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Insights and Experience Sharing with Patient-Reported Outcome Data Analysis in FDA's Submission

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ABSTRACT

This paper discusses the implementation of recent FDA guidance on patient-reported outcome (PRO) data in regulatory submissions, including practical challenges, methodological adjustments, and benefits for clinical trials. Drawing on experiences in FDA submissions, we highlight key elements from guidance documents, such as standardized data analysis, presentation methods, and compliance requirements, to improve PRO data quality and review efficiency.

INTRODUCTION

Patient-reported outcomes (PROs) have become an increasingly important component of clinical trials, offering critical insights into treatment tolerability, patient symptoms, and quality of life. We witnessed this growing recognition by the FDA, which has begun incorporating PRO information into product labels to amplify the patient's voice in decision-making.

This paper shares our experiences working with PRO data in compliance with FDA guidelines, particularly during the NDA submission process. We discuss insights gained from adopting FDA's recommendations, practical decision-making for data analysis, and the challenges of aligning legacy methods to new technical specifications.

RECENT FDA GUIDANCE ON PRO DATA

Over recent years, the FDA has released several guidance documents aimed at improving methodologies for collecting and analyzing PRO data. These efforts are part of the FDA's patient-focused drug development initiative. Key guidance include:

1. Draft Guidance in 2022: *Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments (Series 3).*
2. Draft Guidance in 2023: *Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making (Series 4).*
3. Final Technical Specification in 2023: *Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments Using Item Response Theory.*
4. Additional Guidance in 2024:
    - *Submitting Patient-Reported Outcome Data in Cancer Clinical Trials.*
    - *Core Patient-Reported Outcomes in Cancer Clinical Trials.*

These guidance aim to standardize terminology, data collection, and analysis, enhancing data quality and supporting the FDA's ability to evaluate PROs during product review. This emphasis indicates the FDA's recognition of PROs as valuable complements to traditional clinical endpoints, helping assess risks, benefits, and treatment impact on patients' everyday lives.

Implementing Guidance: Analytical Measures and Outputs

FDA guidance strongly recommends standardizing data presentation formats, including specific tables and graphs, tailored to evaluating PRO measures in cancer clinical trials. Below are the key analysis elements adopted from our end:

1.Patient Disposition Table:

A structured summary by visit, emphasizing expected PRO data at each timepoint. This table includes a cumulative "death" column, providing transparency about patient status across visits.

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%)

Table 1. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population) from Guidance.

2.Compliance Analysis Tables:

- Available Data Rate Table: Evaluates questionnaires assessing clinical benefit, using randomized patients as the denominator.
- Completion Rate Table: Focuses on safety and tolerability questionnaires, with patients expected to complete PROs at each visit as the denominator.

Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Completed, n (%)	PRO Not Completed[8] (excluding Death), n (%)	Reason for PRO Not Completed,[9] n (%)					Death, n (%)
					Patient Unable to Complete due to Disease Progression	Patient Unable to Complete due to Adverse Event (AE)	Patient Refusal	Device Failure	Reason Unknown,[10] n (%)	
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	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%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	556 (92.7%)	39 (6.5%)	8 (1.3%)	25 (4.2%)	6 (1.0%)	0 (0.0%)	0 (0.0%)	5 (0.8%)
	Treatment	602	551 (91.5%)	44 (7.3%)	3 (0.5%)	36 (6.0%)	5 (0.8%)	0 (0.0%)	0 (0.0%)	7 (1.2%)
Cycle 3 Day 1	Control	600	542 (90.3%)	45 (7.5%)	14 (2.3%)	26 (4.3%)	0 (0.0%)	5 (0.8%)	0 (0.0%)	13 (2.2%)
	Treatment	602	539 (89.5%)	47 (7.8%)	10 (1.7%)	32 (5.3%)	5 (0.8%)	0 (0.0%)	0 (0.0%)	16 (2.7%)

Table 2. Available Data Rate for Clinical Benefit (Denominator = Randomized Population) from Guidance Table A6.

Analysis Visit	Treatment Arm	PRO Expected[12] (N)	PRO Completed, n (%)	PRO Not Completed, n (%)	Reason for PRO Not Completed,[13] n (%)			
					Patient Refusal	Patient Unable to Complete due to AE	Device Failure	Reason Unknown,[14] 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	564	542 (96.1%)	22 (3.9%)	6 (1.1%)	16 (2.8%)	0 (0.0%)	0 (0.0%)
	Treatment	572	536 (93.7%)	36 (6.3%)	5 (0.9%)	31 (5.4%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	0 (0.0%)	10 (1.9%)	5 (1.0%)	0 (0.0%)
	Treatment	542	516 (95.2%)	26 (4.8%)	5 (0.9%)	21 (3.9%)	0 (0.0%)	0 (0.0%)

Table 3. Completion Rate for Safety and Tolerability (Denominator- PRO Expected Population) from Guidance Table A7.

