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A review of approaches to select instruments and items to measure patient reported tolerability in clinical trials in oncology

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Background and Objectives

- Patient-reported outcomes (PROs) are increasingly recognised as essential in oncology clinical trials for assessing treatment tolerability from the patient's perspective (1).
- Instruments such as the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)(2), instrumental in quantifying patient-reported symptomatic AEs.
- However, the selection of appropriate instruments and items to measure tolerability remains inconsistent across trials, with limited methodological guidance on how to choose measures and align them with trial objectives and regulatory expectations(3,4).
- This rapid targeted review aimed to synthesise information from guidance documents and publications to identify approaches for selecting PRO instruments to capture patient-reported tolerability across oncology trials, and their acceptability to key stakeholders.

Methods

- A rapid, targeted review of relevant publications and guidance was conducted in June 2025 using PubMed, regulatory websites (EMA/FDA/PMDA), Industry websites (ISPOR/ISOQOL) and key oncology conferences (ESMO Congress (European Society for Medical Oncology) and ASCO Annual Meeting (American Society of Clinical Oncology)). The following search terms were combined: 'tolerability', 'adverse event', 'side effects', 'patient reported', and 'patient reported-outcome common terminology criteria for adverse events (PRO-CTCAE)''.
- Abstracts and guidance documents were reviewed to identify those which contained information relating to the selection of instruments or items to measure patient-reported tolerability in oncology trials.

References:

1. Core Patient-Reported Outcomes in Cancer Clinical Trials. Guidance for Industry. FDA. October 2024. **2.** Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE®). **3.** Zhao Q et al. Quality Care/Health Services Research, American Society of Clinical Oncology. 2025, e23193. **4.** Crossnohere N et al. Quality of Life Research. 2021, 39(1): 21-40 **5.** Giesinger JM et al. Value Health. 2021, 24(4):585-591. **6.** Emerson et al. J Clin Oncol. 2023, 41:1579-1579. **7.** Friends of Cancer Research. White paper: Broadening the definition of tolerability in cancer clinical trials to better measure the patient experience. 2018. **8.** Veitch Z et al. JNCI: Journal of the National Cancer Institute. 2021, 113(8):980–98. **9.** Trask PC et al. Clinical Trials. 2018, 15(6):616-623. **10.** Piccinin C et al.. Lancet Oncol. 2021, 24(2):e86-e95. **11.** Minasian LM et al. Patient Relat Outcome Meas. 2022 8 913): 249-258. **12.** Chung et al. Journal of the American Medical Informatics Association. 2019, 26(4): 276–285. **13.** Reeve BB et al. J Natl Cancer Inst. 2014, 106(7):dju129. **14.** Janse van Rensburg J et al. Br J Cancer. 2023,129: 612–619. **15.** Roth ME et al. JNCI: Journal of the National Cancer Institute. 2023,115(1):21–28. **16.** Kato K et al. J Clin Oncol. 2024,42: e19516-e19516. **17.** Snyder RA et al. Annals of Surgery. 2023, 278(4):598-608. **18.** Gunter M et al. BMC Cancer. 2023, 23: 629. **19.** Feldman E et al. ESMO Open. 2023, 8(1): 100775. **20.** Christiansen MG et al. J Patient Rep Outcomes. 2023, 7:72. **21.** Geurts YM et al. Qual Life Res. 2024, 33:3013–3026. **22.** FDA Patient Focussed Drug Development Guidance Series. **23.** FDA DDT COA #000009: Non small cell lung cancer symptom assessment questionnaire (NSCLC-SAQ). **24.** The FACIT Group. **25.** EORTC Quality of Life. **26.** EMA. Reflection Paper on the use of patient reported outcome 5 (PRO) measures in oncology studies. June 2014. **27.** EMA. Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man. The use of patient-reported outcome (PRO) measures in oncology studies. April **28.** Bottomley A et al. Value In Health. 2024, 27(12): S518-S519 ISPOR. **29.** SISAQOL-IMI. Public Launch of the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints (SISAQOL-IMI) Recommendations. 2025.

