

What Do “None,” “Mild,” “Moderate,” “Severe,” and “Very Severe” Mean to Patients With Cancer? Content Validity of PRO-CTCAE™ Response Scales

Accurate capture of the symptom experience is essential to gauging efficacy, safety, and tolerability of cancer treatments.¹ The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)² was developed by the National Cancer Institute to allow direct patient self-reporting of symptomatic adverse events in cancer clinical trials.^{3–5} Its content validity has been established in accordance with recommended practices for novel patient-reported outcome (PRO) instruments.^{6,7}

Although we previously reported that the PRO-CTCAE response options were acceptable to respondents,⁵ this analysis extends those findings by focusing on comprehension of the response options. For example, can patients delineate between PRO-CTCAE response options for a given attribute? Does “never/none/not at all” indicate the absence of a symptom, or is it interpreted as the patient is not experiencing a noticeable attribute of that symptom (i.e., a symptom is not severe)? Our aims were to determine if PRO-CTCAE response options are 1) accurately comprehended, including that “never/none/not at all” is selected when the respondent is not experiencing a given symptom and 2) nonoverlapping, that is, able to distinguish respondents with different symptom experiences.

Data were drawn from two studies (NCT01031641 and NCT02158637). For the qualitative phase (NCT01031641), we analyzed data from one-on-one cognitive interviews conducted with 127 patients (59% female, 72% white/non-Hispanic, 35% high-school education or less) receiving treatment for cancer.⁵ For any symptomatic adverse events (AEs) where a PRO-CTCAE attribute was reported as >0, interviewers asked (for a minimum of two symptoms and their respective attributes per interview): “For this

item you chose x, what makes that a better choice than (x + 1)? What makes that a better choice than (x – 1)?” The purpose of this probing was to establish that the patient was considering the difference between proximal responses along the continuum of options.

To confirm the monotonicity of PRO-CTCAE response choices, we analyzed data from a psychometric study (NCT02158637) of 940 patients currently undergoing treatment for cancer (57% female, 63% white/non-Hispanic, 32% high-school education or less).⁴ Patients completed PRO-CTCAE and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).⁸ We compared mean EORTC QLQ-C30 Health-Related Quality of Life (HRQL) summary scores⁹ across subgroups with worsening PRO-CTCAE item scores using Jonckheere-Terpstra tests.¹⁰

Seventy-two of 78 PRO-CTCAE symptom terms (92%) were probed. All respondents with a PRO-CTCAE item response >0 (99/127) were able to differentiate between adjacent response choices. In the subsample of respondents who selected “never/none/not at all” (35/127) for one or more PRO-CTCAE items, all participants correctly explained to the interviewer that this response choice meant that they were not experiencing a symptom. For example, a patient was asked about how much dizziness interfered with their usual activities. They selected “some-what,” defined as “something that might interfere with plans—you wouldn’t take the chance of going somewhere alone.” To this patient, “quite a bit” meant “you wouldn’t be able to go anywhere, even if you had someone with you and needed to get something done.” Another patient was asked why they selected “none” in response to pain severity, to which they responded “I do not experience pain at all.” Additional examples are displayed in [Table 1](#). In the psychometric study, significant (all $P < 0.05$) monotonically decreasing mean HRQL scores were observed across worsening PRO-CTCAE score groups for the majority (108/124 [87%]) of PRO-CTCAE items ([Fig. 1](#)).

In response to probing, all study participants provided accurate and meaningful explanations for selection of a given PRO-CTCAE response over its proximal alternatives. Moreover, all participants indicated that choosing “never/none/not at all” meant the symptom was absent. Statistically significant, conceptually relevant associations between PRO-CTCAE response choices and HRQL were seen across a substantial majority of the PRO-CTCAE items.

