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ePRO: A View from Statistical Programmer

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ABSTRACT

Assessing patients experiences and perspectives into their clinical care is an important mechanism for evaluating the Quality of Life (QoL) of patients participating in cancer clinical trials. Patient-Reported Outcomes (PROs) commonly would capture patient perspective systematically and could assist in the development of new cancer therapies. European Organization for Research and Treatment of Cancer (EORTC) created and developed an integrated, modular approach for evaluating the QoL of patients participating in cancer clinical trials. This led to the development of the EORTC Quality of Life Questionnaire (QLQ) QLQ-C30, a quality of life instrument for cancer patients. Furthermore, EORTC developed various types of Questionnaires within various types of cancers. This paper primarily focuses on statistical programming aspects of PRO analysis for questionnaires (QLQ-C30, QLQ-LC13 and EQ-5D-5L) collected in Lung Cancer Indication trials. Details on the mapping process from collected data to Study Data Tabulation Model (SDTM), creation of Analysis Data Model (ADaM) datasets and various types of analysis reports typically included in a Clinical Study Report (CSR) will be discussed in this paper.

BACKGROUND

Patient-reported outcomes (PRO) measures are commonly assessed in cancer trials and they represent important mechanism of incorporating patients' experience and their perspectives in their care so overall participation in delivering cancer care is greatly enhanced. 'Patient' can be considered as the center for any healthcare system. As per US-FDA, a PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [11]. Though medical technology allows to measure physical, physiological or biochemical data of the patient; it is not able to give all the data about the treatment or the disease. Some data can be obtained only from the patient. Further to add, in some cases, disease survival is not the goal of the treatment, but quality of life also plays an essential role in the treatment.

There are various types of PRO measures assessing quality of life of the patients. The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials. An essential component of the EORTC QLQ development strategy involves the use of supplementary questionnaire modules which, when employed in conjunction with the QLQ-C30, can provide more detailed information relevant to evaluating the QoL in specific patient populations.

Some of the following modules are currently available for general use, to supplement the core EORTC QLQ-C30.

- Breast cancer module: QLQ-BR23
- Head & neck cancer module: QLQ-H&N35

• Lung cancer module: QLQ-LC13
• Oesophageal cancer module: QLQ-OES24
• Ovarian cancer module: QLQ-OV28

Similarly, EuroQol Group developed EQ-5D, a standardized measure of health status to provide a simple, generic measure of health for clinical and economic appraisal. Below are the versions available in EQ-5D.

• The 3-level EQ-5D version (EQ-5D-3L).
• The 5-level EQ-5D version (EQ-5D-5L).

This paper primarily focuses on statistical programming aspects of ePRO analysis of questionnaires (QLQ-C30, QLQ-LC13 and EQ-5D-5L) and especially with respect to Lung cancer trials.

SDTM MAPPING

Typically, above mentioned questionnaires are mapped to QS (Questionnaire) domain regardless of SDTM IG version (3.1.1, 3.1.3 or 3.2). This paper mainly discusses with respect to SDTM IG 3.1.3. Questions from each of the questionnaire is generally mapped to QSTEST/QSTESTCD and the results associated with the questions are mapped to QSORRES/QSSTRESC/QSSTRESN variables. QSORRES (Original result) would capture the original result as it was collected and QSSTRESC/QSSTRESN captures the numeric part of the original result in character and numeric formats respectively.
The information related to administration method, completion status and version is also captured and mapped in SDTM. If there are multiple questionnaires being mapped to QS domain, QSCAT is used to differentiate it.

ADAM

All the TLFs generated to support ePRO analysis will make use of ADaM datasets. To support this analysis, three individual ADaM datasets (ADPRO (Analysis Dataset for PRO), ADTTD (PRO Time-to-True-Deterioration) and ADPLDA (Analysis Dataset for PRO Longitudinal Data Analysis) are developed and conformed to ADAM IG 1.1 and belong to the class of BDS (Basic Data Structure). Implementing ADaM compliant (in this case BDS) is essential to the Clinical Data Interchange Standards Consortium (CDISC) compliance of total submission package. However, implementing BDS datasets especially the Questionnaire data is quite challenging. To guide and create mentioned datasets, programmers typically follow company specific dataset specifications which is usually in excel format.

