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IMPUTING QOL SCORES IN SURVIVAL ANALYSIS

**Imputing Missing Quality of Life Data as Covariate in Survival Analysis of
the International Breast Cancer Study Group Trials VI and VII**

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Abstract

Quality of life (QoL) was an important endpoint in the adjuvant breast cancer trials International Breast Cancer Study Group (IBCSG) Trial VI and VII. Here, QoL was considered as a time-dependent effect. The hypothesis explored is that poorer QoL throughout the trial is associated with poorer disease-free survival (DFS) and vice-versa. Potential bias in the parameter estimates is an important concern associated with missing observations. Standard simple and multiple imputation methods were applied to missing QoL assessments before analysis in a time-dependent Cox model. There was no evidence that the patient's QoL is related to the patient's DFS.

Keywords

quality of life; time-dependent Cox model; potential bias; simple imputation; multiple imputation; informative missing data

1. Introduction

Clinical judgment of treatment regimens for breast cancer is based on balancing efficacy with adverse effects. It is usual that the main treatment comparisons in breast cancer clinical trials are based on disease-free survival (DFS) and overall survival (OS). Traditional endpoints such as these do not reflect the patient's sense of well-being and thus it is becoming increasingly common for quality of life to be assessed throughout the study (Fairclough 2010, p.1).

The patient's ability to carry out day to day activities and how the patient feels will influence the patient's perception of whether a treatment is beneficial and the patient's perception of his or her health (Fairclough 2010, p.1). However, these factors are not reflected in traditional endpoints of efficacy and increasingly endpoints which address the patient's perception of his or her health are included in clinical trials. The question of whether good quality of life is associated with good prognosis is of clinical interest in breast cancer clinical trials (e.g. Epplein et al. 2011; Kenne Sarenmalm et al. 2009; Coates et al. 2000).

The potential problems associated with missing observations, such as missing quality of life assessments, include bias of the parameter estimates and loss of power to detect clinically important differences among treatment groups over time (Fairclough 2010, chapter 6; Little and Rubin 2002, chapter 1 and 3). Methods for dealing with analysis of data with missing observations, such as imputation-based procedures, where the missing values are filled-in and the completed data are analysed by standard methods, have been proposed in the statistical literature (e.g. Rubin 1987; Little and Rubin 2002; Molenberghs and Kenwood 2007).

Here, standard imputation methods were applied to missing quality of life assessments before analysis in a time-dependent Cox model (referring to a Cox proportional hazards model with a

time-dependent explanatory variable). The hypothesis explored is that poorer quality of life throughout the trial is associated with poorer DFS and conversely better quality of life throughout the trial is associated with better DFS. The influence of missing data on explanatory variables in time-dependent Cox model analysis is explored by imputing missing quality of life scores by standard imputation methods before analysis of DFS. The performance of the standard imputation methods is considered by comparing the parameter estimates for quality of life and corresponding standard errors. In exploring the hypothesis that quality of life is related to DFS, it may be of interest to consider prognostic factors in breast cancer as covariates. An expanded time-dependent Cox model based on Herring et al. (2004) was also considered for postmenopausal patients (Trial VII).

2. Patients and Methods

2.1. IBCSG Trial VI and VII

Summary of IBCSG Trial VI and VII

IBCSG Trial VI was designed to examine different durations and timing of adjuvant chemotherapy in premenopausal and perimenopausal patients. The trial schema is shown in Figure 1. In postmenopausal patients, tamoxifen alone or together with different durations and timing of chemotherapy was compared in IBCSG Trial VII. Between July 1986 and April 1993, 1554 premenopausal and perimenopausal patients were randomized to Trial VI and during the same time period 1266 postmenopausal patients were randomized to Trial VII. Data on patient's self-assessed quality of life were prospectively collected throughout the study. Baseline quality of life was assessed on, or as close as possible to, the first day of adjuvant therapy. Quality of life was recorded approximately 3 months after randomization, then every 3 months until 24 months

or recurrence, and again at 1 and 6 months after recurrence. The status of coping scores over time is summarized in Table 1.

