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Quality of Life Measures for Patients Receiving Adjuvant Therapy for Breast Cancer: an International Trial

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Serial quality of life (QL) assessments are being obtained every 3 months for 2 years from patients with operable breast cancer in two ongoing International Breast Cancer Study Group (IBCSG) randomised clinical trials of adjuvant treatment. The QL-assessments include patient-derived perceived coping (PACIS, personal adjustment to chronic illness scale), well-being (Bf-S, Befindlichkeitsskala von Zerssen), mood, physical well-being and appetite (LASA, linear analogue self assessments). The first assessment within 6 weeks of surgery was performed by 70% of the patients. The analysis of serial assessments for 265 patients with each of the first four assessments completed showed that all measures improved with increasing time from study entry; that the degrees of improvement for the four major language groups were similar; and that measures were sensitive to treatment difference. In conclusion, measurement of QL related aspects in a multicultural clinical trial is feasible and possibly relevant for the evaluation of treatment results.
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INTRODUCTION

BREAST CANCER is a chronic disease which may relapse many years after initial treatment. Adjuvant treatments given postoperatively may be associated with considerable early subjective toxic effects, while treatment benefits may accrue only after long follow-up periods. Because treatment effects so far achieved are modest, adjuvant treatment for this disease can best be studied in large randomised clinical trials. In order to improve assessment of the cost-benefit balance in a trial comparing adjuvant therapies of differing intensity and duration, we considered it important to measure quality of life (QL) related aspects prospectively. A separate hypothesis, namely that QL scores might carry prognostic information was also of interest. The present study therefore applied QL measures for both these purposes. We chose QL indicators for their psychometric properties (validity, reliability and sensitivity) and, most importantly, for their feasibility in a large international trial. The choice was also influenced by the fact that the study period included a considerable time during which patients were not receiving any therapy.

In this report we show that it is feasible to conduct a prospective QL-oriented study within a large, multicentre, multicultural clinical trial and present the impact of time, language and treatment groups on the QL scores.

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Members of the International Breast Cancer Study Group are listed in Appendix 1.
Part of this data was presented at Annual Meetings of the American Society of Clinical Oncology (ASCO), May 1990 and 1991.
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PATIENTS AND METHODS

The trials

In the ongoing International Breast Cancer Study Group (IBCSG) trials VI and VII, premenopausal and postmenopausal stage II breast cancer patients are randomised within 6 weeks of primary treatment. Eligibility criteria have been reported previously [1]. The objectives of the trial for premenopausal patients are to evaluate the efficacy of adding reintroduction chemotherapy to an initial course of adjuvant combination chemotherapy after a treatment-free interval, as compared with administering an initial course of adjuvant treatment alone, and to determine if three cycles of initial adjuvant chemotherapy are as effective as six cycles (trial VI). For postmenopausal patients the trial is designed to evaluate the efficacy of adding early combination chemotherapy and late reintroduction chemotherapy to adjuvant tamoxifen, as compared with administering tamoxifen alone (trial VII). The trial designs and the timing of the quality of life assessments are shown in Fig. 1. The participating institutions from ten countries are displayed in Appendix 1. Table 1 shows the languages used by the patients for completion of the QL form and the numbers of patients per treatment arm included in the main analysis.

The quality of life investigations

Timing of QL assessments. For evaluation of quality of life, serial assessments over time are necessary. Each patient is assessed at baseline (within 6 weeks of diagnosis) and then every 3 months for 2 years (i.e. beyond the duration of the longest chemotherapy treatment arm).

Selection of instruments. One of the most relevant determinants of QL is the coping process and its resulting adjustment influencing general well-being and psychological well-being,

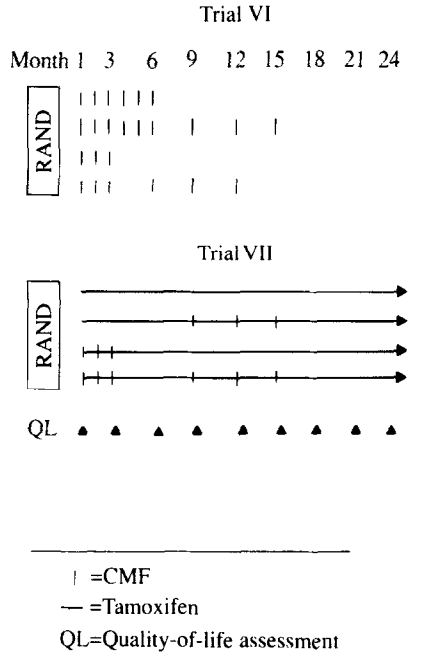

Fig. 1. Protocol designs for the IBCSG trial VI (premenopausal and perimenopausal patients) and trial VII (postmenopausal patients). QL assessments done at months 1, 3, 6, 9, 12, 15, 18, 21 and 24 after randomisation. Two additional assessments also done after relapse.