Common subject level variables (Core variables) are carried from Subject Level Analysis Dataset (ADSL) to all the datasets, similarly core variables are also carried to ePRO related datasets, besides we also carry important variables such as disease progression date etc from other efficacy datasets to support further analysis. Since this is QS data, all the questions that are mapped to QSTESTCD/QSTEST variables in SDTM/QS domain are directly mapped to paramcd/param of ADPRO. Along with directly mapped parameters, additional parameters are derived to support intended analysis. Following paragraphs describes each of the analysis datasets (ADPRO, ADTTD and ADPLDA) in detail.

ADPRO

Table 1, Table 2 and Table 3 provides parameters related to Questionnaire QLQ-C30, QLQ-LC13 and EQ-5D-5L respectively. In table 1, Functional scales (paramcd Q1-Q7, Q20-Q27), Symptom scales/items (paramcd Q8-Q19, Q28), Global health status/QoL (paramcd Q29-Q30), are directly mapped from QSTEST/QSTESTCD of SDTM/QS domain and rest of the parameters are derived in analysis dataset.

Similarly, in table 2 and table 3, Symptom scales/items (paramcd LC1-LC12) and paramcd (Mobility to EQ VAS) are directly mapped from QSTEST/QSTESTCD of SDTM/QS domain and rest of the parameters are derived in analysis dataset.

In questionnaire QLQ-C30 and QLQ-LC13, parameters that are directly mapped from SDTM/QS domain has AVAL mapped directly from QSSTRESN variable. Whereas, in questionnaire EQ-5D-5L AVAL is decoded from character response (QSSTRESC) to numeric value. Typically assigned values range from 1 to 5 i.e., no problem to extreme problem.

Procedure of calculating analysis value, AVAL (in this case score) in questionnaire QLQ-C30 and QLQ-LC13 for derived param is explained in detail in subsequent paragraphs. Score is calculated for each subject and at each time point (analysis visit (AVISIT), analysis date (ADT) etc). Parameter category 1(PARCAT1) is used to identify different Questionnaire forms. The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Parcat2 captures types of scales.

PARAM	**PARAMCD**	**PARCAT2**
Trouble with Strenuous Activities	Q1	Functional scales
Trouble Taking Long Walk	Q2	Functional scales
Trouble Taking Short Walk	Q3	Functional scales
Bed or Chair During Day	Q4	Functional scales
Need Help Caring For self	Q5	Functional scales
Limited Daily Activities	Q6	Functional scales
Limited Hobbies or Leisure	Q7	Functional scales
Short of Breath	Q8	Symptom scales/items
Had Pain	Q9	Symptom scales/items
Need Rest	Q10	Symptom scales/items
Trouble Sleeping	Q11	Symptom scales/items
Felt Weak	Q12	Symptom scales/items
Lacked Appetite	Q13	Symptom scales/items
Felt Nauseated	Q14	Symptom scales/items
Vomited	Q15	Symptom scales/items
Constipated	Q16	Symptom scales/items
Diarrhea Scale	Q17	Symptom scales/items
Tired	Q18	Symptom scales/items
Pain Interfere with Daily Activities	Q19	Symptom scales/items
Difficulty Concentrating	Q20	Functional scales
Feel Tense	Q21	Functional scales
Worry	Q22	Functional scales
Feel Irritable	Q23	Functional scales

PARAM	PARAMCD	PARCAT2
Feel Depressed	Q24	Functional scales
Difficulty Remembering	Q25	Functional scales
Condition Interfered with Family Life	Q26	Functional scales
Condition Interfered with Social Life	Q27	Functional scales
Condition Caused Financial Difficulty	Q28	Symptom scales/items
Overall Health	Q29	Global health status/QoL
Overall Quality of Life	Q30	Global health status/QoL
Global health status/QoL	QL2	Global health status/QoL
Physical functioning	PF2	Functional scales
Role functioning	RF2	Functional scales
Emotional functioning	EF	Functional scales
Cognitive functioning	CF	Functional scales
Social functioning	SF	Functional scales
Fatigue	FA	Symptom scales/items
Nausea and vomiting	NV	Symptom scales/items
Pain	PA	Symptom scales/items
Dyspnoea	DY	Symptom scales/items
Insomnia	SL	Symptom scales/items
Appetite loss	AP	Symptom scales/items
Constipation	CO	Symptom scales/items
Diarrhea	DI	Symptom scales/items
Financial difficulties	FI	Symptom scales/items
Questionnaire Completion Status (C30)	CSTAT1	

