and delivery. Dr. Wagner reports personal fees from Celgene, Inc. and Athenex, Inc. outside the submitted work, and grants from the NCI during the study period. Dr. Sparano reports holding a patent (WO 2009140304 A1) related to tests to predict chemotherapy responsiveness, and grants from NCI during the study period. Dr. Cella is an unpaid board member of the PROMIS Health Organization, reports NIH funding for PROMIS, and is President of FACIT.org.

Conflicts of Interest

Drs. Garcia, Gray, Sparano, Tevaarwerk, Carlos, Yanez, Gareen, Whelan, Sledge, Cella and Wagner report NCI grant funding during the study period. Dr. Wagner reports personal fees from Celgene, Inc. and Athenex, Inc. outside the submitted work. Dr. Sparano reports holding a patent

(WO 2009140304 A1) related to tests to predict chemotherapy responsiveness. Dr. Cella is President of FACIT.org.

Contributions:

SFG: conceptualization; methodology; visualization; writing original draft, review and edit

RJG: conceptualization; methodology; formal analysis; data curation; visualization; writing, review and edit

JAS: conceptualization; methodology; funding acquisition; review and edit

AJT: writing original draft, review and edit

RCC: conceptualization; writing original draft, review and edit

BY: writing original draft, review and edit

IFG, TJW & GWS: review and edit

DC: conceptualization; writing original draft, review and edit

LIW: conceptualization; methodology; investigation; funding acquisition; writing, review and edit

Acknowledgements: The authors acknowledge: Jeff Abrams, MD, Sheila Taube, PhD, Lori Minasian, MD, and Ann O'Mara, PhD, Una Hopkins, RN, DNP, ECOG-ACRIN Operations staff, the Cancer Trials Support Unit, and Mary Lou Smith.

Lay summary:

TAILORx participants with early-stage hormone receptor-positive breast cancer, and intermediate risk of recurrence, were randomly assigned to endocrine (E) versus chemoendocrine therapy (CT+E). 458 women reported fatigue and endocrine symptoms at baseline, 3, 6, 12, 24, and 36 months. Both groups reported greater symptoms at early follow-up compared to baseline. Increases in fatigue were greater for CT+E than E at three and six months but not later. The CT+E group reported greater changes in endocrine symptoms compared to the E group at three months but not later.

Precis:

TAILORx participants randomized to chemoendocrine therapy reported significant increases in fatigue and endocrine symptoms three months after randomization, which decreased through 36 months. Those randomized to endocrine therapy also reported increased symptoms from baseline, although of lesser magnitude.

ABSTRACT

Background: TAILORx prospectively assessed fatigue and endocrine symptoms among women with early-stage hormone receptor-positive breast cancer, and mid-range risk of recurrence, randomized to endocrine (E) versus chemoendocrine therapy (CT+E).

METHODS: Participants completed the Functional Assessment of Chronic Illness Therapy Fatigue, Patient Reported Outcomes Measurement Information System Fatigue Short Form, and Functional Assessment of Cancer Therapy Endocrine Symptoms at baseline, 3, 6, 12, 24, and 36 months. We used linear regression to model outcomes on baseline symptoms, treatment and other factors.

RESULTS: Participants (n=458) in both treatment arms reported greater fatigue and endocrine symptoms at early follow-up compared to baseline. The magnitude of change in fatigue was significantly greater for CT+E than E at 3 and 6, but not at 12, 24, and 36 months. The CT+E arm reported significantly greater changes in endocrine symptoms from baseline to 3 months compared to E; change scores were not significantly different at later timepoints. Endocrine symptom trajectories by treatment were different by menopausal status, with the effect larger and increasing for post-menopausal patients.

CONCLUSIONS: Adjuvant CT+E was associated with greater increases in fatigue and endocrine symptoms at early timepoints compared to E. These differences lessened over time, demonstrating early more than long-term chemotherapy effects. Treatment arm differences in endocrine symptoms were more evident in post-menopausal patients.

Keywords: breast neoplasms; patient-reported outcomes; drug therapy; fatigue; hormones

Number text pages: 18

Number tables: 2

Number figures: 3

Number supporting files: 2

Breast cancer remains the most common cancer in women[1] but mortality rates are declining, partially due to widespread adjuvant therapy[2]. Hormone receptor-positive (HR+) cases account for roughly two thirds of breast cancers, and can be treated with chemotherapy and/or endocrine therapy[3]. Although less toxic than chemotherapy, long-term endocrine therapy[4,5] can produce symptoms (arthralgias, vasomotor symptoms, sexual dysfunction) that impact health-related quality of life (HRQoL)[6] and medication non-adherence[7,8], which in turn decreases treatment efficacy[9].

Beyond being acutely toxic, chemotherapy may also result in future health consequences, including persistent fatigue[10]. Following the Early Breast Cancer Trialists Group meta-analysis[11], adjuvant chemotherapy became standard for most localized breast cancers[12,13]. The ensuing "over-treatment," led to development of the 21-gene assay[4,14,15] to predict: risk of distant recurrence more accurately than classical clinicopathologic features in patients with HR+ breast cancer[14,16], and benefit of adding adjuvant chemotherapy to endocrine therapy in that population[5,7].

The Trial Assigning Individualized Options for Treatment (TAILORx), randomized women with HR+, human epidermal growth factor receptor 2 (HER2)-negative, axillary node-negative early breast cancer and intermediate recurrence scores (RSs=11-25) to chemotherapy followed by endocrine therapy (CT+E) versus endocrine therapy (E).[17,18]. TAILORx demonstrated highly favorable outcomes for patients with RSs 0–25 receiving endocrine therapy, indicating that women with intermediate or low RSs, can be spared chemotherapy.[16,19] TAILORx provided an unparalleled opportunity to prospectively evaluate the trajectory of HRQoL among women randomized to CT+E versus E for breast cancer.

Patient-reported outcome (PRO) measures are ideal for assessing subjective symptoms, and can inform treatment[20,21]. TAILORx allowed us to examine the unique contributions of chemotherapy to fatigue[22] and endocrine symptoms[6]. The substudy's primary objective was to compare those longitudinal patient-reported symptoms among women with early HR+ breast cancer randomized to adjuvant CT+E versus E.

METHODS

Design & Participants

The ECOG-ACRIN Cancer Research Group coordinated TAILORx (ClinicalTrials.gov: NCT00310180)[17,18], which enrolled patients from 4/2006–10/2010. In January 2010, a PRO substudy was approved by participating institutions' human investigations committees. Eligibility was consistent with TAILORx[17,18]: women 18-75 years old, diagnosed with HR+, HER2-negative, axillary node-negative breast cancer, meeting guidelines for adjuvant chemotherapy. Participants provided informed consent and completed PRO measures at baseline (pre-randomization) and 3, 6, 12, 24 and 36 months afterward. Given menopausal status was among the TAILORx stratification factors, we conducted subset analyses to examine its relationships to fatigue and endocrine symptoms. We retrieved data in February, 2016.

Measures

The Patient Reported Outcomes Measurement Information System Fatigue Short Form (PROMIS Fatigue 7) is a seven-item measure of fatigue using a 5-point Likert response scale[23]. PROMIS measures are reported on a T score metric, with higher scores indicating greater symptomatology. It has demonstrated good precision and reliability[24]. Here, Cronbach's alpha was 0.874.

The Functional Assessment of Chronic Illness Therapy Fatigue (FACIT Fatigue) Scale is a 13-item measure using a 5-point Likert scale[25], with higher scores indicating *less* fatigue (i.e., higher HRQoL). It has demonstrated reliability and validity in clinical trials. Cronbach's alpha was 0.956.

The Functional Assessment of Cancer Therapy Endocrine Symptoms (FACT-ES) is a 19-item measure using a 5-point Likert response scale, with higher scores indicating *less* symptomatology. It has demonstrated suitability for clinical trials[26]. Cronbach's alpha was 0.844. Trial participants completed additional PROs (Functional Assessment of Cancer Therapy–Cognitive Function [FACT-Cog][27,28], FACT-General[29] & Assessment of Survivor Concerns)[30], with results reported separately[31].

Analysis

Our primary analysis compared TAILORx participants who received the treatments to which they were randomized. These per-protocol analyses excluded patients based on post-randomization treatment decisions, which may introduce bias. To examine their robustnes, we also performed intention-to-treat (ITT) analyses. Our primary endpoints were fatigue and endocrine symptom score differences between treatment arms at 3 months, controlling for baseline scores. Most women on CT+E received 12-week regimens and were expected to experience maximum chemotherapy side effects at 3 months. We also examined treatment differences at subsequent timepoints. The PRO substudy was designed to have 90% power for a 4.5 point difference in mean change from baseline to 3 months in FACT-Cog (primary PRO endpoint) between CT+E and E[31]; a sample of 235 women per arm was required. We expected comparable power for differences of similar magnitude in the three PRO measures examined here.

We computed means and SDs using all cases at a timepoint. When comparing treatment arms at timepoints, the analysis fits a linear model with arm (binary covariate) and baseline levels (continuous linear covariate), with the test and estimated effect based on the coefficient of treatment effect. We also computed mean changes from baseline and standard errors. We included only cases with assessments at baseline and follow-up timepoint. We excluded cases with baseline assessments >7 days after treatment initiation. We conducted analyses with R 3.5.1[32].