3.Response Distribution Analysis:

Presentation includes both tables and graphs at the item level. Percentages reflect proportional responses, summing to 100% per row. This dual format ensures robust interpretation via both numerical and visual inputs.

Analysis Visit	Treatment Arm	PRO Expected[16]	PRO Completed, n (%)	PRO Not Completed, n (%)	Response Categories,[17] n (%)			
					Not at all	A little	Quite a bit	Very much
Baseline	Control	600	600 (100.0%)	0 (0.0%)	332 (55.3%)	220 (36.7%)	31 (5.2%)	17 (2.8%)
	Treatment	602	602 (100.0%)	0 (0.0%)	313 (52.0%)	228 (37.9%)	38 (6.3%)	23 (3.8%)
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	299 (55.2%)	188 (34.7%)	34 (6.3%)	21 (3.9%)
	Treatment	572	536 (93.7%)	36 (6.3%)	268 (50.0%)	199 (37.1%)	41 (7.6%)	28 (5.2%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	225 (44.1%)	189 (37.1%)	63 (12.4%)	33 (6.5%)
	Treatment	542	516 (95.2%)	26 (4.8%)	203 (39.3%)	193 (37.4%)	71 (13.8%)	49 (9.5%)

Table 4. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example) from Guidance Table A8.

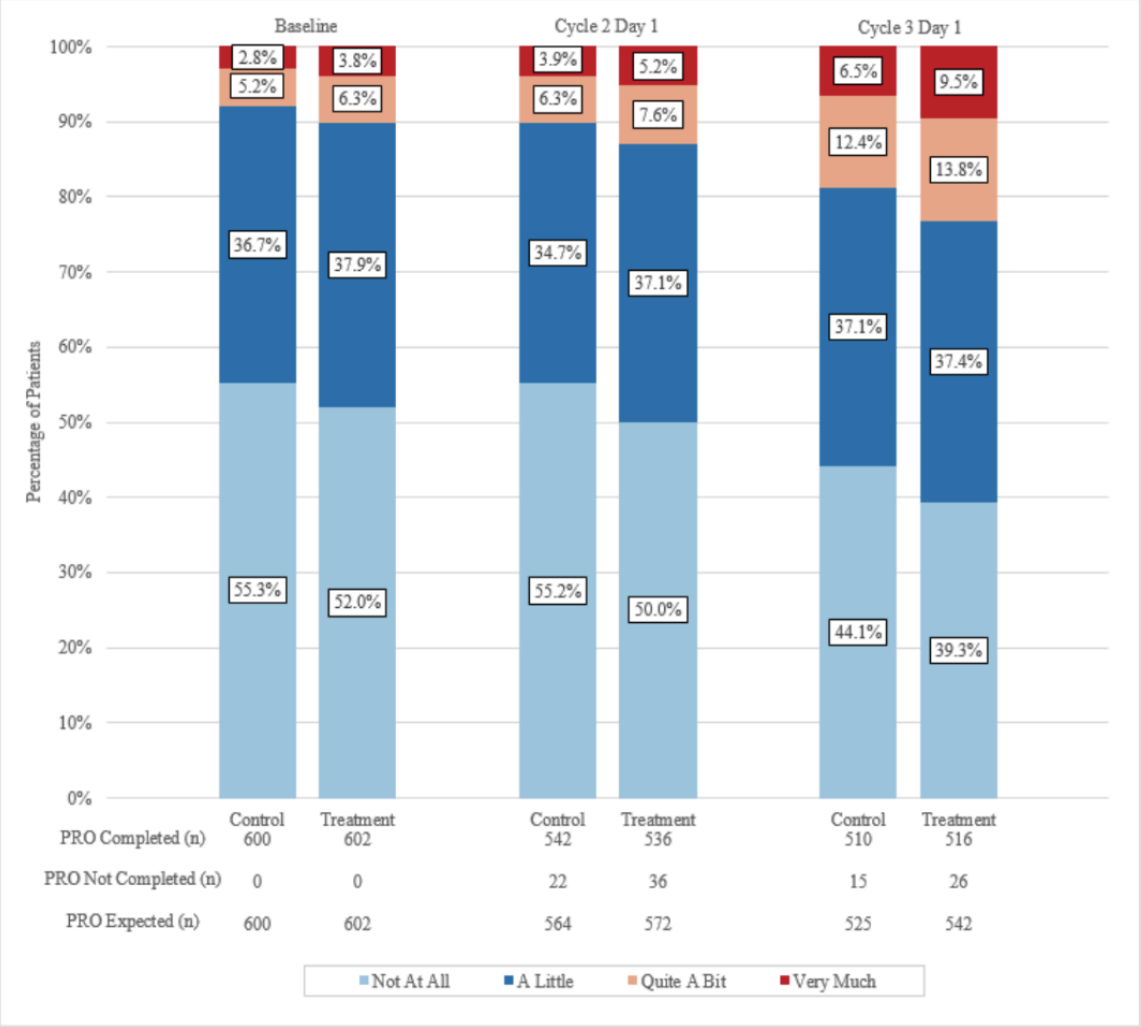