TABLE 1. Parameters related to Questionnaire QLQ-C30

PARAM	PARAMCD	PARCAT2
Amount of Cough	LC1	Symptom scales/items
Cough Up Blood	LC2	Symptom scales/items
Short of Breath Rested	LC3	Symptom scales/items
Short of Breath Walked	LC4	Symptom scales/items
Short of Breath Stairs	LC5	Symptom scales/items
Sore Mouth or Tongue	LC6	Symptom scales/items
Trouble Swallowing	LC7	Symptom scales/items
Tingling Hands or Feet	LC8	Symptom scales/items
Hair Loss	LC9	Symptom scales/items
Chest Pain	LC10	Symptom scales/items

Arm or Shoulder Pain	LC11	Symptom scales/items
Pain in Other Body Parts	LC12	Symptom scales/items
Dyspnoea	LCDY	Symptom scales/items
Coughing	LCCO	Symptom scales/items
Haemoptysis	LCHA	Symptom scales/items
Sore mouth	LCSM	Symptom scales/items
Dysphagia	LCDS	Symptom scales/items
Peripheral neuropathy	LCPN	Symptom scales/items
Alopecia	LCHR	Symptom scales/items
Pain in chest	LCPC	Symptom scales/items
Pain in arm or shoulder	LCPA	Symptom scales/items
Pain in other parts	LCPO	Symptom scales/items
Questionnaire Completion Status (LC13)	CSTAT2	

TABLE 2. Parameters related to Questionnaire QLQ-LC13

PARAM	**PARAMCD**
Mobility	MOBILITY
Self-Care	SELFCARE
Usual Activities	ACTIVITY
Pain or Discomfort	PAIN
Anxiety or Depression	ANXIETY
EQ VAS Score	EQVAS
Questionnaire Completion Status (EQ-5D)	CSTAT3

TABLE 3. Parameters related to Questionnaire EQ-5D-5L

Additional parameters from above table QL2-FI are derived in the analysis dataset. Figure 2 provides details regarding number of items, item range and item number to calculate the score for each of the parameter. For example, Global health status/QoL (QL2) consider item numbers Q29, Q30 (number of items as 2) which has minimum response as 1 and maximum response as 7 which gives item range of 6. Please refer to EORTC QLQ-C30 sample specimen provided at end of this paper.

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					

Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

FIGURE 2. Scoring of the QLQ-C30

* Item range is the difference between the possible maximum and the minimum response to individual items.

Scoring of the lung cancer module

The questionnaire QLQ-LC13 includes dyspnoea scale assessment which includes multi-item, and all other scales such as assessing pain (pain in chest, pain in arm or shoulder, pain in other parts), coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis.

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single items of the QLQ-C30.

Scale name	Scale	Number of items	Item range	QLQ-LC13 Item numbers	†
Symptom scales / items					
Dyspnoea†	LCDY	3†	3	3,4,5	X
Coughing	LCCO	1	3	1	
Haemoptysis	LCHA	1	3	2	
Sore mouth	LCSM	1	3	6	
Dysphagia	LCDS	1	3	7	
Peripheral neuropathy	LCPN	1	3	8	
Alopecia	LCHR	1	3	9	
Pain in chest	LCPC	1	3	10	
Pain in arm or shoulder	LCPA	1	3	11	
Pain in other parts	LCPO	1	3	12	

† The dyspnoea scale should only be used if all three items have been answered.