Statistical Analysis of Quality of Life in IBCSG Trial VI and VII

Hürny et al. (1996) found that between baseline and 18 months, there was a significant improvement of quality of life over time. There was a significant adverse impact of delayed chemotherapy on all quality of life measures. Of note, Hürny et al. (1996) suggested that the patient's quality of life described by the coping score may be related to anticipation of future chemotherapy. This implies that the missing coping scores are likely to be informative missing data. Previous work by Coates et al. (2000) indicated that in the IBCSG dataset DFS was not significantly predicted by quality of life scores at baseline or month 18, or by changes in quality of life score between baseline and months 3 or 18. However, Herring et al. (2004) indicated that poor baseline quality of life was associated with improved prognosis in postmenopausal patients. This may reflect the fact that chemotherapy treatment is fairly toxic.

The further analysis of quality of life in Trial VI and VII reported here explored the hypothesis that the patient's quality of life as measured by coping score was related to the patient's DFS. The linear analogue scale ('How much effort does it cost you to cope with your illness') ranged from 0 ('no effort at all') to 100 ('a great deal of effort'). Standard imputation methods are applied to impute the missing coping scores in the IBCSG dataset. The square root of the coping score (S_{Pacis}) together with an indicator for delayed chemotherapy is used in a time dependent Cox model for DFS. The high proportion of missing coping scores (Table 1) and findings from previous statistical analysis of quality of life indicated that imputation is appropriate. Time-dependent Cox model analyses without imputation was carried out to provide parameter

estimates for reference and illustrative purposes (Table S2; online appendix only). Schoenfeld residuals against time were plotted for the explanatory variables in this time-dependent Cox model analysis (Figure S1; online appendix only). The dataset for the analysis of all available coping scores contains patients with a monotone missing data pattern and patients with intermittent missing coping scores. The time-dependent Cox model analysis of all available coping scores considered 2544 patients. An expanded time-dependent Cox model analysis based on Herring et al. (2004), which consider prognostic factors in breast cancer as covariates, was also performed on the postmenopausal patients (Trial VII) (Table 3).

Parameters in the Time Dependent Cox Model

The statistical analysis of efficacy (The International Breast Cancer Group 1996; The International Breast Cancer Group 1997) and previous statistical analysis of quality of life by Herring et al. (2004) suggested also including an indicator for sufficient early chemotherapy and estrogen positive receptor status in the time dependent Cox model. Sufficient early chemotherapy was defined as 6 initial cycles of CMF in Trial VI and 3 initial cycles of CMF in Trial VII. This was not done in the analyses reported here to keep the model parsimonious and for ease of comparison of the standard imputation methods.

Parameters in the Expanded Time Dependent Cox Model for Postmenopausal Patients (Trial VII)

The expanded time-dependent Cox model analysis for postmenopausal patients included the covariates and interaction terms considered by Herring et al (2004). The treatment covariates are coded so that women who took tamoxifen only are the reference group. Interaction terms for treatment and age and interaction terms for treatment and estrogen receptor status were

considered. As in Herring et al. (2004), the original coping score was reversed so that higher coping scores indicated higher quality of life. However, as the full IBCSG Trial VII dataset is used, instead of an indicator for whether the patient's primary language is German, 9 language/culture groups were defined. The reference language/culture group is German/Germany and Switzerland.

Standard Imputation Methods

The standard simple imputation methods applied to the IBCSG dataset were:

- i) LOCF
- ii) median imputation by patient
- iii) linear regression with previous coping score(s)

Fifty repetitions of standard multiple imputation methods were performed. The standard multiple imputation methods applied to the IBCSG dataset were:

- i) bootstrapping: subgroups defined by baseline coping score or previous coping score
- ii) nearest neighbor imputation
- iii) predictive mean matching
- iv) pattern mixture models – Curran's analytical technique

2.2. Technical Details of Standard Imputation Methods

As noted, there were 2687 patients randomized to Trial VI and VII. However, some patients could not be considered in the time-dependent Cox model analysis following standard imputation methods. The 456 patients with a missing baseline coping score (approximately randomization) were only considered in the time-dependent Cox model analysis after median imputation by patient.

When considering the remaining standard imputation methods, 15 patients where using the expected dates of assessment for missing coping scores led to intervals of less than 1 day for the time-dependent Cox model analysis were not considered. The corresponding number was 18 patients when considering median imputation by patient. The status of the coping scores considered for time-dependent Cox model analysis at each time point considered is summarized in Table S1 (online appendix only).

