PharmaSUG 2017 - Paper PO04

# Implementing Patient Report Outcome Data in Clinical Trials Analysis

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## ABSTRACT

Over the recent decades, Health-Related Quality of Life (HRQoL) end points have been increasingly adopted in oncology and hematology clinical trials. This paper will focus on analyzing HRQoL data accumulated from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Acute Lymphoblastic Leukemia Symptom Scale (ALLSS). This paper will introduce various statistical methods to analyze the HRQoL data; and present some challenges and considerations in developing ADaM data specifications and performing statistical analysis.

## INTRODUCTION

The aim of this paper is to propose/introduce some standard statistical methods and Patient Report Outcome (PRO) CDISC ADaM data structure and derivation rules on EORTC and ALLSS HRQOL analyses for Oncology and Hematology trails.

PRO analysis in Oncology and Hematology may be very challenging due to

- Lack of standard scoring software and methods.
- Lack of standard statistical analysis methods.
- Lack of standard reference documents on CDISC.
- Dealing with lots of missing data (missing date, missing assessment, missing visit)

PRO analysis may also have more opportunities due to

- Increased need on HRQol in labeling claims and endpoints in clinical trials because survival and progress free survival are improving in oncology patients
- The unique perspective on medical therapy provided by PROs, because of some effects of a health condition and its therapies that are known only to patients

We will show how we successfully performed PRO analysis in our clinical study to support primary analysis. Our PRO analysis has been reported in ASCO, ASH and EHA conferences and published in some journals.

## INSTRUMENTS AND SCORING

Generic instruments such as SF-8/12/36, EQ-5D, VAS are widely used and have software to provide standard scoring methods in a straightforward and simple way. However there is no tool nor standard scoring method for some disease specific instruments such as EORTC and ALLSS. EORTC is valid instrument but lacks the related reference documents in industry practice. ALLSS is a newly developed for Acute Lymphoblastic Leukemia; it's not valid instrument, and no standard scoring methods can be referenced.

This paper is focused on EORTC QLQ-C30 and ALLSS PRO data analysis.

### EORTC QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ-C30)

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 clinical trials. The analysis we performed was based on the latest version 3.

The EORTC QLQ-C30 is a 30-item questionnaire that incorporates fifteen multi-item scales: a global health status/ quality-of-life scale, five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and 6 single items (dyspnea, insomnia,

appetite loss, constipation, diarrhea, financial difficulties).

The two items of the overall health and quality of life scales use a 7-point categorical scale ranging from 1-“Very poor” to 7-“Excellent”. All other items are scored on a 4 point categorical scale ranging from 1 “Not at All’ to 4 “Very Much”. All scales and single items are linearly transformed to a 0-100 scale. For the five functioning scales and the global quality of life scale, a higher score represents a better level of functioning. For the symptom scales and items, a higher score corresponds to a higher level of symptomatology/problems.

### ACUTE LYMPHOBLASTIC LEUKEMIA SYMPTOM SCALE (ALLSS)

The Acute Lymphoblastic Leukemia Symptom Scale (ALLSS) is a 12 item measure assessing the presence of ALL-specific symptoms. The symptoms in ALLSS include: fatigue (2 items), bleeding, bruising, joint/bone pain, fever, frequent infections, lack of appetite, night sweats, swollen nodes, and itch (one item for each symptom). Each item uses one of two 5-point response scales from 0 to 4 where 0 is for ‘Not at All’ or ’Never’ and 4 is for ‘Extremely’ or ’Always’ depending in the question. A higher score represents a worse conditions, with the exception of the question regarding ability to eat, in which we revised the score in our analysis. Scores will be derived as the sum of the 12 scores and can take any integer value from 0 to 48.

## ANALYSIS METHODS

Per Statistical Analysis Plan, the statistical analyses include:

- Descriptive Summaries by visit: Summary tables of change from baseline in EORTC QLQ-C30 scales/items, sum of the scores, and ALLSS itemized scores; Plots on cumulative distribution and mean changes from baseline by treatment group.
- Time to deterioration in EORTC QLQ-C30 GHS/QoI, all EORTC QLQ-C30 subscales, and ALLSS sum score: summary tables with hazard ratios, Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles, the number of subjects with events, the number of subjects censored, and the pattern of censoring; Kaplan Meier Plot of Time to Deterioration.
- Repeated measure analysis for EORTC QLQ-C30 subscales
- Subgroup analysis of time to deterioration in EORTC QLQ-C30 GHS/QoL including age group, prior salvage status, prior HSCT status, gender, ethnicity, race, region, baseline bone marrow blasts level

## ADAM STRUCTURE AND SPECIFICATIONS

We developed two efficacy datasets (ADQS and ADTTEQS) for PRO data, both use ADaM Basic Data Structure (BDS) and have a data structure of one record per subject per parameter per visit.