For all scales, the *Raw Score*, *RS*, is the mean of the component items:

Raw Score=RS= (I_1 +I_2+…..+ I_n□□*n,* Where I is individual item(question) in the Questionnaire form

XNUM = N (OF I_1 I_2…..I_n);
XMEAN = MEAN (OF I_1 I_2…..I_n);

XNUM is used to count the number of non-missing items, which should be at least half the total NITEMS items in the scale to derive a score i.e. *xnum >= nitems / 2*

To calculate the **Functional scale score**:

$$Score = \left\{1 - \frac{(RS - 1)}{RANGE}\right\} * 100$$

To calculate **Symptom scales / items** and **Global health status / QoL:**

$$Score = \left\{\frac{(RS - 1)}{RANGE}\right\} * 100$$

As mentioned earlier, since analysis datasets conform to ADaM class of BDS structure, Baseline flag (ABLFL), Baseline value (BASE), Change from Baseline (CHG), analysis visit (AVISIT) are derived to support analysis. Baseline column, BASE is identified for each subjid and parameter and then ABLFL is set to Y on the record whose analysis value is mapped to variable BASE. Change from baseline at each time point is calculated by difference of AVAL and BASE. AVISIT is used to describe analysis visit or analysis time point. Based on the value of change from baseline, different categories (stable, improved and deteriorated) are derived in Change from Baseline Category 1(CHGCAT1). Please refer to following Table 4 for complete derivation.

QUESTIONNAIRE	PARAM/PARAMCD	PARCAT2	CHGCAT1
QLQ-C30	Global health status/QoL (QL2)	Global health status/QoL	CHG>=10, Improved -10<CHG<10, Stable . < CHG <= -10, Deteriorated
QLQ-C30	Physical functioning (PF2)	Functional scales	CHG>=10, Improved -10<CHG<10, Stable . < CHG <= -10, Deteriorated
QLQ-C30	Role functioning (RF2)	Functional scales	CHG>=10, Improved -10<CHG<10, Stable . < CHG <= -10, Deteriorated
QLQ-C30	Emotional functioning (EF)	Functional scales	CHG>=10, Improved -10<CHG<10, Stable . < CHG <= -10, Deteriorated
QLQ-C30	Cognitive functioning (CF)	Functional scales	CHG>=10, Improved -10<CHG<10, Stable . < CHG <= -10, Deteriorated

QUESTIONNAIRE	PARAM/PARAMCD	PARCAT2	CHGCAT1
QLQ-C30	Social functioning (SF)	Functional scales	CHG>=10, Improved -10<CHG<10, Stable . < CHG <= -10, Deteriorated
QLQ-C30	Fatigue (FA)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Nausea and vomiting (NV)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Pain (PA)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Dyspnoea (DY)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Insomnia (SL)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Appetite loss (AP)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Constipation (CO)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Diarrhea (DI)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved
QLQ-C30	Financial difficulties (FI)	Symptom scales/items	CHG>=10, Deteriorated -10<CHG<10, Stable . < CHG <= -10, Improved

TABLE 4. QLQ-C30 CHGCAT Derivation based on respective scale and category

Analysis Record Flag (ANL01FL) is derived to identify the records considered into analysis. Completion status of all forms is captured in QS and is directly mapped (CSTAT1, CSTAT2, CSTAT3) to AVAL/AVALC variable in ADPRO.

ADPLDA

Derived parameters related to QLQ-C30 (QL2,PF2,RF2,EF,CF,SF,FA,NV,PA,DY,SL,AP,CO,DI,FI), QLQ-LC13 (LCDY,LCCO,LCHA,LCSM,LCDS,LCPN,LCHR,LCPC,LCPA,LCPO) and EQ-5D-5L (EQVAS) in ADPLDA are directly carried from ADPRO by filtering respective predefined analysis flag to support longitudinal data analysis. Details regarding longitudinal data analysis is described in analysis and reporting section of this paper.

Apart from the above parameters, completion status from ADPRO dataset is mapped to new parameter to accommodate any new derived information in case of missing completion status for any visit. Missing completion status is derived based on predefined derivation rules.

ADTTD

Time-to-deterioration (TTD)

For the EORTC QLQ-C30 and QLQ-LC13, a 10 points or greater worsening from baseline for each scale represents a clinically relevant deterioration based on prior literature. Time-to deterioration is defined as the time to first onset of 10 or more (out of 100) deterioration from baseline in a given scale/sub-scale/item and confirmed by a second adjacent 10 or more deterioration from baseline under a right-censoring rule. Typically, endpoint of interest for lung cancer trial is the composite endpoint of cough (QLQ-LC-13 Item 1), chest pain (QLQ-LC-13 Item 10), or dyspnoea (QLQ-C30 Item 8).