Table 1. *Patients with at least one quality of life form received by language, and patients included in the Multivariate Analysis of variance of PACIS**

At least one QL form	Premenopausal	Postmenopausal
English	143	70
Finnish	1	1
French	42	40
German	78	66
Greek	4	1
Italian	65	83
Slovenian	56	41
Spanish	8	1
Swedish	66	88
Total	463	391
Included in multivariate analysis of PACIS		
treatment		
A (6 mo CT)	37	--
B (6 mo + late CT)	38	--
C (3 mo CT)	34	--
D (3 mo + late CT)	45	--
E (TAM)	--	29
F (TAM + late CT)	--	19
G (TAM + early CT)	--	35
H (TAM + early + late CT)	--	28
Language		
English	80	30
Italian	27	39
Swedish	25	26
German	22	16
Total	154	111

* Requires all of the first four assessments available and four main languages only.
CT = chemotherapy, TAM = tamoxifen.

especially mood. The PACIS (perceived adjustment to chronic illness scale [2]) is a one-item scale comprising a global patient rating of the amount of effort it costs to cope with the illness. It is derived from a multi-item life event scale [3] and has been shown to be a reasonable indicator of coping in earlier studies [2, 4–8]. As indicators of side-effects of treatment and symptoms of the disease, one-item linear analogue self assessment scales (LASA) for physical well-being and appetite were chosen. LASA-scales have been repeatedly used and proven to be valid and reliable in breast cancer patients [9–12]. Emotional wellbeing/mood was assessed with one LASA and a specific, more precise standard scale, the Bf-S. This 28-item, one-dimensional adjective check-list is very sensitive to anxiety [13] and, especially, depression [13, 14]. It was initially developed by von Zerssen for serial assessments of mood in longitudinal psychopharmacological studies [15] and has become a standard measure for mood alterations in different clinical settings. It has been validated in German and French-speaking populations [16] and used in cancer patients [17, 18]. The five scales are incorporated in a two-page questionnaire for patient self-administration (available from C.H.). Sociodemographic data (living situation, education, employment status, and income level) was assessed by the treating physican using a simple classification. In a separate study [13] the four QL-indicators and the adjective checklist showed good concurrent validity against standard scales including FLIC [19], POMS [20] and HAD [21]. Acceptable test–retest reliability was established for the LASA-scales within 1 and 24 hours (0.66–0.80; [12]).

Crosscultural issues. Substantial differences in QL-responses might be expected across cultures, especially with different languages, and have to be considered in the evaluation of subjective treatment effects in a multinational trial. The instruments for this study were translated into 11 languages (English, German, Swedish, Slovenian, Italian, French, Spanish, Greek, Finnish, Danish and Norwegian) by professional translaters, carefully tested in the centres with patients by their physicians and adjusted with their feedback in order to assure not only linguistic, but also conceptual equivalence of the questionnaire. The relative frequency of languages used is displayed in Table 1.

Statistical analysis. The impact of time, treatment and language on QL variables was evaluated using a multivariate repeated measures analysis of variance (MANOVA) model [22] with SPSS-X [23]. The repeated measures MANOVA is a method for testing for differences among means when multiple observations are obtained from each subject. Tests of significance of any given factor are done controlling for all other factors in the model. Every patient must have measures at each point in order to fit the MANOVA model. The disadvantage is that cases with missing measurements at one or more time points must be dropped from the analyses. The advantage, however, is that comparisons across time are done using data from the same patient.

RESULTS

Compliance

The studies were started in July 1986. As of 30 June 1989, 1228 newly randomised patients have entered the studies. Of these, 854 (70%) had at least on evaluable QL form as of 1 November 1989. The analysis is based on QL data available at this date, including the first 9 months of adjuvant treatment. The actual, updated compliance is higher, at baseline 87% of

Table 2. Descriptive statistics on QL measures for the baseline assessment, by menopausal status

Measure	Menopausal status	n	Mean (S.D.)	Quartiles Q1	Median	Q3
BFS	Pre	375	16 (13)	6	13	25
	Post	331	16 (12)	7	14	22
PACIS	Pre	392	43 (28)	20	40	67
	Post	337	40 (27)	20	40	59
Physical	Pre	394	27 (24)	6	19	45
	Post	337	28 (24)	7	21	48
Mood	Pre	391	35 (27)	10	31	51
	Post	336	32 (25)	8	29	50
Appetite	Pre	395	22 (25)	3	11	36
	Post	337	24 (27)	3	10	38

the expected QL forms have been received. Over time the compliance drops continuously to 72% at month 9. It varies substantially from centre to centre, from 58–100% at baseline and 19–94% at month 9 (only centres with more than 30 patients included).

