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Comparison of patient reported quality of life and impact of treatment side effects experienced with a taxane-containing regimen and standard anthracycline based chemotherapy for early breast cancer: 6 year results from the UK TACT trial (CRUK/01/001)

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Abstract ***Background:*** The TACT trial (CRUK/01/001) compared adjuvant sequential FEC-docetaxel (FEC-D) chemotherapy with standard anthracycline-based chemotherapy of similar duration in women with early breast cancer. Results at a median of 5 years suggested no improvement in disease-free survival with FEC-D. Given differing toxicity profiles of the regimens, the impact on quality of life (QL) was explored.

Methods: Patients from 44 centres completed standardised QL questionnaires before chemotherapy, after cycles 4 and 8, at 9, 12, 18 and 24 months and at 6 years follow-up. Patient diaries assessed frequency, associated distress and impact on daily activity of 15 treatment related side effects.

Findings: 830 patients (415 FEC-D; 415 controls) contributed assessments during 0–24 months; 362 of whom participated again at 6 years. During chemotherapy, FEC-D impaired global health/QL and depression rates and significantly more QL domains than standard regimens. Novel diary card ratings highlighted significantly more distress and interference with daily activities due to FEC-D side effects compared with standard treatment. In both groups, most QL parameters returned to baseline levels by 2 years and were unchanged at 6 years.

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Interpretation: Within expected negative effects of chemotherapy on wide ranging QL domains FEC-D patients reported greater toxicity, disruption and distress during treatment with no improvement in disease outcome at 5 years than patients receiving standard anthracycline-based chemotherapy. Findings should inform future patients of relative costs and benefits of adjuvant chemotherapy.

1. Introduction

The toxicity experienced by women with early breast cancer undergoing adjuvant chemotherapy concerns both patients and clinicians, especially when more intensive, toxic regimens result in small or no overall survival gains. In meta-analyses of randomised controlled trials [1] comparing taxane-containing chemotherapy with control regimens of similar duration, results showed no statistically significant reduction in the risk of recurrence (relative risk (RR): 0.96, standard error (SE):0.05; $p > 0.1$) or death (RR: 0.96, SE: 0.06; $p > 0.1$). These analyses were heavily influenced by the UK Taxotere® as Adjuvant Chemotherapy Trial (TACT, CRUK/01/001, ISRCTN79718493) [2] which, with median 62 months follow-up, did not demonstrate an overall gain in disease-free (hazard ratio (HR): 0.95, 95% CI: 0.85–1.08) or overall survival (HR: 0.99 (0.86–1.14)). In this context the prospective assessment of patient reported toxicity and quality of life (QL) incorporated in TACT is particularly important although its relevance extends to other clinical scenarios where a small incremental benefit for taxane based regimens has been seen [1].

The impact of adjuvant chemotherapy on QL is widely recognised. However, the assessment of taxane toxicity in breast cancer clinical trials has been based largely on clinical assessments [2–10] and considered 'acceptable' [5], 'tolerable' [3] or 'manageable' [9] when it is known that some clinicians' ratings of key symptoms and distress may not reflect those of patients [11–14]. Nevertheless, health professionals increasingly acknowledge that differences in toxicity profiles potentially influence choice of adjuvant treatment [3], and that there is a need to improve the QL of patients receiving taxanes and better identify those more likely to benefit from treatment, to justify the trade off with toxicity [6–8]. Others have argued that toxicity is transient and some women may accept acute toxicity for the chance of a small survival benefit [15,16]. However, longer term effects from chemotherapy, such as hot flushes, amenorrhoea and sexual dysfunction have also been consistently reported [17], especially following a menopausal transition [18]. Patient preferences are highly variable and so discussion of treatment options should be informed by patient reported outcomes of the impact of treatment on QL so that expectations are realistic. In an era where the duration of adjuvant therapy and/or accompanying toxicity has increased, even 'transient' treatment effects can extend over 6 months.

The TACT QL sub-study provides a randomised comparison of patient evaluated treatment related side effects in terms of severity, distress and disruption as well as the impact on a range of QL parameters, during treatment and over 6 years follow-up.

2. Methods

2.1. Patients

Details of the TACT trial patient population, treatment regimens and procedures were previously reported [2]. Briefly, women with operable invasive breast cancer who had undergone complete tumour excision and were to be prescribed adjuvant chemotherapy were eligible. Participating centres chose at the outset of the trial whether to participate in the QL sub-study. To minimise bias, centres were encouraged to offer the QL sub-study to all TACT patients able to read and understand English. Specific informed consent for the QL sub-study was obtained.

2.2. Procedures

2.2.1. Treatment

Women were randomised to receive fluorouracil$_{600}$/epirubicin$_{60}$/cyclophosphamide$_{600}$ for four cycles followed by docetaxel$_{100}$ for four cycles (FEC-D) or one of two standard regimens (choice declared by each centre at trial outset): $F_{600}E_{60}C_{600}$ for eight cycles (FEC) or epirubicin$_{100}$ for four cycles followed by cyclophosphamide$_{600x2}$/methotrexate$_{40x2}$/fluorouracil$_{600x2}$ for four cycles (E-CMF) [19]. Women receiving E-CMF had a slightly longer overall duration of treatment as CMF was given over four-weekly cycles (all other cycles given over three weeks). Following chemotherapy, tamoxifen was prescribed for 5 years in patients with oestrogen receptor and/or progesterone receptor positive tumours, or (from 2005) an aromatase inhibitor could be prescribed according to local policy. Radiotherapy commencing within four weeks of completion of chemotherapy was mandatory after breast conserving surgery and according to local clinical guidelines following mastectomy.

2.2.2. QL assessments

Consenting women completed a baseline QL questionnaire booklet, administered by their hospital team in the outpatient clinic, before randomisation. Subsequent booklets were mailed by ISD Cancer Clinical Trials Unit Scotland (CaCTUS) for completion at home (after checking the individual's health status with their hospital team or family doctor), after cycles 4 and 8 of chemotherapy, then at 9, 12, 18 and 24 months. A single prompt was made if booklets were not returned within 8 weeks.

QL was evaluated using the EORTC (European Organisation for the Research and Treatment of Cancer) general cancer scale QLQ-C30 [20] and breast cancer module, BR23 [21]. The QLQ-C30 comprises five functional subscales (physical, role, emotional, cognitive, social), three symptom subscales (fatigue, nausea/vomiting, pain), five symptom items and one item reporting financial difficulties. Questionnaire items had a 4-point response format (not at all, a little, quite a bit, very much). Two items captured global health and global QL, each rated on a 7-point numeric scale. The BR23 comprises four functional subscales/items (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom subscales/items including systemic side effects. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) [22].

A trial specific patient self-report diary (see web appendix) was constructed and piloted, based on a prototype developed for cancer trials [23,24]. Patients rated the extent to which side effects of anthracycline and taxane-based chemotherapy were experienced (rated daily) and/or caused distress or interfered with daily activities (rated once for each cycle assessed); all 14 items were rated on a 4-point scale (not at all, a little, quite a bit, very much). Diary cards were administered by the hospital for completion on days 1–21 of cycles 1, 5 and 8 and mailed by patients to CaCTUS. At 9, 12, 18 and 24 months post-randomisation the same diary card items concerning distress and interference of side effects were incorporated into the QL booklet.

