QUALITY OF LIFE ASSESSMENT IN INTERNATIONAL BREAST CANCER STUDY GROUP (IBCSG) TRIALS: PRACTICAL ISSUES AND FACTORS ASSOCIATED WITH MISSING DATA

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SUMMARY

We report on our experience of quality of life (QL) assessment in adjuvant clinical trials of the International Breast Cancer Study Group (IBCSG), with special emphasis on cultural and logistical aspects of international organization that are unique to this group. Data are presented regarding submission rates of assessments before and after treatment failure, and timing of assessments relative to chemotherapy administration. To identify areas where rates might be improved, we investigated the association between missing data and sociodemographic and biomedical factors, treatment assignment, institution, chemotherapy compliance and toxicity in a trial of adjuvant chemoendocrine therapy for post-menopausal patients with breast cancer (IBCSG VII). The factors most highly associated with missing data were institution and chemotherapy compliance.

INTRODUCTION

The International Breast Cancer Study Group (IBCSG) conducts large-scale phase III trials to evaluate adjuvant therapies for patients with operable breast cancer (chemotherapy, endocrine

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therapy, and their combinations). The group is currently composed of 30 main centres in 10 countries. Many of the main centres collaborate with affiliated smaller hospitals, clinics and private practices. At each main centre there is a principal investigator and data manager responsible for the protocol adherence and the organization of all data collection. The central co-ordination office is located in Bern, Switzerland. The central data management is performed in Amherst, New York, U.S.A. The statistical centre is located in Boston, Massachusetts, U.S.A.

The IBCSG began studying quality of life (QL) issues in 1986. The first trials incorporating QL enrolled patients with node-positive breast cancer.¹ There are two global hypotheses investigated in IBCSG QL trials: (i) QL of the patients is different for different treatment arms within each trial; (ii) the level of early coping/well-being and social support of the patient can be used as a prognostic indicator of outcome. In addition, a quality adjusted survival analysis is used to compare treatments with respect to overall and disease-free survival, adjusted for the preferences of patients for various clinical health states.²

For practicality, the QL form used in the first IBCSG trials incorporating QL assessment (trials VI–IX) was restricted to two pages.³ Four single-item linear analogue self-assessment (LASA) scales⁴–⁶ were developed as short indicators of components of QL: physical well-being; mood; appetite, and perceived adjustment (PACIS).⁷ As a reference scale, a 28-item adjective checklist for emotional well-being (Bf-S) was also included in these trials.⁸

The QL form was devised for the more recent trials with QL assessment (trials 10-93 to 14-93), which were activated in 1993. The revised form is designed to address the endpoints more specifically while still keeping it short and practical for the international setting. It consists of a one-page ‘core’ form which includes the four LASA scales from the original (1986) version, plus six additional single-item indicators also in the LASA format. The multi-item reference scale was discontinued based on findings that the mood LASA scale was very efficient at detecting changes in mood and easier to complete.⁹ The revised QL form was substituted for the original version for all ongoing trials. In addition, we use QL ‘modules’ to address other specific questions in some trials.

DATA COLLECTION AND MANAGEMENT

Practical guidelines and strategies

The IBCSG has adopted special procedures to achieve good compliance and data quality. Our practical guidelines are summarized in Table I.¹⁰,¹¹ Many of these also apply to trials within a single country, but they are especially important within a multi-centre international trial.

A key problem is that the logistics for managing patient care differ widely among institutions. For example, in some institutions patient care following completion of chemotherapy is provided by the oncologists, while in other institutions it is provided by general practitioners or gynaecologists. Since QL is assessed within clinical routine, our central data management staff have had to design procedures that are flexible enough to accommodate many local variations.

We have found it essential to have one person in each local institution responsible for co-ordination of QL assessment and for communication both within the local institution and with the central data managers and the study co-ordinator. This person generally is responsible for non-QL aspects of the trials as well.
Table I. Practical guidelines of the IBCSG for QL assessment in large-scale international cancer clinical trials

**Study design and protocol development**
Quality of life assessment as an integral part of the trial, not optional; objectives, methods and guidelines explicitly stated in the protocol
Consultation with all study participants during protocol development, including with patients in pilot phase

**Central data management**
Central study co-ordinator with regular, ongoing contact with responsible local co-ordinators; individualized feedback complementing regular standardized feedback across all institutions
At the time of randomization, notification of all required assessment dates to the local data managers and later on a regular basis by prospective reminder
Reminding the physician at randomization to have the patient fill in the baseline questionnaire
Joint organization of management of quality of life data and biomedical data
Promotion of exchange of experience across institutions by annual group meeting
Training of the local data managers concerning goals and methodology of the study and of the need for a standardized data collection setting
Feedback to institutions about evolution of the study (compliance, preliminary results) on a regular basis (group meetings, newsletter, site report)