RESULTS

Sample

734 women enrolled in the PRO substudy (Figure 1). They had generally similar characteristics to the larger TAILORx[31]. Participants were eligible to continue on PRO substudy if they experienced a recurrence or new primary breast cancer while enrolled on TAILORx. Table 1 gives the demographic and clinical characteristics for patients (n= 458) in the per-protocol analysis with data on at least one of the PRO measures at baseline and 3 months. As previously reported, the characteristics of participants in the PRO study, as compared to the larger trial sample randomized to treatment, were generally very similar, with a slightly higher proportion of postmenopausal patients, low recurrence score and very small (< 1cm) tumors in

the PRO study.[31] The per-protocol dataset had slightly lower proportions of older patients and lower RSs, low-grade and very small tumors on the CT+E arm (such patients may have been more likely to refuse chemotherapy).

Treatment Arm-related Differences

In the per-protocol analysis, women in CT+E reported significantly greater increases in *PROMIS Fatigue 7* scores from baseline to 3 and 6 months compared to women in E; change scores were comparable between treatment arms at at later timepoints (Table 2). The trajectories of longitudinal PROMIS Fatigue change scores by treatment arm converged more over time because the CT+E arm reported decreased fatigue after a sharp increase post-baseline (while receiving chemotherapy). However, both arms reported more fatigue at all follow-up assessments compared to baseline (Figure 2a).

Women receiving CT+E reported significantly greater increases in *FACIT Fatigue Scale* scores from baseline to 3 months, and approaching significantly greater fatigue at 6 months, compared to women on E; change scores were comparable between treatment arms at at later timepoints (Table 2). Change scores in a *negative* direction indicate *more* fatigue. Change scores by treatment arm converged over time because the CT+E arm reported decreased fatigue post-chemotherapy (Figure 2b). However, scores for the CT+E arm remained worse than baseline at all follow-up timepoints.

Women randomized to CT+E reported significantly greater increases in *FACT-ES* scores from baseline to 3 months compared to women randomized to E; change scores were not significantly different between treatment arms at later timepoints (Table 2). Change scores in a *negative* direction indicate *more* symptomatology. Both arms reported significantly more endocrine symptoms at all follow-up assessments compared to baseline (Figure 2c). For all three PROs, we observed similar result patterns using ITT analysis (supplemental materials).

Meaningful Change

We calculated the percentage of per-protocol participants whose symptoms meaningfully changed across assessments (Figure 3). Using a prior approach[33], we conservatively used 0.5 SD as the threshold for meaningful change. The estimated SD of baseline *PROMIS Fatigue* was 8.2, so we defined 'Better' as decrease of >4.1 points, 'Same' as change within +/- 4.1, and 'Worse' as increase of >4.1. At 3 months, 59% of women receiving CT+E reported worse fatigue compared to 34% among E; at 6 months it was 47% (CT+E) versus 33% (E). The magnitude of

difference between arms is lower later (e.g., 40% CT+E vs 36% E at 12 months). Nevertheless, a sizable proportion of women on both arms reported worsened fatigue at long-term follow-up (35-44%, 24 & 36 months). We observed similar results with FACIT-Fatigue. Using an estimated SD 9.4, for *FACT-ES* baseline scores ('Better':+>4.7 points; 'Same':+/- 4.7; 'Worse':- >4.1), women randomized to CT+E had worsened endocrine therapy-related symptoms at 3 and 6 months (50%, 52%) relative to E (39%, 44%, respectively).

Differences by Menopausal Status

We examined symptom change scores by menopausal status. Fatigue trajectories by treatment appear to be different for pre- versus postmenopausal women (Figures 2a&b), with the effect larger and more persistent for postmenopausal women. Postmenopausal women appear to have had a larger influence on the overall treatment arm differences in fatigue changes from baseline to 3 months. Post-menopausal women in the CT+E arm reported significantly higher increases in fatigue compared to those in the E arm at 24 months. However, menopause-by-treatment interactions were non-significant at all timepoints for both fatigue measures (Table 2).

Endocrine symptom trajectories by treatment were also different for pre- versus postmenopausal women (Figure 2c), with the effect larger and increasing over time for post-menopausal women. Menopause-by-treatment interactions were significant at 24 and 36 months (Table 2). Post-menopausal women in the CT+E arm reported significantly higher increases in endocrine symptoms compared to those in E.

DISCUSSION

Women receiving treatment for early-stage breast cancer commonly report fatigue and endocrine symptoms. Chemotherapy-related fatigue is expected, given known mechanisms of action[34], and often assumed to be reversible a sufficient time from completion. However, long-term data to demonstrate resolution has been lacking and complicated by receipt of radiation and endocrine therapy. Chemotherapy may also produce endocrine symptoms by inducing transient or persistent ovarian failure in premenopausal patients[35]. Similarly, tamoxifen and aromatase inhibitor (AI) side effects[36] differ by menopausal status[37].

TAILORx allowed examination of the unique contribution of chemotherapy to fatigue and endocrine symptoms, as well as symptom trajectories extending into post-treatment. Symptoms were greater at follow-up timepoints compared to baseline for both arms. Women on

CT+E reported significantly greater increases in fatigue and endocrine symptoms during chemotherapy, compared to those on E. While endocrine therapy is assumed to be well-tolerated, a considerable proportion of women on both arms reported fatigue at long-term follow-up that exceeded a conservative threshold for meaningful worsening. At 12-36 months, increases in fatigue and endocrine symptoms were not significantly different between arms; the trajectories of women on CT+E converged with those on E. That there was some fatigue resolution in the chemoendocrine arm should be reassuring to women who may benefit from chemotherapy based on clinicopathologic features and RSs. For women who can safely skip chemotherapy, our findings on the significant, acute chemotherapy-related symptoms support the value of precision guided therapy sparing uneccesary toxicity.

Treatment arm fatigue trajectories appeared different for pre- versus postmenopausal women, with the effect larger and more persistent in the latter, although the differences did not reach statistical significance. The trajectories of endocrine symptoms by treatment also appeared different by menopausal status, with the effect larger and increasing over time for post-menopausal patients, and menopause-by-treatment interactions significant at later timepoints. Patients randomized to CT+E began endocrine therapy after completing chemotherapy. Therefore, endocrine symptoms would not develop in the CT+E arm until later timepoints.

These findings suggest earlier results demonstrating prior chemotherapy is associated with greater treatment side effect bother (which predicted *higher* risk of early AI discontinuation[38]) may be explained by more endocrine symptoms among women on CT+E. Yet, TAILORx demonstrated a significantly *lower* risk of early endocrine therapy discontinuation among women on CT+E[39]. While we speculated chronic symptom burden may diminish endocrine therapy tolerability[40], results indicate further study is needed. Endocrine therapy adherence remains a complex challenge; interventions must be comprehensive[41] and PROs have predictive value in identifying women at risk for early discontinuation[38,42].

This study's strengths include the randomized prospective design, long-term follow-up and well-validated measures. Limitations include missing data, including some attrition, which may have introduced bias (although we observed overall good retention). Sample characteristics were similar to the overall trial—supporting generalizability. The per-protocol analysis may introduce bias; however, our ITT analysis yielded similar results. Therapy regimens were selected using clinician judgment, which introduced variability. The majority of women

randomized to chemotherapy received docetaxel-cyclophosphamide, so it is possible we underestimated symptom burden associated with other regimens. The amount of patients receiving particular endocrine treatments were not assessed at all time points. We were unable to evaluate the impact of tamoxifen versus AI treatment in our analyses of menopausal status subgoups. Lastly, we were unable to define the contribution of radiation or surgery.

Results demonstrate the: fatigue experienced acutely during chemotherapy and decreasing afterward, long-term endocrine symptom trajectories, and significant proportions of women with persistent symptoms. Our findings support the importance of providing long-term, symptom assessment and management. In quantifying the unique contributions of chemotherapy to fatigue and endocrine symptoms, study results add to the research identifying women with breast cancer unlikely to benefit substantially from chemotherapy relative to associated HRQoL impact. Findings illustrate the symptom burden that women with early stage HR+ breast cancer, and intermediate RSs, can be spared when electing to receive endocrine versus chemoendocrine therapy. They also provide valuable longitudinal data on the trajectories of common, distressing symptoms from the patient perspective.

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Table 1. Demographic & Clinical Characteristics (n=458*)

		E (n=238)	CT+E (n=220)
Mean age (SD) years		56 (9)	55 (8)
Age			
	≤50	78 (33%)	68 (31%)
	51-65	115 (48%)	126 (57%)
	>65	45 (19%)	26 (12%)
Race			
	White	196 (82%)	181 (82%)
	Black	15 (6%)	13 (6%)
	Asian	16 (7%)	8 (4%)
	Other/Unknown	11 (5%)	18 (8%)
Ethnicity			
	Hispanic	12 (5%)	18 (8%)
	Non-Hispanic	210 (88%)	183 (83%)
	Unknown	16 (7%)	19 (9%)
Menopause			
	Pre	74 (31%)	80 (36%)
	Post	164 (69%)	140 (64%)
Recurrence score			
	11-15	101 (42%)	82 (37%)
	16-20	81 (34%)	80 (36%)

	21-25	56 (24%)	58 (26%)
Tumor size, cm			
	<=1.0	37 (16%)	21 (10%)
	1.1- 2.0	149 (63%)	140 (64%)
	2.1- 3.0	40 (17%)	50 (23%)
	3.1- 4.0	11 (5%)	5 (2%)
	>4.0	1 (0%)	4 (2%)
	Unknown	0	0
Histology grade			
	Low	75 (32%)	59 (27%)
	Medium	123 (53%)	127 (58%)
	High	33 (14%)	32 (15%)
	Unknown	7	2
Estrogen receptor			
	Negative	0 (0%)	0 (0%)
	Positive	238 (100%)	220 (100%)
Progesterone receptor			
	Negative	14 (6%)	18 (8%)
	Positive	216 (94%)	195 (92%)
	Unknown	8	7
Surgery			
	Tumorectomy	175 (74%)	152 (69%)
	Mastectomy	63 (26%)	68 (31%)
Initial endocrine therapy			
	Aromatase inhibitor	139 (58%)	127 (58%)
	Tamoxifen	87 (37%)	83 (38%)
	Tamoxifen & Aromatase inhibitor	3 (1%)	5 (2%)
	Ovarian function suppression	7 (3%)	0 (0%)
	Other	1 (0%)	0 (0%)
	None reported	1 (0%)	5 (2%)
Changed endocrine therapy			
	Tamoxifen to Aromatase inhibitor	31 (13%)	41 (19%)

