Linguistic validation of the Spanish version of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

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Abstract
Purpose The U.S. NCI's PRO-CTCAE is a library of self-report items for assessing symptomatic adverse events in cancer clinical trials from the patient perspective. The aim of this study was to translate and linguistically validate a Spanish version.
Methods PRO-CTCAE's 124 items were translated from English into Spanish using multiple forward and back

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translations. Native Spanish speakers undergoing cancer treatment were enrolled at six cancer treatment sites. Participants each completed approximately 50 items and were then interviewed using cognitive probes. The interviews were analyzed at the item level by linguistic themes, and responses were examined for evidence of equivalence to English. Items for which ≥20 % of participants experienced difficulties were reviewed, and phrasing was revised and then retested in subsequent interviews. Items where <20 % of respondents experienced difficulties were also reviewed and were considered for rephrasing and retesting.

Results One hundred nine participants from diverse Spanish-speaking countries were enrolled (77 in Round 1 and 32 in Round 2). A majority of items were well comprehended in Round 1. Two items presented difficulties in ≥20 % of participants and were revised/retested without further difficulties. Two items presented difficulties in <20 %, and when retested exhibited no further difficulties. Two items presented difficulties in <20 %, but were not revised due to lack of alternatives. Sixteen items presented difficulties in ≤12 % and were not revised because difficulties were minor.

Conclusions The Spanish PRO-CTCAE has been developed and refined for use in Spanish-speaking populations, with high levels of comprehension and equivalence to the English PRO-CTCAE.

Trial registration: ClinicalTrials.gov:NCT01436240

Keywords Translation · Spanish · PRO-CTCAE · Cancer · Adverse events · Toxicity · Patient-Reported outcomes

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Background

Historically, adverse events (AEs) occurring in cancer clinical trials have been reported by clinicians using the Common Terminology Criteria for Adverse Events (CTCAE) [1]. The CTCAE, which is maintained by the U.S. National Cancer Institute (NCI), is a lexicon used by clinicians to describe and document AEs, with each AE graded using an ordinal severity scale [2]. In 2008, the U.S. National Cancer Institute (NCI) began developing a library of patient-reported outcome (PRO) items to complement the CTCAE, called the PRO-CTCAE [3].

The process of developing the PRO-CTCAE item library is described elsewhere [4]. Of the 790 AEs in CTCAE version 4, 78 were identified as symptomatic AEs that would be amenable to patient self-reporting. For each of these symptomatic AEs, between 1 and 3 PRO items were created to evaluate the attributes of symptom frequency, severity, and/or interference with usual or daily activities. The particular attributes selected for a given AE in the PRO-CTCAE were determined based on the grading criteria for that AE in the CTCAE. The PRO-CTCAE item library is comprised of a total of 124 items, representing 78 symptomatic AEs.4. In any given trial, investigators select a subset of these items for evaluation, based on study hypotheses, prior research, and knowledge of the anticipated regimen-related toxicities.

The generic phrasing structure for PRO-CTCAE items and response options are shown below. Each item includes a plain language term for the symptomatic AE and the attribute of interest. The standard recall period is “the past 7 days.”

- Frequency item: How OFTEN did you have _____?
- (Never / Rarely / Occasionally / Frequently / Almost constantly)
- Severity item: What was the SEVERITY of your _____ at its WORST?
- (None / Mild / Moderate / Severe / Very severe)
- Interference item: How much did _____ INTERFERE with your usual or daily activities?
- (Not at all / A little bit / Somewhat / Quite a bit / Very much)

A U.S. multi-site cognitive interviewing study previously evaluated the 124 PRO-CTCAE items in English and found the items to be well understood and meaningful to patients undergoing cancer treatment [5]. Robust quantitative measurement properties including construct validity and reliability were previously demonstrated in a large validation study conducted at multiple sites around the U.S. [6].

Development and testing of a Spanish language version of the PRO-CTCAE was prioritized by the NCI because a substantial proportion of the U.S. population, and hence participants in U.S. cancer clinical trials, are Spanish-speaking.

Linguistic validation of the Spanish PRO–CTCAE in a large and diverse sample was considered important to ensure that the Spanish PRO-CTCAE was well understood and meaningful to Spanish speakers receiving cancer treatment.