In a separate but related initiative, patients who were disease-free and continuing in follow-up at 6 years were invited to participate in a cross-sectional QL assessment focusing on residual systemic therapy effects in the survivorship context (to be reported separately). Data from patients who also participated in the original QL substudy were included in the longitudinal analyses reported here.

2.3. Endpoints

The co-primary endpoints were EORTC QLQ-C30 global health/QL and psychological distress (HADS anxiety and depression subscales). Secondary endpoints included other subscales and items of specific interest from the EORTC questionnaires (including fatigue, pain, nausea/vomiting and systemic side effect subscales) and patient diaries.

2.4. Scoring and statistical analysis

EORTC questionnaires were scored according to standard procedures [25]. Change from baseline values on any subscale was considered clinically relevant with a difference of $\geqslant 10$ [26] and statistically significant if $p \leqslant 0.05$ (primary endpoints) or $p \leqslant 0.01$ (all other endpoints).

Recommended threshold scores for HADS anxiety and depression were used: scores $\geqslant 11$ indicated probable case disorder, scores 8–10 indicated borderline disorder and scores < 8 were considered normal. Prevalence rates refer to borderline and probable case categories combined.

The study design included at least 500 patients, with an approximate 5% attrition rate, providing 97% power to detect difference of 20% or more in any proportion (1% significance) and 78% power for differences of 15% or, alternatively, 90% power to detect a standardised difference of 0.35 (1% significance). Due to rapid accrual to the main trial the final size of the sample was larger than originally anticipated, increasing the power of comparisons.

Analyses comparing FEC-D to control were according to intention-to-treat, adjusted for centre's choice of standard control regimen. Dichotomised outcomes were adjusted for baseline score and analysed by logistic regression (with odds ratios (OR) reported). Subscale scores were compared between randomised groups using analysis of covariance with change from baseline adjusted for baseline scores. Mean differences in change from baseline (FEC-D − control) are reported with 95% (primary endpoints)/99% (secondary endpoints) confidence intervals. Categorised anxiety and depression subscale scores were compared using generalised ordinal logistic regression [27]. Treatment side effects (diary card data) were analysed by Cochran–Mantel–Haenszel test (no baseline data were available for adjustment). Time points for formal analysis were cycle 8, and 9 and 24 months from randomisation. Generalised estimating equations were used for longitudinal analysis. These models (not shown) gave similar results to single time point analyses. Subgroup analyses by centre's choice of control regimen (i.e. comparing FEC-D to FEC and FEC-D to E-CMF), menopausal status and sensitivity analyses assessing robustness to missing data and time windows of questionnaire response and excluding questionnaires completed after a disease event (not shown) were consistent with the main analysis results unless otherwise stated. Analyses were conducted in STATA v10.1.

2.5. Study oversight

TACT (ISRCTN79718493), including the QL sub-study, was approved by the national South East Multi-Research Ethics Committee (MREC00/1/59) and the local ethics committees of all participating centres. The Cancer Research UK funded Clinical Trials and Statistics Unit (ICR-CTSU) at The Institute of Cancer Research had overall responsibility for trial co-ordination and undertook all statistical analyses; a central QL co-ordinator at CaCTUS was responsible for QL project management.

2.6. Role of the funding sources

TACT was funded by Cancer Research UK (C1491/A2645, C1491/A4129, C1491/A6852, C1491/A9895) and educational grants from collaborating pharmaceutical companies: Sanofi-Aventis, Pfizer and Roche. Funders had no role in study design, collection, analysis, interpretation of data, or writing of the report. All authors had access to study data and the corresponding author had final responsibility for the decision to submit for publication.

3. Results

Between July 2001 and August 2002, 830 women (415 FEC-D; 415 Control), from 44 UK centres, entered the QL sub-study (Fig. 1). 797/830 (96.0%) patients returned a baseline questionnaire and form the primary analysis population. Questionnaire return rates were high (Fig. 1) although decreased over the 2 years to 78.9% (control) and 79.1% (FEC-D). Diary card return rate during treatment was 57.8%, 58.3% and 55.3% for cycles 1, 5 and 8, respectively increasing to 78.9% at 9 months and 69.9% at 2 years. At 6 years, 349/538 (64.9%) patients (171 control; 178 FEC-D) completed QL booklets.

Baseline characteristics of QL patients (Table 1) were similar to those of the 540 TACT patients at centres participating in the QL substudy who were ineligible, not approached or chose not to enter the QL substudy.

3.1. Global health/QL and psychological distress

Patients' ratings showed a clinically relevant impairment of global health/QL during treatment, which was statistically significantly worse for the FEC-D group compared with controls at cycle 8 (mean difference in change from baseline: −6.32 (95% CI: −9.42 to −3.23), $p < 0.0001$) (Fig. 2). This difference was consistent when FEC-D was compared with each control regimen separately (test for heterogeneity: $p = 0.95$). Recovery to baseline levels occurred for women in both regimens by 12 months and scores were similar and unchanged from baseline at 2 and 6 years (Fig. 2). Anxiety prevalence was greatest (44.3%) pre-treatment reducing over time to affect 30–35% women post-treatment with no significant differences between the regimens (Fig. 3). In contrast, depression affected 11.9% women at baseline but increased during treatment (Fig. 3) and was significantly worse for FEC-D patients compared with controls at cycle 8 (30.6% versus 23.9%; OR = 1.63 (1.11–2.39), $p = 0.01$). No differences were seen at later time points and there was no evidence of heterogeneity by control regimen. The prevalence of anxiety remained greater than depression throughout follow-up.

3.2. General treatment side effects

Patients' ratings of general treatment toxicity are reflected in the BR23 systemic side effects subscale and the QLQC30 fatigue, pain and nausea and vomiting symptom subscales (Fig. 2). A clinically relevant increase in systemic side effects was shown for control and FEC-D regimens from baseline to mid treatment. At cycle 8 this increase was significantly greater for FEC-D patients (mean difference in change from baseline 4.02, 99% CI: 0.33–7.72, $p = 0.005$) with no evidence of heterogeneity by control regimen ($p = 0.87$). Fatigue and pain were also worse in FEC-D patients at cycle 8 whilst control patients reported more nausea and vomiting (Fig. 2).

In terms of individual systemic side effects, at cycle 8, the odds of rating BR23 symptom items as 'quite a bit' or 'very much' were significantly greater in the FEC-D group for different taste and sore/watery eyes; odds of reporting hot flushes and dry mouth were significantly greater in control patients (web appendix Table 1a and b). All systemic effects except dry mouth reduced similarly in both treatment groups over follow-up to 24 months but did not recover to baseline levels. Odds of reporting dry mouth at 2 years were greater in control than FEC-D patients (OR = 0.34 (0.13–0.86), $p = 0.003$). Moderate or marked hot flushes were prevalent and persistent for patients in both regimens, increasing from 18.4% FEC-D and 12.5% control at baseline to 38.9% and 46.7% respectively at cycle 8; levels peaked at 9 months (58.2% and 48.6% respectively) affecting around 50% women to 2 years and were reported by more than a quarter of women at 6 years (web appendix Table 1a).