Various endpoints for TTD defined in protocol or SAP are derived in ADTTD dataset. ADTTD follows time to event analysis dataset structure per ADAM IG.

PARAMCD	ADT	CENSOR	EVENT DESCRIPTION
TTDXX	Select ADPRO records with parameter "XXX" (for example Pain in Chest, LCPC) and in conjunction with predefined analysis flags, select the earliest record with Change category (CHGCAT1) as "Deteriorated" confirmed by the following assessment {Event} If there is no event, then select most recent date of post baseline records, if at least one post-baseline record exists with non-missing Change from Baseline {Censor} Else ADT = TRTSDT	0 if event, 1 if censor	If there is an event, then "Deteriorated from Chest Pain" If there is no event and there is at least one valid post-baseline record, then "Censored at last assessment"; If there is no event and there is no valid post-baseline, then "Censored at first dose date";
TTDCOMP	In case of composite endpoint, select required parameters based on above logic, combine all of them and select earliest record.	0 if event, 1 if censor	Event description would be based on analysis date from which parameter it was derived from. In case of ties, then we need to go with alphabetic order. In case of no event, use same logic as described above.

Time-to-Event Origin Date (STARTDT) is typically randomization date or treatment start date. Analysis value is calculated based on difference of analysis date (ADT) and STARTDT +1.

ANALYSIS AND REPORTING

The above described analysis datasets (ADaM) are created to support PRO related endpoints defined in protocol such as mean change in scores and time to deterioration. Along with these endpoints, there are exploratory endpoints such as analysis of overall improvement and stability, for example Proportion

improved/stable in Global Health Status/QoL scale are also supported. Apart from the endpoints, Completion and compliance of Questionnaires by visit and by treatment will also be analyzed. The details regarding all these Analysis and Reporting formats are explained in subsequent paragraphs.

Mean Change in Score

To calculate mean change from baseline at intended timepoint (visit) in the derived QLQ-C30 global health status/quality of life score (i.e., QL2 parameter from ADPRO), cLDA model will be used for analysis.

To assess the treatment effects on the PRO, for each continuous endpoint defined, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [1] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will include the PRO score as the response variable, with covariates including treatment by study visit interaction, and the same stratification factors as used in the stratified analyses of efficacy endpoints. The treatment difference in terms of mean PRO score change from baseline at prespecified timepoint (time defined by time windows instead of study visit) will be estimated and tested from this model.

Above model is described as below in SAS code and sample display of report is also mentioned below.

```
Proc mixed data=dataset;

Class avisitn usubjid stratum;

Model y = avisitn stratum Trt*Time/ DDFM=KR;

Repeated Time / Subject=usubjid Type = un R;

Lsmeans Trt*Time / CL Pdiff e;

Run;
```

	Baseline		Week X		Change from Baseline at Week X		Pairwise Comparison	Inv. Drug vs. Control
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)	Difference in LS Means (95% CI)	p-value
Inv.Drg	X	xx.x (xx.xxx)	X	xx.xx (xx.xxx)	X	xx.xx (xx.xx)	xx.xx (xx.xx)	x.xx
Control	X	xx.xx (xx.xxx)	X	xx.xx (xx.xxx)	X	xx.xx (xx.xx)		

Time-to-deterioration (TTD)

The TTD is defined as the time to first onset of 10 or more points deterioration from baseline with confirmation under right-censoring rule. The non-parametric Kaplan-Meier method will be used to estimate the deterioration curve in each treatment group. The estimate of median time to deterioration and its 95% confidence interval will be obtained from the Kaplan-Meier survival estimates. The treatment difference in TTD will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling and with a single treatment covariate will be used to assess the magnitude of the treatment difference (hazard ratio). SAS code to achieve above analysis is explained below and display of table is also mentioned below. TTD is also represented in Kaplan Meier plots representing time in X axis and no deterioration rate in Y axis.

proc lifetest data= dataset method=LT intervals=**t1 t2** alpha=**0.05**;
time aval* censor (0);
strata treatment;
survival out= xx conftype=LOGLOG;
run;