**Institution**
Support by the head of the department by providing time and space for quality of life assessments
Avoiding patient selection for quality of life assessment (for example, by socio-economic status, or exclusion of patients from a distant satellite clinic)
One responsible person for local co-ordination of data collection and management who is fluent in the language in which the study is being conducted

**Local data management**
Information to the patient about goals of the study and need for completion of the questionnaire
Assistance to the patient in questionnaire completion (as much as necessary, as little as possible)
Clarification of misunderstandings (for example, questionnaire not a psychodiagnostic tool, or a substitute for physician–patient interview)
Explanation of reasons for repetitive assessments and motivation of the patient

**Questionnaire (self-rating)**
Simple self-explanatory instruction
One page ‘core’ questionnaire, short enough to be filled in within routine clinical visit
Complementary modules for selected trials only, and including no more than one additional page
Uniform response format (LASA)

Modified from Húrny et al.\textsuperscript{10} and Bernhard et al.\textsuperscript{11}

Adequate training of the data managers in the local institutions is crucial. Staff that are well informed about how to approach a patient with a QL form and understand the goals of the QL research can better encourage patient participation. A QL manual has been developed which explains the importance of data quality and provides some practical help for clinical staff in their contact with patients. Because accrual and follow-up in these trials takes many years, changes in local staff are likely to occur and staff education is a continuous process.

To aid the local data managers in planning clinical visits, we developed a ‘Patient Clinical Visits and QL Assessment Schedule’, which is sent to the local centre at the time the patient is randomized and is to be incorporated into the patient file. This schedule lists the dates of all...
required QL assessments for a given patient and reminds clinical staff of the documentation required. However, because there may be delays in the administration of chemotherapy, it does not always reflect the actual patient situation. A future goal is to develop data management tools that can be updated individually by the local data managers.

Frequent and effective communication and feedback between the central data management office and the local data managers is critical for quality monitoring and supervision. It is essential that the central data management office monitors QL compliance within the participating centres and gives relevant feedback. We recently developed individual centre site reports to inform centres on a regular basis of their current submission rates and the accuracy of QL assessment timing. These are complemented by prospective reminders informing centres in advance of upcoming QL assessments which must be scheduled. These measures have been recently implemented and their impact is currently being evaluated.

SUBMISSION RATES AND ACCURACY OF TIMING OF ASSESSMENTS

At present, most IBCSG trials require a baseline QL assessment on day 1 of adjuvant therapy (chemotherapy and/or endocrine therapy), and subsequently every 3 months during the first year and every 6 months during the second year. Since 1995, assessments are also required annually during years 3 to 6 of patient follow-up. The assessment schedule differs slightly from this in some trials. During chemotherapy, assessments are required on the first day of specified cycles, before the patient receives her chemotherapy. The assessment schedule changes following treatment failure, when assessments are required within one month of treatment failure and at six months after failure.

Pre-failure submission rates

Figure 1 shows the total number of required pre-failure QL assessments during the first 2 years following randomization and the number completed according to year across all closed and ongoing IBCSG trials. ‘Required form’ is defined as any QL form required of any randomized patient (that is, including patients with language problems) according to the assessment schedule in the protocol. The number of assessments has increased steadily since we started assessing QL in 1986, except for a drop in 1993 with the commencement of the present generation of trials.

Table II shows QL submission rates at baseline and during the first 2 years of follow-up, at time points when patients are assigned to receive chemotherapy and at time points when patients are not assigned to receive chemotherapy according to year. Submission rates are highest at baseline and they are higher at time points when patients are to receive chemotherapy than when they are not to receive chemotherapy. Overall, the QL pre-failure submission rates have improved over the past 7 years. However, this tendency is not consistent across institutions; some show a substantial improvement, others a deterioration (data not shown). There is considerable variation among the 30 institutions in all trials, providing a possibility for improvement. For example, the current submission rates after completing chemotherapy vary between 13 and 100 per cent in the first 24 months. There is strong evidence that the main factors affecting submission rates are site specific. In particular, the commitment of the local principal investigator has been found to be a key factor.
Figure 1. Number of pre-failure QL assessments required across all IBCSG trials during the first 2 years from randomization and number completed according to year