Figure 1. Distribution of Categorical Response for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed) from Guidance Figure A5.

4.Distribution in Change of Responses from Baseline
Visual and numerical evaluations of response changes from baseline. Data completeness and evolving response distributions are summarized, enhancing clarity and visualization.

Analysis Visit	Treatment Arm	PRO Expected[2]	PRO Completed n (%)	PRO Not Completed, n (%)	Change in Response Categories,[25] n (%)						
					Improving 1	Improving 2	Improving 3	No Change	Worsening 1	Worsening 2	Worsening 3
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	38 (7.0%)	11 (2.0%)	3 (0.6%)	303 (55.9%)	132 (24.4%)	38 (7.0%)	17 (3.1%)
	Treatment	572	536 (93.7%)	36 (6.3%)	33 (6.2%)	14 (2.6%)	6 (1.1%)	296 (55.2%)	141 (26.3%)	32 (6.0%)	14 (2.6%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	50 (9.8%)	24 (4.7%)	10 (2.0%)	261 (51.2%)	126 (24.7%)	29 (5.7%)	10 (2.0%)
	Treatment	542	516 (95.2%)	26 (4.8%)	44 (8.5%)	28 (5.4%)	11 (2.1%)	261 (50.6%)	123 (23.8%)	39 (7.6%)	10 (1.9%)

Table 5. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example) from Guidance Table A10.

