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A Programmer's Perspective on Patient Reported Outcomes in Oncology Trials

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ABSTRACT

Patient reported outcomes (PRO) are used in clinical trials to assess the quality of life from the patient's perspective. Patients are asked to respond to questionnaires related to physical functioning, adverse effects of treatment, and the overall burden of such adverse effects. In addition to overall quality of life, PROs also measure treatment benefit or risk and are helpful in supporting the labelling claims and reimbursement positioning for the drug. Since PROs are directly reported by the patient, they have gained increased utility for determining the quality-of-life endpoints of a clinical trial.

This paper takes a closer look at the data collection process and the issues we may come across in PRO data in the context of clinical trials in an oncology setting. It also discusses some of the common PRO instruments in such trials and statistical analysis methods for those instruments.

INTRODUCTION

PROs are a critical data source for improving quality of care, therapies, and interventions, and for making informed decisions. For a while now, FDA has emphasized on systematically capturing patients' voice as part of the drug development process. As a part of this initiative, FDA is developing Patient Focused Drug Development (PFDD), guidance documents to address collection and submission of patient experience data and regulatory decision making. In addition, PROs play a major role in Health Technology Assessments (HTA) across different countries which can have implications on access and pricing as well.

SELECTION OF PRO STRATEGY FOR THE CLINICAL TRIAL

The first step in designing the patent reported data collection starts with defining the study endpoints for the patient report data. PRO planning should begin in the early phases of clinical trial design so that the selected PRO instruments can be implemented within clinical trial. Selection of appropriate PRO instrument for meeting the study objectives involves a good understanding of the disease or condition. FDA encourages collaboration among key stakeholders and leveraging the existing literature on PRO measurements to fit the specific needs of the study objectives. Patient and caregiver perspectives, clinician and expert perspectives can also help in understanding the disease. Specific constructs that the PRO should measure should be identified. Summarize the target population. A targeted literature review should be conducted to identify the key concepts and constructs of interest.

Existing PRO instruments for the specific disease that can effectively meet the study objectives and with high-quality evidence for good measurement properties should be assessed properly before selecting a specific instrument. PRO instruments should have reliability (produce the same results on repeated trials), ability to detect change over time, and validity (measure what it is intended to measure). Any regulatory or market access requirements should also be considered while deciding the PRO strategy. Along with feasibility to utilize the instrument in the given trial, which can be determined by patient, interviewer or clinician, and administrative factors.

PRO DATA COLLECTION

PROs are increasingly collected on a tablet or smart phone directly entered by the patient which are referred as ePRO's. Electronic data collection helps with real-time analysis of the data pinpointing the exact time of patient experience. As an alternative PRO's can be answered on a paper form.

While planning the PRO, implementation teams should identify potential risks to data collection like poor compliance by the site or subject, language skills, health literacy, etc. Mitigation strategies should be implemented for these risks in the data collection process.

STATISTICAL ANALYSIS OF PRO INSTRUMENTS

The choice of a PRO instrument should be well-defined and reliable with conceptual framework, content validity, and adequate measurement properties. The following section discusses two of the PRO instruments used in oncology trials, NCI PRO-CTCAE and PROMIS (Patient-Reported Outcomes Measurement Information System).

NCI PRO-CTCAE

PRO-CTCAE characterizes the frequency, severity, interference, and presence/absence of toxicity symptoms like pain, fatigue, diarrhea, and cutaneous side effects such as numbing or tingling in hands or feet, rash, etc. PRO-CTCAE instrument is intended to enhance the precision and reproducibility of adverse event reporting in oncology trials. It complements the information reported by the clinician on the adverse events and represents the patient experience of symptomatic adverse events.

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
1a.	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
2a.	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Figure 1: Sample Questionnaire for PRO-CTCAE

In Figure 1, items are scored from 0 to 4, with 0 representing no symptoms and 4 representing very severe or frequent symptoms or symptoms, that interfere with daily life very much.

The following statistical analyses can be performed on the PRO-CTCAE scores:

1. Summary of change in scores from baseline to post baseline at each timepoint
2. Descriptive statistics of each category at each timepoint
3. Shift tables to analyze the summary of shifts from baseline to post-baseline scores

PROMIS (Patient-Reported Outcomes Measurement Information System)

PROMIS evaluates physical, mental, and social health of adults and children.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Figure 2: Sample PROMIS Questionnaire

PROMIS scores helps in generating T-scores. T-scores are standardized scores with a mean of 50 and a standard deviation (SD) of 10. The procedure below explains the conversion of raw scores collected from the PROMIS to a T-score (as represented in Figure 2).

For adults, each question has 5 response options ranging in value from 1 to 5. To find the total raw score for a short form with all questions answered, sum the values of the response to each question.
Example: For the adult 10-item form, the lowest possible raw score is 10; the highest possible raw score is 50 (see all short form scoring tables in Appendix 1).