### ADQS - QUESTIONNAIRES ANALYSIS DATA

PRO efficacy analysis data (ADQS) includes EORTC-QLQ-C30 global health status/quality of life (GHS/QoL) scale, 5 functional scales, 3 symptom scales, 6 single items, acute lymphoblastic leukemia symptom scale (ALLSS) summary score, and 12 individual item scores.

The key derived parameters are listed below:

| Variable Name | Parameter Code | Parameter | Comments |
|---|---|---|---|
| EORTC Parameters | | | |
| AVAL | EC30_PF | EORTC-QLQ-C30 Physical Functioning | At each Subject/Visit level if at least half the values of QS.AVAL are non-missing where QS.PARAMCD in ('C30_01', 'C30_02', 'C30_03', 'C30_04', 'C30_05') then calculate a raw score<br>raw score=mean of the non-missing QS.QSSTRESN (i.e. ($I_1$ + $I_2$ + ... $I_n$)/n), where n=number of non-missing AVALs)<br><br>Set AVAL to be (1-(raw score-1)/3)*100 |
| AVAL | EC30_RF | EORTC-QLQ-C30 Role functioning | At each Subject/Visit level if at least half the values of QS.AVAL are non-missing where QS.PARAMCD in ('C30_06', 'C30_07') then calculate a raw score<br>raw score=mean of the non-missing QS.QSSTRESN (i.e. ($I_1$ + $I_2$ + ... $I_n$)/n), where n=number of non-missing AVALs)<br><br>Set AVAL to be (1-(raw score-1)/3)*100 |
| AVAL | EC30_EF | EORTC-QLQ-C30 Emotional Functioning | At each Subject/Visit level if at least half the values of QS.AVAL are non-missing where QS.PARAMCD in ('C30_21', 'C30_22', 'C30_23', 'C30_24') then calculate a raw score<br>raw score=mean of the non-missing QS.QSSTRESN (i.e. ($I_1$ + $I_2$ + ... $I_n$)/n), where n=number of non-missing AVALs)<br><br>Set AVAL to be (1-(raw score-1)/3)*100 |
| AVAL | EC30_CF | EORTC-QLQ-C30 Cognitive Functioning | At each Subject/Visit level if at least half the values of QS.QSSTRESN are non-missing where QS.PARAMCD in ('C30_20', 'C30_25') then calculate a raw score<br>raw score=mean of the non-missing scores (i.e. ($I_1$ + $I_2$ + ... $I_n$)/n), where n=number of non-missing AVALs)<br><br>Set AVAL to be (1-(raw score-1)/3)*100 |
| AVAL | EC30_SF | EORTC-QLQ-C30 Social Functioning | At each Subject/Visit level if at least half the values of QS.QSSTRESN are non-missing where QS.PARAMCD in ('C30_26', 'C30_27') then calculate a raw score<br>raw score=mean of the non-missing QS.AVAL (i.e. ($I_1$ + $I_2$ + ... $I_n$)/n), where n=number of non-missing AVALs)<br><br>Set AVAL to be (1-(raw score-1)/3)*100 |
| AVAL | EC30_F | EORTC-QLQ-C30 Fatigue | At each Subject/Visit level if at least half the values of QS.QSSTRESN are non-missing where QS.PARAMCD in ('C30_10', 'C30_12','C30_18') then calculate a raw score<br>raw score=mean of the non-missing QS.AVAL (i.e. ($I_1$ + $I_2$ + ... $I_n$)/n), where n=number of non-missing AVALs)<br><br>Set AVAL to be ((raw score-1)/3)*100 |