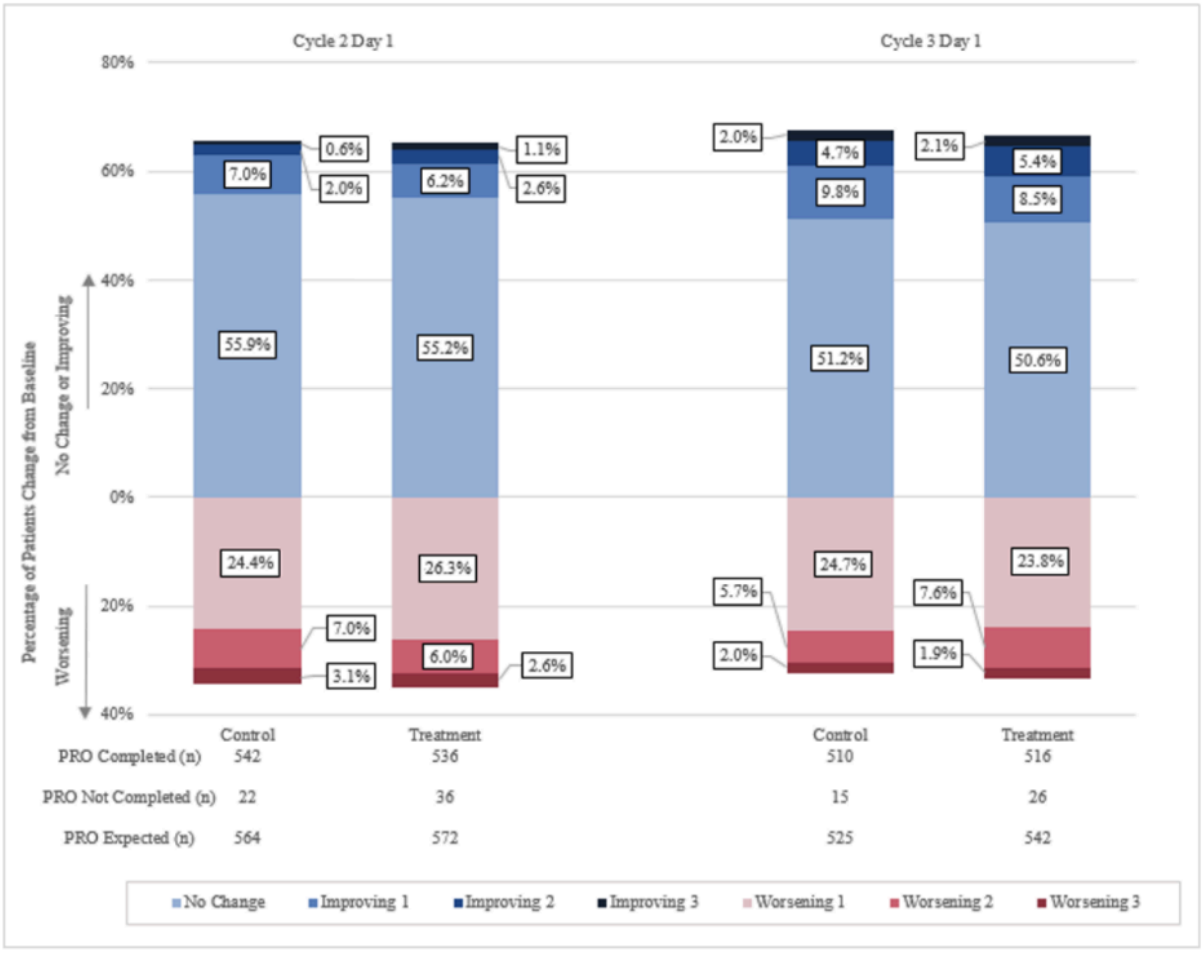

Figure 2. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed) from Guidance Figure A7.

Structuring Data: Technical and Analytical Perspectives

FDA guidance expects PRO data compliance with CDISC standards. Key requirements include:

SDTM Data Sets:

QS Domain: Captures questionnaire name, specific question details, and completion status. Missing records must be marked as 'Not Done,' with reasons summarized in analysis.

Trial Design Domain: Highlights parameters indicating adherence to Oncology PROs Technical Specifications Guidance.

ADaM Data Sets:

Data is organized using the Basic Data Structure (BDS), with newly derived variables:

Expected Flag: for each subject to specify whether the PRO parameter corresponds to a planned PRO assessment per protocol. This derivation not only reflects the patient's status at specific timepoints but also determines the appropriate timeframe for analyses. Questionnaires assessing clinical benefit are evaluated up to the end of study or patient death. Questionnaires assessing safety and tolerability are evaluated up to the end of treatment.

Complete Flag: The FDA guidance requires the inclusion of a "Complete Flag" to denote whether a PRO item or summary score was completed at a planned assessment.

Phantom Records: Missing data are accounted for through phantom record imputation, addressing skipped visits or intercurrent events that impacted data collection. The reason for non-performance is also documented, ensuring transparency in data handling.

Adding a Parameter of death visit for summarizing cumulative death by visit in Completion Rate Table: For patients with recorded death, "death by visit" is calculated. This involves: Comparing the date of death with the planned PRO visit dates, assigning the visit at which death occurred, tabulating this information at a population level, in conjunction with completion rates.

Practical Considerations

While the FDA guidance simplifies some aspects of PRO analysis, it introduces complexities when applied to real-world data. Challenges include:

- Adapting templates that consolidate large data volumes into single-page formats.
- Addressing ambiguities in the guidance that require careful interpretation.
- Balancing the inclusion of core traditional practices with newer guidance recommendations to avoid overwhelming outputs.

Through proactive planning, limitations can be mitigated by focusing on the key value derived from questionnaires and aligning data sets across studies for scalability. Drawing upon prior experience ensures efficient utilization of resources while managing potential regulatory risks.

CONCLUSION

The FDA's new guidance on patient-reported outcomes (PRO) represents a significant step forward in harmonizing PRO data analysis with the estimand framework. By thoroughly studying the guidance and incorporating it proactively into study designs, sponsors can successfully meet regulatory expectations. While implementing the recommendations can present challenges, careful preparation, thoughtful decision-making, and leveraging past experiences provide a foundation for robust and scalable PRO analyses.

Adhering to these principles ensures that data sets and outputs not only meet regulatory standards but also provide meaningful insights into patient-reported data in clinical trials.

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