3.3. Pattern of QL changes over time

Patients' self-reports of other QL domains mirrored those of their side effects, with clinically relevant worsening of multiple QL domains for both FEC-D and control regimens (Fig. 2). Statistically significant differences in subscale change scores between the

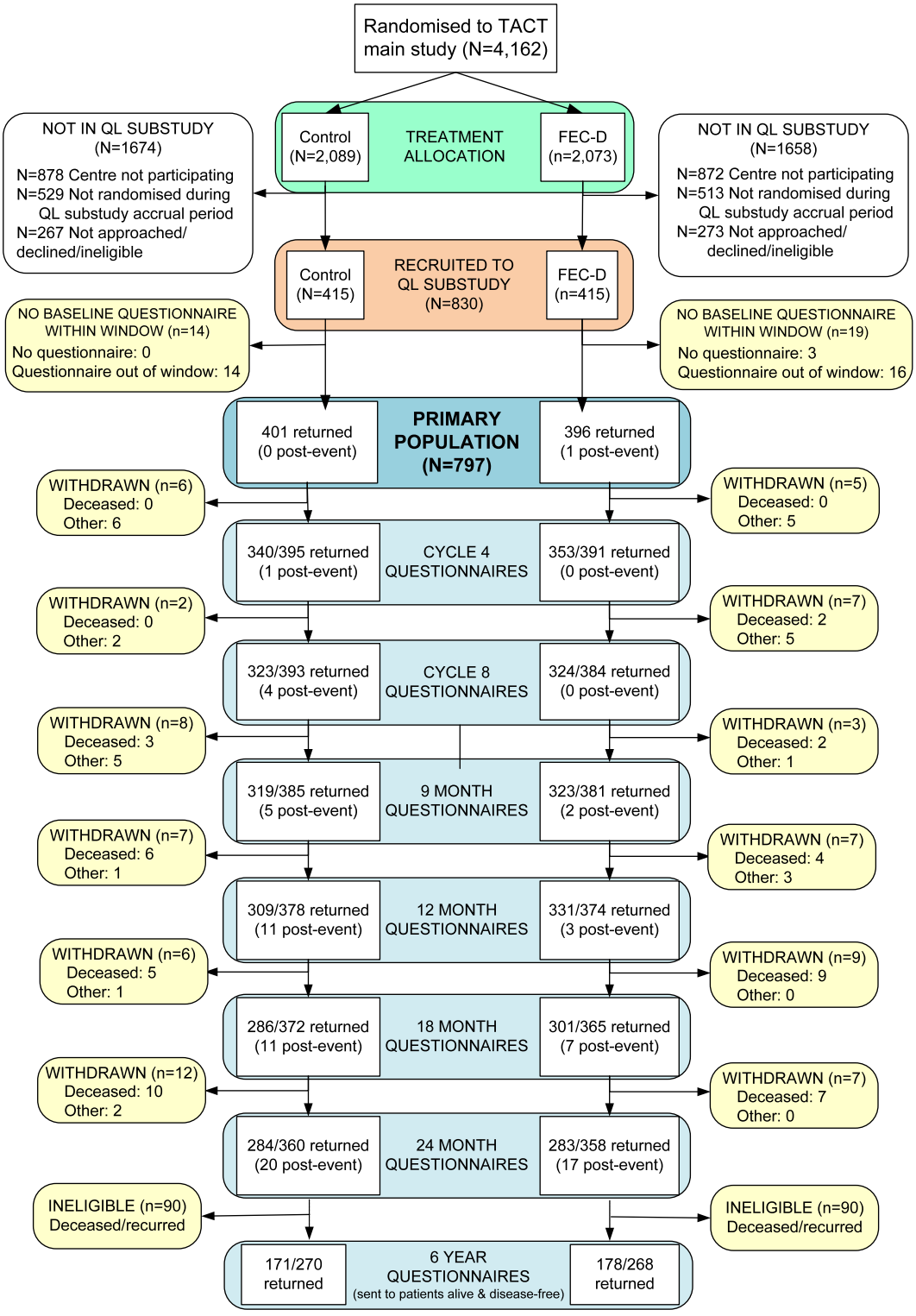

Fig. 1. Study profile.

regimens at cycle 8 indicated more severe side effects and functional disruption in the FEC-D regimen (Fig. 2) but differences were not considered clinically relevant. Most QL subscale scores improved post treatment to near baseline values, although women's ratings of their body image and sexual functioning took longer to resolve. No further changes were observed at 6 years.

3.4. Diary cards: impact of treatment on side effects

Patients' diary ratings provided new insight into the prevalence and impact of a large range of specific treatment-related side effects (Fig. 4, Tables 2 and 3). First, a wide variability in the proportion of women rating 'quite a bit' or 'very much' experience of individual side

Table 1
Baseline characteristics by randomised group.

		Control ($N = 415$)		FEC-D ($N = 415$)		Total ($N = 830$)	
		N	%	*N*	%	*N*	%
Control arm	FEC	268	64.6	271	65.3	539	64.9
	E-CMF	147	35.4	144	34.7	291	35.1
Age (years)	Mean (SD)	47.7	(8.7)	49.5	(8.4)	48.6	(8.6)
	<40	96	23.1	65	15.7	161	19.4
	40–49	145	34.9	131	31.6	276	33.3
	50–59	143	34.5	176	42.4	319	38.4
	60+	31	7.5	43	10.4	74	8.9
Menopausal status	Post-menopasual	187	45.1	218	52.5	405	48.8
	Not menopausal (i.e. pre or peri)	228	54.9	197	47.5	425	51.2
Ethnicity	White	391	94.2	394	94.9	785	94.6
	Other	15	3.6	16	3.9	31	3.7
	Not known	9	2.2	7	1.7	16	1.9
Type of surgery	Mastectomy	210	50.6	225	54.2	435	52.4
	Local excision	205	49.4	190	45.8	395	47.6
Radiotherapy given	Yes	357	86.0	354	85.3	711	85.7
	No	44	10.6	39	9.4	83	10.0
	Not known	14	3.4	22	5.3	36	4.3
Nodal status	Positive	332	80.0	333	80.2	665	80.1
	Negative	83	20.0	82	19.8	165	19.9
Tumour grade	I	19	4.6	21	5.1	40	4.8
	II	149	35.9	140	33.7	289	34.8
	III	246	59.3	251	60.5	497	59.9
	Not known	1	0.2	3	0.7	4	0.5
Tumour size	<2 cm	227	54.7	226	54.5	453	54.6
	2–5 cm	143	34.5	146	35.2	289	34.8
	>5 cm	45	10.8	43	10.4	88	10.6
	Not known	0	0.0	0	0.0	0	0.0
Oestrogen receptor (ER) status	Positive	279	67.2	275	66.3	554	66.7
	Negative	136	32.8	140	33.7	276	33.3
Progesterone receptor status	Positive	99	23.9	93	22.4	192	23.1
	Negative	96	23.1	94	22.7	190	22.9
	Not known	220	53.0	228	54.9	448	54.0
Endocrine therapy received	None (ER negative)	136	32.8	140	33.7	276	33.3
	Tamoxifen only	173	41.7	186	44.8	359	43.3
	Aromatase inhibitor (AI) only	18	4.3	6	1.4	24	2.9
	Tamoxifen and switched to AI	78	18.8	78	18.8	156	18.8
	None (ER positive)	10	2.4	5	1.2	15	1.8
HER2 status	Negative	290	69.9	281	67.7	571	68.8
	Positive	80	19.3	91	21.9	171	20.6
	Positive and received Herceptin	7	1.7	6	1.4	13	1.6
	Not known	45	10.8	43	10.4	88	10.6
Combined ER/HER2 status	ER+/HER2+	44	10.6	47	11.3	91	11.0
	ER+/HER2–	205	49.4	198	47.7	403	48.6
	ER+/HER2 not known	30	7.2	30	7.2	60	7.2
	ER-/HER2+	36	8.7	44	10.6	80	9.6
	ER-/HER2–	85	20.5	83	20.0	168	20.2
	ER-/HER2 not known	15	3.6	13	3.1	28	3.4
EORTC QLQ-C30	Global health/QL median (IQR)	75	(58.3, 83.3)	75	(58.3, 83.3)	75	(58.3, 83.3)
HADS anxiety	Normal (<8)	222	53.5	233	56.1	455	54.8
	Borderline disorder (8–10)	86	20.7	83	20.0	169	20.4
	Probable case disorder (⩾11)	105	25.3	94	22.7	199	24.0
	Not known	2	0.5	5	1.2	7	0.8
HADS depression	Normal (<8)	359	86.5	364	87.7	723	87.1
	Borderline disorder (8–10)	37	8.9	32	7.7	69	8.3
	Probable case disorder (⩾11)	16	3.9	14	3.4	30	3.6
	Not known	3	0.7	5	1.2	8	1.0

