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Time-to-Deterioration for Patients Reported Outcomes

Christine Teng, MRL, Merck & Co., Inc., Rahway, NJ, USA

ABSTRACT

In oncology studies, time-to-deterioration (TTD) in Patient-Reported Outcomes (PRO) assessments serves as an important endpoint, measuring how cancer treatment affects a patient's quality of life and symptom burden. TTD is typically defined as the duration from a specified starting point—such as the initiation of treatment or a baseline assessment—until a patient indicates a clinically decline in their health status. This decline may be reflected by heightened symptoms, diminished quality of life, or an increased need for medical intervention. The definitions of TTD can vary depending on the primary focus of the specific disease area, and the intended objectives of the assessment.

The two common applied definitions of TTD for PROs evaluation are (1) time to first deterioration and (2) time to first confirmed deterioration. This paper seeks to discuss a method for designing ADaM analysis datasets (ADPRO/ADPROTTE) that effectively support both types of TTD analyses.

BACKGROUND

Patient-reported outcomes (PRO) measures are commonly assessed in cancer trials, representing an important mechanism for incorporating patients' experiences and perspectives into their care. This approach greatly enhances overall participation in delivering cancer care. According to the U.S. 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, where a PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. There are various types of PRO measures that assess the quality of life of patients. Time-to-Deterioration (TTD), as measured by patient-reported outcomes, offers critical insights into the real-world impacts of cancer treatments on patients' lives. By focusing not just on survival but also on quality of life, oncology clinical trials can provide a more holistic understanding of treatment efficacy and patient well-being.

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. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) will be used to illustrate the ADaM specifications and code design to support TTD analysis setup. However, the statistical analysis of TTD data is out of the scope of this paper.

Below shows an example of TTD endpoint and definition from a statistical analysis plan (SAP).

Objective/Hypothesis	Endpoint
• Objective: To evaluate changes from baseline and TTD in HRQoL scores in all treatment groups, using two general instruments (EORTC QLQ-C30, and EuroQoL EQ-5D-5L)	• Change from baseline in the global health status/QoL of the EORTC QLQ-C30 (items 29 and 30) • Change from baseline in the physical functioning scales of the EORTC QLQ-C30 • Change from baseline in the VAS as assessed using the EQ-5D-5L • **TTD in the global health status/QoL of the EORTC QLQ-C30** • TTD in the EQ-5D-5L VAS

TTD is defined as the time from baseline to first onset of PRO deterioration. Deterioration in the global health status/quality of life is defined as a 10 points or greater worsening from baseline, with or without subsequent confirmation, under a right-censoring rule by censoring at the last assessment prior to cutoff date if it has no event of deterioration prior to cutoff date.

ADAM BASIC DATA STRUCTURE (BDS) and SPECIFICATIONS

There are two ADaM BDS datasets: ADPRO and ADPROTTE. The ADPRO dataset includes both the raw details and the derived analysis data, incorporating changes from baseline scores to identify whether a patient's outcome over time is worsening, stable, or improving. Conversely, ADPROTTE is specifically designed to capture time-to-event (TTE) analysis data based on the change from baseline category information derived from ADPRO. The events in this analysis can represent either improvement or deterioration. Although this paper will emphasize time-to-deterioration (TTD), the programming concepts applicable to TTE will remain consistent for time-to-improvement as well.

EORTC QLQ-C30

The EORTC QLQ-C30 is the most utilized cancer-specific measure of health-related quality of life (HRQoL), comprising 30 items that assess five functional dimensions: physical functioning (PF2), role functioning (RF2), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF). Additionally, it includes three symptom items: fatigue (FA), nausea/vomiting (NV), and pain (PA), alongside six single items that evaluate dyspnea (DY), sleep disturbance (SL), appetite loss (AP), constipation (CO), diarrhea (DI), and financial impact (FI). The instrument also features a global health and quality of life scale (QL2). In the global health status/quality of life and functional scales, higher scores indicate better functioning, whereas higher values in the symptom scales and items signify greater symptom severity. PARCAT1 is used to keep the measure name(s) and version(s), which is typically included in QS.QSCAT. PARAM has the description of the analysis parameter (e.g., individual item or summary score). The value of PARAM may match the value stored in QS.QSTEST for parameters existing in the input SDTM QS dataset. Individual parameters are needed for each summary score. PARCAT2 is created for PRO measures where summary scores are calculated to indicate whether PARAM represents an item or a summary score, where the summary score calculated is dependent on the instrument scoring manual. PARAMN is numeric representation of PARAM.