Therefore, a study was designed for translation and linguistic validation of the PRO-CTCAE, including two stages: (i) translation into Spanish and (ii) cognitive testing in native Spanish-speaking cancer patients, with modifications and retesting as appropriate. The large number of individual items in the PRO-CTCAE item library, and the necessity of conducting interviews in a diverse sample with respect to country of origin and educational attainment, required that we enroll a relatively large sample compared to most linguistic validation studies. The simultaneous evaluation of 124 PRO-CTCAE items, some of which are gender-specific, in a single study also required that the PRO-CTCAE items be distributed methodically across different questionnaires customized by gender.

Methods

Translation procedure

A translation procedure was developed based on current best practices and guidance [7–10]. The overall approach was designed to render terminologies and phrasing that are meaningful across a heterogeneous population of Spanish speakers residing in the USA (with various countries of origin and levels of acculturation and education) and to optimize equivalence with the English source across three principal categories: (1) semantic/linguistic equivalence (i.e., the item means the same thing in the source and translated language); (2) content equivalence (i.e., the item is relevant in both languages and cultures), and (3) conceptual equivalence (i.e., the underlying construct is similar in both languages and cultures) [11].

Figure 1 provides an overview of the procedure for translation. This procedure was conducted by personnel at FACITtrans, an organization specializing in translation of PRO measures (www.facit.org), with direct oversight and involvement by the study's principal investigator (EB) and the NCI PRO-CTCAE Science Officer (SAM). A team of native Spanish speakers representing different Spanish-speaking regions (Argentina, Colombia, Dominican Republic, Mexico, Puerto Rico, Spain) was assembled and coordinated by the FACITtrans scientific lead (BA). This team initially conducted a translatability assessment to identify possible linguistic and conceptual difficulties, anticipate translation issues, and suggest preliminary translation wording to ensure item clarity, cultural relevance, and equivalence. Next, item definitions were created to serve as a glossary of the terms and concepts contained in the 124 PRO-CTCAE items, providing a standardized resource to translators and linguists. Two independent forward translations by native Spanish-speaking translators were performed, followed by a reconciliation of the two forward translations by a third native Spanish-speaking translator. Back-translation of the reconciled version was performed by a native English speaker fluent in Spanish and familiar with cultural considerations in translation methods, who had not seen the original English PRO-CTCAE items. A comparison of source and back-translated versions was conducted by the team to identify

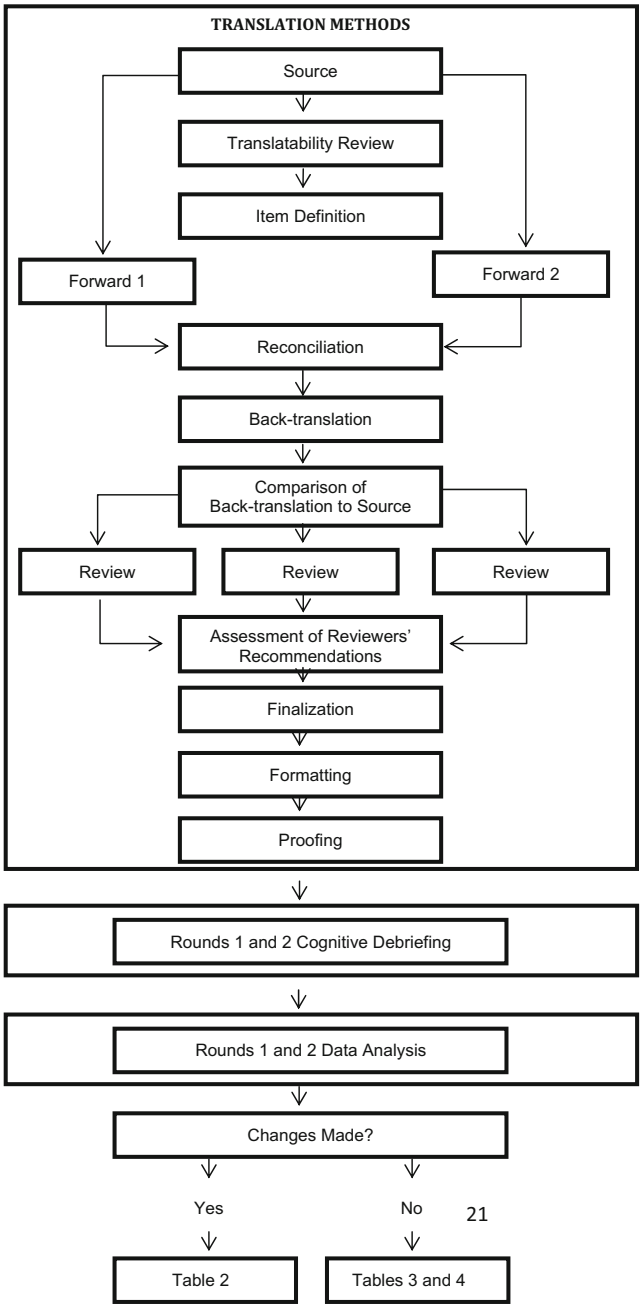

Fig. 1 Procedure for linguistic adaptation (translation and linguistic validation) of the PRO-CTCAE from English to Spanish