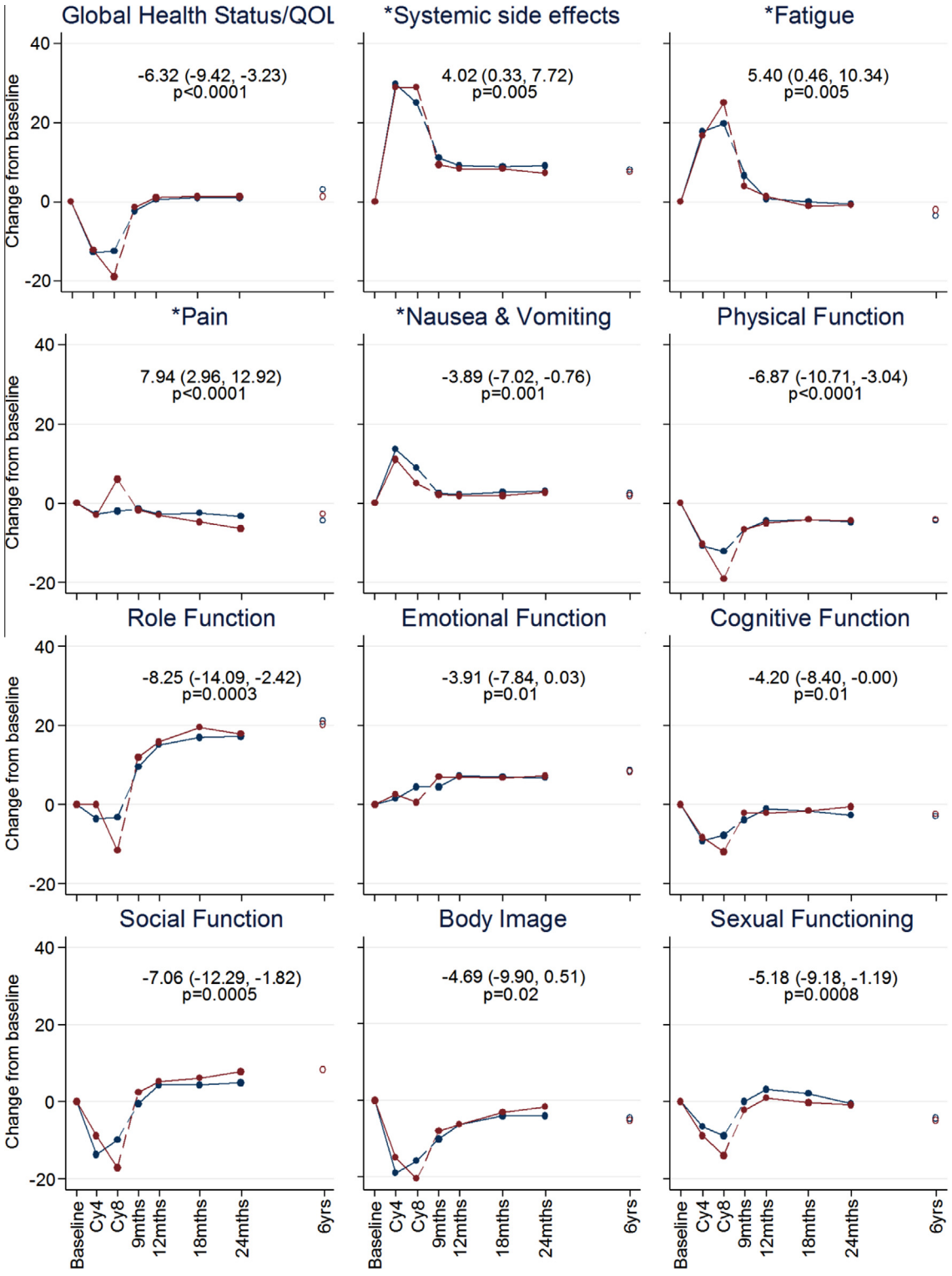

Fig. 2. Change from baseline in EORTC QLQ-C30 and BR23 functional and symptom subscales scores at each time point. Text shows mean difference in change from baseline[†] (FEC-D minus control, with confidence interval[‡] and p value) at cycle 8. Red = FEC-D, blue = control. [†]Change from baseline scores are adjusted for baseline score, chosen control and randomised treatment group using an analysis of covariance (ANCOVA) model. [*]Positive change from baseline indicates a worsening of symptoms; otherwise deterioration in function is shown by a negative change score. [‡]95% confidence interval is given for the primary endpoint of global health/QL, 99% confidence intervals for all other subscales. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

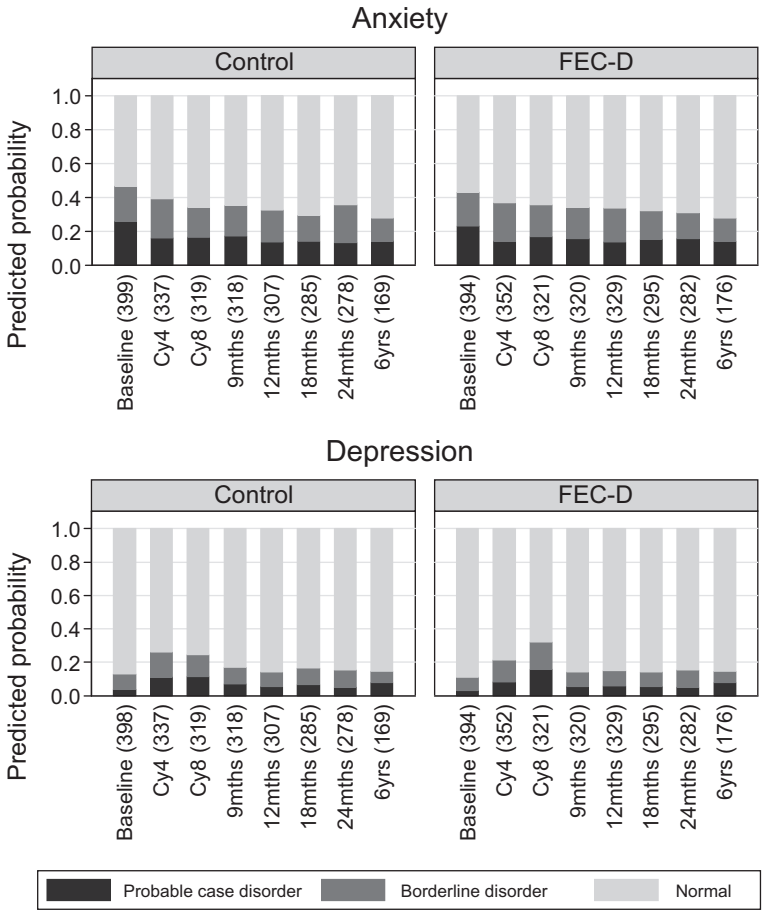

Fig. 3. HADS anxiety and depression ratings (probable case disorder, borderline disorder, normal) by regimen at each time point. Graph shows predicted probabilities from generalised ordinal logistic regression models adjusting for baseline score, chosen control and randomised treatment. Number of observations at each time point are given in parentheses.