Table II. Number of QL assessments required (N) and per cent completed* (%) at baseline, on and off chemotherapy (first 2 years) according to year in trials VI to IX and 10-93 to 14-93

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<td>During follow-up</td>
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<tr>
<td>on chemotherapy</td>
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<td>83</td>
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<tr>
<td>off chemotherapy</td>
<td>4929</td>
<td>73</td>
<td>1953</td>
<td>76</td>
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<td>78</td>
</tr>
<tr>
<td></td>
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<td>70</td>
<td>5967</td>
<td>71</td>
<td>6722</td>
<td>72</td>
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</tbody>
</table>

* Forms received by co-ordinating centre by 5 September 1996, across 30 main institutions

Pre-surgery assessment

One particular IBCSG trial has represented a special challenge. This trial (trial 10-93) investigates surgical therapy with or without axillary node clearance for breast cancer in older women (≥60 years old). All patients receive adjuvant therapy with Tamoxifen following surgery. QL is a primary endpoint for this trial, and both the ‘core’ form and a trial-specific ‘module’ form are used to record patients’ subjective experience. The baseline QL assessment is scheduled before primary surgery, which is different from the routine in other IBCSG trials. The submission rates of the baseline form have been lower due to this requirement. As of February 1996, compliance is 67 per cent, with a range of 60 to 100 per cent among the participating institutions with at least 15
patients. In comparison, in this trial we have received 70 per cent of the QL forms required within 1 month after surgery and 76 per cent of the follow-up forms between months 3 and 18. Patients’ advanced age may further affect form submission. Because of the poor compliance, the IBCSG decided in 1997 to require completion of the baseline QL form as an eligibility requirement for randomization.

**Post-failure submission rates**

Assessing QL data after treatment failure represents another challenge. Overall, across all IBCSG trials the QL *post-failure* submission rates have been substantially deteriorating over the past 9 years, from 51 per cent to less than 40 per cent across all centres. This is due in part to the simpler logistics for collecting QL data after treatment failures that occur early compared with those that occur years later. Patients who recur may not be seen by the IBCSG participating centre because they are being followed by their family doctors or at other health facilities not connected with the IBCSG. Medical staff in these situations may not be aware of the details of protocol requirements. Not surprisingly, the submission rate for the second post-failure QL form (six months after failure) is higher than for the first one (within 1 month after failure). Centres appear to have more time to organize the data collection at 6 months and can plan in advance. As a consequence of this problem, the IBCSG in 1996 changed the post-failure QL assessment schedule, requiring assessments on the same schedule for all patients, without regard to disease status.

**Timing of quality of life assessment**

In the first generation of IBCSG trials with QL assessment (trials VI to IX) we observed more difficulties with correct timing than anticipated. During the time patients are receiving chemotherapy, QL assessments are to be done on the first day of cycles, before the patient receives her chemotherapy. In trials VI and VII, where patients received a combination of Cyclophosphamide, Methotrexate and 5-fluorouracil (CMF), the percentage of assessments done on the first day of CMF cycles ranged from 27 to 61 per cent among the various time points and treatment arms.

Over the years, the timing of QL assessment has substantially improved. Steps to improve awareness and sensitivity to proper QL assessment timing have been stressed at all data management continuing education sessions by discussing observed cases. In trials VIII and IX, 52 per cent of the assessments between 1988 and 1993 were done on the first day of CMF cycles, compared with 67 per cent between 1994 and February 1996. In the trials which started in 1993, where some patients receive an anthracycline (Doxorubicin or Epirubicin) plus Cyclophosphamide (AC) in addition to CMF, timing has improved further, with 75 per cent of all assessments on the first day of the cycle.

Analysis of baseline QL scores has shown that exact timing of QL assessment is important. In trials VI and VII, scores on assessments done either before or after day 1 of CMF can differ substantially from those done on day 1.12 In a subsequent analysis, timing of QL forms has been shown to have an effect on patient self-estimation also at month 3 in patients receiving CMF.13 It has to be assumed that timing at later time points or in relation to other drugs similarly affect the QL scores at chemotherapy cycles and possibly within treatment gaps (that is, interruptions between two cycles).

FACTORS AFFECTING PRE-FAILURE COMPLIANCE

To investigate the relative importance of various factors in predicting QL submission rates prior to treatment failure, we did an in-depth analysis of IBCSG trial VII. This trial was conducted between July 1986 and April 1993, and enrolled 1212 eligible post-menopausal patients with node-positive operable breast cancer from 9 countries on 3 continents. All patients received Tamoxifen daily for 5 years. Tamoxifen alone was compared with chemoendocrine therapy adding 3 early cycles of CMF, 3 delayed single CMF cycles at 3-month intervals, or both early and delayed CMF. Clinical details of the trial are presented elsewhere and the QL endpoints are described by Hürny et al.