The study population with QL data was compared to the population without QL data. No difference in language distribution, sociodemographic and biomedical characteristics was observed. We can therefore consider the group with QL data representative for the whole study population.

The rate of missing and nonevaluable scores in completed QL forms ranged from 1–5% for the different measures, was constant over time, and highest for the Bf-S, the most complex scale.

Impact of time, language and treatment

Table 2 shows the mean, standard deviation, and quartile values of the five measures at baseline. The distributions of individual scores exhibit a large variability and are skewed toward low values (i.e. better QL) for all measures. The use of the square root transformation of scores for analysis effectively normalised the data as determined by residual probability plots. The results of the multivariate analyses for the first 9 months of the study are displayed in Table 3. Only the four most frequent language groups (English, Italian, German and Swedish) are included in this analysis because the smaller groups have too few cases to give reliable parameter estimates. As stated above, only cases with a QL form for all of the first four time points (months 1, 3, 6 and 9) are included. As this is a preliminary evaluation of an ongoing study, many patients have not been on study long enough to have all four assessments completed. The final analysis will include a much higher proportion of all patients. The number of patients included in the multivariate analysis of variance for the coping scale (PACIS) according to language, treatment and menopausal status is shown in Table 1.

Language is the factor which most influences the QL report for both premenopausal and postmenopausal patients. For premenopausal patients, the language effect is signifiant for the PACIS, physical wellbeing and mood. For postmenopausal patients the language effect is significant for the Bf-S, the PACIS and mood.

Follow-up interval (time) is also a significant factor for several of the QL measures. For both premenopausal and postmenopausal patients, PACIS significantly improves over time. In addition, improvements with time are significant for Bf-S and mood in postmenopausal patients. There are no significant interactions between language and time.

The language and time effects are illustrated in Fig. 2, which shows as an example the means for the PACIS scale by language and time. For both premenopausal and postmenopausal patients there is a general decline in scores over time, indicating that less effort is required to cope with the disease with time. The responses of the patients to the English scale are consistently lower than for other language scales for both premenopausal and postmenopausal women and the Italian scale yields responses that are higher for the premenopausal group. The pattern of scores across time is similar throughout, illustrating the absence of a language by time interaction. Thus, analyses of QL changes over time can be based upon data pooled across language.

Table 3. Significance levels (P values) of tests from repeated measures MANOVA of follow-up interval (time), treatment and language

	Bf-S wellbeing	PACIS coping scale	LASA physical wellbeing	LASA mood	LASA appetite
Premenopausal	(n=143)	(n=154)	(n=154)	(n=155)	(n=156)
Time	0.06	0.01	0.99	0.23	0.29
Treatment	0.50	0.68	0.05	0.16	0.13
Language	0.09	0.001	0.04	0.03	0.27
Treatment × time	0.89	0.57	0.91	0.96	0.06
Language × time	0.75	0.99	0.27	0.16	0.09
Language × treatment	0.94	0.94	0.65	0.61	0.71
Language × treatment × time	0.89	0.99	0.80	0.39	0.02
Postmenopausal	(n=107)	(n=111)	(n=115)	(n=113)	(n=117)
Time	0.001	0.02	0.15	0.04	0.18
Treatment	0.87	0.19	0.61	0.61	0.15
Language	0.001	0.001	0.24	0.004	0.67
Treatment × time	0.02	0.46	0.54	0.09	0.26
Language × time	0.85	0.24	0.48	0.44	0.87
Language × treatment	0.12	0.12	0.02	0.30	0.78
Language × treatment × time	0.21	0.26	0.31	0.15	0.81

