Danish Translation and Linguistic Validation of the U.S. National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

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Abstract

Context. The Common Terminology Criteria for Adverse Events (CTCAE) is the basis for standardized clinician-based grading and reporting of adverse events in cancer clinical trials. The U.S. National Cancer Institute has developed the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) to incorporate patient self-reporting of symptomatic adverse events.

Objectives. The aim of the study was to translate and linguistically validate a Danish language version of PRO-CTCAE.

Methods. The U.S. English language PRO-CTCAE was translated into Danish using forward and backward procedures with reconciliation. The linguistic validity of the PRO-CTCAE Danish was examined in two successive rounds of semistructured cognitive interviews in a sample of 56 patients equally distributed by gender and cancer type (prostate, head and neck, lung, breast, gynecological, gastrointestinal, and hematological cancer), and who were currently undergoing cancer treatment.

Results. In the first round of linguistic validation ($n = 42$), the phrasing of five symptomatic toxicities was adjusted, and the refined phrasing was retested in a second round of interviews ($n = 14$). Agreement about phrasing that was both culturally acceptable and semantically comprehensible was achieved in the second round. Statements from participants describing the meaning of the PRO-CTCAE symptomatic toxicities support conceptual equivalence to the U.S. English language version.

Conclusion. Availability of the NCI PRO-CTCAE in languages beyond English will support international congruence in self-reporting of side effects of cancer treatment. A rigorous methodology was used to develop the Danish language version of PRO-CTCAE. Results provide preliminary support for the use of PRO-CTCAE in cancer clinical trials that include Danish speakers. J Pain Symptom Manage 2016;52:292−297.

Key Words

Patient-reported outcomes, PRO-CTCAE, linguistic validation, symptomatic toxicity, treatment adverse events, cancer clinical trials

Introduction

The Common Terminology Criteria for Adverse Events (CTCAE) developed by the U.S. National Cancer Institute (NCI) is a standard lexicon for grading and reporting adverse events by clinicians.[1,2] Approximately 10% of the adverse events in the CTCAE are symptomatic toxicities that rely on patient reporting of symptoms. At present, symptomatic toxicities

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Accepted for publication: February 5, 2016.

http://dx.doi.org/10.1016/j.jpainsymman.2016.02.008

assessed during visits are interpreted and graded by clinicians and entered on case report forms.[2]

Clinician-based evaluation of symptoms has been challenged,[3] and evidence suggests that in cancer clinical trials, symptomatic toxicities may be underreported.[4,5] Thus inclusion of PROs may enhance precision and comprehensiveness in the capture of symptomatic adverse effects of cancer treatment.[6–8]

It is suggested that patient-reported outcome measures described as "measurements of any aspects of a patient's health status that comes directly from the patient" [9] could complement clinicians' reports in cancer treatment trials, and reports from patients and clinicians together might provide a more comprehensive view of the adverse events of cancer treatment. The U.S. NCI recently developed a patient-reported outcome version of the CTCAE (PRO-CTCAE) comprising 78 symptomatic toxicities that can be meaningfully reported by patients.[1,10] The 78 symptomatic toxicities are evaluated with 124 PRO-CTCAE items that assess the presence/absence, frequency, severity, and/or interference with daily activities associated with each symptomatic toxicity.[1] The default recall period is the past seven days. For more information about PRO-CTCAE, visit http://healthcaredelivery.cancer.gov/pro-ctcae/. The validity and reliability of the U.S. English version of PRO-CTCAE has been tested thoroughly.[11] Translation and linguistic validation of the PRO-CTCAE in Spanish and German have been reported.[12,13] Availability of a Danish language version of the PRO-CTCAE provides the foundation to incorporate patient self-reporting of symptomatic toxicities into cancer clinical trials in Denmark and encourages data harmonization and comparison across studies. The aim of this study was to develop a Danish language version of the U.S. English PRO-CTCAE.

Methods

A research collaboration (represented by the authors of this article) was established between a Danish Steering Group and representatives from the U.S. NCI PRO-CTCAE Study Group to ensure optimal methodology and interpretation of results. The study design was approved by the Danish Data Protection Agency (File number 2014-41-3059).

The U.S. English PRO-CTCAE was translated according to the guidelines of the International Society for Pharmacoeconomics and Outcomes Research for translation and cultural adaption of PRO instruments.[14] Forward translation was done independently by two native Danish-speaking professional translators, and the steering group agreed on one reconciled version on the basis of culture, customary clinical dialogue between clinicians and patients, and congruence with the meaning of the U.S. English phrasing. One native U.S. and one British English-speaking professional translator, both residing in Denmark, made independent backward translations.