Taken together, these results provide strong evidence that PRO-CTCAE response options are well comprehended and that each of the ordinal response choices is nonoverlapping, serving to distinguish

Table 1
Example Patient Explanations of Response Options by Attribute and Adverse Event (N = 127)

Attribute	Symptomatic Adverse Event	Patient Definition of Response		
		(X - 1)	(X)	(X + 1)
Severity	Pain	Moderate—"when you are in pain and it hurts 'bad, bad'"	Severe—"when you are in pain and it's getting worse"	Very severe—"when you are in pain and it doesn't stop and it hurts a lot"
Severity	Problems with concentration	Mild—"able to get the task done but may take more time to focus"	Moderate—"takes even more time to get a task done"	Severe—"unable to accomplish a task"
Severity	Shortness of breath	Mild—"breathe through the nose only, at a faster pace"	Moderate—"need to breathe through the nose and mouth"	Severe—"fainting or passing out due to the inability to catch a breath"
Severity	Felt like nothing could cheer you up	None—"not there"	Mild—"does not feel if it is a reaction"	Moderate—"can recognize it and realize it is a problem"
Frequency	Nausea	Occasionally—"every other day or so"	Frequently—"every day I felt some sort of nausea"	Almost constantly—"constantly experiencing nausea"
Frequency	Headache	Never—"never happens"	Rarely—"some time during the day"	Occasionally—"three or four times a week"
Frequency	Hot flashes	Never—"not once in the last week"	Rarely—"one or two times"	Occasionally—"every other day or so"
Interference	Arm or leg swelling	Somewhat—"interfering with 25%–50% of activities in a day"	Quite a bit—"interfering with 50%–75% of activities in a day"	Very much—"interfering with 75%–100% of activities in a day"
Interference	Fatigue	A little bit—"doesn't interfere with daily activities much—wouldn't put off gardening"	Somewhat—"would put off gardening but be able to do something less strenuous"	Quite a bit—"wouldn't be able to do another activity that was more strenuous than gardening"
Interference	Frequent urination	A little bit—"I'm aware of it and may have to compensate for it"	Somewhat—"you have to make more compensation but not interfering too much (don't have to call in sick to work)"	Quite a bit—"having to miss work or social events"
Amount	Hair loss	Not at all—"none, not noticeable"	A little bit—"hair falling out naturally"	Somewhat—"noticing more than usual on the brush"

X refers to the patient response, with X - 1 representing the proximal lower response choice and X + 1 representing the proximal higher response choice on the response scale for a specific attribute.

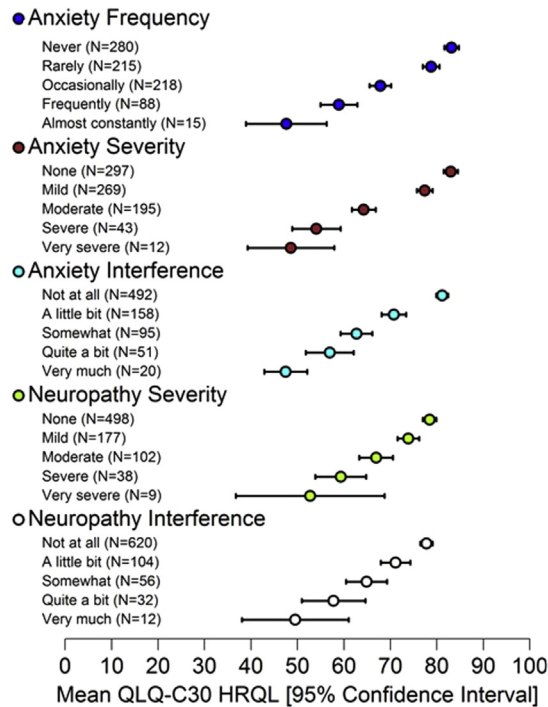


Fig. 1. Mean European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Health-Related Quality of Life (HRQL) summary scores (higher scores represent better HRQL) show statistically significant declines across worsening Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events Item Response.

respondents with meaningfully different symptom experiences.

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