Aromatase inhibitor to Tamoxifen	14 (6%)	21 (10%)
Chemotherapy		
Taxane & cyclophosphamide	--	153 (70%)
Anthracycline +/- taxane	--	44 (20%)
CMF	--	18 (8%)
Other	--	5 (2%)
None	238 (100%)	0 (0%)
Comorbidities		
Hypertension: No	140 (59%)	134 (62%)
Yes	97 (41%)	83 (38%)
Unknown	1	3
Hyperlipidemia: No	165 (70%)	164 (76%)
Yes	71 (30%)	51 (24%)
Unknown	2	5
Depression: No	186 (79%)	172 (80%)
Yes	50 (21%)	43 (20%)
Unknown	2	5
Diabetes: No	210 (89%)	192 (89%)
Yes	25 (11%)	23 (11%)
Unknown	3	5
Osteoarthritis: No	214 (90%)	191 (88%)
Yes	23 (10%)	25 (12%)
Unknown	1	4
Osteopenia/Osteoporosis: No	199 (85%)	201 (94%)
Yes	36 (15%)	13 (6%)
Unknown	3	6

- The per-protocol analytic data set was specified a priori and consists of patients (n= 458) with data on at least one of the patient-reported outcome measures at baseline and 3 months

Table 2. Per Protocol Analysis - Changes from Baseline

Subset	Timepoint	n	E	CT+E	Raw Diff	LM Diff	p.LM
FACT-ES							
All	3-month	458	-3.61 (0.59)	-5.56 (0.60)	-1.95 (0.84)	-1.62 (0.79)	0.04
All	6-month	467	-4.24 (0.60)	-5.63 (0.55)	-1.39 (0.81)	-0.97 (0.76)	0.20
All	12-month	451	-5.62 (0.67)	-6.96 (0.68)	-1.34 (0.95)	-1.08 (0.90)	0.23
All	24-month	385	-5.31 (0.75)	-6.81 (0.68)	-1.50 (1.02)	-1.05 (0.96)	0.27
All	36-month	337	-5.17 (0.80)	-7.14 (0.85)	-1.97 (1.17)	-1.69 (1.10)	0.13
Pre-Menopausal	3-month	154	-5.96 (1.14)	-7.62 (1.02)	-1.65 (1.53)	-1.44 (1.47)	0.33
Pre-Menopausal	6-month	151	-6.19 (1.15)	-8.34 (1.03)	-2.15 (1.54)	-1.63 (1.45)	0.26
Pre-Menopausal	12-month	148	-8.95 (1.16)	-7.94 (1.28)	1.01 (1.73)	1.06 (1.64)	0.52
Pre-Menopausal	24-month	118	-10.39 (1.53)	-8.29 (1.27)	2.09 (1.99)	2.27 (1.84)	0.22
Pre-Menopausal	36-month	102	-10.84 (1.70)	-8.96 (1.66)	1.88 (2.38)	2.18 (2.25)	0.34
Pre-Menopausal	3-month	304	-2.55 (0.66)	-4.39 (0.72)	-1.83 (0.98)	-1.49 (0.92)	0.11
Post-Menopausal	6-month	316	-3.41 (0.69)	-4.19 (0.61)	-0.78 (0.93)	-0.45 (0.87)	0.60
Post-Menopausal	12-month	303	-4.10 (0.79)	-6.45 (0.78)	-2.34 (1.12)	-2.04 (1.06)	0.06
Post-Menopausal	24-month	267	-3.23 (0.80)	-6.10 (0.80)	-2.87 (1.13)	-2.39 (1.06)	0.03
Post-Menopausal	36-month	235	-2.87 (0.82)	-6.28 (0.97)	-3.41 (1.26)	-3.17 (1.18)	0.008
FACIT Fatigue							
All	3-month	452	-2.48 (0.66)	-8.77 (0.74)	-6.29 (0.99)	-5.32 (0.94)	0.00000002
All	6-month	466	-1.97 (0.64)	-4.37 (0.61)	-2.40 (0.88)	-1.55 (0.83)	0.06
All	12-month	452	-2.14 (0.70)	-4.01 (0.64)	-1.86 (0.95)	-1.01 (0.87)	0.25
All	24-month	382	-1.49 (0.74)	-4.27 (0.82)	-2.77 (1.11)	-1.76 (1.03)	0.09
All	36-month	336	-1.83 (0.81)	-3.67 (0.88)	-1.84 (1.19)	-0.90 (1.07)	0.40
Pre-Menopausal	3-month	152	-3.87 (1.41)	-8.01 (1.13)	-4.14 (1.79)	-3.11 (1.64)	0.06
Pre-Menopausal	6-month	150	-1.66 (1.19)	-3.26 (0.96)	-1.60 (1.51)	-0.82 (1.43)	0.57
Pre-Menopausal	12-month	149	-1.32 (1.51)	-2.99 (1.14)	-1.67 (1.88)	-1.12 (1.64)	0.50
Pre-Menopausal	24-month	116	-2.52 (1.60)	-2.45 (1.44)	0.07 (2.16)	1.02 (2.07)	0.62
Pre-Menopausal	36-month	102	-2.11 (1.76)	-1.60 (1.71)	0.51 (2.45)	1.46 (2.12)	0.49
Post-Menopausal	3-month	300	-1.87 (0.72)	-9.22 (0.96)	-7.35 (1.18)	-6.42 (1.14)	0.00000004
Post-Menopausal	6-month	316	-2.10 (0.76)	-4.97 (0.77)	-2.87 (1.09)	-1.99 (1.02)	0.05
Post-Menopausal	12-month	303	-2.52 (0.75)	-4.55 (0.76)	-2.03 (1.07)	-1.16 (1.02)	0.26
Post-Menopausal	24-month	266	-1.09 (0.82)	-5.14 (1.00)	-4.05 (1.28)	-3.02 (1.17)	0.01
Post-Menopausal	36-month	234	-1.71 (0.89)	-4.67 (1.00)	-2.95 (1.34)	-2.01 (1.22)	0.10
PROMIS Fatigue							
All	3-month	446	1.70 (0.44)	6.10 (0.50)	4.39 (0.67)	3.68 (0.63)	0.00000001
All	6-month	462	1.26 (0.44)	3.51 (0.50)	2.25 (0.66)	1.52 (0.62)	0.01
All	12-month	442	1.45 (0.50)	2.76 (0.53)	1.31 (0.73)	0.60 (0.67)	0.37
All	24-month	379	1.34 (0.58)	3.35 (0.61)	2.01 (0.85)	1.11 (0.77)	0.15

All	36-month	330	1.42 (0.61)	2.86 (0.64)	1.44 (0.89)	0.93 (0.80)	0.25
Pre-Menopausal	3-month	150	1.66 (0.85)	7.34 (0.83)	5.69 (1.19)	4.18 (1.13)	0.0003
Pre-Menopausal	6-month	147	1.12 (0.74)	3.50 (0.89)	2.38 (1.16)	0.85 (1.11)	0.44
Pre-Menopausal	12-month	144	0.41 (0.93)	2.92 (0.95)	2.51 (1.33)	1.28 (1.18)	0.28
Pre-Menopausal	24-month	117	1.90 (1.12)	2.68 (1.16)	0.78 (1.61)	-0.74 (1.53)	0.63
Pre-Menopausal	36-month	98	0.73 (1.26)	2.36 (1.06)	1.63 (1.66)	0.41 (1.52)	0.79
Post-Menopausal	3-month	296	1.72 (0.52)	5.41 (0.62)	3.69 (0.80)	3.33 (0.76)	0.00002
Post-Menopausal	6-month	315	1.32 (0.55)	3.52 (0.60)	2.19 (0.81)	1.83 (0.75)	0.02
Post-Menopausal	12-month	298	1.92 (0.59)	2.67 (0.64)	0.75 (0.87)	0.25 (0.82)	0.76
Post-Menopausal	24-month	262	1.10 (0.69)	3.68 (0.72)	2.57 (1.00)	1.97 (0.88)	0.03
Post-Menopausal	36-month	232	1.70 (0.70)	3.09 (0.81)	1.39 (1.06)	1.21 (0.94)	0.20

ACFB= average change from baseline; Raw Diff= Arm CT+E ACFB minus Arm E ACFB; LM Diff= estimated treatment difference (CT+E minus E) from linear regression of score at timepoint on treatment and baseline score; p.LM= p-value for treatment difference from linear model.