A score can be approximated if a participant skips a question. If items are missing responses, check how many items were answered. For short forms with at least 5 items, confirm that 4 or 50% of items, whichever is greater, were answered. For example, a 5-item short form can be scored as long as 4 items were answered. A 10-item short form can be scored as long as the participant answered at least 5 items. After confirming that enough responses were provided, sum the response scores from the items that were answered (not including any screening question). Multiply this sum by the total number of items in the short form. Finally, divide by the number of items that were answered.

Example: If a respondent answered 5 of 8 questions and answered all items with the second lowest response option (2), you would sum all responses (10), multiply by the number of items in the short form (8) and divide by the number of items that were answered (5). Here (10x8)/5=16. If the result is a fraction, round up to the nearest whole number. This is a pro-rated raw score.

Again, the formula is:

(Raw Sum x Number of items on the short form) / Number of items that were answered

Locate the applicable score conversion table in Appendix 1 and use this table to translate the total raw score or pro-rated score into a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person with a T-score of 40 is one SD below the mean.

For the adult PROMIS Physical Function 10a short form, a raw score of 10 converts to a T-score of 14.1 with a standard error (SE) of 3.3 (see scoring table for the 10a short form in Appendix 1). Thus, the 95% confidence interval around the observed score ranges from 7.7 to 20.5 (T-score + (1.96*SE) or 14.1 + (1.96*3.3).

For pro-rated scores, this calculation assumes that responses are missing at random. This isn't always true. Therefore, use caution when interpreting the final pro-rated T-score.

Appendix 1-Scoring Tables 2018

Adult v2.0 – Physical Function 6b		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
6	21.0	3.8
7	25.0	2.7
8	27.1	2.4
9	28.8	2.2
10	30.1	2.1
11	31.3	2.0
12	32.3	2.0
13	33.2	1.9
14	34.2	1.9
15	35.0	1.9
16	35.9	1.9
17	36.8	1.9
18	37.6	1.9
19	38.5	1.9
20	39.3	1.9
21	40.2	1.9
22	41.2	1.9
23	42.1	1.9
24	43.2	2.0
25	44.3	2.0
26	45.6	2.2
27	47.1	2.3
28	48.9	2.7
29	51.3	3.0
30	59.0	6.2
*SE = Standard Error on T-score metric		

A Higher T-score indicates better physical functioning. PROMIS scores are statistically analyzed by summarizing the T-scores at each visit as shown in figure 3.

Total T-Score (higher T-Score score means better physical functionning)	
Baseline	
n	13
Mean (SD)	41.1 (8.7)
Median	38.5
Q1, Q3	35.1 , 42.1
Minimum, maximum	33, 59
95% CI	(35.8,46.37)
Number of missing questions[a] (Mean[SD])	0.0 (0.0)
Cycle 1 Day 1	
n	18
Mean (SD)	41.3 (8.8)
Median	40.7
Q1, Q3	34.3 , 46.8
Minimum, maximum	29, 59
95% CI	(36.91,45.64)
Number of missing questions[a] (Mean[SD])	0.0 (0.0)

Figure 3: Statistical Analysis of T-scores

MISSING DATA HANDLING

Missing data is very common in PRO data collection. Patients may fail to report the questionnaires, skip visits, or withdraw from the trial before its completion. The resulting missing data can introduce bias and interfere with the ability to compare effects in the test group with the control group. To understand the extent and impact of missing data, FDA recommends providing either a table summary of missing data or summarizing missingness by visits or time points as shown below:

Bothered by side effects of treatment	
Baseline	
Not at all (n, %)	3 (33)
A little bit (n, %)	2 (22)
Somewhat (n, %)	2 (22)
Quite a bit (n,%)	0
Very much (n, %)	0
Missing (n, %)	2 (22)

Figure 4: Missing Data Summary

The clinical trial protocol should mention how the missing data will be handled. To avoid the bias from missing data, it is recommended that the patient should continue the trial, even if they discontinued the treatment, and should continue to report the PRO data.

FREQUENCY AND DURATION OF PRO ASSESSMENTS

The frequency and duration of PRO assessments should correspond with the specific research questions being addressed. It is important to consider whether the clinical trial's duration is of adequate length to support the proposed claim and assess a durable outcome in the disease or condition being studied. Frequency of assessments depends on the length of recall asked by the instrument's response options, demonstrated instrument measurement properties, the disease or condition's natural history, the treatment's nature, and planned data analysis.

CONCLUSIONS

Patient Reported Outcomes emphasize the patient's voice in the drug development. Patient Reported Outcomes in oncology studies provide valuable information to the stakeholders and are powerful tools to inform about the patient. Adverse event and relative comparative symptomatic toxicity profiles of therapies can guide treatment choice and enhance its value proposition.

Clinical exams and medical technologies do not provide all the data. PRO instruments, when used appropriately, can help to determine treatment effect as part of an endpoint (primary, secondary, or exploratory).

REFERENCES

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