| Variable Name | Parameter Code | Parameter | Comments |
|---|---|---|---|
| EORTC Parameters | | | |
| AVAL | EC30_NV | EORTC-QLQ-C30 Nausea and Vomiting | At each Subject/Visit level if at least half the values of QS.AVAL are non-missing where QS.PARAMCD in ('C30_14', 'C30_15') then calculate a raw score<br>raw score=mean of the non-missing QS.AVAL (i.e. $(I_1 + I_2 + ... I_n)/n$), where n=number of non-missing AVALs)<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_PA | EORTC-QLQ-C30 Pain | At each Subject/Visit level if at least half the values of QS.QSSTRESN are non-missing where QS.PARAMCD in ('C30_09', 'C30_19') then calculate a raw score<br>raw score=mean of the non-missing QS.AVAL (e.g. $(I_1 + I_2 + ... I_n)/n$), where n=number of non-missing AVALs)<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_DY | EORTC-QLQ-C30 Dyspnea | At each Subject/Visit level if QS.PARAMCD='C30_8' then calculate raw score=QS.AVAL<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_SL | EORTC-QLQ-C30 Insomnia | At each Subject/Visit level if QS.PARAMCD='C30_11' then calculate raw score=QS.QSSTRESN<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_AP | EORTC-QLQ-C30 Appetite Loss | At each Subject/Visit level if QS.PARAMCD='C30_13' then calculate raw score=QS.AVAL<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_CO | EORTC-QLQ-C30 Constipation | At each Subject/Visit level if QS.PARAMCD='C30_16' then calculate raw score=QS.AVAL<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_DI | EORTC-QLQ-C30 Diarrhea | At each Subject/Visit level if QS.PARAMCD='C30_17' then calculate raw score=QS.QSSTRESN<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_FI | EORTC-QLQ-C30 Financial Difficulties | At each Subject/Visit level if QS.PARAMCD='C30_28' then calculate raw score=QS.QSSTRESN<br><br>Set AVAL to be ((raw score-1)/3)*100 |
| AVAL | EC30_GHS | EORTC-QLQ-C30 Global Health Status / QoL | At each Subject/Visit level if at least half the values of QS.AVAL are non-missing where QS.PARAMCD in ('C30_29', 'C30_30') then calculate a raw score<br>raw score=mean of the non-missing QS.QSSTRESN (i.e. $(I_1 + I_2 + ... I_n)/n$), where n=number of non-missing AVALs)<br><br>Set AVAL to be ((raw score-1)/6)*100 |

| Variable Name | Parameter Code | Parameter | Comments |
|---|---|---|---|
| ALLSS parameters | | | |
| AVAL | ALLSSTOT | ALLSS Total score | The integer part of sum of AVAL of ALLSS questions 1 through 12 (ALLSS1-ALLSS12), total score can take any integer value from 0 to 48. The Scores on question 11 "Able to eat" need to be reversed to obtain a uniform direction of all scales, so that for all ALLSS questions higher scores correspond to dis-improvement<br>At each Subject/Visit level if the values of QS.AVAL are non-missing where QS.PARAMCD contains ('ALLSS') then calculate a raw total score. raw total score=int(sum of non-missing QS.QSSTRESN (i.e. (I1 + I2 + ... In))), where n=number of non-missing AVALs),<br>If any item of ALLSS is missing, a sum score on ALLSS will not be calculated. |
| AVAL | ALLSSRSP | ALLSS Response | ALLSS responder if the change at a visit in ALLSS sum score from baseline is larger than or equal to half of the standard deviation of the ALLSS sum score at baseline<br>0 if std(CHG) of post-baseline ALLSSTOT <50%; 1 if sdt(CHG) of post-baseline ALLSSTOT >=50%; missing if PCHG of post-baseline ALLSSTOT is missing. |

## ADTTEQS - QUESTIONNAIRES ANALYSIS DATA

Time to event PRO efficacy analysis data (ADTTEQS) were organized by endpoints (PARAM/PARAMCD). Time to events endpoints include time to deterioration/death (or deterioration only) in EORTC GHS/QoL, functional/symptom subscales, and ALLSS summary score or individual item scores

The key derived parameters are listed below:

| Variable Name | Parameter Code | Parameter | Comments |
|---|---|---|---|
| EORTC Parameters | | | |
| EVNTDESC | TTDDEGHS | Time to Deterioration/Death in EORTC-QLQ-C30 Global Health Status/QoL (day) | 'DETERIORATION' if subject had >= 10-point decrease from baseline in GHS/QoLwhere PARAMCD='C30_QL2';<br>For subject who died (ADSL.DTHDT is not missing):<br>a. "NO DATA" if subject has missing ADQS.CHG and didn't die;<br>b. 'DEATH' if subject died before or on safety follow up;<br>c. 'DEATH' if subject died and didn't have safety follow up visit,<br>d. 'NO DETERIORATION/DEATH' if subject died after safety follow up visit or subject died in LTFU period (ADSL.DTHDT > . and ADSL.LTFUPFL='Y');<br>e. "NO DETERIORATION/DEATH' if subjects who missed safety follow up visit but did have a long term follow up and then died after LTFU;<br>f. 'NO DETERIORATION/DEATH' if subjects died on the same day as the SFU visit (from the LOOKUP_VISIT dataset) and also has a LTFU visit on the same date.<br><br>if a subject died and had deterioration, then the earliest event (deterioration or death), whichever comes first.<br><br>Otherwise, set to 'NO DETERIORATION/DEATH'. |
| CNSR | TTDDEGHS | Time to Deterioration/Death in EORTC-QLQ-C30 Global Health Status/QoL (day) | if EVNTDESC eq 'DETERIORATION' or 'DEATH' then 0<br>else 1; |