QL forms were completed in 7 major languages. QL indicators were to be assessed on day 1 of cycles 1 and 3 of early CMF, on day 1 of each cycle of delayed CMF, and at intervals of 3 months while not receiving CMF, to 2 years following randomization. We examined QL submission rates for the first 18 months, by which time all patients had completed protocol chemotherapy. The 15 per cent of the patients who had a recurrence during the first 18 months on study have been excluded, leaving 1025 included in this analysis.

The factors which we investigated for their relationship with forms submission included institution, treatment-related factors and patient-related factors. Treatment-related factors included whether or not the patient was assigned to receive early and/or delayed chemotherapy, whether or not she completed her full assigned course of chemotherapy, and degree of toxicity, ranging from 0 for none to 4 for life threatening. Patient-related factors included sociodemographic factors (marital status, living situation, education level, income and professional position), disease-related factors (oestrogen and progesterone receptor status, tumour size, number of positive nodes and type of surgery) and other biomedical factors (age, presence of concurrent chronic disease and performance status).

Forward stepwise logistic regression with an entry significance level of 0.05 was used to examine the relative importance of various factors in predicting QL form submission and to investigate the multivariate relationships. A separate model was fit for each of the 7 assessment time points. For the analysis of effects across the entire trial, all factors were eligible for entry, including institution, with each of the 7 major institutions eligible for entry into the model separately and the remaining institutions pooled as the reference group. In a second step, the institution variables were forced into the models, and all other factors were analysed. To examine differences among institutions, stepwise logistic models were fit at each assessment time point for each of the 7 largest institutions.

Forms submission across all institutions

Institution was the most important predictor of forms submission. In the stepwise logistic regression procedures, at each time point an institution was the first variable to enter the model. Table III shows submission rates across the first 7 assessments (18 months) for all 21 institutions that participated in IBCSG trial VII, listed according to number of patients. The submission rate across all 21 institutions was 75 per cent. The rates for the institutions which contributed at least 50 patients to the analysis ranged from 40 per cent to 85 per cent.

After controlling for institution, the most important predictor of forms submission was whether or not the patient completed her full assigned course of chemotherapy. At each time point, including baseline, this was the first factor to enter the logistic regression model after controlling.
Table III. QL form submission rates for first 18 months of study according to institution for 1025 patients in IBCSG trial VII who did not recur within 18 months

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>QL form submission rates, %</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>216</td>
<td>79</td>
</tr>
<tr>
<td>B</td>
<td>111</td>
<td>40</td>
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<tr>
<td>C</td>
<td>103</td>
<td>80</td>
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<tr>
<td>D</td>
<td>90</td>
<td>82</td>
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<tr>
<td>E</td>
<td>72</td>
<td>85</td>
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<tr>
<td>F</td>
<td>62</td>
<td>94</td>
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<tr>
<td>G</td>
<td>57</td>
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<td>H</td>
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<td>I</td>
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<td>K</td>
<td>28</td>
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<tr>
<td>L</td>
<td>25</td>
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<td>M</td>
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<td>U</td>
<td>6</td>
<td>50</td>
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<tr>
<td>Total</td>
<td>1025</td>
<td>75</td>
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</table>

for institution. Twelve per cent of the patients assigned to receive chemotherapy did not receive the full course. The most frequent reason for stopping therapy early was patient refusal. Patients who completed the full course of chemotherapy were more likely to complete their QL assessments; the rates ranged from a difference of 85 per cent versus 70 per cent at baseline to 76 per cent versus 45 per cent at 18 months.

Factors affecting compliance within institutions

Because submission rates varied so much across institutions, we investigated rates within each of the 7 largest institutions to determine whether the factors associated with submission rates differed among institutions. Sixty-nine per cent of the patients in this analysis were enrolled from these 7 centres and each of them contributed at least 50 patients.