Treatment	N	Deterioration (Events) %	Median TTD (Months) (95% CI)	vs. Control	
				Hazard Ratio (95% CI)	p-Value
Inv drug	X	X (X.XX)	X (X.XX)	xx.xx (x.xx, x.xx)	x.xx
Control	X	X (X.XX)	X (X.XX)	---	---

Analysis of Overall Improvement/Stability

Overall Improved/Stable rate will be calculated as the percentage of subjects who have 10 point or more improvement or less than 10 points worsening in score from baseline at any time during the trial and confirmed by a 10 point or more improvement or a less than 10 points worsening at the next consecutive visit. The stratified Miettinen and Nurminen method will be used for comparison of the overall improvement/stability rate between the treatment groups. The difference in overall improvement/stability rate and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided.

Treatment	N	Number of patients with Improvement/Stability	Proportion with Improvement/Stability % (95% CI)	Inv drug vs Control	
				Difference of Improvement/Stability % (95% CI)	p-Value
Inv drug	xxx	xx	xx.x (xx.x, xx.x)		
Control	xxx	xx	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	x.xx

Compliance reports

Completion and compliance of QLQ-C30, LC13 and EQ-5D-5L by visit and by treatment will be described within the specified population. Numbers and percentages of complete and missing data at each visit will be summarized for each of the treatment groups.

Completion Rate is defined as the percentage of observed visit over number of randomized subjects at each time points.

$$\text{Completion Rate} = \frac{\text{Number of Subjects who Complete at least one Item}}{\text{Number of Randomized Subjects}}$$

The completion rate is expected to shrink in the later visit during study period due to the subjects who discontinued early. Therefore, another measurement, Compliance Rate, defined as the percentage of observed visit over number of eligible subjects who are expected to complete the PRO assessment (not including the subjects missing by design (such as death, discontinuation, translation not available) will be employed as the support for completion rate).

$$\text{Compliance Rate} = \frac{\text{Number of Subjects who Complete at least one Item}}{\text{who are Expected to Complete}}$$

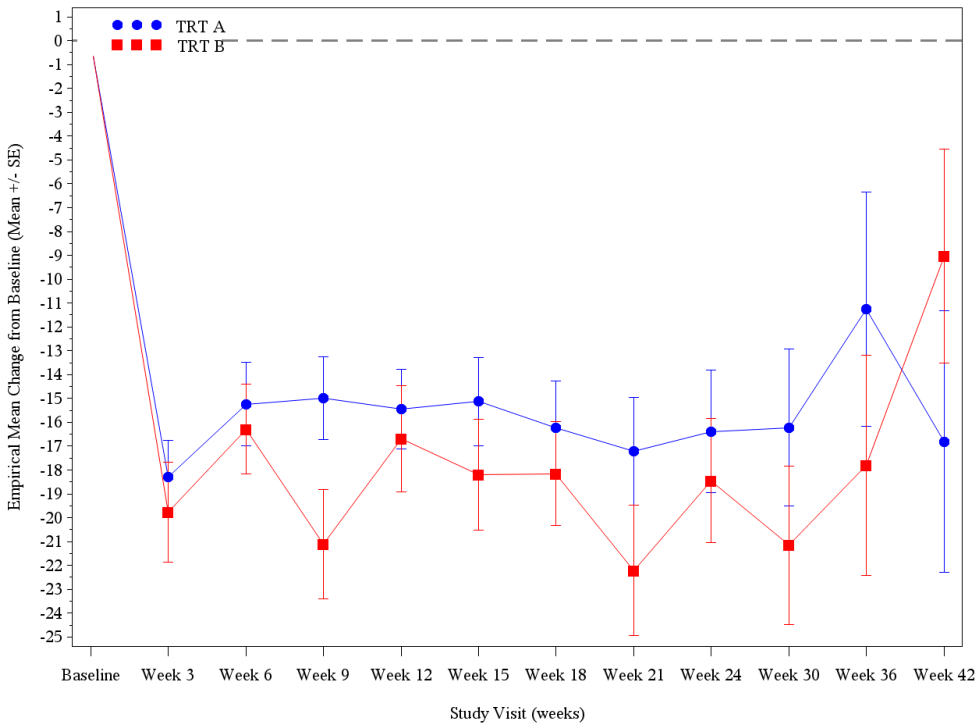
For example, Compliance of EORTC QLQ C30 by Visit and by Treatment is shown below