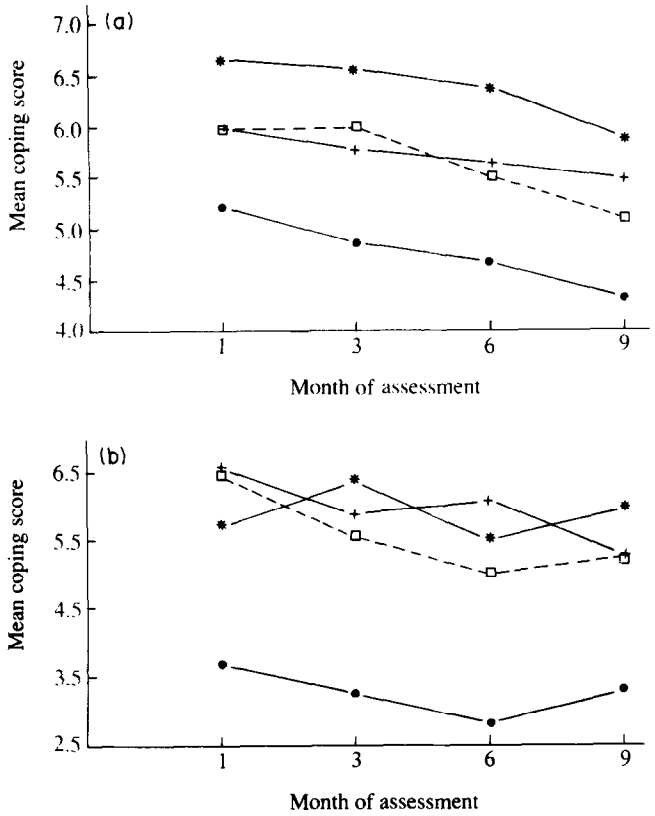

Fig. 2. Mean of the square roots of QL scores for the PACIS (coping) scale according to language for 154 premenopausal (a) and 111 postmenopausal (b) patients. -●- = English, + = German, * = Italian and -□- = Swedish.

The effect of treatment group is significant only for physical wellbeing in premenopausal patients. The treatment by time interaction is significant only for the Bf-S in postmenopausal patients. The other effects which are significant are the language by treatment interaction for physical wellbeing in postmenopausal women and the language by treatment by time interaction for appetite in premenopausal women (Table 3).

Figure 3 shows mean quality of life scores for the PACIS coping scale for the first four assessment times according to treatment assignment for the premenopausal patients. The closed symbols refer to time points at which the patients are receiving chemotherapy, while the open symbols indicate times when no chemotherapy is administered. At time points without chemotherapy, QL is improved. This pattern is representative of that seen for all five QL measures. Thus, while overall treatment differences are not statistically significant in the multivariate analyses, the measures are sensitive to the presence or absence of chemotherapy effects. Given the large variability in the measures (Table 2) a large number of cases would be required to achieve statistical significance. A sufficient number of cases will be available after additional follow-up of the patient cohort.

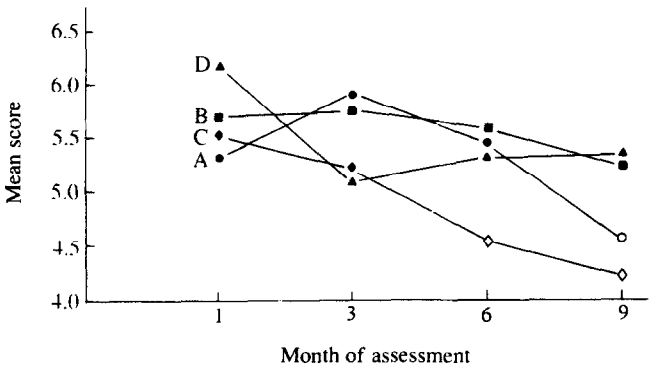

Fig. 3. Mean of the square roots of QL scores for the PACIS (coping) scale across time by treatment assignment for 154 premenopausal patients. Includes only patients with all four assessments and one of the four main languages. Filled sumbols denote chemotherapy delivered at the assessment, empty symbols denote no chemotherapy delivered at that assessment. A = 6 months chemotherapy, B = 6 months plus late chemotherapy, C = 3 months chemotherapy, D = 3 months plus late chemotherapy.