FACIT-ES menopause-by-treatment interaction: p=0.97, 0.41, 0.11, 0.02, 0.02, at 3, 6, 12, 24, 36 months

FACIT Fatigue menopause-by-treatment interactions: p=0.13, 0.49, 0.85, 0.06, 0.17, at 3, 6, 12, 24, 36 months

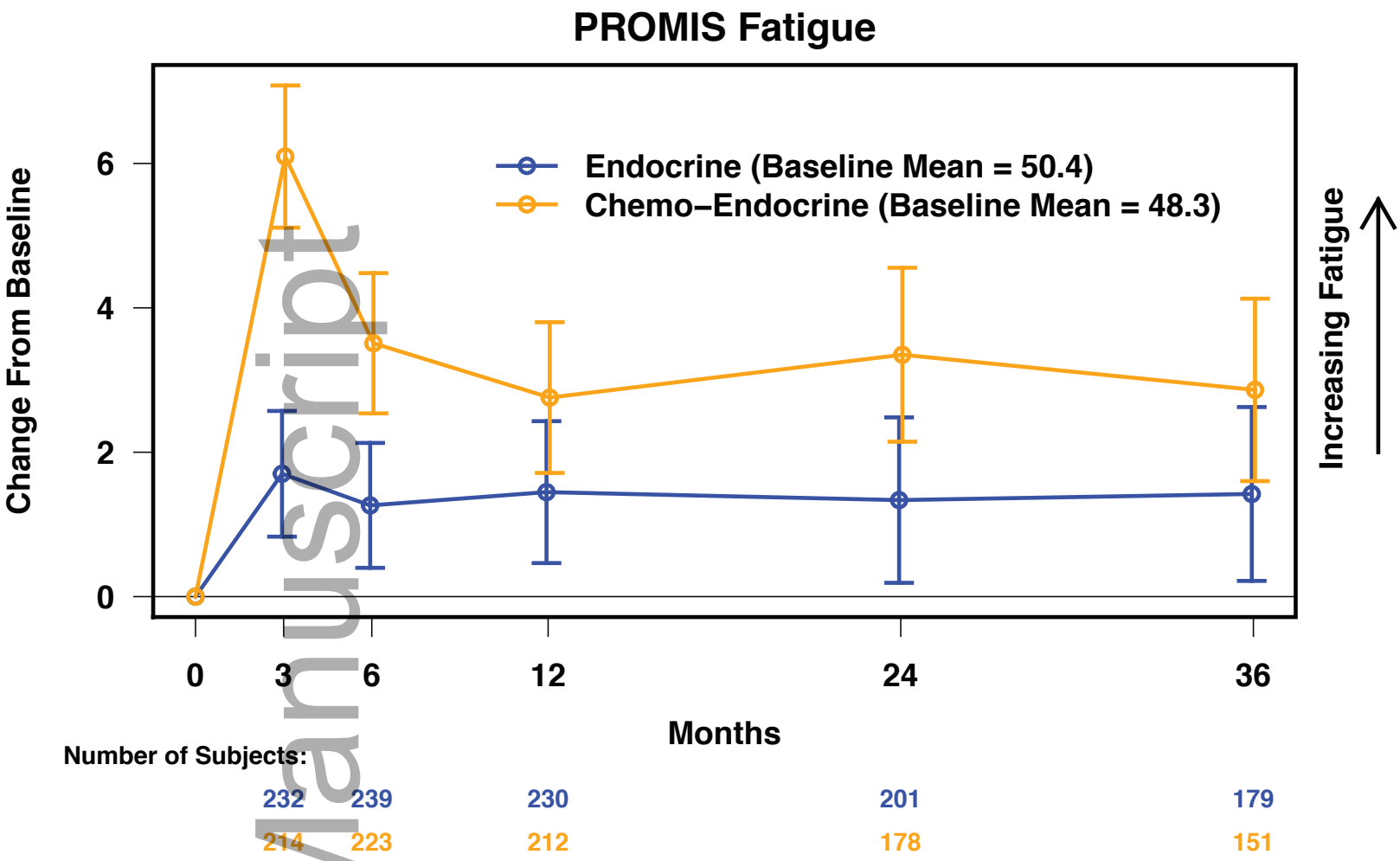
PROMIS Fatigue menopause by treatment interactions: p=0.42, 0.48, 0.34, 0.08, 0.60, at 3, 6, 12, 24, 36 months

Figure Legends

Figure 1. CONSORT diagram – TAILORx PRO substudy

Figure 2. Endocrine and Chemoendocrine Arms, Change over 36 Months

Figure 3. Endocrine and Chemoendocrine Arms: Meaningful Change



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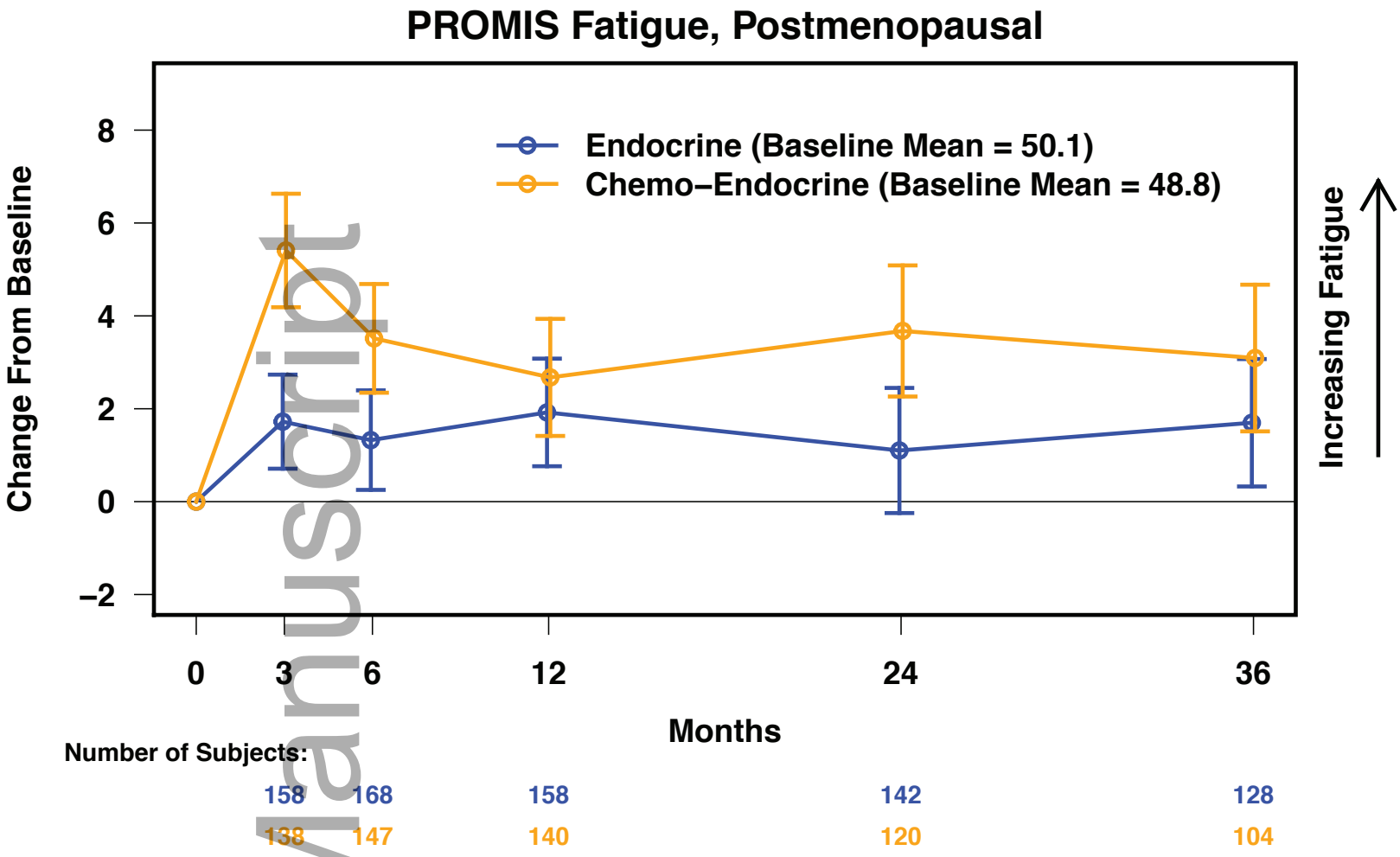

