Data Visualisation of Completion Rate for PRO objectives in Oncology Clinical Trials Supporting PRO Estimands

MSR 36

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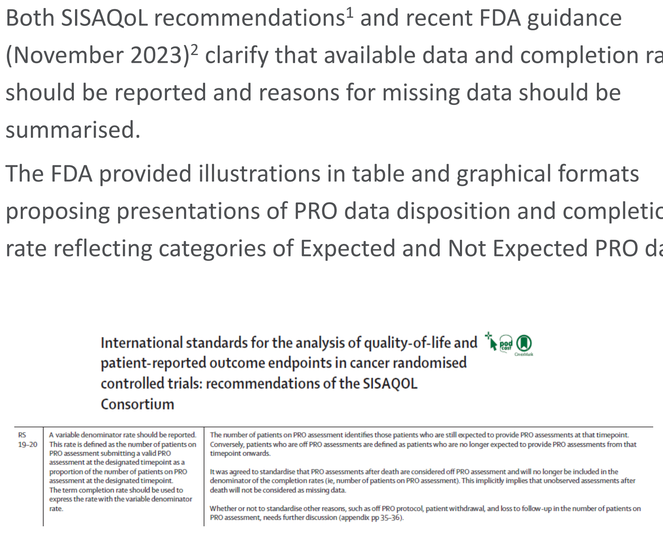
OBJECTIVE

- **Longitudinal analysis** of PRO data in oncology clinical trials is widely used to assess the effect of treatment on patient-reported quality of life, functioning and disease symptoms.
- The introduction of the ICH E9(R1) addendum estimand framework and its application in oncology clinical trials has resulted in development of PRO estimands where discontinuation of treatment, disease progression and death are identified as **intercurrent events**.
- To align with planned PRO estimands, which may focus on-treatment period or prior to disease progression, it is important to distinguish at each visit PRO data which are:
  1. **"Expected" and non-missing**
  2. **"Expected" but missing for other reasons**
  3. **"Not expected"** (e.g. after disease progression or death events)
- Our goal was to develop a data visualization solution to facilitate more effective interpretation of PRO completion rates and intercurrent events over time.

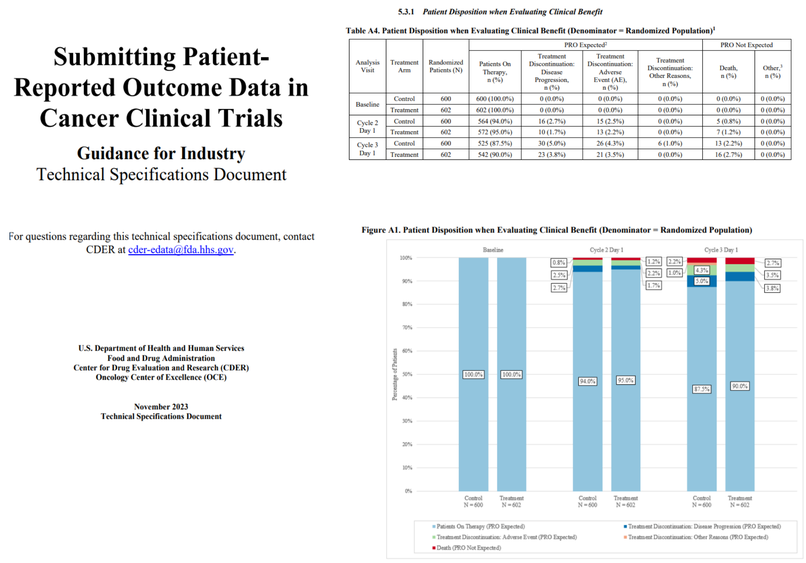
FDA and SISAQoL Guidance

- Both SISAQoL recommendations[1] and recent FDA guidance (November 2023)[2] clarify that available data and completion rate should be reported and reasons for missing data should be summarised.
- The FDA provided illustrations in table and graphical formats proposing presentations of PRO data disposition and completion rate reflecting categories of Expected and Not Expected PRO data



