Methods for Reporting the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Data in Cancer Clinical Trials

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BACKGROUND

- The National Cancer Institute's PRO-CTCAE has been developed to integrate patient perspectives on symptomatic adverse events in cancer trials.
- As a relatively new assessment, there are currently no standard approaches for analyzing and reporting PRO-CTCAE data.
  - Basch et al.[1] provided examples using stacked bar charts and recommended that future directions consider baseline and more frequent reports of PRO-CTCAE data to allow for granular longitudinal analyses.

OBJECTIVE

- To provide a systematic and easy-to-apply approach that can be used to report PRO-CTCAE data in clinical trials for oncology.

METHODS

Challenges of Analyzing and Reporting PRO-CTCAE Data

- The PRO-CTCAE measurement system contains a large item library.[2]
  - 124 PRO-CTCAE items for 80 PRO-CTCAE terms are mapped to 78 CTCAE MedDRA terms (Figure 1 provides an example).[3]
  - For irregular menstruation and depression, two PRO-CTCAE terms are mapped to each one.
- Each term may have 1 to 3 attribute items, where the item is defined as frequency, severity, interference, presence, or amount.
  - 45 PRO-CTCAE terms involve a single item (21 for presence, 20 for severity, 2 for frequency, and 2 for amount).
  - 26 terms have 2 items (severity, frequency, and/or interference).
  - 9 terms have 3 items (severity, frequency, and interference).
- Most items (59 items) on the PRO-CTCAE are scored from 0 to 4.
  - 21 presence items are scored from 0 (absent) to 1 (present).
  - The PRO-CTCAE scores and CTCAE grades are not comparable for the same symptom
- There are no standardized scoring rules for how to combine attribute items (frequency, severity, interference), and no summation score exists for the PRO-CTCAE. As such, terms and corresponding attributes must be presented separately.
- Weekly data collection is recommended for full coverage of the treatment period.
- The frequency of data collection, the size of the PRO-CTCAE item library, and the lack of summation scores result in many data points for analysis.

Proposed Method

- We propose two sets of analyses for baseline and postbaseline PRO-CTCAE data.
  - Analysis of baseline data provides background information on disease burden in the clinical trial patient population.
  - The postbaseline analysis focuses on treatment comparisons, although it can also be used in single-arm trials.
  - The postbaseline analysis is relative to baseline and shows trends in patients' perceptions of their symptomatic adverse events over time.
- Example figures were generated using SAS statistical software (SAS Institute, Cary, NC) with simulated data.

RESULTS

Reporting of Baseline PRO-CTCAE Data

- As shown in Figure 2, horizontal bars make it easy to list 20-30 items per page to show the toxicity/symptom burden in the clinical trial patient population.
- The paneled figure provides a unified display of PRO-CTCAE terms with various attribute items.
- High granularity is retained in stacked bars because the percentage of each score level is presented.
- The visual presentation makes it easy to identify prevalent symptoms.
- The order of the score level makes it easy to dichotomize the scores. In our example, it can be easily seen that approximately 20% of the patients have constipation score ≥ 3, and approximately 90% have constipation score ≥ 1.
- Sample sizes presented beside each bar allow for assessing completion/compliance.

Reporting of Postbaseline PRO-CTCAE Data

- To compare treatment differences, we define an outcome in three categories: improved, no change (i.e., stable), or worsened from baseline (Figure 3).
  - It is important to assess both the percentage of improved and percentage of worsened symptoms when the direction of treatment impact on the symptom is unknown. It is also possible that the treatment improves some symptoms while worsening others.
- The visual presentation makes it easy to identify symptoms that are responsive to treatment.
- In Figures 4 and 5, both improved and worsened scores are relative to baseline and are displayed longitudinally and in one figure.
  - The total length of the bar shows the percentage of patients with a changed (improved or worsened) symptom score (the longer the bar, the less percentage in the "no change" category).
  - Treatment groups are displayed side by side for easy comparison.
- High granularity is retained in divergent stacked bars (Figure 5) because the percentage of each change score level is presented.
  - The proposed order of the improving (or worsening) categories makes it easy to see the percentage of improvement (or worsened scores) using various cutoff criteria (e.g., improved by 4, improved by at least 3) in one figure (Figure 5).
- Sample sizes presented beside each bar allow for assessing completion/compliance.
  - This is especially informative because loss to follow-up due to disease progression or adverse events is common in cancer clinical trials.

CONCLUSIONS

- The presentation provides a simple and informative solution to PRO-CTCAE data reporting that considers both the baseline and longitudinal assessments that can be routinely implemented in clinical trials.
- Programs have been developed using the SAS software, which is preferred for regulatory submission.
- The visualization of the results makes it easy to identify symptoms that matter to patients and are responsive to treatments.

REFERENCES

1. Basch E, Rogak LJ, Dueck AC. Methods for implementing and reporting patient-reported outcome (PRO) measures of symptomatic adverse events in cancer clinical trials. Clin Therapeut. 2016 Apr 1;38(4):821-30.
2. National Cancer Institute, NCI- PRO-CTCAE™ ITEMS (Item Library Version 1.0, Version date: 12/20/2017) Available at: https://healthcaredelivery.cancer.gov/pro-ctcae/pro-ctcae_english.pdf Accessed March 8, 2018.
3. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). J Natl Cancer Inst. 2014 Sep 29;106(9):pii:dju244.