When considering multiple imputation methods, calculations during the imputation by the MI procedure in SAS were based on standardised values of S_Pacis. Further details on implementing the standard imputation techniques are described below.

Bootstrapping

The patients were divided into 9 subgroups according to i) the baseline coping score and ii) the previous coping score as defined in Table S3 (online appendix only). For each missing coping score, the set of potential imputed values is all the observed coping scores at the same time period among the patients in the same subgroup as the patient with the missing coping score. The imputed coping score was selected at random from the set of potential imputed values by proc surveyselect in SAS.

Nearest Neighbor Imputation and Predictive Mean Matching

A monotone missing monotone pattern was created by imputing non-monotone missing coping scores by LOCF. Nearest neighbor imputation (Rubin 1987, chapter 5; Van Buuren et al. 1999) was then implemented by using the regpredmeanmatch procedure option in the monotone statement in the MI procedure in SAS. During the imputation, predicted values for patients with both observed values and missing observation were generated from a linear regression model.

The linear regression model for S_Pacis considered at each time point was based on the previous coping score(s). Predictive mean matching (Rubin 1987, p.168, Rubin and Schenker 1991; Heitjan and Landis 1994) was implemented similarly to nearest neighbor imputation. The five patients with an observed value where the predicted value was closest value to the predicted value for the patient with the missing value were considered when selecting the imputed value.

Pattern Mixture Models (Curran's Analytic Technique)

Pattern mixtures models (Little 1993; Little 1994; Little 1995) is a modelling approach to multiple imputation. The method stratifies incomplete data by the pattern of missing values and formulates distinct models within each stratum (Little and Wang, 1996). It is common that the parameters for many of these models can only be estimated by imposing restrictions (Fairclough 2010, p. 213). Thus, restrictions such as the complete case missing value restriction (CCMV) have been proposed for longitudinal data with monotone missing data. Under the CCMV restriction, the data for patients with complete data are used to predict the means for the missing observations in the remaining patterns. Curran (2000) proposed an analytic technique for such restrictions using multiple imputation by the Markov chain Monte Carlo (MCMC) method of data augmentation.

A monotone missing data pattern was created by imputing non-monotone missing coping scores by LOCF. Curran's analytic technique was then implemented using the MI procedure in SAS (see algorithm in the online appendix). During the imputation, S_Pacis Y_h ($h = 1, \dots, 9$) were assumed to follow a multivariate Normal distribution. Default settings for the MCMC statement applying MCMC methods in the MI procedure in SAS were used. Therefore, during the

imputation i) a single chain was used and ii) a non-informative Jeffreys prior was used to derive the posterior mode from the EM algorithm as the starting values.

3. Results

The plots of Schoenfeld residuals (Schoenfeld 1982) against time for S_Pacis and delayed chemotherapy from the time-dependent Cox model analysis of all available coping scores is shown in Figure S1 (online appendix only). Beyond approximately 11 years (~ 4000 days), the plots no longer indicated a zero slope for delayed chemotherapy (Figure S1B). However, this did not raise concerns about the time-dependent Cox model. The parameter estimates from this time-dependent Cox model analysis are shown in Table S2 (online appendix only). The bias in considering all available coping scores in the IBCSG dataset makes it difficult to interpret the parameter estimates. The results from the time-dependent Cox model analysis following standard imputation methods are shown in Table 2.

Applying Standard Imputation Methods to the IBCSG Dataset

Given the indication that the missing coping scores in the IBCSG dataset are informative missing data, it is unlikely that the assumptions for the standard simple imputation methods hold. Many multiple imputation methods assume a monotone missing data pattern, which is not the case the IBCSG dataset. In the standard multiple imputation methods except from bootstrapping, the non-monotone missing data patterns were imputed by LOCF.

Parameter Estimate of Square Root for Coping Score and Delayed Chemotherapy

The parameter estimate for S_Pacis was positive, favoring a positive relationship between quality of life and DFS, for all standard imputation methods (Table 2). The multiple imputation methods showed hazard ratios which were similar for each repetition. The parameter estimate for

S_Pacis was close to 0 for all standard imputation methods. As noted, in Herring et al. (2004) poor baseline coping score was associated with improved relapse-free survival in postmenopausal patients. However, considering coping scores throughout the study in a time-dependent Cox model led to parameter estimates in the opposite direction and of a smaller magnitude. There was no evidence from the standard simple or standard multiple imputation methods of a statistically significant or clinically important relationship between quality of life and DFS. This was consistent with the expanded time-dependent Cox model analysis of postmenopausal patients (Trial VII) based on Herring et al (2004) (Table 3).