International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium

RS 19–20	A variable denominator rate should be reported. This rate is defined as the number of patients on PRO assessment submitting a valid PRO assessment at the designated timepoint as a proportion of the number of patients on PRO assessment at the designated timepoint. The term completion rate should be used to express the rate with the variable denominator rate.	The number of patients on PRO assessment identifies those patients who are still expected to provide PRO assessments at that timepoint. Conversely, patients who are off PRO assessments are defined as patients who are no longer expected to provide PRO assessments from that timepoint onwards. It was agreed to standardise that PRO assessments after death are considered off PRO assessment and will no longer be included in the denominator of the completion rates (ie, number of patients on PRO assessment). This implicitly implies that unobserved assessments after death will not be considered as missing data. Whether or not to standardise other reasons, such as off PRO protocol, patient withdrawal, and loss to follow-up in the number of patients on PRO assessment, needs further discussion (appendix pp 35–36).



Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Oncology Center of Excellence (OCE)

November 2023
Technical Specifications Document

5.3.1 *Patient Disposition when Evaluating Clinical Benefit*

Table A4. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)[1]

Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Expected[2]				PRO Not Expected	
			Patients On Therapy, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Treatment Discontinuation: Adverse Event (AE), n (%)	Treatment Discontinuation: Other Reasons, n (%)	Death, n (%)	Other,[3] n (%)
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	564 (94.0%)	16 (2.7%)	15 (2.5%)	0 (0.0%)	5 (0.8%)	0 (0.0%)
	Treatment	602	572 (95.0%)	10 (1.7%)	13 (2.2%)	0 (0.0%)	7 (1.2%)	0 (0.0%)
Cycle 3 Day 1	Control	600	525 (87.5%)	30 (5.0%)	26 (4.3%)	6 (1.0%)	13 (2.2%)	0 (0.0%)
	Treatment	602	542 (90.0%)	23 (3.8%)	21 (3.5%)	0 (0.0%)	16 (2.7%)	0 (0.0%)

Figure A1. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)