effects was observed, with the highest rates for tiredness and the lowest for diarrhoea. Second, the pattern of side effect frequency over each cycle was similar for each treatment group (Fig. 4) but significantly more patients in the FEC-D group experienced moderate or marked effects compared with controls. Third, novel observations showed that at cycle 8 the FEC-D regimen accounted for significantly increased distress and/or interference with activities, rated by patients as 'quite a bit' or 'very much' for eight side effects (skin changes, tingling hands/feet, tiredness, breathlessness, swollen hands/feet, nail changes, muscle/joint pains and painful/gritty eyes); women in the control group rated significantly worse distress and/or interference in activities from nausea and vomiting (Tables 2 and 3). Subgroup analyses by centre's choice of control regimen had minimal effect on overall findings (see web appendix Tables 2a,b and 3a,b); the only statistically significant interaction between randomised treatment and centre's choice of control regimen was for diarrhoea at cycle 8 (FEC-D more distress than FEC but FEC-D less distress than E-CMF).

Peak severity of side effects was mainly at cycle 8 but earlier for sore mouth, nausea and mouth ulcers. Of note, there was persistence of some distress and or interference with activities beyond completion of chemotherapy. At 9 months significantly more distress/interference was observed due to tingling hands/feet and nail changes in the FEC-D group and to tiredness in the control group. Differences between the regimens resolved by 24 months. Centre's choice of control regimen was not a significant factor in analyses at 9 and 24 months.

4. Discussion

The findings of this large study of QL and toxicity provide clear evidence of women's experience of greater toxicity and disruption to diverse aspects of their QL over many months from taxane-containing treatment compared to standard adjuvant chemotherapy. Whilst established QL subscales provide broad coverage, details of the impact of toxicity are better reflected using the diary card approach. These results build usefully on the well-established but more limited reporting of adverse effects in other such clinical trials [3–10], TACT patients were able to report not only the severity and duration of side effects, but also the unique distress and disruption to daily life that each symptom caused.

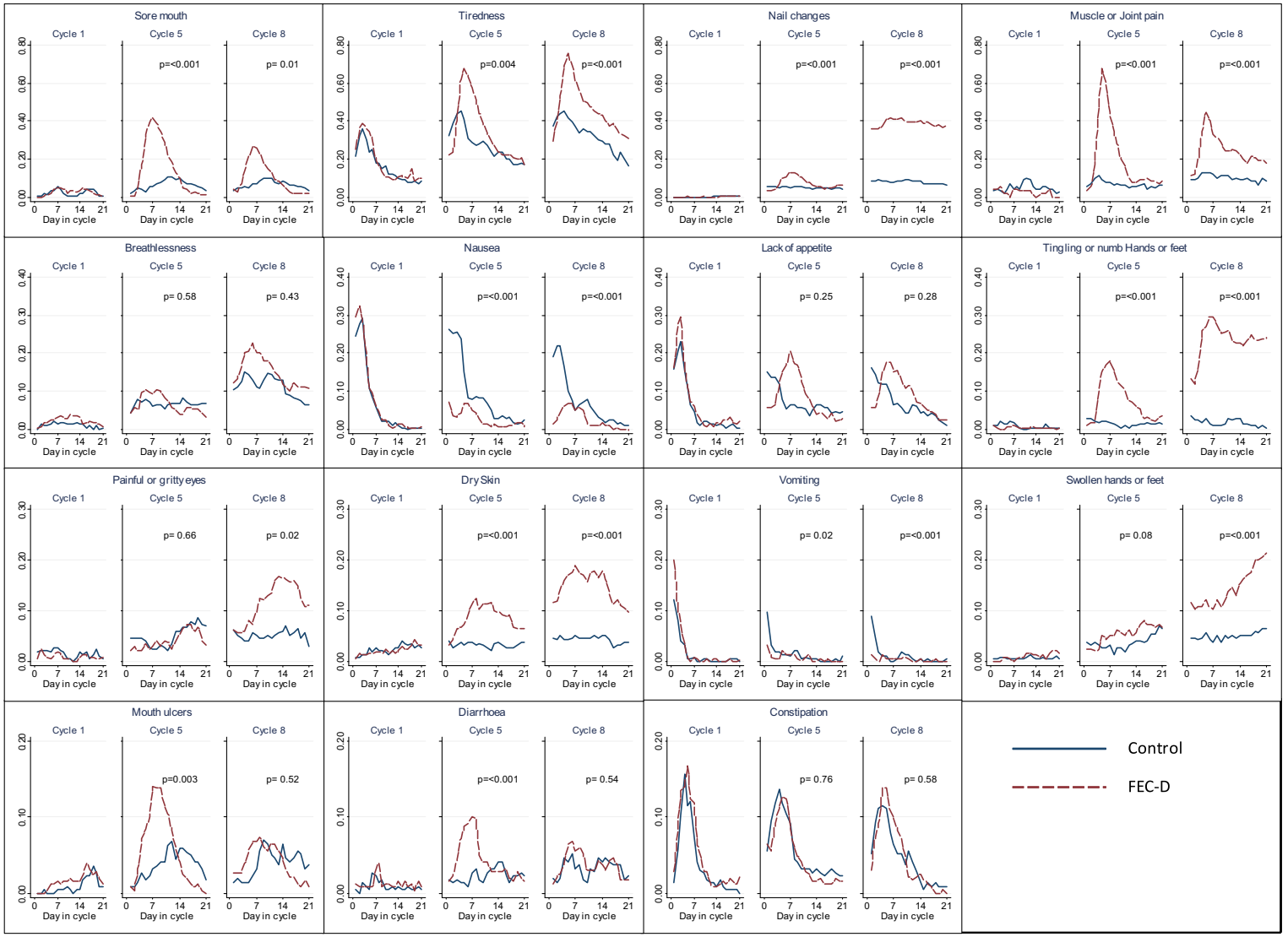

Fig. 4. Diary card: Proportion experiencing side effect 'quite a bit' or 'very much' during treatment by regimen. *P*-values compare area under the curve by Mann–Whitney *U* test. Note scale of vertical axis differs on each row.

Table 2
Diary card ratings of side effect experience, distress and interference with activities: proportion rating as 'quite a bit'/'very much'.