Treatment Visit	Category	Inv Drug N = XX n (%)	Control N = XX n (%)
T1	Missing by Design	x (x.x)	x (x.x)
	Discontinued due to adverse event		
	Discontinued due to death		
	Discontinued due to physician decision		
	Discontinued due to progressive disease		
	Discontinued due to clinical progression		
	Discontinued due to withdrawal by subject		
	Discontinued due to other		
	Translation not available in subject's language		
	Subject died		
	No visit scheduled		
	Expected to Complete Questionnaires		
	Not Complete		
	Subject did not complete due to disease under study		
	Not completed due to site staff error		
	Subject in hospital or hospice		
	Subject was physically unable to complete		
	Subject lost to follow-up/unable to contact		
	Subject did not complete due to side effect of treatment		

Graphs

Empirical mean change Graph

The empirical mean change (with 95% CIs) from baseline across time will be displayed graphically for the following scale as an example: EORTC QLQ-C30 GHS/QoL (QL2 from ADPRO).

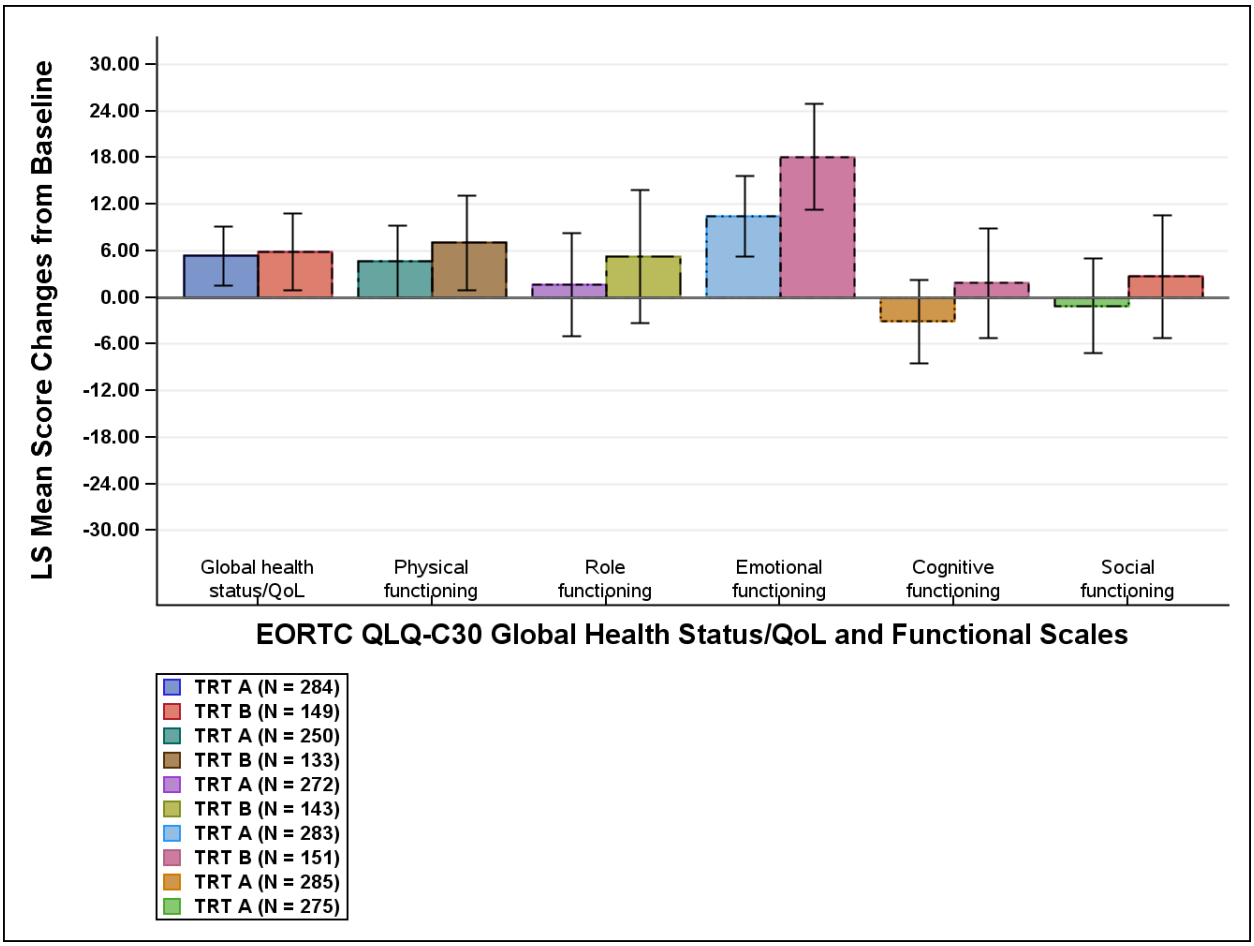


TRT A	261	234	211	192	197	189	180	150	114	83	41	30
TRT B	153	130	130	116	120	115	106	86	71	47	29	17

Note: Above data has been constructed for example purpose.

LS mean change Graph