The steering group compared the two backward translations according to similarity in the meaning of the symptom phrasing and then compared congruence with the original U.S. English text for each symptomatic toxicity. Based on consensus in the steering group, this process resulted in a reconciled version that was advanced for cognitive interviews with patients. Still, a number of symptoms were classified as potentially problematic if the steering group found inconsistencies between the different translated versions because of culture or customary clinical dialogue, and these symptoms were flagged for special attention in the cognitive interviews.

The comprehensibility of the PRO-CTCAE Danish item library was examined in two successive rounds of individual semistructured cognitive interviews.[15] We aimed to include 55 patients equally distributed by gender and seven cancer types; 55 patients were anticipated to be adequate to achieve representativeness of the different cancer patient subgroups, including gender and educational attainment.

In May and June 2014, patients were identified consecutively from a list of patients scheduled for chemotherapy from each of the seven teams treating the different cancer types at the Department of Oncology, Rigshospitalet, University Hospital of Copenhagen. The hospital is a specialist hospital and offers oncology treatments for patients from the regional area as well as special oncology treatments for patients on a national basis. Inclusion criteria for participation in the study were as follows: 1) aged 18 years or older, 2) diagnosed with prostate, head and neck, lung, breast, gynecological, gastrointestinal, or hematological cancer, 3) had received at least one prior treatment with chemotherapy within the last three months, 4) able to speak and understand Danish, and 5) able to provide informed consent. Sixty-five eligible patients were invited to participate, of whom 56 (86%) participated (Fig. 1). The patients were equally distributed according to gender and cancer type, and the a priori sampling goal of including at least 10% of respondents with primary school as their highest education was fulfilled (Table 1).

This research, because of Danish law, was exempt from review by an institutional review board or ethical authority. Informed consent was obtained from all individual participants included in the study.

Cognitive interviews were performed focusing on the comprehension and cultural relevance of the question phrasing including the PRO-CTCAE

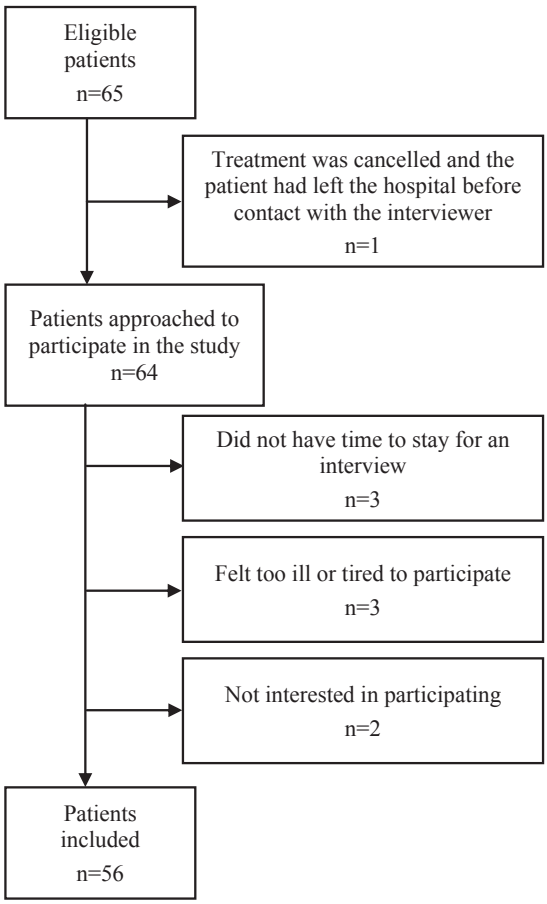

Fig. 1. Flowchart of sample recruitment in Rounds 1 and 2.

Table 1
Characteristics of the 56 Patients Who Participated in the Linguistic Validation in Rounds 1 and 2

Median age (range in yrs)	63 (25–79)
Gender, *N* (%)	
Female	28 (50)
Male	28 (50)
Disease site, *N* (%)	
Prostate	8 (14)
Head and neck	8 (14)
Lung	8 (14)
Breast	8 (14)
Gynecological	8 (14)
Gastrointestinal	8 (14)
Hematological	8 (14)
Current disease status, *N* (%)	
Localized	13 (23)
Advanced or metastatic	43 (77)
Highest attained education, *N* (%)	
Basic or high school	9 (16)
Vocational education	15 (27)
Higher education, 2–4 yrs	25 (44)
Higher education, ≥5 yrs	7 (13)
Employment status, *N* (%)	
Student	3 (5)
Working full time	17 (30)
Working part time	8 (14)
Unemployed	2 (4)
Retired	26 (46)
Marital status, *N* (%)	
Single	10 (18)
Married or cohabiting	38 (68)
Widowed	4 (7)
Divorced or separated	4 (7)

symptomatic toxicities, attributes (e.g., frequency, severity, and interference), and the response choices. Two rounds of interviews were planned with 42 participants (Round 1) and 14 participants (Round 2). If saturation was not achieved after the two rounds of interviews, additional interview rounds could be added.