The parameter estimate for delayed chemotherapy was negative, favoring a positive relationship between further treatment with delayed chemotherapy and DFS, for all standard imputation methods (Table 2). The time-dependent Cox model analysis indicated a trend towards a positive relationship between delayed chemotherapy and DFS.

Standard Error of Parameter Estimate for Square Root of Coping Score and Delayed Chemotherapy

The standard error of the parameter estimate for S_Pacis (~0.011) and delayed chemotherapy (~0.054) following simple imputation methods (Table 2) was approximately equal to the standard error considering all available coping scores (Table S2). The standard errors of the parameter estimates following simple imputation have not increased to reflect the uncertainty in the imputed values. In contrast, the standard errors of the parameter estimates following multiple imputation showed a small increase to reflect this uncertainty. The standard error of the parameter estimate for S_Pacis and delayed chemotherapy increased by ~14% to ~0.0125 (Table

2) compared to ~ 0.011 (Table S2) and by $\sim 4\%$ to ~ 0.056 (Table 2) compared to ~ 0.054 (Table S2) respectively.

Expanded Time-Dependent Cox Model Analysis for Postmenopausal Patients

The expanded time-dependent Cox model analysis of postmenopausal patients (Trial VII) considered three scenarios: i) all available coping score, ii) simple imputation by LOCF and iii) multiple imputation by bootstrapping, subgroups defined by baseline coping score. For each of the 3 scenarios, there was no evidence of a clinically a statistically significant or clinically important relationship between quality of life and DFS. The parameter estimate for S_Pacis was close to 0 (Table 3).

4. Summary

We investigated the influence of missing quality of life values, as assessed by coping score, when exploring the relationship between quality of life and DFS in a time-dependent Cox model. Preliminary investigations indicated that imputation is appropriate for the IBCSG dataset. Standard imputation methods were applied to the IBCSG dataset before analysis in a time-dependent Cox model. While the standard imputation methods are not necessarily good estimation techniques in this context due to the assumptions relating to the missing data mechanism and the missing data pattern, this provides insight into the influence of the missing quality of life assessments in the time-dependent Cox model analysis.

There are only limited circumstances when it is appropriate to draw inferences from the parameter estimate resulting from simple imputation. Justification should be provided if the parameter estimates are considered (Molenbergs and Kenward 2007, Chapter 4). However, the purpose of applying simple imputation methods is generally as part of a sensitivity analyses into

the sensitivity of results to the assumptions about the missing data. Many multiple imputation methods assume a monotone missing data pattern, which is not the case the IBCSG dataset. In the standard multiple imputation methods except bootstrapping, the non-monotone missing data patterns were imputed by LOCF. This gives the advantage of generating multiple completed datasets compared to LOCF imputation.

The parameter estimate for S_Pacis was positive, favoring a positive relationship between quality of life and DFS, for all standard imputation methods. There was no evidence from the standard imputation methods of a statistically significant or clinically important relationship between quality of life and DFS in the IBCSG dataset. As noted, the standard error of the parameter estimates following simple imputation did not increase compared to considering all available coping scores and thus did not reflect the uncertainty in the imputed values. In contrast, there was a small increase in the standard error of the parameter estimates following the standard multiple imputation methods. The parameter estimates for delayed chemotherapy showed a trend towards a positive relationship between delayed chemotherapy and DFS. This is consistent with the finding from the main efficacy analysis that there may be a therapeutic benefit from delayed chemotherapy.

The parameter estimates for S_Pacis and delayed chemotherapy following the standard imputation methods were similar to those from the all available analysis. This is similar to the fact that the parameter estimates for baseline coping score in Herring et al. (2004) were little influenced by the different models accounting for missing data. However, as noted, the bias from the selection of patients considered in the all available analysis makes it difficult to interpret the values of the parameter estimates. The small increase in the standard error of the parameter

estimates compared to the all available analysis was similar following each of the standard multiple imputation methods. The similarities in the parameter estimates and standard errors may be influenced by the fact there is no evidence of a statistically significant or clinically important relationship between quality of life and DFS in the IBCSG dataset.