| Variable Name | Parameter Code | Parameter | Comments |
|---|---|---|---|
| EORTC Parameters | | | |
| EORTC Parameters | TTDDEGHS | Time to Deterioration/Death in EORTC-QLQ-C30 Global Health Status/QoL (day) | if EVNTDESC eq "NO DETERIORATION/DEATH" then do;<br>1) 'DEATH AFTER SAFETY FOLLOW UP' if subject died after safety follow up visit and didn't enter LTFU<br>2) else 'DEATH DURING LONG TERM FLOLLOW UP' if subject died in LTFU period;<br>3) else 'LAST ASSESSMENT SHOWING NO DETERIORATION/DEATH' |
| ADT | TTDDEGHS | Time to Deterioration/Death in EORTC-QLQ-C30 Global Health Status/QoL (day) | 1) if EVNTDESC in ( "DETERIORATION",'DEATH'), then the earliest deterioration or death, whichever comes first.<br>a. the first QS.QSDTC where CHG <= -10.0 and PARAMCD='C30_QL2';<br>b. If subject died before or on safety follow up;<br><br>2)if EVNTDESC is "NO DETERIORATION/DEATH" then subject censored on their last EORTC QLQ-C30 subscale assessment date (last ADQS.ADT or planned visit date where QS.QSSTRESN > . and ADQS.PARAMCD='C30_QL2').<br><br>ADT is missing if QS.QSDTC is missing. |
| STARTDT | TTDDEGHS | Time to Deterioration/Death in EORTC-QLQ-C30 Global Health Status/QoL (day) | First Exposure to Treatment date (ADSL.TRTSDT) |
| ALLSS Parameters | | | |
| EVNTDESC | TTDATOT | Time to Deterioration in ALLSS Total score (day) | "NO DATA" if subject has missing ADQS.CHG, 'DETERIORATION' if subject had CHG of post-baseline >=50% std of baseline (ADQS.CHG>=0.5 std (ADQS.BASE)) in ALLSS sum score where ADQS.PARAMCD='ALLSSTOT'; Otherwise 'NO DETERIORATION' |
| CNSR | TTDATOT | Time to Deterioration in ALLSS Total score (day) | If EVNTDESC in ("DETERIORATION") then 0;<br>else if EVNTDESC eq "NO DETERIORATION" then 1; |
| CNSDTDSC | TTDATOT | Time to Deterioration in ALLSS Total score (day) | if EVNTDESC eq "NO DETERIORATION" then 'LAST ASSESSMENT SHOWING NO DETERIORATION' |
| ADT | TTDATOT | Time to Deterioration in ALLSS Total score (day) | 1) if EVNTDESC in ( "DETERIORATION"), then the earliest deterioration<br><br>2)if EVNTDESC is "NO DETERIORATION" then subject censored on their last ALLSS sum score assessment date (last ADQS.ADT where PARAMCD='ALLSSTOT');<br><br>ADT is missing if ADQS.ADT is missing. |
| STARTDT | TTDATOT | Time to Deterioration in ALLSS Total score (day) | First Exposure to Treatment date (ADSL.TRTSDT) |

## CONSIDERATIONS AND DISCUSSION

### MISSING DATA

Per FDA Guideline: The resulting missing data can introduce bias and interfere with the ability to compare effects between testing groups.

Missing data are not imputed in our analysis due to various reasons. There are about 15% missing data and some data imputation rules were applied. The data imputation may increase the analysis complexities but can reduce bias.

### SDTM/ADAM MAPPINMG STRATEGY

Both subject reported date and study coordinator reported date are collected in CRF. The decision on which date should be used in AdaM data could be tricky. Analysis date is especially important for time to event analysis, patient reported date can have high incidents of missing data, but study coordinator date may not be as accurate as patient report date.

## CONCLUSION

This paper provides some examples of statistical methods and ADaM data specifications in implementing EORTC and ALLSS HRQOL Patient Report Outcomes data. It explores in detail on establishing ADaM BDS data with examples on derivations of computing scores in ADaM data specifications. Lastly, this paper explains the tradeoff of having data imputation in ADaM datasets and limitations in incorporating imputation.

## REFERENCES

EORTC QLQ-C30 Scoring Manual http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_qlq-c30_english.pdf)

Patient-Reported Outcomes to Support Medical Product Labeling Claims: FDA Perspective http://ac.els-cdn.com/S1098301510606377/1-s2.0-S1098301510606377-main.pdf?_tid=b042a3fe-ecc7-11e6-a67b-00000aacb35e&acdnat=1486425488_bff8910bc26e95356e7a1f2db05a51bd

Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf

## ACKNOWLEDGMENTS

Appreciation goes to Wenyun Ji for reviewing this paper and providing the comments.

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