Results

Published Literature

Overview

- The PRO-CTCAE was most commonly used to collect patient-reported AE data from the studies identified and is widely cited (1,5,6).
- Use of PRO measures other than the PRO-CTCAE was commonplace to asses overall AE burden on patients, drug specific AEs not in the PRO-CTCAE and other outcomes of importance such as physical functioning (7).
- The PRO-CTCAE has also been used to show that reporting rates for AEs differ between patients and clinicians (8).

The Patient reported-outcome common terminology criteria for adverse events (PRO-CTCAE)

- An item library comprising 124 items representing 78 symptomatic toxicities from the clinician-reported CTCAE (2).
- Developed and validated using well-established measurement principles and guidance.
- Each item represents a toxicity that can be meaningfully reported from the patient perspective
- Paediatric and caregiver versions are available

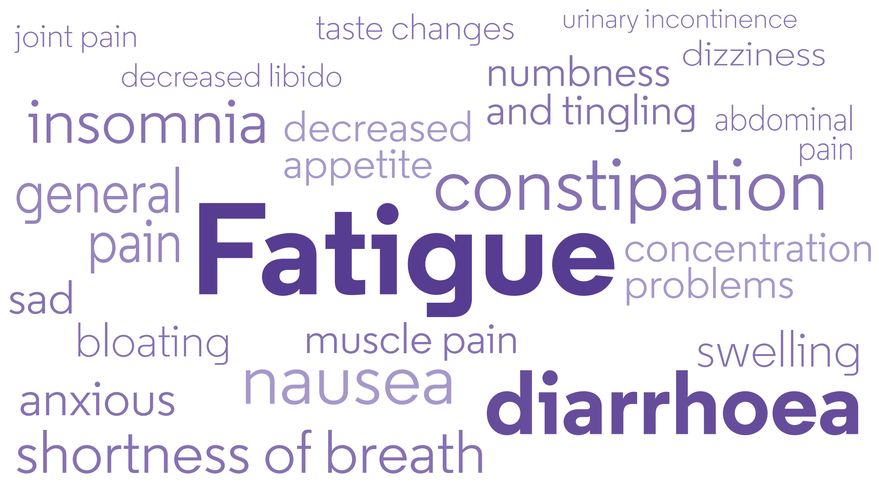
Selecting items from the PRO-CTCAE library

- The most comprehensive recommendations for item selection were developed by Trask et al. who define separate methodological recommendations for selecting PRO-CTCAE items for both early and late phase trials (9).
- Piccinin et al. recommend a range of methods for item selection which are broadly aimed at all item libraries for patient reported outcome measurement in oncology trials, and can be applied to the PRO-CTCAE (10).
- Additional practical recommendations for implementing the PRO-CTCAE in oncology trials were also identified (9, 11,12).

Examples of PRO-CTCAE item set development

- 10 articles describing the development of 12 PRO-CTCAE item sets for specific patient populations were identified in the literature; these are summarised in Table 1.
- Despite the availability of guidance for PRO-CTCAE item selection, studies varied in their methods used to select items and several involved no direct patient input.
- We compared the symptoms that comprised the 12 PRO-CTCAE item sets in the 10 articles identified. A total of 60 symptoms were included across the 12 item sets.
- Figure 1 shows the relative number of times each symptom was included in an item set, for the 21 symptoms which were included in five or more of the item sets.

Figure 1: A word cloud to show the relative frequency of the most common symptoms included in the n=12 PRO-CTCAE item sets identified in the literature



Relative frequency is represented by text size with larger text denoting higher frequency. Includes only those symptoms included in 5 or more item sets.

Table 1: Examples of methods used to select PRO-CTCAE items for use in specific patient populations