Considering coping scores throughout the study in a time-dependent Cox model led to parameter estimates in the opposite direction and of a smaller magnitude than when considering baseline quality of life in Herring et al. (2004). There are differences of note in the time-dependent Cox model analyses described here compared to Herring et al. (2004). Firstly, here premenopausal patients and postmenopausal patients outside Switzerland were considered, giving a broader and larger population of patients. Secondly, the outcome of relapse-free survival considered by Herring et al. (2004) did not include second primary cancer or death without prior event as events. Lastly, further covariates such as age and interaction terms were considered in the analysis by Herring et al. (2004), whereas the time-dependent Cox model analysis was parsimonious. Of note, the expanded time-dependent Cox model analysis of postmenopausal patients (Trial VII) based on Herring et al (2004) also found no evidence of a statistically significant or clinically important relationship between quality of life and DFS.

It is possible that the performance of the standard imputation methods in this setting is influenced by the fact that here there was no evidence of a relationship between quality of life and DFS. It would be of interest to investigate if the performance of the standard imputation methods is influenced by the relationship between quality of life and DFS in datasets where quality of life was associated with DFS.

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Table 1. Summary of Status of Coping Scores in IBCSG Trial VI and VII.

		Observed	Missing	Post- recurrence	Lost to follow-up	Dead
Time 1	Baseline	2231 (83.0)	456 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time 2	Month 3	1918 (71.4)	744 (27.7)	25 (0.9)	0 (0.0)	0 (0.0)
Time 3	Month 6	1871 (69.6)	751 (27.9)	56 (2.1)	1 (0.0)	8 (0.3)
Time 4	Month 9	1817 (67.6)	745 (27.7)	103 (3.8)	1 (0.0)	21 (0.8)
Time 5	Month 12	1812 (67.4)	662 (24.6)	173 (6.4)	3 (0.1)	37 (1.4)
Time 6	Month 15	1692 (63.0)	711 (26.5)	215 (8.0)	3 (0.1)	66 (2.5)
Time 7	Month 18	1616 (60.1)	707 (26.3)	266 (9.9)	5 (0.2)	93 (3.5)
Time 8	Month 21	1556 (57.9)	693 (25.8)	294 (10.9)	5 (0.2)	139 (5.2)
Time 9	Month 24	1502 (55.9)	666 (24.8)	339 (12.6)	5 (0.2)	175 (6.5)

Data are n (%)

Table 2. Summary of Time Dependent Cox Model Analysis Considering Square Root of Coping Score (S_Pacis) and Delayed Chemotherapy Stratified by Trial.

Square root of coping score (S_Pacis)						
Method	Detail	Parameter estimate	Range	Standard error	t statistic	95% CI for hazard ratio
LOCF		0.0047		0.0112	0.42	(0.983, 1.027)
Median	by patient	0.0136		0.0107	1.27	(0.993, 1.035)
Linear regression	previous coping scores	0.0069		0.0124	0.56	(0.983, 1.032)
Bootstrap	baseline coping score	0.0046	-0.0096 to 0.0195	0.0130	0.35	(0.979, 1.030)
	previous coping score	0.0070	-0.0027 to 0.0194	0.0125	0.56	(0.983, 1.032)
Nearest neighbor		0.0030	-0.0037 to 0.0108	0.0118	0.25	(0.980, 1.026)
Predictive mean matching	initial steps as described for NNI	0.0043	-0.0026 to 0.0149	0.0121	0.36	(0.981, 1.028)
Pattern mixture models		0.0127	0.0061 to 0.0231	0.0123	1.03	(0.989, 1.037)
Delayed Chemotherapy						
Method	Detail	Parameter estimate	Range	Standard error	t statistic	95% CI for hazard ratio
LOCF		-0.0929		0.0555	-1.67	(0.817, 1.016)
Median	by patient	-0.1124		0.0521	-2.16	(0.807, 0.990)
Linear regression	previous coping scores	-0.0937		0.0556	-1.69	(0.817, 1.015)
Bootstrap	baseline coping score	-0.0929	-0.0968 to -0.0884	0.0556	-1.67	(0.802, 1.020)
	previous coping score	-0.0937	-0.0976 to -0.0907	0.0556	-1.69	(0.802, 1.020)
Nearest neighbor		-0.0926	-0.0948 to -0.0905	0.0560	-1.65	(0.802, 1.021)
Predictive mean matching	initial steps as described for NNI	-0.0928	-0.0963 to -0.0909	0.0555	-1.67	(0.803, 1.020)
Pattern mixture models		-0.0956	-0.1009 to -0.0933	0.0556	-1.72	(0.800, 1.018)