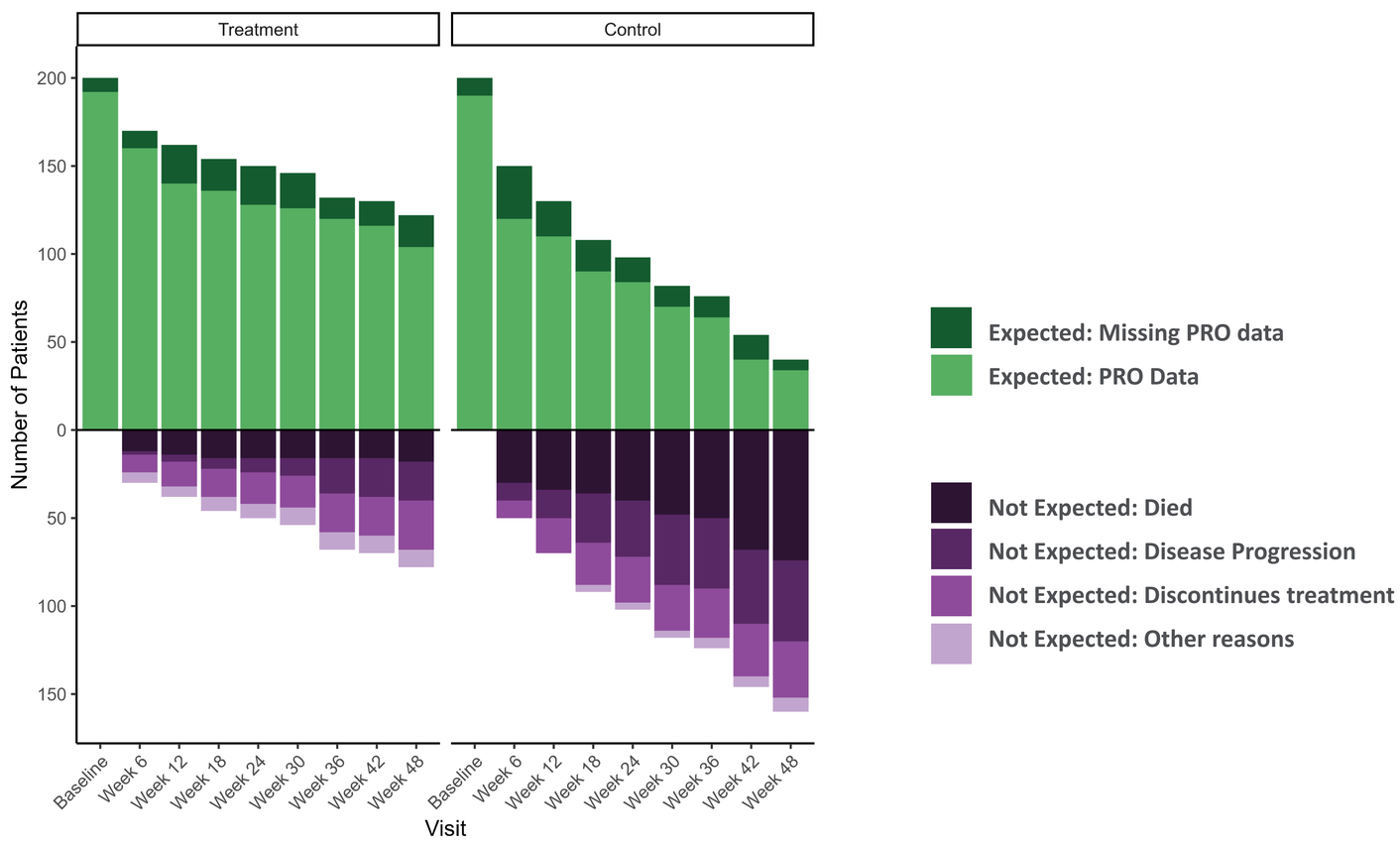
DATA VISUALISATION OF COMPLETION RATE: DIVERGENT BAR CHART

PRO DATA EXPECTED

- Above the line: green bars show "Expected" PRO data so that it is easy to view the **completion rate** and the **amount of missing data** in each treatment arm

PRO DATA NOT EXPECTED

- Below the line, bars in purple reflects data "not expected"
- The dark purple bar below the line shows the cumulative incidence of death over time – which is key in ability to interpret PRO data summaries
- The other purple bars below the line indicate visualise the impact of other intercurrent events and that PRO data is "not expected"



IMPLEMENTATION

1) Create a summary of the **counts of the number of patients in each category over time** – based on data in ADQS dataset (ADSL variables which should be copied into ADQS). In this example, PRO data collected whilst on treatment. Therefore, PRO data is not expected after stopping treatment e.g. due to either disease progression or adverse events
2) From ADQS, variable PROEXPFL can be used to identify patients at each AVISIT for PRO Expected or PRO Not Expected
3) Not expected: Died: The cumulative frequency of deaths over time (by visit) is required: compare DTHDT with nominal AVISIT date to determine deaths at each visit
4) Not expected: For each patient at AVISIT when PRO is "not expected" but patient alive use the reasons for treatment discontinuation (DCTREAS)
5) Expected: PRO data present – or PRO data is missing
6) Use the summary of counts in each category. Also possible to present as **% of randomized population** in each treatment arm (e.g. if 2:1 randomization ratio)