Side Effect		Cycle 1				Cycle 5				Cycle 8				9 Months				12 Months				18 Months				24 Months			
		Control N = 226		FEC-D N = 254		Control N = 226		FEC-D N = 258		Control N = 219		FEC-D N = 240		Control N = 321		FEC-D N = 334		Control N = 314		FEC-D N = 342		Control N = 293		FEC-D N = 311		Control N = 287		FEC-D N = 293	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Nausea	Experience	108	(47.8)	134	(52.8)	103	(45.6)	41	(15.9)	79	(36.1)	35	(14.6)																
	Distress	60	(26.5)	79	(31.1)	58	(25.7)	20	(7.8)	39	(17.8)	15	(6.3)	12	(3.7)	15	(4.5)	9	(2.9)	6	(1.8)	6	(2.0)	3	(1.0)	1	(0.3)	6	(2.0)
	Interference	63	(27.9)	75	(29.5)	53	(23.5)	17	(6.6)	35	(16.0)	14	(5.8)	9	(2.8)	7	(2.1)	6	(1.9)	3	(0.9)	6	(2.0)	4	(1.3)	1	(0.3)	4	(1.4)
Vomiting	Experience	44	(19.5)	73	(28.7)	36	(15.9)	22	(8.5)	33	(15.1)	11	(4.6)																
	Distress	34	(15.0)	58	(22.8)	29	(12.8)	10	(3.9)	18	(8.2)	4	(1.7)	4	(1.2)	2	(0.6)	3	(1.0)	2	(0.6)	2	(0.7)	2	(0.6)	0	(0)	2	(0.7)
	Interference	36	(15.9)	55	(21.7)	23	(10.2)	7	(2.7)	19	(8.7)	4	(1.7)	5	(1.6)	1	(0.3)	4	(1.3)	1	(0.3)	3	(1.0)	1	(0.3)	1	(0.3)	4	(1.4)
Skin	Experience	26	(11.5)	24	(9.4)	22	(9.7)	63	(24.4)	18	(8.2)	67	(27.9)																
	Distress	5	(2.2)	7	(2.8)	6	(2.7)	30	(11.6)	7	(3.2)	26	(10.8)	30	(9.3)	37	(11.1)	14	(4.5)	18	(5.3)	14	(4.8)	14	(4.5)	17	(5.9)	13	(4.4)
	Interference	1	(0.4)	5	(2.0)	2	(0.9)	14	(5.4)	5	(2.3)	4	(1.7)	8	(2.5)	11	(3.3)	4	(1.3)	5	(1.5)	4	(1.4)	5	(1.6)	8	(2.8)	6	(2.0)
Tingling/numb hands/ feet	Experience	12	(5.3)	10	(3.9)	12	(5.3)	76	(29.5)	17	(7.8)	100	(41.7)																
	Distress	4	(1.8)	3	(1.2)	5	(2.2)	29	(11.2)	10	(4.6)	56	(23.3)	29	(9.0)	75	(22.5)	33	(10.5)	45	(13.2)	26	(8.9)	28	(9.0)	25	(8.7)	27	(9.2)
	Interference	1	(0.4)	0	(0)	4	(1.8)	26	(10.1)	6	(2.7)	32	(13.3)	20	(6.2)	34	(10.2)	18	(5.7)	22	(6.4)	13	(4.4)	13	(4.2)	10	(3.5)	12	(4.1)
Tiredness	Experience	140	(61.9)	182	(71.7)	165	(73)	216	(83.7)	161	(73.5)	207	(86.3)																
	Distress	55	(24.3)	79	(31.1)	83	(36.7)	128	(49.6)	80	(36.5)	114	(47.5)	94	(29.3)	83	(24.9)	64	(20.4)	57	(16.7)	61	(20.8)	59	(19)	54	(18.8)	46	(15.7)
	Interference	78	(34.5)	102	(40.2)	106	(46.9)	147	(57.0)	85	(38.8)	129	(53.8)	94	(29.3)	69	(20.7)	58	(18.5)	44	(12.9)	48	(16.4)	37	(11.9)	44	(15.3)	43	(14.7)
Diarrhoea	Experience	26	(11.5)	31	(12.2)	35	(15.5)	74	(28.7)	41	(18.7)	51	(21.3)																
	Distress	10	(4.4)	11	(4.3)	10	(4.4)	40	(15.5)	19	(8.7)	17	(7.1)	9	(2.8)	10	(3.0)	6	(1.9)	6	(1.8)	6	(2.0)	9	(2.9)	11	(3.8)	5	(1.7)
	Interference	5	(2.2)	8	(3.1)	10	(4.4)	31	(12.0)	16	(7.3)	12	(5.0)	4	(1.2)	6	(1.8)	3	(1.0)	2	(0.6)	5	(1.7)	6	(1.9)	7	(2.4)	4	(1.4)
Constipation	Experience	62	(27.4)	86	(33.9)	56	(24.8)	64	(24.8)	56	(25.6)	53	(22.1)																
	Distress	25	(11.1)	35	(13.8)	28	(12.4)	32	(12.4)	27	(12.3)	24	(10.0)	16	(5.0)	16	(4.8)	11	(3.5)	5	(1.5)	9	(3.1)	10	(3.2)	16	(5.6)	5	(1.7)
	Interference	11	(4.9)	21	(8.3)	16	(7.1)	21	(8.1)	9	(4.1)	13	(5.4)	7	(2.2)	7	(2.1)	4	(1.3)	4	(1.2)	5	(1.7)	6	(1.9)	9	(3.1)	2	(0.7)
Sore mouth	Experience	31	(13.7)	37	(14.6)	49	(21.7)	144	(55.8)	58	(26.5)	87	(36.3)																
	Distress	18	(8.0)	20	(7.9)	29	(12.8)	100	(38.8)	31	(14.2)	53	(22.1)	8	(2.5)	20	(6.0)	5	(1.6)	9	(2.6)	7	(2.4)	7	(2.3)	10	(3.5)	7	(2.4)
	Interference	6	(2.7)	12	(4.7)	24	(10.6)	61	(23.6)	16	(7.3)	29	(12.1)	9	(2.8)	12	(3.6)	4	(1.3)	5	(1.5)	4	(1.4)	4	(1.3)	6	(2.1)	5	(1.7)
Mouth ulcers	Experience	12	(5.3)	18	(7.1)	28	(12.4)	59	(22.9)	36	(16.4)	35	(14.6)																
	Distress	8	(3.5)	15	(5.9)	17	(7.5)	50	(19.4)	27	(12.3)	29	(12.1)	4	(1.2)	14	(4.2)	3	(1.0)	6	(1.8)	6	(2.0)	5	(1.6)	5	(1.7)	7	(2.4)
	Interference	1	(0.4)	8	(3.1)	12	(5.3)	32	(12.4)	17	(7.8)	16	(6.7)	7	(2.2)	11	(3.3)	3	(1.0)	5	(1.5)	6	(2.0)	4	(1.3)	2	(0.7)	4	(1.4)
Breathlessness	Experience	15	(6.6)	22	(8.7)	38	(16.8)	53	(20.5)	61	(27.9)	72	(30.0)																
	Distress	11	(4.9)	15	(5.9)	27	(11.9)	41	(15.9)	31	(14.2)	54	(22.5)	27	(8.4)	25	(7.5)	25	(8.0)	17	(5.0)	19	(6.5)	13	(4.2)	18	(6.3)	16	(5.5)
	Interference	10	(4.4)	17	(6.7)	28	(12.4)	40	(15.5)	37	(16.9)	57	(23.8)	28	(8.7)	23	(6.9)	23	(7.3)	19	(5.6)	15	(5.1)	11	(3.5)	19	(6.6)	14	(4.8)
Swollen hands/feet	Experience	6	(2.7)	11	(4.3)	27	(11.9)	49	(19.0)	31	(14.2)	82	(34.2)																
	Distress	3	(1.3)	2	(0.8)	9	(4.0)	19	(7.4)	13	(5.9)	39	(16.3)	37	(11.5)	54	(16.2)	37	(11.8)	33	(9.6)	22	(7.5)	32	(10.3)	23	(8.0)	19	(6.5)
	Interference	1	(0.4)	3	(1.2)	9	(4.0)	14	(5.4)	12	(5.5)	28	(11.7)	21	(6.5)	33	(9.9)	26	(8.3)	17	(5.0)	16	(5.5)	19	(6.1)	17	(5.9)	10	(3.4)