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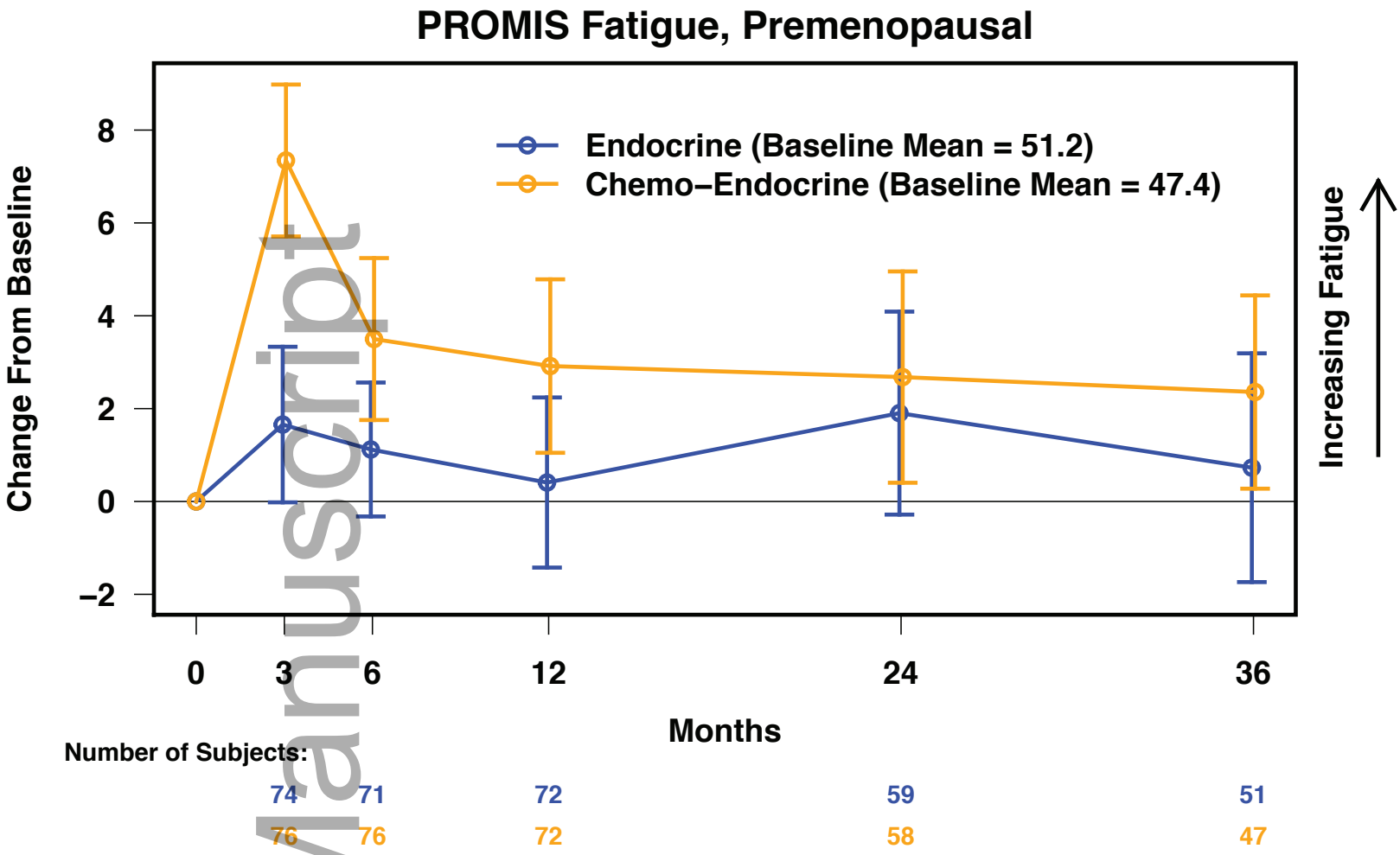

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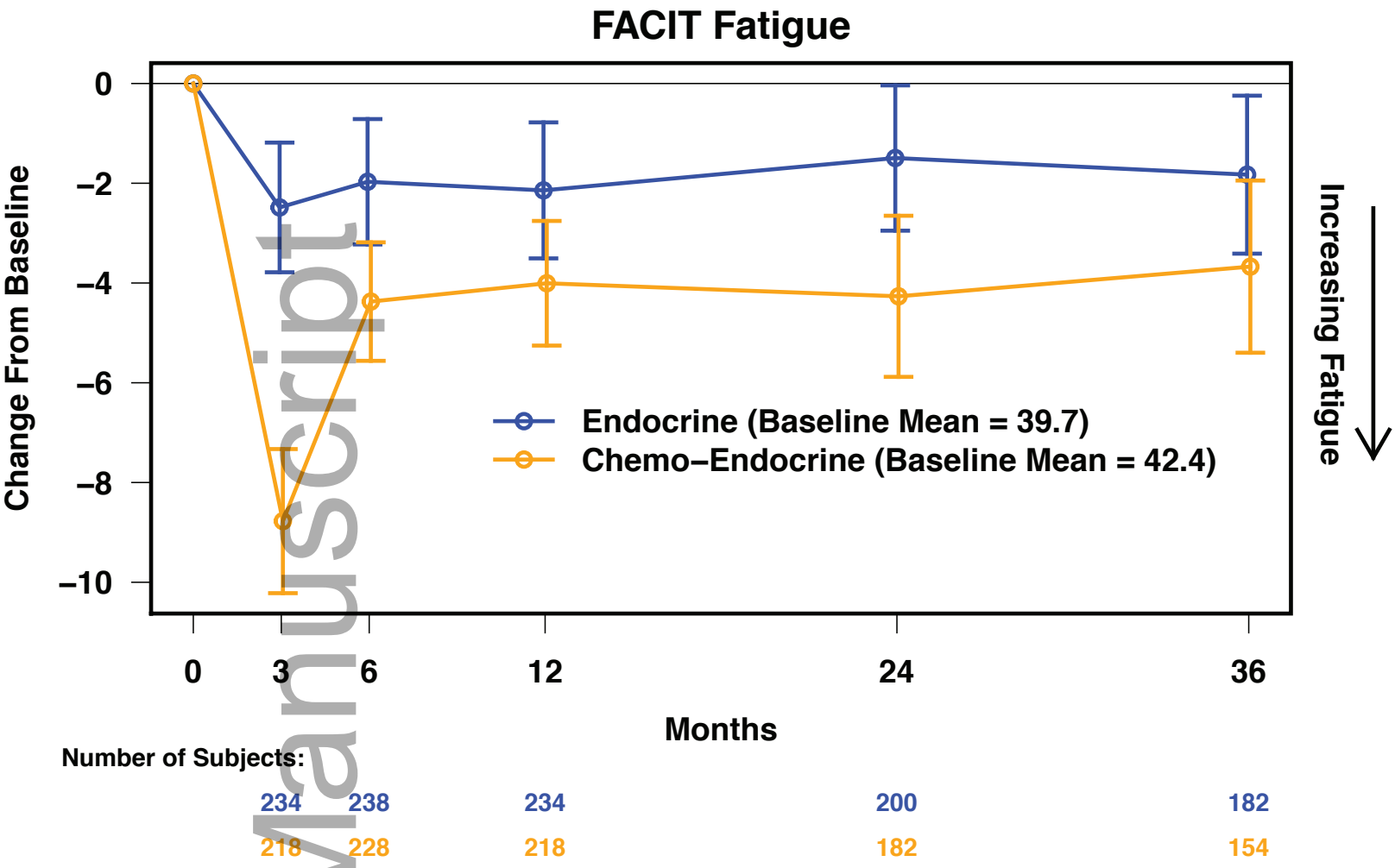

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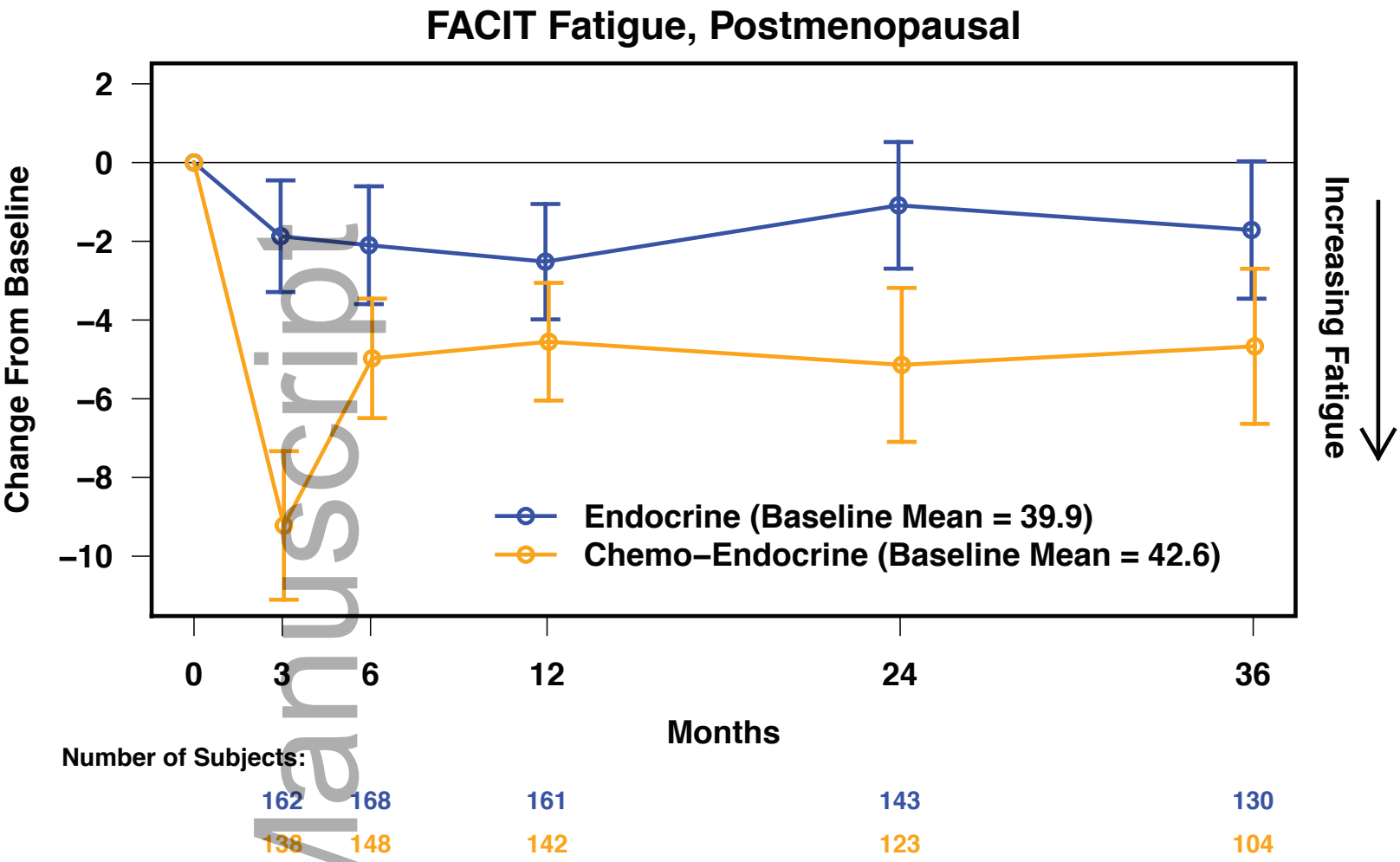