Implementation in R

This part creates the negative counts for the divergent bar chart

Use ggplot to create the divergent stacked bar chart

```r
#Modify counts to display below x-axis for Not Expected type
comp_rates <- comp_rates %>%
              mutate(COUNT_MOD = ifelse(
                     grepl('Not Expected:', comp_rates$CATEGORY, fixed = TRUE),
                     -1*comp_rates$COUNT, comp_rates$COUNT))

#Divergent Stacked Bar plot
breaks_values <- seq(-200, 200, by=50)

ggplot (data = comp_rates, aes(x = AVISIT, y = COUNT_MOD, fill = CATEGORY)) +
  geom_bar(stat = "identity") +
  fillScale +
  scale_x_discrete(name = ("Visit"),  guide = guide_axis(angle = 45)) +
  scale_y_continuous(name = ("Number of Patients"), breaks = breaks_values, labels = abs(breaks_values)) +
  theme_classic() +
  facet_grid(~ARM) +
  geom_hline(yintercept = 0) +
  theme(legend.position = "none")
```

Implementation in SAS

This part adds a -1 for creation of the divergent bar chart

```
/*NOTE 1: Syntax below requires a dataset (D_FIG), by treatment group, counts across completion types over timepoints*/
/*NOTE 2: Need to create formats for your completion types and treatment groups*/
/*1) Prep the dataset*/
DATA D_FIG1;
    SET D_FIG;

    /*N_COUNT is your subject count*/
    IF MISSING(N_COUNT) THEN N_COUNT = 0;
    IF CMR_TYPE > 2     THEN N_COUNT = -1 * N_COUNT; /*Creates the Divergent Bar Chart*/

    N_PERCENT = 100*(N_COUNT/N_POP);
RUN;
```

After setting up your colours and labels, use PROC SGPANEL to create the bar chart

```
%LET FONT = COURIER;
%LET FONT_SIZE = 8PT;
PROC SGPANEL DATA = D_FIG DATTRMAP = ATTR_MAP;
    FORMAT CMR_TYPE  CMR_TYPE_F.
           ARMCD     ARMCD_F.;

    /*PANEL/PLOT INFO*/
    PANELBY ARMCD / NOVARNAME HEADERATTRS=(SIZE=&FONT_SIZE. FAMILY="&FONT");
    VBAR AVISIT   / RESPONSE = N_PERCENT GROUP = CMR_TYPE GROUPDISPLAY = STACK GROUPORDER = DESCENDING MISSING NAME = "VBAR" ATTRID = SID;

    /*LEGEND INFO*/
    KEYLEGEND "VBAR" /POSITION=BOTTOM TITLEATTRS=(FAMILY="&FONT" SIZE=&FONT_SIZE.) VALUEATTRS=(FAMILY="&FONT" SIZE=&FONT_SIZE.);

    /*AXES INFO*/
    COLAXIS LABEL="Timepoint"  VALUEATTRS=(SIZE=&FONT_SIZE. FAMILY="&FONT") LABELATTRS=(SIZE=&FONT_SIZE. FAMILY="&FONT") FITPOLICY=ROTATE;
    ROWAXIS VALUES = (-100, -80, -60, -40, -20, 0, 20, 40, 60, 80, 100") VALUESDISPLAY=('100' '80' '60' '40' '20' '0' '20' '40' '60' '80' '100')
            LABEL="Pecent (%)" VALUEATTRS=(SIZE=&FONT_SIZE. FAMILY="&FONT") LABELATTRS=(SIZE=&FONT_SIZE. FAMILY="&FONT");
RUN;QUIT;TITLE;FOOTNOTE;
```

RGB colour codes (in order)

c("#145B2F","#57AF62", "#C2A5CE", "#8E4B9B", "#582864", "#2D1433")

CONCLUSIONS

Data visualisation of available PRO data and completion rate together with clinical events in a patients' journey enables clearer quantification of the potential impact of death and progression on the availability of PRO data, as well as the amount of missing data. This improves the ability to interpret PRO data over time in context of the defined PRO estimand.

[1]FDA: Submitting Patient-Reported Outcome Data in Cancer Clinical Trials: Technical Specifications Document November 2023: https:/www.fda.gov/media/173581/download

[2]Coens C, et al; Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol. 2020 Feb;21(2):e83-e96.

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