ADPRO PARAM Value for QLQ-C30

Collected PARAM	PARAMN	PARCAT2
Trouble with Strenuous Activities	1	Functional scales
Trouble Taking Long Walk	2	Functional scales
Trouble Taking Short Walk	3	Functional scales
Bed or Chair During Day	4	Functional scales
Need Help Caring For self	5	Functional scales
Limited Daily Activities	6	Functional scales
Limited Hobbies or Leisure	7	Functional scales
Short of Breath	8	Symptom scales/items
Had Pain	9	Symptom scales/items
Need Rest	10	Symptom scales/items
Trouble Sleeping	11	Symptom scales/items
Felt Weak	12	Symptom scales/items
Lacked Appetite	13	Symptom scales/items
Felt Nauseated	14	Symptom scales/items
Vomited	15	Symptom scales/items
Constipated	16	Symptom scales/items
Diarrhea Scale	17	Symptom scales/items
Tired	18	Symptom scales/items
Pain Interfere with Daily Activities	19	Symptom scales/items
Difficulty Concentrating	20	Functional scales
Feel Tense	21	Functional scales
Worry	22	Functional scales
Feel Irritable	23	Functional scales
Feel Depressed	24	Functional scales
Difficulty Remembering	25	Functional scales
Condition Interfered with Family Life	26	Functional scales
Condition Interfered with Social Life	27	Functional scales
Condition Caused Financial Difficulty	28	Symptom scales/items
Overall Health	29	Global health status/QoL
Overall Quality of Life	30	Global health status/QoL

Derived PARAM	PARAMCD	PARCAT2
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

Table 1. Parameters related to Questionnaire QLQ-C30

ADPRO Categorical Variables used by ADPROTTE (QL2 and PF2 only in this example)

Variable Name	Variable Label	Define Derivation
CHGCAT1	Change from Baseline Category 1	Derive the Improved/Stable/Worsened status based on change from baseline: 1. For PARAMCD in ("QL2" and "PF2") and PARCAT2 of "Functional scales" or "Global health status/QoL": Change >= 10 is a status of Improved, <= -10 is Worsened and change > -10 and < 10 is Stable
CHGCAT1N	Change from Baseline Category 1 (N)	Numeric code for CHGCAT1. 1: Improved 2: Stable 3: Worsened

Table 2. ADPRO variable CHGCAT1N is referenced in ADPROTTE

ADPRO Window Based Variables

Variable Name	Variable Label	Define Derivation
ADT	Analysis Date	QS.QSDTC
AVISIT	Analysis Visit	_awtgt

AWTARGET	Analysis Window Target	_awtgt
AWTDIFF	Analysis Window Diff from Target	The absolute difference between ADY and AWTARGET when both are valued
AWLO	Analysis Window Beginning Timepoint	_awtgt
AWHI	Analysis Window Ending Timepoint	_awtgt
ANL01FL	Analysis Flag 01	For each participant and each parameter and each AVISIT, flag the one with smallest AWTDIFF and largest ADTM and sequence number.

Table 3. _awtgt is a method to define window range as specified in SAP

Key Variables and Value (QLQ0101-QLQ0130 are collected result)

Dataset	Parameter Identifier	Variable	Define Derivation
ADPRO	QLQ0101, QLQ0102, QLQ0103, QLQ0104, QLQ0105, QLQ0106, QLQ0107, QLQ0108, QLQ0109, QLQ0110, QLQ0111, QLQ0112, QLQ0113, QLQ0114, QLQ0115, QLQ0116, QLQ0117, QLQ0118, QLQ0119, QLQ0120, QLQ0121, QLQ0122, QLQ0123, QLQ0124, QLQ0125, QLQ0126, QLQ0127, QLQ0128, QLQ0129, QLQ0130, QL2, PF2, RF2, EF, CF, SF, FA, NV, PA, DY, SL, AP, CO, DI, FI	PARCAT1	EORTC QLQ-C30
ADPRO	QLQ0101, QLQ0102, QLQ0103, QLQ0104, QLQ0105, QLQ0106, QLQ0107, QLQ0120, QLQ0121, QLQ0122, QLQ0123, QLQ0124, QLQ0125, QLQ0126, QLQ0127, PF2, RF2, EF, CF, SF	PARCAT2	Functional Scales