Nail changes	Experience	3	(1.3)	5	(2.0)	20	(8.8)	54	(20.9)	26	(11.9)	120	(50.0)																	
	Distress	1	(0.4)	0	(0)	6	(2.7)	31	(12.0)	13	(5.9)	69	(28.7)	36	(11.2)	93	(27.8)	16	(5.1)	30	(8.8)	16	(5.5)	16	(5.1)	16	(5.6)	15	(5.1)
	Interference	0	(0)	0	(0)	1	(0.4)	20	(7.8)	4	(1.8)	33	(13.8)	11	(3.4)	32	(9.6)	1	(0.3)	11	(3.2)	8	(2.7)	9	(2.9)	11	(3.8)	5	(1.7)
Lack of appetite	Experience	86	(38.1)	113	(44.5)	68	(30.1)	94	(36.4)	59	(26.9)	70	(29.2)																	
	Distress	20	(8.8)	18	(7.1)	19	(8.4)	20	(7.8)	18	(8.2)	20	(8.3)	15	(4.7)	16	(4.8)	11	(3.5)	7	(2.0)	4	(1.4)	10	(3.2)	7	(2.4)	7	(2.4)
	Interference	15	(6.6)	14	(5.5)	16	(7.1)	15	(5.8)	6	(2.7)	9	(3.8)	13	(4.0)	6	(1.8)	8	(2.5)	5	(1.5)	3	(1.0)	3	(1.0)	4	(1.4)	5	(1.7)
Muscle/joint pain *	Experience	18	(19.1)	14	(15.1)	42	(20.5)	165	(72.1)	61	(28.0)	142	(59.2)																	
	Distress	6	(6.4)	6	(6.5)	19	(9.3)	125	(54.6)	31	(14.2)	91	(37.9)	89	(27.7)	100	(29.9)	71	(22.6)	80	(23.4)	63	(21.5)	65	(20.9)	64	(22.3)	56	(19.1)
	Interference	8	(8.5)	7	(7.5)	21	(10.2)	118	(51.5)	29	(13.3)	83	(34.6)	69	(21.5)	60	(18.0)	53	(16.9)	51	(14.9)	43	(14.7)	40	(12.9)	49	(17.1)	34	(11.6)
Painful/ gritty eyes	Experience	20	(8.8)	18	(7.1)	39	(17.3)	43	(16.7)	43	(19.6)	64	(26.7)																	
	Distress	8	(3.5)	8	(3.1)	32	(14.2)	37	(14.3)	28	(12.8)	51	(21.3)	17	(5.3)	23	(6.9)	8	(2.5)	17	(5.0)	15	(5.1)	15	(4.8)	15	(5.2)	8	(2.7)
	Interference	5	(2.2)	7	(2.8)	21	(9.3)	21	(8.1)	17	(7.8)	36	(15)	12	(3.7)	13	(3.9)	5	(1.6)	7	(2.0)	8	(2.7)	6	(1.9)	8	(2.8)	4	(1.4)

* The item on muscle/joint pain was added in November 2001 when this was identified as a relevant side effect. During treatment only, this item is summarised as % of non-missing, and was completed by (Control and FEC-D): cycle 1–94 and 93 patients; cycle 5–205 and 229 patients; cycle 8–218 and 240 patients.

For instance, nail changes, swollen and/or tingling hands or feet may be regarded clinically as manageable or of nuisance value, but were not only more prevalent, and distressing but also interfered more with daily life in women receiving FEC-D than those treated with standard regimens. This supports evidence from smaller studies exploring more specific taxane toxicities [4,28–30], and may help explain delayed emotional recovery, reduced compliance or early discontinuation of taxane containing chemotherapy [31,32]. The introduction of TACT diary cards gave unique insights into the impact of adjuvant chemotherapy; to our knowledge similar findings have not previously been reported in an adjuvant breast cancer clinical trial.

Assessment of multiple QL domains highlighted the social, psychological and physical reality of undergoing adjuvant chemotherapy, with worsening and improvement in these domains mirroring that of toxicity. Most functional and psychosocial domains as well as side effects reduced substantially after the end of treatment. Exceptions were slow recovery of body image and sexual function and persistent tiredness and joint pains, irrespective of regimen, possibly secondary to changes in hormonal status. The onset of a menopause after chemotherapy is an important survivorship concern [33], whilst younger patients report both more menopausal concerns [34] and greater concerns about fertility than age matched controls [35]. Women in the TACT trial who underwent a menopausal transition may have experienced such concerns and so clinical teams need to distinguish QL issues due to these problems in order to give appropriate support and advice.

It is implicit in QL evaluation that findings will be taken into account in trial outcomes and translated into clinical practice. Together with the TACT clinical results [2] these findings can aid clinicians' discussion with patients. The indication to use taxanes in combination with trastuzumab or similar agents means that a substantial minority of women will be exposed to this increased toxicity. Moreover, appropriate support and advice are needed to mitigate distress and optimise side effect management. Similar considerations exist for women with metastatic disease where the burden of toxicity must be balanced against treatment efficacy in the palliative setting.

Our findings were consistent across QL domains but interpretation may be affected by several factors. Eighty-eight (21.2%) controls and 66 (15.9%) FEC-D patients stopped treatment early; the majority of those in the FEC-D group received at least one taxane cycle but had higher systemic side effect scores than those completing treatment. Control group patients stopping early had slightly lower side effect scores than those completing treatment but differences between these subgroups were not clinically relevant. Diary cards discriminated well between the treatment regimens but completion

Table 3
Odds ratios (OR)[†] for diary card reports of side effect experience, distress and interference with activities as 'quite a bit' or 'very much'.