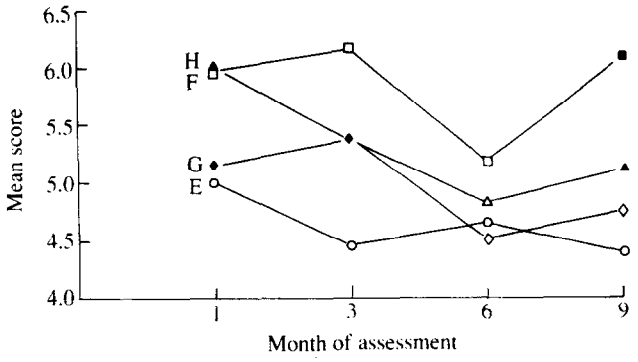

Fig. 4. Mean of the square root of QL scores for the PACIS (coping) scale across time by treatment assignment for 111 postmenopausal patients. Includes only patients with all four assessments and one of the four main languages. Filled symbols denote chemotherapy delivered at the assessment, empty symbols denote no chemotherapy delivered at that assessment. E = tamoxifen only, F = tamoxifen plus late chemotherapy, G = tamoxifen plus 3 months chemotherapy, H = tamoxifen plus 3 months and late chemotherapy.

Figure 4 shows the similar analyses of the PACIS scale for the postmenopausal patients. The open symbols represent times at which only tamoxifen (no chemotherapy) is administered. Although the variability among treatments is quite large with only 20–25 patients evaluable in each group, in most cases the tamoxifen-only group (treatment E) has the best quality of life scores. Furthermore, a worsening quality of life score is observed at 9 months for patients who receive late chemotherapy (treatments F and H). In the group without chemotherapy in the beginning (treatment F) the scores at the start of chemotherapy are reaching baseline levels reflecting the anticipatory anxiety of the patients. In several measures the scores of premenopausal patients who after 6 months of chemotherapy have to face reintroduction at 9 months increase substantially from baseline. This corresponds to the clinical experience of patients' difficulties with chemotherapy increasing with each cycle. To begin treatment again after a long negative experience and only a short break of 2 months may be more distressing than to begin with.

Several tests were done to address the question of whether or not dropping patients with one or more missing values for the first four timepoints introduced a bias. An ANOVA tested for a difference in the initial QL measures between those patients who had all four values and those patients who were missing at least one of the subsequent three values, controlling for language and treatment. None of the five measures showed a significant difference. Simultaneous pairwise t tests were done to test for differences between adjacent time points using all patients with

both adjacent measurements available. Results were consistent with the MANOVA results. To test for language and treatment differences, univariate one-way analyses of variance were done at each time point using all data available at each timepoint. Again, results were consistent with the MANOVA results.

DISCUSSION

In introducing subjective QL measures into a large international trial, two major problems were anticipated: compliance with the QL study and crosscultural or semantic differences in the perception of QL-related aspects. After 3 years of data collection, the results of our first evaluation are encouraging and allow preliminary analysis of treatment effects.

Our compliance rate compares favourably with other published studies [10, 24, 25] reflecting the long experience of the group in the logistics of data collection and the simple design of our measurement instrument. The assessment instrument in an international trial must be short, easily understandable and require a minimum of instructions. The fact that patients in our study were generally in good health may also contribute to a higher compliance than that obtained with sicker patients [24].

After the first 2 years of data collection a feasibility query was sent to the principal investigators at 20 centres (two centres did not yet participate). Fifteen (75%) responded. In 11 of these 15 centres a specific person, mostly a data-manager, was in charge of QL coordination. These were usually also the centres with the highest QL compliance. The person presenting the QL form to the patient was usually the treating oncologist.

In twelve centres, no special difficulties were reported in motivating the patients to participate in the study, but in one centre the staff felt that patients with heavy toxicity could not be bothered with forms and in one centre staff felt it difficult to motivate their patients. The most frequent problems encountered were related to language (especially with the Bf-S). Investigators also found it difficult to remember to give the follow-up forms to the patients.

The compliance during the first 3 years of data collection in the IBCSG trials VI/VII demonstrates that longitudinal assessment of QL is feasible and yields acceptable data, provided the instrument is compact and the cooperative group experienced.

Alternative instruments which might have been used in our study include the FLIC [19], the questionnaire by Selby *et al.* [26], the POMS [20], HAD [21] and the EORTC core questionnaire [27], but the need for simplicity led us to choose four aspects of quality of life which cover the physical state, the emotional state and the coping style of the patient. Social functioning was not taken into account as so far to our knowledge, there is no appropriate indicator for our purpose. Furthermore, we established the concurrent validity of our simple measures against some of these longer scales in a separate study [13]. Since many patient groups were not receiving treatment during a substantial period of the study, our assessment focussed on adjustment and wellbeing, with less emphasis on specific treatment side-effects. LASA-scales have been tested in different clinical settings as reliable and valid, but relatively rough indicators of subjective states [28]. The relative benefit of an additional more sophisticated standard wellbeing scale (Bf-S) cannot yet be estimated in this analysis. Although the advantages of standard scales are clear cut (psychometric properties, normative data, internal reference scale) the disadvantages due to impaired feasibility have to be taken into account.