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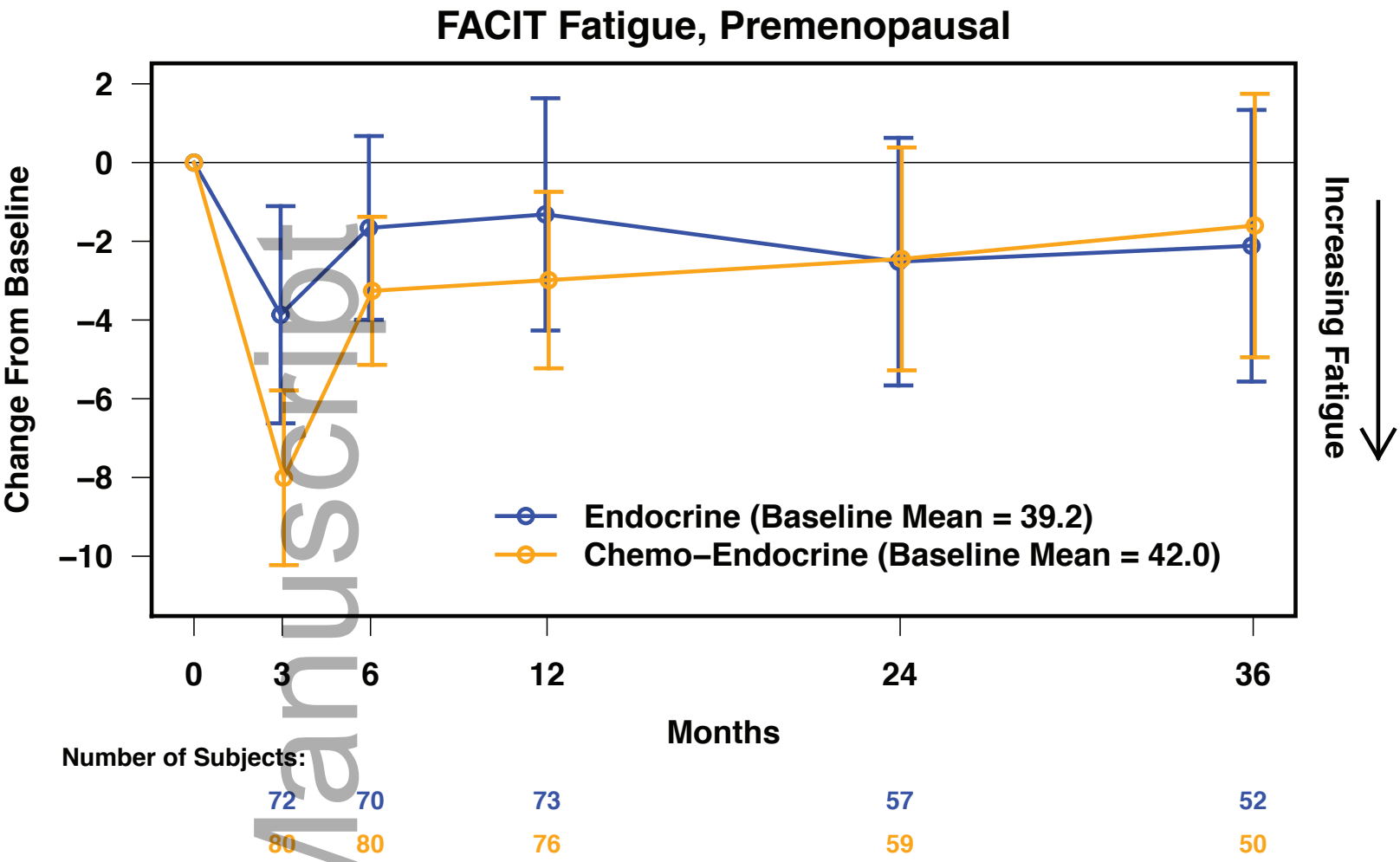

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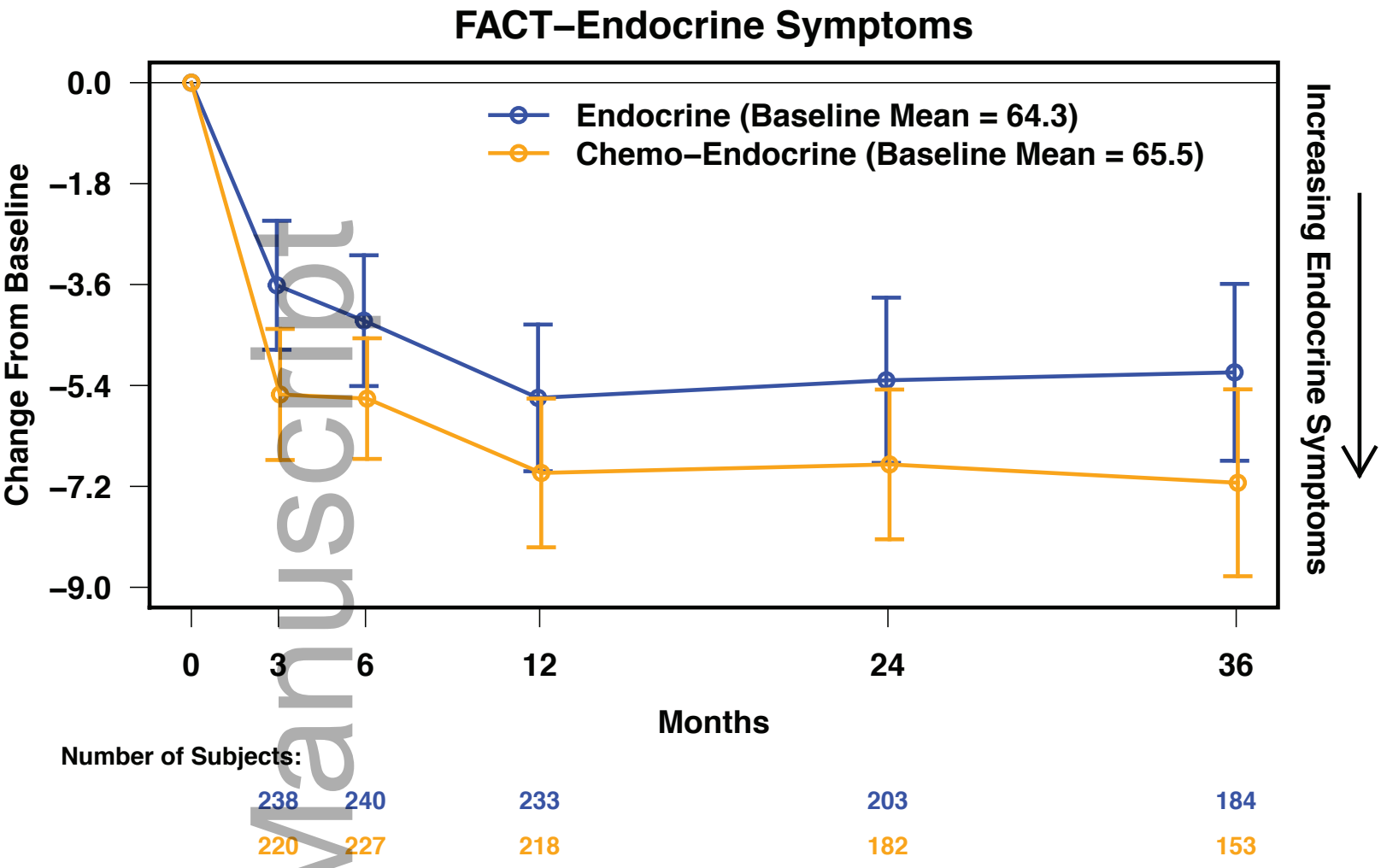