Table IV lists the factors which entered each of the logistic regression models, listed in the order in which they entered. In 3 of the 7 institutions (C, D and E), stopping chemotherapy early is the most important factor, just as it is the most important factor (after institution) in the overall analysis. However, it is not the most important factor within either of the two institutions with the
Table IV. Summary of stepwise logistic regression for each of the 7 largest institutions

<table>
<thead>
<tr>
<th>Month</th>
<th>Institution (QL form submission rate)</th>
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<tbody>
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<td>A (79%)</td>
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<tr>
<td>Baseline</td>
<td>tox</td>
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<td>3</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td># + nodes</td>
</tr>
<tr>
<td>12</td>
<td>—</td>
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<tr>
<td>15</td>
<td>—</td>
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<tr>
<td>18</td>
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</table>

# + nodes: number of positive nodes  
age: age at randomization  
delayed CT: assigned to receive delayed chemotherapy  
chronic dis: concomitant chronic disease present  
early CT: assigned to receive early chemotherapy  
educ: education  
ER: oestrogen receptor status (positive/negative)  
income: income level  
stop CT: patient did not receive full course of assigned chemotherapy  
tox: toxicity during chemotherapy  
tumour size: ≤2cm versus >2cm

lowest QL submission rates (institutions B and F). In institution B the primary factor associated with forms completion is whether or not the patient is assigned to receive chemotherapy at the given timepoint. QL assessments are more likely to be completed by the patients who are coming in for chemotherapy than by those patients who are not. For example, during the time period when delayed chemotherapy is administered (months 9 to 15), the patients assigned to receive delayed chemotherapy completed 48 per cent of their QL assessments compared with 19 per cent for the patients not assigned to receive delayed chemotherapy. In institution F, the other institution with a low QL submission rate, toxicity is the primary factor associated with compliance. The worse the toxicity, the better the forms completion. In the two remaining institutions (A and G) there are no factors consistently associated with QL forms submission across the 18 months.
The IBCSG has shown that good pre-failure submission rates for QL data are feasible in a multi-cultural, international setting. Submission rates with post-failure assessments and exact timing in collecting QL data require improvement. The IBCSG recently introduced several changes in an effort to improve submission rates. Starting in 1996, QL assessments are required on the same schedule for all patients, without regard to disease status. In addition, centres periodically receive lists of all upcoming required QL assessments and three times a year receive summary reports on their submission rates and timing.

To identify areas where rates might be improved, we investigated factors associated with missing forms prior to treatment failure in IBCSG trial VII. In this trial, institution is the factor most highly associated with QL form submission rates. Differences among institutions might in part be explained by cultural differences. Filling in forms is quite possibly something that some cultures are more accepting of than others. However, factors associated with missing forms varied among institutions. In the analysis of institutions with at least 50 patients (7 institutions), within the two institutions with low submission rates, the major factors appear to be logistical. In one of these institutions, patients who are assigned to receive CMF at a given time point are more likely to complete assessments. In the other patients who have high toxicity are more likely to complete assessments. One possible explanation for this is that submission rates might be associated with the level of interaction with clinic staff. The more attention a patient receives from the medical staff, the more likely she will to be asked to complete a QL form. On the other hand, the missing QL assessment could be a marker for incomplete toxicity information; the same patients who are not willing to provide the QL information may also not be telling their physicians about their toxicity.

In those institutions with higher submission rates, missing forms are more likely explained by the degree to which a patient is willing and able to participate. The primary factor associated with missing QL data in 3 of 5 of these institutions is whether or not the patient completed the assigned course of chemotherapy. In these cases the patient is probably both refusing chemotherapy and refusing to complete the QL form. It is noteworthy that chemotherapy compliance is associated with QL compliance even at baseline, suggesting that ‘compliers are compliers.’

The factors associated with QL compliance in the IBCSG trial VII study are not very useful for adjustments in analytic models. The randomization was stratified according to institution, minimizing the potential bias in QL estimates associated with this most important compliance factor. Other QL non compliance factors such as chemotherapy non compliance and low levels of toxicity are not very prevalent across the study cohort and are, therefore, not likely to have a large effect on model adjustments. Fairclough et al.\(^1\) explore the usefulness of various approaches to the analysis of the QL data collected in IBCSG trial VII. They describe the different QL estimates that can be obtained from a variety of model-based methods (including covariates) and compare the results to the complete case and all available data estimates. The estimates from the model-based methods are quite close to the all available data estimates, indicating that the incorporation of covariate information is not useful in this case. Because analytic methods require assumptions on the missing data mechanism, and the validity of these assumptions cannot always be adequately tested, the best approach to the missing data problem is to implement procedures to reduce the risk of missing data in cancer clinical trials.
APPENDIX: INTERNATIONAL BREAST CANCER STUDY GROUP, PARTICIPANTS AND AUTHORS TRIALS VI TO IX AND 10 TO 14-93

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