Multivariate analysis of QL data has shown time from diagnosis and language to be important determinants of the five measured variables (Bf-S, PACIS, LASA-mood, LASA-physical well-being, LASA-appetite). The impact of time and language exceeds the impact of the different treatment modalities. Nevertheless some interesting treatment effects have been observed. First, contrary to intuitive prediction, no substantial deterioration in QL was seen during initial cytotoxic therapy. This is of major importance in applying our data to the evaulation of the cost–benefit balance of such therapy. The differences observed with subsequent reintroduction therapy both demonstrate the sensitivity of the QL measures and shed light on the different costs associated with the treatments being compared.

The significance tests for treatment effects done in this preliminary analysis address only the questions of whether or not the average scores across all time points are the same for all treatments (the test for the treatment effect), and whether or not the overall pattern of means across time are the same for all treatments (the test for a treatment by time interaction). With further follow-up more specific hypotheses can be tested; for example, in trial VI, we could ask whether the quality of life during the follow-up time during which patients are receiving no chemotherapy is the same for patients who have received three cycles of adjuvant chemotherapy as for those who have received six cycles.

The coping process and its resulting adaptation have been extensively studied in the last 20 years and different theoretical models have been proposed. On one point all the theories agree: time is an essential determinant of the coping process and adaptation. All of our measures are sensitive to time. Over 9 months after diagnosis and initial treatment psychological wellbeing, mood, physical wellbeing and appetite are gradually improving; the perceived effort to cope as measured by the PACIS is decreasing. The plausible pattern of change over time supports the capacity of the measures to validly assess some relevant aspect of adaptation.

So far, little attention has been paid to crosscultural problems in QL research in oncology. In the field study of the EORTC core questionnaire comparing groups of cultures, i.e. southern versus northern European countries, no differences of the psychometric properties of the instrument were found, except for the Japanese [29]. Hence, this is the first time that substantial differences of mean QL scores among language groups are reported. Our results probably reflect true cultural differences and not merely a translation artefact, because with few exceptions the pattern of differences is consistent across instruments and time points, English-speaking patients showing lowest, German and Swedish intermediate and Italian highest mean values. This pattern fits the notion of northern people being more reserved and complaining less than southerners. Crosscultural issues are of importance in international clinical trials, especially in Europe, and have to be investigated in more depth.

There are no consistent differences among the language groups in the pattern of change over time. The PACIS again shows significant differences of mean values for the different languages and, within language groups, significant changes over time, confirming previous studies indicating that this simple scale is a sensitive indicator for the assessment of the patient's perception of coping.

In this analysis, there are relatively few assessments available in each of the eight treatment groups. Nevertheless, the average scores reported by patients were better when they were not receiving chemotherapy than when they were receiving treatment. The current analysis also includes only those patients who

have all of the first four assessments, excluding those who experienced a relapse within this time period. Adjustments will be required for future analyses as a less toxic but less effective treatment will have more drop-outs. Intra-individual changes over time for which the patient acts as her own control will be used as additional information becomes available from the quality of life investigations being conducted by the group.

Evaluation of the prognostic significance of QL-scores in the present trials must await more prolonged follow-up of the conventional endpoints. A theoretical framework for such analysis is presented elsewhere [30].

Disease-free survival (DFS) and overall survival (OS) can no longer be considered the only appropriate endpoints in the evaluation of adjuvant treatment for breast cancer. Because the potential benefits in terms of prolongation of DFS and OS must be balanced against the toxicity of treatment, our group has proposed two new quality of life oriented endpoints: TWiST (time without symptoms and toxicity) and Q-TWiST (quality-adjusted survival) [31–33]. Both of these endpoints can be applied retrospectively to studies in which QL has not been measured. However, TWiST and Q-TWiST both involve arbitrary physician judgments. In the current trial we decided to introduce prospective QL assessment by the patients in order to integrate their subjective experience into treatment evaluation [34].

The IBCSG studies aim to develop an integrated model of adjuvant treatment evaluation incorporating the traditional treatment endpoints, the toxicity and disease variables rated by physicians, and subjective wellbeing rated by the patients themselves. This model of evaluation of clinical trials will allow the clinician to better adapt the treatment to the needs of the individual patient.

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APPENDIX

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