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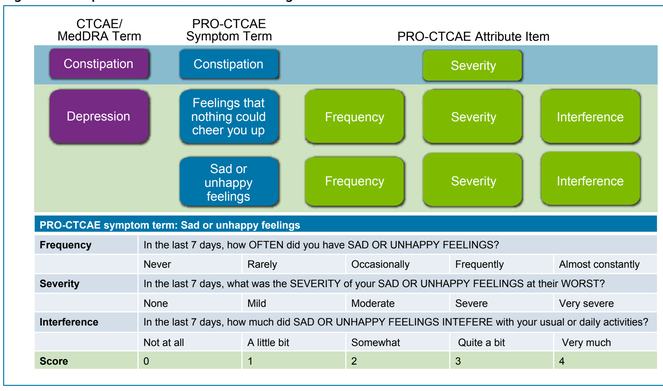
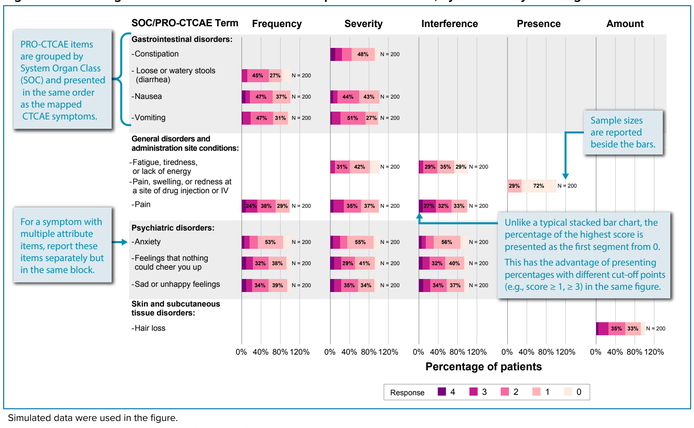
Figure 1. Example PRO-CTCAE Items and Scoring



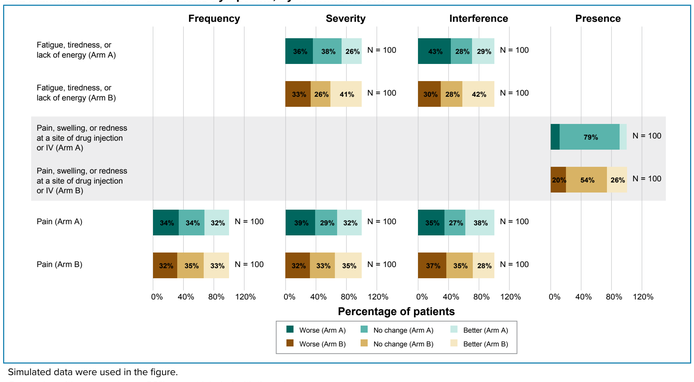
PRO-CTCAE symptom term: Sad or unhappy feelings					
Frequency	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	Never	Rarely	Occasionally	Frequently	Almost constantly
Severity	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	None	Mild	Moderate	Severe	Very severe
Interference	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTEFERE with your usual or daily activities?				
	Not at all	A little bit	Somewhat	Quite a bit	Very much
Score	0	1	2	3	4

Figure 2. Percentage of Patients With PRO-CTCAE Responses at Baseline, by Item and System Organ Class



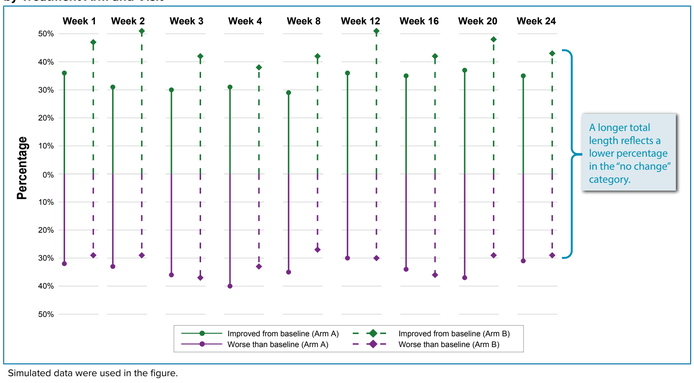
Simulated data were used in the figure.
Categories with a percentage < 24% are not labeled with the value.

Figure 3. Stacked Bar Chart for the Percentage of Categories of Change From Baseline to Week 4 in General Disorders and Administration Site Conditions Symptoms, by Treatment Arm



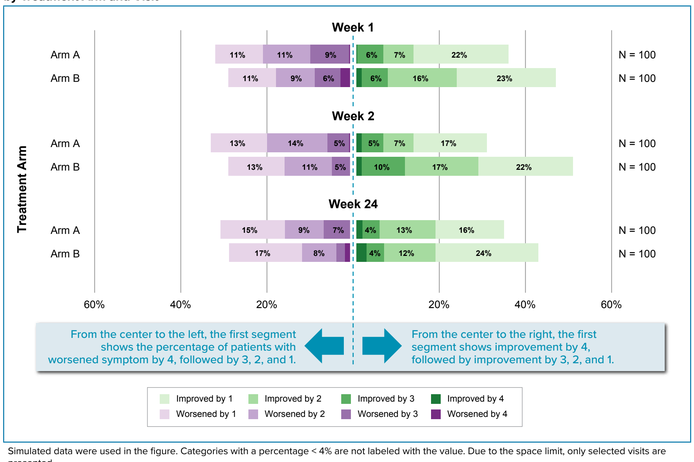
Simulated data were used in the figure.
Categories with a percentage < 20% are not labeled with the value.

Figure 4. Divergent Lollipop Chart for Percentage of Patients With Improvement or Worsening in Constipation Severity, by Treatment Arm and Visit



Simulated data were used in the figure.

Figure 5. Divergent Stacked Bar Chart for Percentage of Patients With Improvement or Worsening Constipation Severity, by Treatment Arm and Visit



Simulated data were used in the figure. Categories with a percentage < 4% are not labeled with the value. Due to the space limit, only selected visits are presented.

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