In the first round, three different interview schedules were constructed for men and three for women. Fourteen core symptomatic toxicities (anxiety; constipation; decreased appetite; fatigue, tiredness or lack of energy; insomnia [including difficulty falling asleep, staying asleep, or waking up early]; loose or watery stools [diarrhea]; mouth or throat sores; nausea; numbness or tingling in your hands or feet; pain; rash; sad or unhappy feelings; shortness of breath; vomiting), reflecting highly prevalent symptomatic toxicities of cancer treatment, were included in all six questionnaires.[11] The remaining 64 PRO-CTCAE symptomatic toxicities were distributed across the six interview schedules in different combinations. Each interview schedule contained a maximum of 57 symptomatic toxicities including 0–2 gender-specific symptomatic toxicities. After feedback from the first round of cognitive interviews, the second round of interviews was performed using two gender-matched interview schedules that incorporated 14 core symptomatic toxicities, a subset of the remaining 64 symptomatic toxicities, and the revised phrasings from Round 1.

Two specially trained interviewers (with a Master's degree in public health and bachelor's degree in psychology, respectively) conducted the cognitive interviews. In the interviews, retrospective probing was used [15] in which patients first completed a PRO-CTCAE survey on article; this was followed by discussion about their responses.[11] In each interview round, participants first filled in the questionnaire independently. For each question, they were asked to indicate if they found a question difficult to understand or confusing. Observations concerning a patient's attitude and body language were recorded, and the interviewer noted any PRO-CTCAE items where participants seemed to hesitate or were uncertain about their responses. The interviewer asked respondents to reflect on their thoughts as they answered each question and invited them to discuss any problems they experienced in understanding the meaning of the questions. Respondents were asked specifically about their interpretation of the instructions, the attribute terminology (frequency, severity, and interference),[11] and were encouraged to explain the terms in their own words. Special attention was given to questions marked as difficult to understand or confusing and symptomatic toxicities identified as

"potentially problematic" during the translation procedure. The interviews were audio-recorded and field notes were prepared.

An item history, including participants' comments about their interpretation of the symptomatic toxicities, PRO-CTCAE Danish phrasing, questions marked as problematic, the duration of the interview, and the interviewer's observations were systematically documented, together with participant demographic and clinical characteristics. When symptomatic toxicities were identified as problematic by three or more respondents, the steering group evaluated the comments to determine whether they were related to the phrasing of the PRO-CTCAE item, interpretation of the symptomatic toxicity, the patient's experience of the symptom, or a more general problem in the construction of the question. On the basis of this evaluation, the steering group decided whether the Danish phrasing of the symptomatic toxicity should be changed, or whether the comment could be addressed by a general explanation of the structure of the questionnaire in an introduction. The study participants' comprehension of the phrasing of question stem elements "how often," "severity at its worst," and "interfere with usual or daily activities," as described in their own words, was evaluated in a consensus process by the study group.

To develop the final version of the PRO-CTCAE Danish, the research group reviewed summaries of the interviews and attained an item history to reflect decisions made during the process of developing the final version of the PRO-CTCAE.

Results

There was full agreement of the two forward and the two backward translations for 28 and 27 symptomatic toxicities, respectively. For the remaining 50 symptomatic toxicities, no major differences were found between the Danish language versions in the forward translation. In the backward translation, no major differences were found in 47 symptomatic toxicities, whereas four symptomatic toxicities were found to be problematic: breast area enlargement or tenderness; fatigue, tiredness or lack of energy; pounding or racing heartbeat (palpitations); spots or lines (floaters) that drift in front of your eyes. The Danish phrasing of these symptomatic toxicities was adjusted to ensure the most precise cultural and clinical description without compromising the meaning of the symptomatic toxicity.

Eligible patients were identified over a period of two months. The cognitive interviews took place at the hospital on days where the patients were scheduled for treatment, visits, or other activities. The average duration of the interview was 18 minutes (range 9–42), in addition to the time patients spent on filling in the questionnaire. No problems were found in the

Table 2
Symptoms Marked as Problematic by Patients

Symptoms With Minimum Three Patient Comments Resulting in Modification		
Initial Version	Modified Version Retested in Round 2	Reason for Modification
Body odor	Body odor other than normal	To clarify that the body odor is different from usual
Feeling that nothing could cheer you up	Nothing could cheer you up	The sentence was too long and difficult to read
Lose control of your stools	Lose control of your stools (problems holding feces back)	The parenthetical phrase was added to clarify the meaning of the symptom and to distinguish it from the symptoms diarrhea and constipation
Mouth or throat sores	Problems from the mucosa in your mouth or throat[a]	The Danish word for "sores" was too specific
An unexpected decrease in sweating	Any decrease in sweating from normal	The word "unexpected" confused some patients