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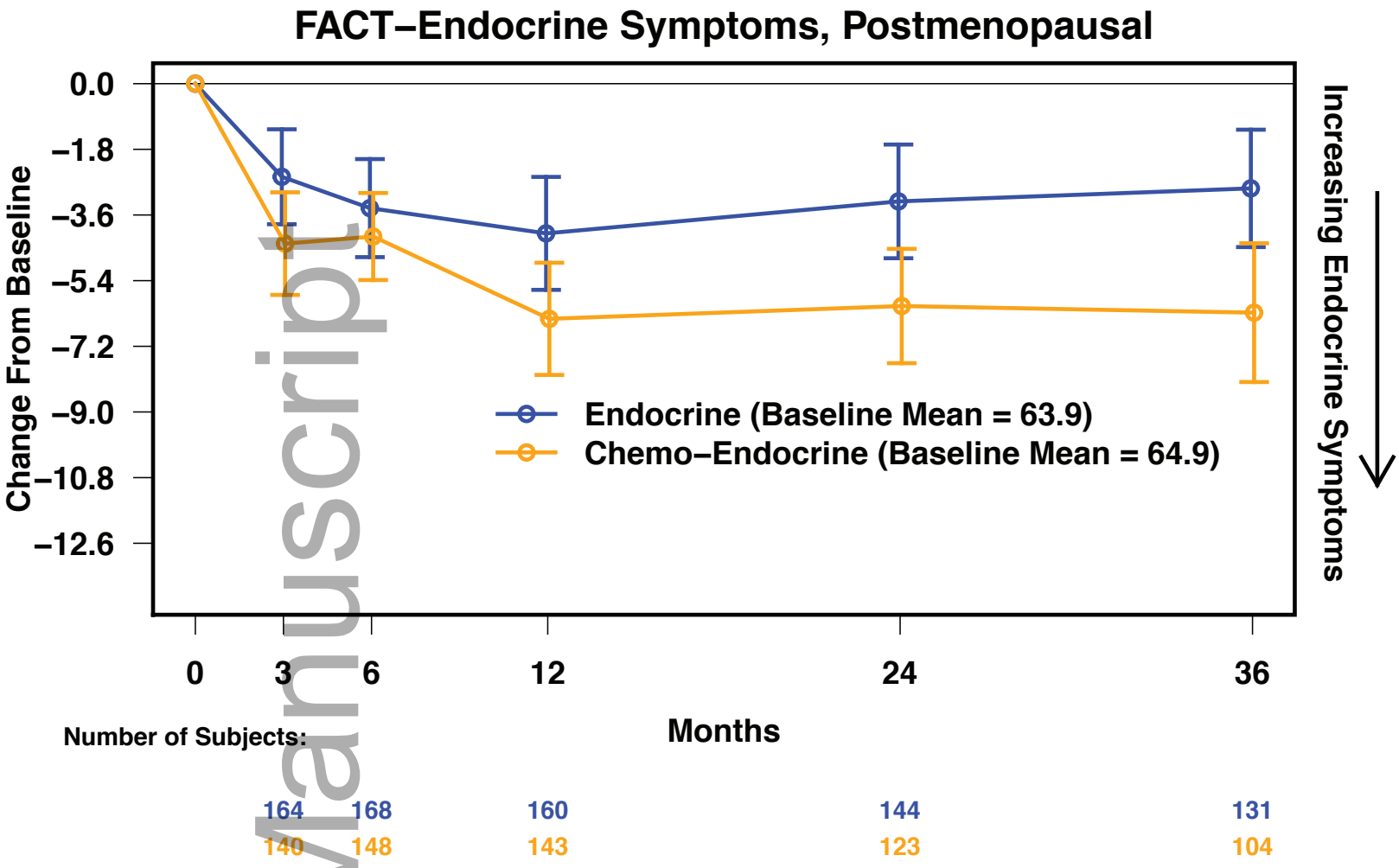

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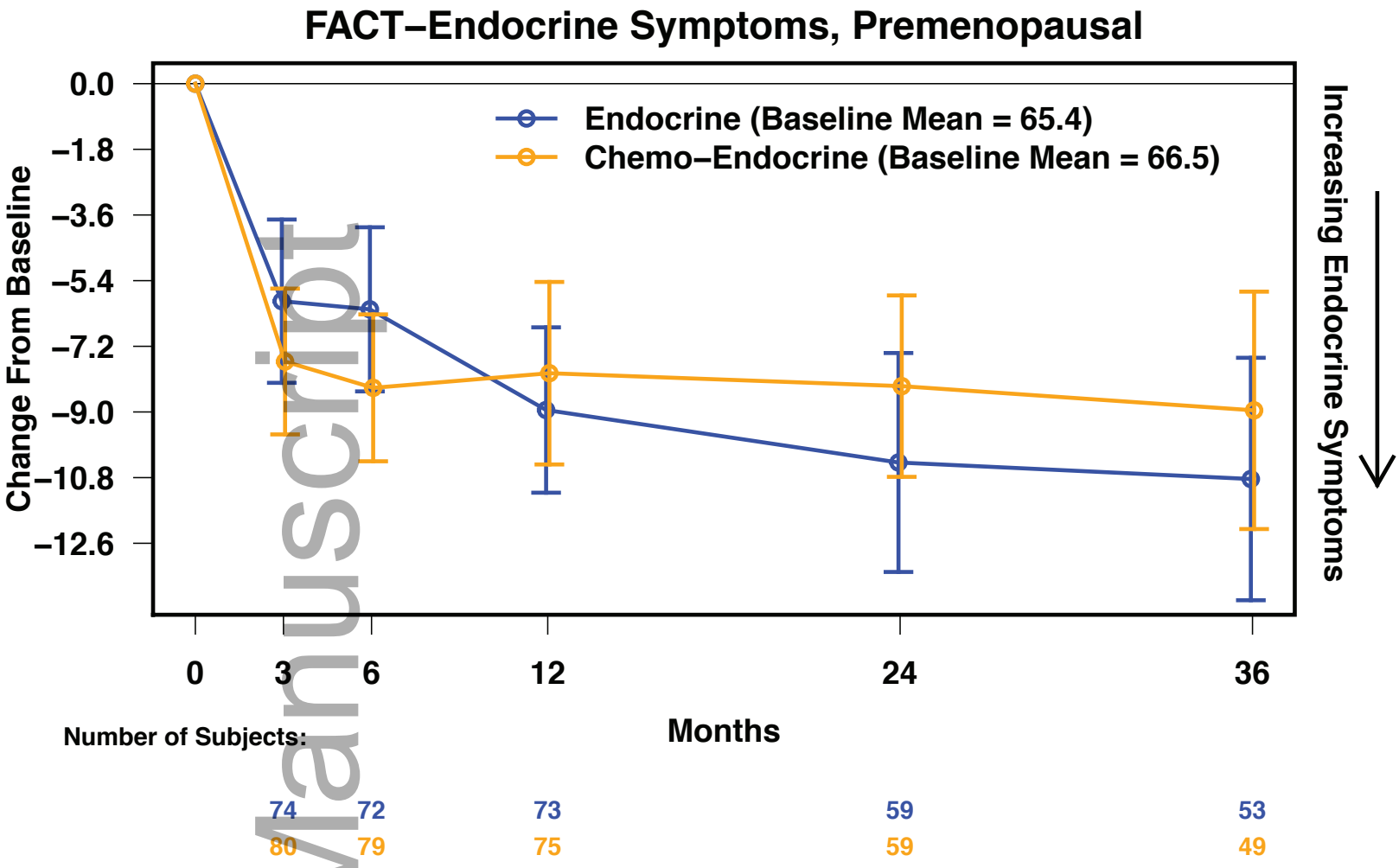

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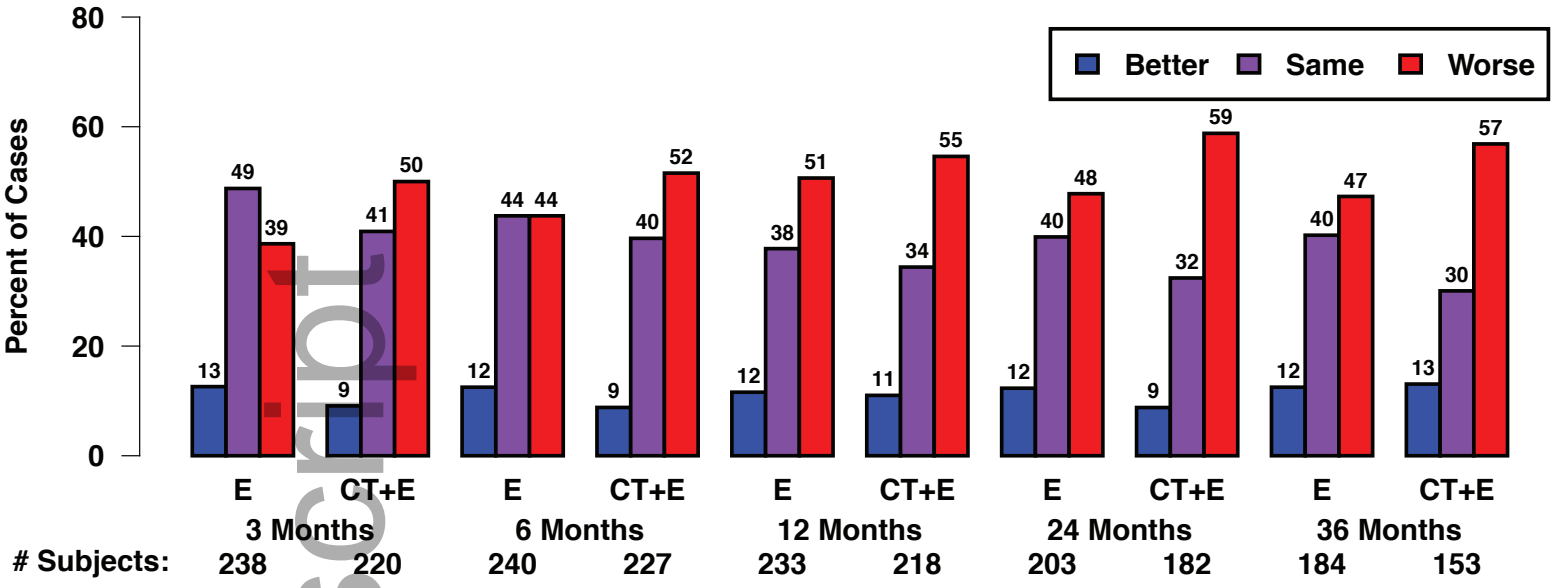