		Cycle 8			9 Months			24 Months		
		OR	(99% CI)	*P*-value	OR	(99% CI)	*P*-value	OR	(99% CI)	*P*-value
Nausea	Experience	0.30	(0.16, 0.56)	<0.0001						
	Distress	0.30	(0.13, 0.70)	0.0001	1.22	(0.44, 3.36)	0.62	5.98	(0.36, 98.04)	0.06
	Interference	0.32	(0.13, 0.76)	0.0004	0.75	(0.20, 2.80)	0.58	3.91	(0.22, 69.63)	0.19
Vomiting	Experience	0.27	(0.10, 0.69)	0.0001						
	Distress	0.19	(0.05, 0.81)	0.001	0.48	(0.05, 4.42)	0.39	–[*]	(–, –)	0.16
	Interference	0.18	(0.04, 0.76)	0.0005	0.19	(0.01, 3.18)	0.09	3.97	(0.22, 73.31)	0.19
Skin	Experience	4.34	(2.02, 9.31)	<0.0001						
	Distress	3.87	(1.24, 12.05)	0.001	1.21	(0.62, 2.36)	0.47	0.73	(0.27, 1.94)	0.4
	Interference	0.77	(0.13, 4.45)	0.7	1.35	(0.40, 4.61)	0.52	0.72	(0.18, 2.98)	0.55
Tingling/numb hands/feet	Experience	8.76	(3.90, 19.66)	<0.0001						
	Distress	7.01	(2.65, 18.52)	<0.0001	2.89	(1.56, 5.34)	<0.0001	1.07	(0.51, 2.25)	0.82
	Interference	5.92	(1.78, 19.68)	<0.0001	1.73	(0.81, 3.70)	0.06	1.17	(0.38, 3.61)	0.72
Tiredness	Experience	2.40	(1.25, 4.61)	0.0004						
	Distress	1.73	(1.03, 2.90)	0.006	0.80	(0.50, 1.26)	0.2	0.80	(0.45, 1.42)	0.32
	Interference	2.09	(1.23, 3.54)	0.0002	0.63	(0.39, 1.00)	0.01	0.94	(0.51, 1.71)	0.78
Diarrhoea	Experience	1.19	(0.65, 2.17)	0.46						
	Distress	0.85	(0.35, 2.07)	0.64	1.05	(0.31, 3.54)	0.91	0.44	(0.11, 1.78)	0.12
	Interference	0.71	(0.26, 1.93)	0.37	1.42	(0.26, 7.60)	0.59	0.55	(0.11, 2.80)	0.34
Constipation	Experience	0.83	(0.47, 1.47)	0.4						
	Distress	0.79	(0.37, 1.71)	0.43	0.96	(0.38, 2.43)	0.9	0.29	(0.08, 1.13)	0.01
	Interference	1.37	(0.43, 4.31)	0.48	0.94	(0.23, 3.83)	0.91	0.21	(0.03, 1.61)	0.03
Sore mouth	Experience	1.60	(0.94, 2.71)	0.02						
	Distress	1.80	(0.94, 3.45)	0.02	2.51	(0.84, 7.52)	0.03	0.68	(0.19, 2.45)	0.44
	Interference	1.85	(0.79, 4.35)	0.06	1.27	(0.41, 3.99)	0.58	0.81	(0.17, 3.93)	0.73
Mouth ulcers	Experience	0.88	(0.45, 1.72)	0.63						
	Distress	0.99	(0.47, 2.08)	0.98	3.51	(0.80, 15.47)	0.02	1.38	(0.30, 6.34)	0.58
	Interference	0.87	(0.34, 2.22)	0.69	1.55	(0.44, 5.47)	0.37	1.94	(0.21, 18.32)	0.44
Breathlessness	Experience	1.11	(0.65, 1.90)	0.61						
	Distress	1.91	(0.99, 3.68)	0.009	0.88	(0.42, 1.86)	0.66	0.86	(0.35, 2.12)	0.66
	Interference	1.68	(0.91, 3.12)	0.03	0.77	(0.36, 1.65)	0.38	0.70	(0.27, 1.77)	0.31
Swollen hands/feet	Experience	3.17	(1.69, 5.94)	<0.0001						
	Distress	3.35	(1.39, 8.04)	0.0002	1.49	(0.82, 2.69)	0.08	0.79	(0.35, 1.83)	0.48
	Interference	2.50	(0.98, 6.37)	0.009	1.55	(0.73, 3.30)	0.13	0.55	(0.19, 1.59)	0.14
Nail changes	Experience	7.58	(3.77, 15.26)	<0.0001						
	Distress	7.36	(3.04, 17.79)	<0.0001	3.06	(1.73, 5.39)	<0.0001	0.91	(0.35, 2.37)	0.81
	Interference	9.69	(2.32, 40.58)	<0.0001	2.99	(1.18, 7.58)	0.001	0.43	(0.10, 1.77)	0.11

Lack of appetite	Experience	1.12	(0.65, 1.93)	0.59							
	Distress	1.02	(0.42, 2.45)	0.96	1.03	(0.40, 2.65)	0.94	0.98	(0.24, 3.94)	0.96	
	Interference	1.39	(0.35, 5.54)	0.54	0.44	(0.12, 1.59)	0.09	1.20	(0.21, 6.92)	0.78	
Muscle/joint pain	Experience	3.80	(2.20, 6.57)	<0.0001							
	Distress	4.04	(2.13, 7.68)	<0.0001	1.11	(0.71, 1.73)	0.55	0.82	(0.48, 1.39)	0.33	
	Interference	3.77	(1.97, 7.21)	<0.0001	0.80	(0.48, 1.34)	0.27	0.62	(0.33, 1.16)	0.05	
Painful/gritty eyes	Experience	1.51	(0.84, 2.70)	0.07							
	Distress	1.93	(0.98, 3.80)	0.01	1.30	(0.56, 3.04)	0.42	0.51	(0.16, 1.61)	0.12	
	Interference	2.20	(0.98, 4.97)	0.01	1.03	(0.36, 2.95)	0.95	0.48	(0.10, 2.36)	0.22	

† OR is for FEC-D versus control stratified by centre's choice of control regimen with *p*-values from a Cochran Mantel–Haenszel test.
* OR not estimable as no patient in the control group reported symptom.

rates were lower during treatment compared with follow-up: administrative problems may have contributed. It should be noted that statistically significant differences between the experimental and control regimens may not necessarily be clinically relevant. Strengths of this study include the large sample size and the low level of attrition together with detailed and novel reporting of treatment side effects.

It has been reported that doctors 'underestimate' patients' symptoms and distress and therefore patient reported outcomes are more 'accurate', however medical assessments and patients' ratings are drawn from different contexts and are not interchangeable [11,12,36,37]. Biomedical and psychosocial perspectives are complementary [38–40], both providing valuable insights into the treatment experience. This is particularly relevant when considering regimens where the trade-off between toxicity and benefit is small, uncertain or absent. Therefore equal emphasis to the patients' and clinicians' perspectives can provide optimal care for women undergoing adjuvant chemotherapy. As indications for the use of taxanes in the management of early breast cancer evolve the trade-off between clinical benefit and QL will need to be reassessed both in randomised controlled trials and in the decision making process for individual patients.

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Authors contributions

P Hopwood was responsible for the design and management of the QL sub-study, clinical data interpretation and manuscript writing. E Hall was responsible for study design, trial management, statistical data interpretation, manuscript writing and oversaw all statistical analyses. D Cameron was responsible for the design of the QL sub-study and manuscript writing and contributed to data interpretation. P Ellis and P Barrett-Lee were joint Chief Investigators of the main TACT trial and contributed to study design, data interpretation and manuscript writing. J M Bliss was responsible for study design, trial management, data interpretation, contributed to manuscript writing and oversaw all statistical analyses. R Waters conducted the statistical analyses. S Crawford was responsible for trial management and data collection. All authors contributed to manuscript review.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article, including a list of TMG members and contributers to the TACT QL study can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.06.007.

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