Symptoms With Minimum Three Patient Comments Resulting in No Modification[b]	
Initial Version	Examples of Patient Comments
Anxiety	Anxiety was considered individual and not relevant to be categorized by patients themselves
Blurry vision	Uncertain if blurry vision was related to the treatment
Decreased appetite	Regarding decreased appetite, the attributes "interfering" and "at its worst" were confusing
Decreased sexual interest	The symptom was not considered important in the patients' current situation
Pain	Tolerance of pain is individual, need to clarify the location of pain
Sad or unhappy feelings	Unsure if the symptom was related to the disease and difficult to categorize the attribute "severity" in relation to the symptom
Stretch marks	The symptom was perceived as related to pregnancy and overweight and not in relation to cancer treatment
Urine color change	Urine color is also related to food intake and time of day

[a]Modified to "Sores or lesions in the mucosa in your mouth or throat" after second round of linguistic validation and retested in a third round of interviews.
[b]Patients' comments were not related to problems in understanding the phrasing.

two rounds of validation in the patients' description of the symptom attributes and response options for "frequency," "severity," and "interference with usual or daily activities." The first round of validation including 42 patients resulted in 35 symptomatic toxicities with no patient comments (not marked as "difficult to understand"). Eighteen symptomatic toxicities received one patient comment each, 12 symptomatic toxicities received two patient comments, and 13 symptomatic toxicities were commented on by three or more participants (Table 2). The "difficult to understand" marking was used by patients if they had concerns about the question, even if it was not reflecting problems in understanding the phrasing of the symptomatic toxicity. Sometimes, it was due to patients' lack of experience with the symptom, for example, the symptomatic toxicity "stretch marks" was described as difficult to understand by five patients, who thought that the symptom was related only to pregnancy or overweight and not to cancer or its treatment. Eight patient comments were related to uncertainty of a symptom as being due to treatment or not. The 13 symptomatic toxicities on which at least three patients had comments were reviewed by the steering group. Only five of these 13 symptomatic toxicities were difficult for respondents to comprehend or were misinterpreted. The Danish language symptomatic toxicities were rephrased (Table 2), and were retested in Round 2 ($n = 14$). As an example, the symptomatic toxicity "Mouth or throat sores" was found difficult to understand because the Danish word for "sore" was too specific. The term was then modified to "Problems from the mucosa in your mouth or throat."

In the second round, the Danish symptomatic toxicity "Problems from the mucosa in your mouth or throat" still was found difficult to understand and was misinterpreted as "dry mouth," or "problems tasting." Consequently, the Danish language phrasing was adjusted to "Sores or lesions in the mucosa in your mouth or throat." In a third interview round, this phrasing was then tested separately in a new patient cohort ($n = 7$). Saturation was reached, as no study participants expressed comprehension difficulties with this revised phrasing.

Discussion

The forward and backward translations were highly consistent with the meaning of the PRO-CTCAE English language version, with only slight observed differences in phrasing that were easily addressed through minor edits. Minor but important changes were made in the phrasing of five symptomatic toxicities in the Danish language PRO-CTCAE version. Results of the cognitive testing confirm the comprehensibility of the PRO-CTCAE Danish and support its conceptual equivalence to the English source. The PRO-CTCAE Danish is available for use in cancer clinical trials through collaboration agreements with the U.S. NCI.

Strengths of this study include the use of rigorous procedures for translation, linguistic validation in a diverse sample of patients undergoing cancer treatment, and the use of methodologies that have been developed and standardized by the U.S. NCI for linguistic validation of PRO-CTCAE-Spanish and PRO-CTCAE-German.[12,13] Our study was conducted using a sample of Danish speakers drawn from a single site and while adequate for a qualitative study, the sample size was relatively small given the large number of items in the PRO-CTCAE item library. However, the study population adequately represents geographic and socioeconomic variability in the general Danish cancer population.

In conclusion, these results provide evidence of the comprehensibility of the newly developed PRO-CTCAE Danish item library including the symptomatic toxicities, symptom attributes, and response options, and support a conclusion that the Danish language PRO-CTCAE has linguistic equivalence to English. These results provide preliminary support for the use of PRO-CTCAE in cancer clinical trials that include Danish speakers. The next step will be to test the feasibility of using an electronic version of Danish PRO-CTCAE in clinical practice.

Disclosures and Acknowledgments

This study was supported by grants from the Danish Cancer Society (127 12 004-9102) and Department of Oncology, Rigshospitalet, Copenhagen University Hospital. The authors declare that they have no conflicts of interest.

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