Analysis of LS mean change (95% CI) from baseline to time point of interest will be displayed in bar plot format for different questionnaires as mentioned in protocol. For example, see below bar plot displayed for questionnaire EORTC QLQ-C30 global health status and functional scales. LS mean change from baseline is plotted against different scales such as Global health status, Physical Functioning and others as shown below.



Note: Above data has been constructed for example purpose.

APPENDIX

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

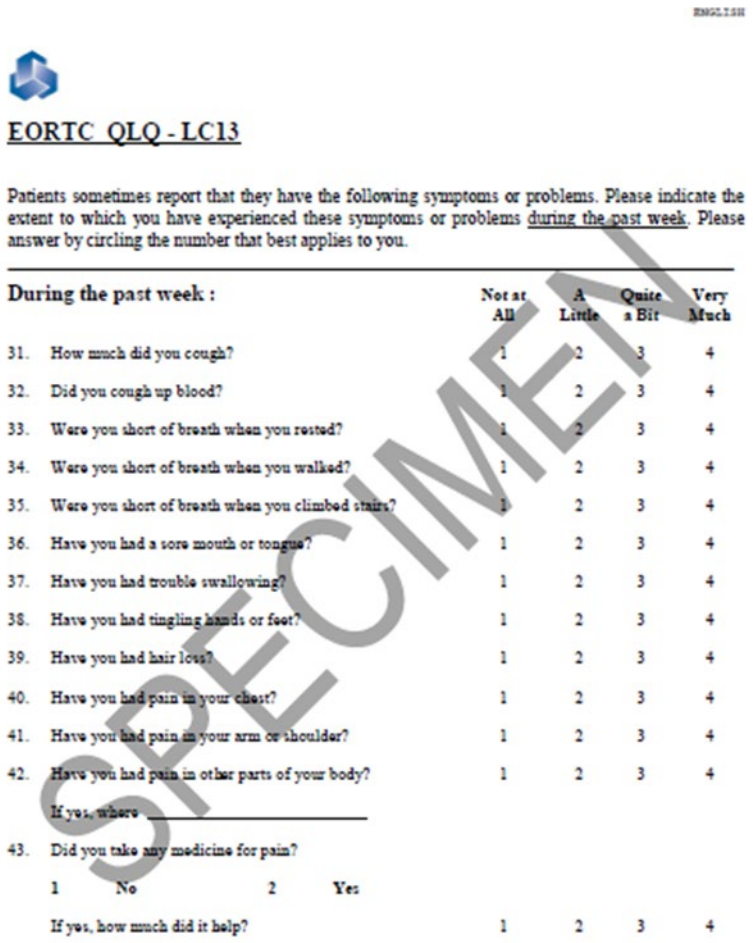
29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

FIGURE 1. EORTC QLQ-C30 Specimen sheet



ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where _____				
43. Did you take any medicine for pain?				
1 No 2 Yes				
If yes, how much did it help?	1	2	3	4

FIGURE 3. EORTC QLQ-LC13 Specimen sheet

CONCLUSION

In recent years, regulatory agencies such as the FDA and EMA have increasingly promoted the use of PRO data in the development and approval of cancer products. Like regular clinical trial data, ePRO data can be analyzed and reported in tables and figures following CDISC guidelines, SDTM and ADaM models.

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