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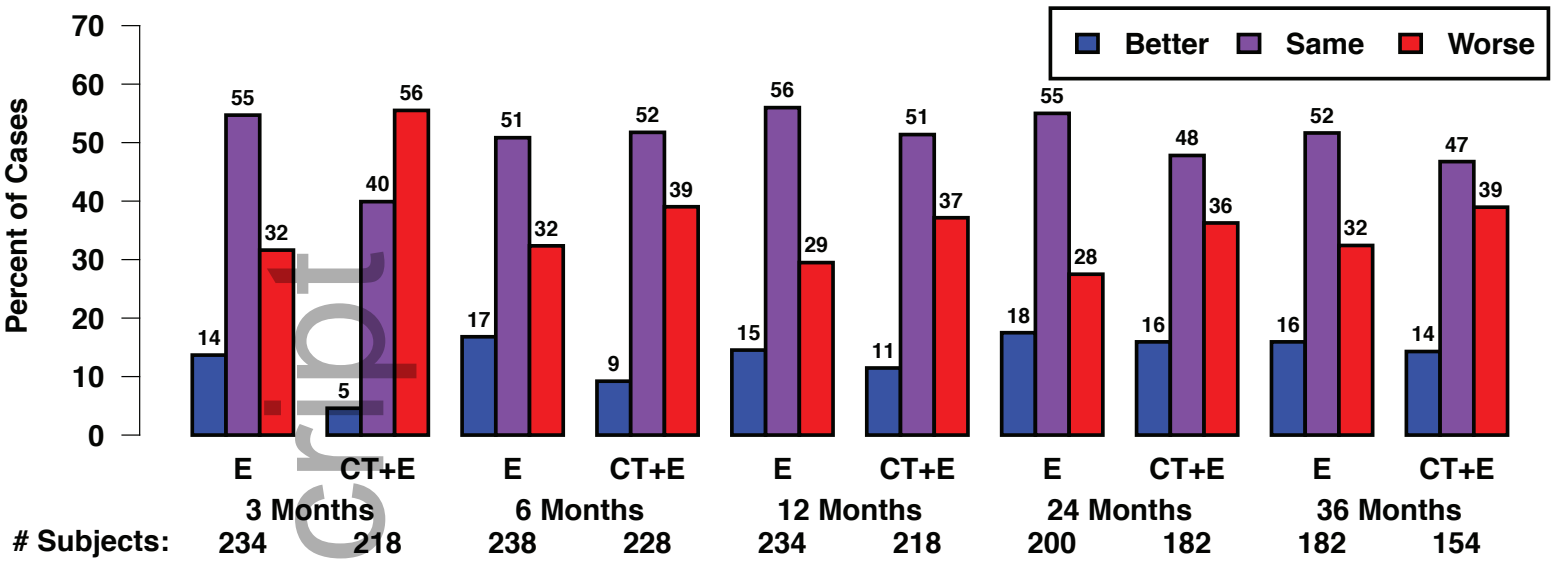

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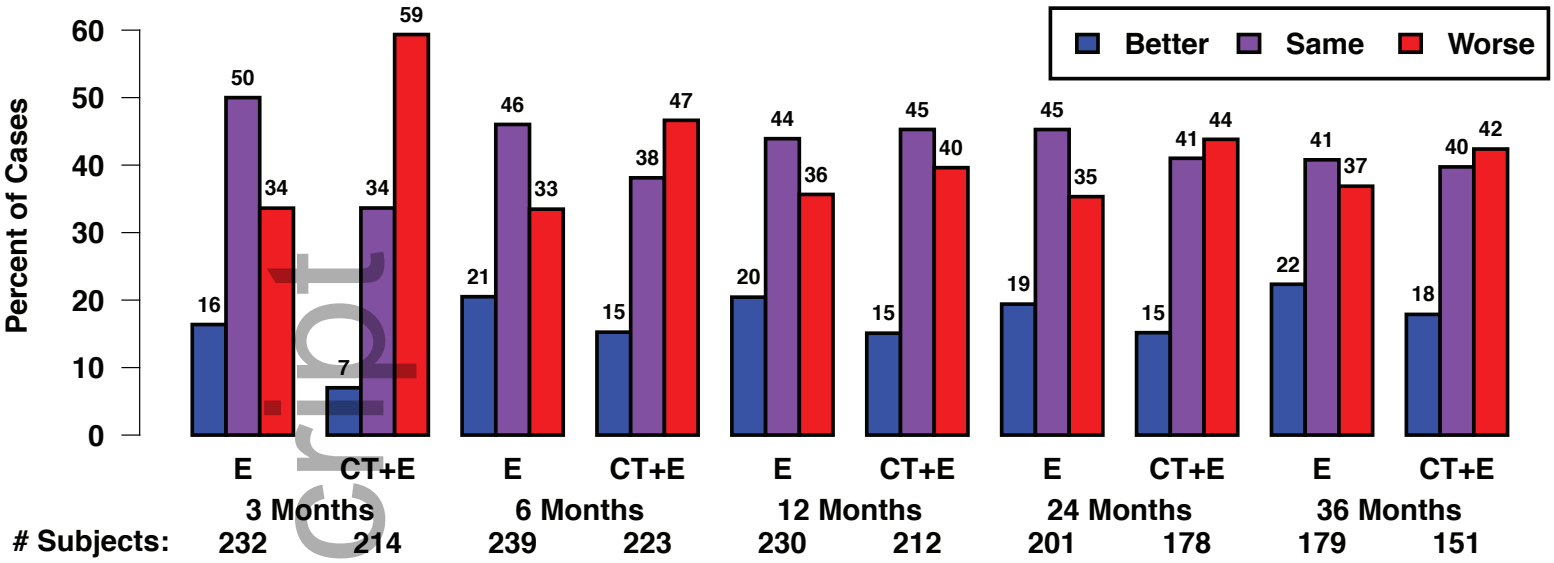

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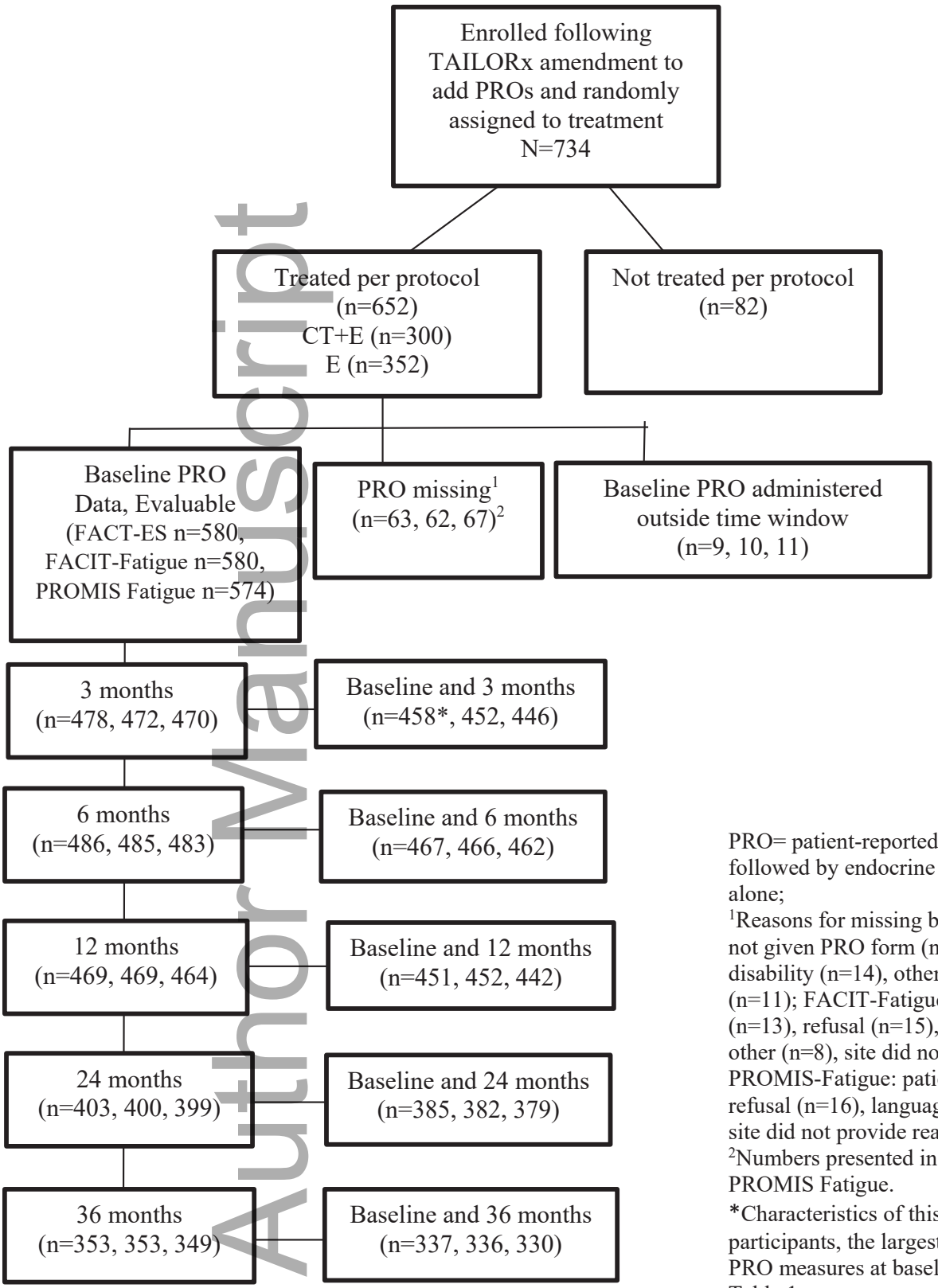

PRO= patient-reported outcome; CT+E= chemotherapy followed by endocrine therapy; E= endocrine therapy alone;

[1]Reasons for missing baseline data: FACT ES= patient not given PRO form (n=15), refusal (n=15), language or disability (n=14), other (n=8), site did not provide reason (n=11); FACIT-Fatigue= patient not given PRO form (n=13), refusal (n=15), language or disability (n=14), other (n=8), site did not provide reason (n=12); PROMIS-Fatigue: patient not given PRO form (n=17), refusal (n=16), language or disability (n=14), other (n=9), site did not provide reason (n=11).

[2]Numbers presented in order FACT-ES, FACIT-Fatigue, PROMIS Fatigue.

*Characteristics of this sample of 458 per protocol participants, the largest with data on at least one of the PRO measures at baseline and 3 months, are presented in Table 1.

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