ADPRO	QLQ0108, QLQ0109, QLQ0110, QLQ0111, QLQ0112, QLQ0113, QLQ0114, QLQ0115, QLQ0116, QLQ0117, QLQ0118, QLQ0119, QLQ0128, FA, NV, PA, DY, SL, AP, CO, DI, FI	PARCAT2	Symptom Scales/items
ADPRO	QLQ0129, QLQ0130, QL2	PARCAT2	Global Health Status/QoL
ADPRO	QLQ0101, QLQ0102, QLQ0103, QLQ0104, QLQ0105, QLQ0106, QLQ0107, QLQ0108, QLQ0109, QLQ0110, QLQ0111, QLQ0112, QLQ0113, QLQ0114, QLQ0115, QLQ0116, QLQ0117, QLQ0118, QLQ0119, QLQ0120, QLQ0121, QLQ0122, QLQ0123, QLQ0124, QLQ0125, QLQ0126, QLQ0127, QLQ0128, QLQ0129, QLQ0130	AVAL	QS.QSSTRESN
ADPRO	QL2, PF2, RF2, EF, CF, SF, FA, NV, PA, DY, SL, AP, CO, DI, FI	AVAL	For each USUBJID and ADT, derive AVAL using the algorithm provided in the QLQC30 manual (i.e., calculate the PRO score for every participant at each time point).
ADPRO	QLQ0101, QLQ0102, QLQ0103, QLQ0104, QLQ0105, QLQ0106, QLQ0107, QLQ0108, QLQ0109, QLQ0110, QLQ0111, QLQ0112, QLQ0113, QLQ0114, QLQ0115, QLQ0116, QLQ0117, QLQ0118, QLQ0119, QLQ0120, QLQ0121, QLQ0122, QLQ0123, QLQ0124, QLQ0125, QLQ0126, QLQ0127, QLQ0128, QLQ0129, QLQ0130	AVALC	QS.QSSTRESC

Table 4. ADPRO PARAMCD

Sample define.xml output for PARCAT1

Variable	Where Condition	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
PARCAT1 VLM		Parameter Category 1	text	14		Assigned See Parameter Value Level Metadata
	PARAMCD IN ("QLQ0101" (QLQ01-Trouble with Strenuous Activities), "QLQ0102" (QLQ01-Trouble Taking Long Walk), "QLQ0103" (QLQ01-Trouble Taking Short Walk), "QLQ0104" (QLQ01-Bed or Chair During Day), "QLQ0105" (QLQ01-Need Help Caring for Self), "QLQ0106" (QLQ01-Limited Daily Activities), "QLQ0107" (QLQ01-Limited Hobbies or Leisure),		text	14		Assigned EORTC QLQ-C30

ADPROTTE (ePRO Data for the Time to Event Analyses)

ADPROTTE reads in ADPRO to identify the specific endpoint designated for analysis. In this instance, we focus solely on the QL2 and PF2 PARAMCD values, along with their corresponding CHGCAT1/CHGCAT1N value that indicate a worsening category. The naming convention for PARAMCD conveys details regarding the type of TTD method and the endpoint. For analyses conducted without confirmation (Traditional), PARAMCD is prefixed with TTDP, which denotes the primary analysis for TTD in this example. Conversely, for analyses conducted with confirmation (True), PARAMCD is prefixed with TTDS, representing a secondary analysis for TTD. The endpoint is appended as a suffix to the PARAMCD (e.g., TTDP**QL2**).

ADPROTTE Key Variables and Value

Dataset	Parameter Identifier	Variable	Define Derivation	Comment
ADPROTTE	TTDPQL2, TTDPPF2, TTDSQL2, TTDSPF2	PARCAT1	EORTC QLQ-C30	
ADPROTTE	TTDPQL2, TTDPPF2, TTDSQL2, TTDSPF2	PARCAT2	"Traditional" - if PARAMCD has prefix "TTDP" "True" - if PARAMCD has prefix "TTDS"	

ADPROTTE	TTDSQL2, TTDSPF2	ADT	Read data from ADPRO where ADPRO.PFASFL="Y" and ADPRO.PARAMCD = "QL2", "PF2" (1) Find the date of the following scenario (event): for records with appropriate ADPRO.PARAMCD as above, find the earliest record with ADPRO.CHGCAT1= "Worsened" and confirmed by the an assessment of ADPRO.CHGCAT1 ="Worsened" in the next consecutive analysis window. (2) If there is no record from (1) ,i.e., censor, then do the following: if there is at least one post-baseline valid record where appropriate ADPRO and ADPRO.AVISITN is greater than 1, then assign ADT to the most recent date of post-baseline valid records. Otherwise, assign ADT= ADSL.TRTSDT.	Note 1: Confirmed deterioration = True deterioration
ADPROTTE	TTDPQL2, TTDPPF2	ADT	Read data from ADPRO where ADPRO.PFASFL="Y" and ADPRO.PARAMCD = "QL2", "PF2, for TTDPQL2, TTDPPF2 , respectively (1) Find the date of the following scenario (event): for records with appropriate ADPRO.PARAMCD as above, find the earliest record with ADPRO.CHGCAT1= "Worsened" (2) If there is no record from (1) ,i.e., censor, then do the following: if there is at least one post-baseline valid record where appropriate ADPRO.PARAMCD , then assign ADT to the most recent date of post-baseline valid records. Otherwise, assign ADT= ADSL.TRTSDT .	Traditional = Deterioration that does not require a confirmation at the next visit window