Reference	Population	Methods for item selection	Number of symptoms/ items*
Reeve et al. 2014 (13)	Adult oncology patients	Multi-disciplinary panel (including patients and clinicians), literature review and analysis of clinical trial and real world datasets	12 symptoms; number of items not specified
Janse van Resenburg et al. 2023 (14)	Adult phase I oncology patients	1. PRO-CTCAE data from previous Phase I oncology trials ranked by a pre-set list of criteria for AE prevalence, severity, interference, frequency, amount and % change in reliability 2. Survey of Phase I trial clinicians	30 symptoms; 58 items (if all symptoms are experienced)
Veitch et al. 2021 (8)	Adult phase I oncology patients	PRO-CTCAE data from Phase I oncology trials. PRO-CTCAE items were selected by those with 10% or greater reporting frequency	50 symptoms; number of items not specified
Roth et al. 2022 (15)	Adolescent and young adult oncology clinical trial patients	Expert task force comprising trial design and HRQoL/PRO experts; items selected using a modified Delphi method	8 core + 4 study specific symptoms; number of items not specified
Kato et al. 2024 (16)	Multiple myeloma (MM)	Semi-structured interviews with patients with multiple myeloma	29 symptoms; number of items not specified
Snyder et al. 2023 (17)	Patients with pancreatic cancer receiving neoadjuvant therapy	PRO-CTCAE data from pancreatic cancer trial. PRO-CTCAE items were selected as representing 'symptomatic adverse events' if they were scored as Grade 3 or higher by at least 10% of patients.	10 symptoms; number of items not specified
Gunther et al. 2023 (18)	Patients with breast cancer (BC), multiple myeloma (MM), and prostate cancer (PC).	PRO-CTCAE data from outpatient cancer centers. PRO-CTCAE items were selected by prevalence and importance as ranked by patients.	21 symptoms (BC), 19 symptoms (MM and PC); number of items not specified
Feldman et al. 2023 (19)	Patients with prostate cancer (PC)	Mixed methods approach; Literature review, interviews with patients with prostate cancer and health care providers, modified Delphi panel	21 symptoms; number of items not specified
Christiansen et al. 2023 (20)	Women with endometrial or ovarian cancer undergoing chemotherapy	Mixed methods approach; literature review to identify common toxicities, patient advisory board feedback, focus groups with clinical experts	44 items covering 21 symptoms
Geurts et al. 2024 (21)	Patients with rectal cancer	Mixed methods approach; literature review, semi-structured interviews with healthcare professionals, modified Delphi panel	16 symptoms; number of items not specified

*Number of items does not always correspond to number of symptoms measured as multiple facets of each symptom may be measured (e.g. frequency, severity)

Regulatory guidance

Overview of regulatory guidance: FDA

- FDA Guidance recommends the inclusion of patient-reported disease-related symptoms, symptomatic AEs, overall side effect impact summary measures, physical function and role function as core domains for tolerability assessment (1,22).
- For symptomatic AEs, the FDA recommends selecting the most important AEs for measurement, via a PRO from an item library, such as PRO-CTCAE with a rationale for the selection of the AE. They note this data is to complement, not to replace safety data.
- Other PRO measures/item banks are provided as examples within the FDA guidance for the collection of disease-related symptoms (23,24,25).

Overview of regulatory guidance: EMA

- The European Medicines Agency (EMA) has not produced detailed, updated guidance on the implementation of PRO measures such as the PRO-CTCAE, creating variability in international trial design. The EMA's 2014 reflection paper (26,27) does not specify the use of any particular PRO instrument for collection of tolerability in oncology clinical trials.
- No further EMA guidance is available on this topic, although from recent meetings with the EMA and the European Organisation for Research and Treatment of Cancer (EORTC), new guidance or information may be released in the future.

Overview of regulatory guidance: PMDA

- No specific guidance was found on the PMDA's website for the use of PROs in oncology clinical trials.

Overview of Industry guidance

- The **Professional Society for Health Economics and Outcomes Research (ISPOR)** was found not to have clear guidance or recommendations for measuring tolerability data via PROs, but did have a number of related posters and conference submissions, which discussed the challenges and need for alignment (28).
- The **International Society for Quality of Life Research (ISOQOL)** was also found not to have any specific guidelines on this topic.
- The **Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI)** have recently established recommendations for the design, analysis, presentation, and interpretation for PRO data in cancer clinical trials (29) but without specific recommendations for collection of patient-reported tolerability data.

Conclusion

For sponsors submitting data to the FDA, there is clear guidance for designing oncology clinical trials. However, there is less specific guidance on which PRO instruments should be selected, how items should be selected in some situations and limited guidance for sponsors collecting and submitting tolerability data via PRO measures outside of the US.

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Financial statement

CB and SK are employees and some are stockholders of Clarivate and provide specialized clinical outcome assessment and patient-centered outcomes consultancy to various pharmaceutical companies.