CI = confidence interval; NNI = nearest neighbor imputation

Note: The standard error shown is the square root of the variance of the parameter estimate. The standard error and the parameter estimate are used to calculate the 95% confidence interval for the parameter estimate. The exponential of the lower and upper 95% confidence limits for the parameter estimate gives the lower and upper 95% confidence limits for the hazard ratio. The t-statistic is the parameter estimate divided by the standard error.

For the multiple imputation methods, the parameter estimate is the mean of the parameter estimate from each of the 50 completed datasets. The variance of the parameter estimate for each of the multiple imputation methods is calculated based on the 50 repetitions of multiple imputation according to Rubin (1987).

Table 3. Summary of Expanded Time-Dependent Cox Model Analysis of Postmenopausal Patients (IBCSG Trial VII).

Parameter	All Available		LOCF		Bootstrapping*
	Estimate	Standard Error	Estimate	Standard Error	Mean Estimate
Main Effects					
Early CMF	-0.3860	0.2369	-0.4347	0.2578	-0.4282
Late CMF	0.1620	0.2284	0.2189	0.2520	0.2225
Full CMF	-0.3038	0.2306	-0.2150	0.2483	-0.2091
Number nodes positive	0.0715	0.0066	0.0807	0.0073	0.0809
Age >= 65	-0.2339	0.1690	-0.2331	0.1869	-0.2361
Positive ER status	-0.1837	0.1827	-0.1246	0.2014	-0.1237
S_Pacis	0.0096	0.0168	0.0095	0.0181	-0.0017
Language/culture Main Effects					
Language/culture EngAusNz	-0.1535	0.1322	-0.2496	0.1417	-0.2604
Language/culture EngSA	-0.1036	0.2029	-0.2193	0.2069	-0.2380
Language/culture FrenchCH	-0.1797	0.1766	-0.2339	0.1978	-0.2334
Language/culture ItalianCH	-0.2073	0.1933	-0.3047	0.1960	-0.3026
Language/culture ItalianI	-0.3780	0.1376	-0.4526	0.1434	-0.4448
Language/culture SlovenianSI	-0.1740	0.1499	-0.2872	0.1640	-0.2758
Language/culture SpanishSp	0.1109	0.2631	0.1350	0.2808	0.1496
Language/culture SwedishSd	-0.3890	0.1274	-0.5387	0.1423	-0.5457
Treatment Interactions					
Early CMF * Age >= 65	0.4623	0.2434	0.3155	0.2720	0.3110
Late CMF * Age >= 65	0.0244	0.2550	0.1357	0.2756	0.1292
Full CMF * Age >= 65	0.3312	0.2416	0.3764	0.2604	0.3823
Early CMF * Positive ER status	0.0161	0.2612	0.1573	0.2850	0.1562
Late CMF * Positive ER status	-0.4555	0.2556	-0.4796	0.2807	-0.4755
Full CMF * Positive ER status	-0.0514	0.2557	-0.1588	0.2757	-0.1618

*For imputation by bootstrapping, the subgroups were defined by baseline coping score. Based on 50 repetitions of multiple imputation, the standard error of the parameter estimate for S_Pacis was 0.0201.

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Note: Higher coping scores indicated higher quality of life

Reference group for treatment is tamoxifen only

Reference group for language/culture is German/Switzerland and Germany

CMF = cyclophosphamide, methotrexate and fluorouracil; ER = estrogen receptor

Abbreviations for language or countries in language/culture groups:

Eng = English; AusNZ =Australia and New Zealand; SA = South Africa; CH = Switzerland; I =

Italy; Sl = Slovenia; Sp =Spain; Sd= Swedan;