ADPROTTE	TTDSQL2, TTDPQL2, TTDSPF2, TTDPPF2	EVNTDESC	If there is an event for PARAMCD= TTDSQL2, TTDPQL2 then assign "Deteriorated in QoL"; if there is an event for PARAMCD= TTDSPF2, TTDPPF2 then assign "Deteriorated in Physical Function"; Otherwise if there is no event and there is at least one valid post-baseline record, then assign "Censored at last assessment" Otherwise if there is no event and there is no valid post-baseline, then assign "Censored at baseline"	

Table 5. ADPROTTE PARAMCD

SAS MACRO DESIGN for ADPROTTE

As the changes from baseline categories (worsened, stable, improved) have already been established in ADPRO, coding the TTD endpoint becomes more straightforward by providing just two parameters: 1. PARAMCD, which will be used for the endpoint; 2. CONFIRMED, which will help in selecting the TTD approach. Furthermore, utilizing SAS format can reduce the need for hard-coded logic to derive TTD PARAMCD in ADPROTTE. ADPROTTE program can add or remove PARAMCD as needed with minimal update.

```
value $ ttds
  'QL2'='TTDSQL2'
  'PF2'='TTDSPF2';
value $ ttdp
  'QL2'='TTDPQL2'
  'PF2'='TTDPPF2';
value $ ttdparm
  'TTDSQL2'='Time to True Deterioration for QLQ-C30 Global Health Status/QoL
(QL2)'
  'TTDSPF2'='Time to True Deterioration for Physical Functioning (PF2)'
  'TTDPQL2'='Time to First Deterioration for QLQ-C30 Global Health
Status/QoL (QL2)'
  'TTDPPF2'='Time to First Deterioration for Physical Functioning (PF2)';
invalue ttdparmn….
value ttdcat….
```

```
%macro ttdc (paramcd=PF2, confirmed=Y);
:
:
%if &confirmed.=Y %then %do;
      paramcd2=put(paramcd,$ttds.);
      parcat2='True';
```

```
%end;
%else %if &confirmed.=N %then %do;
    paramcd2=put(paramcd,$ttdp.);
    parcat2='Traditional';
 %end;
 param=put(paramcd2,$ttdparm.);
 paramn=input(paramcd2,ttparmn.);
 parcat1=trim(left(put(paramn,ttdcat.)));
:
:
%mend ttdc;
```

```
**TTDS = True/confirmed  TTDP = Traditional/not confirmed;
**Create TTDPPF2 TTDSPF2 TTDPQL2 TTDSQL2 rows;
%ttdc(confirmed=N, paramcd=PF2)
%ttdc(confirmed=Y, paramcd=PF2)
%ttdc(confirmed=N, paramcd=QL2)
%ttdc(confirmed=Y, paramcd=QL2)
```

Since the analysis timepoint is based on window rules, it is likely multiple assessments may fall into the same window (ex: unscheduled visits). In this example, according to the pre-defined confirmation specification ' … confirmed by the an assessment of ADPRO.CHGCAT1 ="Worsened" in the next consecutive analysis window', the two worsened deteriorations (TRUE deterioration) must be one visit window apart.

Example 1: Below True deterioration is on Week 4 (4, 8)

BL	Week 4	Week 8	Week 8	Week 12	Week 36
	Worsened	Stable	Worsened	Worsened	Worsened

Example 2: Below True deterioration is on Week 12 (12, 36)

BL	Week 4	Week 4	Week 8	Week 12	Week 36
	Worsened	Worsened	Stable	Worsened	Worsened

Example 3: Below True deterioration is on Week 12 if it is first and last deterioration

BL	Week 4	Week 8	Week 12
	Stable	Stable	Worsened

SUMMARY

Time to First Deterioration is suitable for the early detection of treatment effects and for capturing rapid patient experiences, while Time to Confirmed Deterioration is appropriate when there is a need for assurance that observed changes are stable and reflect true clinical deterioration. The choice between these two should be based on the specific study design, objectives, and clinical context, as well as considerations regarding regulatory expectations and the importance of capturing meaningful patient experiences. It's not very often both approaches will be used. This paper suggests an ADaM implementation strategy that incorporates ADPRO and ADPROTTE, as well as the PARAMCD naming convention, to streamline the programming derivations for TTD.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Christine Teng
Senior Principal Scientist, Statistical Programming
MRL, Merck & Co., Inc., Rahway, NJ, USA
christine_teng@merck.com