discrepancies, and to consider whether translated items were simple yet grammatically correct and amenable for use across different Spanish language cultural contexts and likely to be comprehensible to those with lower levels of literacy or educational attainment. The resulting items were reviewed and approved for cognitive testing by the multidisciplinary PRO-CTCAE Spanish Translation and Linguistic Validation Study Group, comprised of health outcomes researchers, clinicians, clinical trialists, and experts in qualitative approaches to the translation and content validation of PRO measures (represented by the authors of this manuscript).

Cognitive interviewing procedure

Cognitive interviewing has had increasing use as a means to evaluate questionnaires and other self-report instruments that are translated into multiple languages, and administered across a range of cultural groups [12]. For the current investigation, a cognitive testing protocol, including an informed consent form, was developed and approved by the Institutional Review Board (IRB) of the National Cancer Institute and six participating institutions and their affiliated community sites: Memorial Sloan Kettering Cancer Center, New York, NY (Coordinating Center); Ralph Lauren Center for Cancer Care and Prevention, New York, NY; MD Anderson Cancer Center, Houston, TX; Stroger Hospital (formerly Cook County Hospital), Chicago, IL; St. Joseph's Hospital, Orange, CA; and University of Miami, FL. The study was registered at ClinicalTrials.gov (NCT01436240).

Questionnaire scripts Four Spanish language PRO-CTCAE questionnaire script versions were created for administration to study participants, each consisting of a subset of approximately 50 items (shown in Supplemental Table S1). This approach was employed because the PRO-CTCAE consists of 124 individual items, and administration and probing with a given participant of all items in the PRO-CTCAE item library were considered to be overly burdensome to patients who are undergoing cancer treatment. A prior PRO-CTCAE cognitive debriefing study in English-speaking patients had successfully employed an approach of distributing the items among four interview questionnaires with approximately 50 items per questionnaire [15].

A subset of 14 commonly occurring symptoms [13] was specified a priori; these symptoms were included in all four script versions [4], with the remaining PRO-CTCAE items, including five female-specific and two male-specific symptomatic AEs, distributed across the scripts. In addition, each questionnaire included items collecting information about demographics, education, country of birth, and a validated 4-item measure of acculturation which asks participants about the language they speak at home, think in, and prefer to communicate in [14]. Lower scores indicate lower acculturation as an English speaker and a preference to think and communicate in Spanish.

Participants Adults with cancer who had received chemotherapy or radiation therapy within the prior 6 months were eligible to participate if they lived in the USA, were native Spanish speakers, and were capable of understanding the PRO-CTCAE items in print or when read to them verbatim. Enrollment goals were prespecified to include at least 50 % of participants with high school education or less, 25 % with low acculturation, and to include participants representing key Spanish-speaking regions of origin including (1) Mexico and the USA; (2) Central and South America; and (3) Cuba, the Dominican Republic and Puerto Rico. Study accrual was monitored on a weekly basis with targeted enrollment at sites to meet these goals, as well as to assure diverse representation by age, gender, and cancer type.

Interviewers Trained interviewers at all study sites were Bachelor's and Master's prepared research staff who were bilingual and experienced with cognitive interviewing in clinical research and/or cancer treatment settings. In total, there were 10 interviewers, and all underwent a standard training process to ensure a consistent approach to the interviews.

Interviews As described below, at least two rounds of cognitive interviews were planned with an option to add a third round of interviews if necessary. The cognitive interviewing procedure took place in a private area of the outpatient clinic and consisted of two parts: (a) administration of the questionnaire and (b) a semi-scripted debriefing interview in which cognitive probes were administered. Patients were given a printed copy of the PRO-CTCAE questionnaire but had the option to have the questionnaire read to them verbatim if they were uncomfortable reading text. Patients were directed to complete the questionnaire and to mark questions they found confusing or with which they had difficulty selecting a response. Interviewers did not provide any assistance or advice and encouraged patients to complete questions to the best of their ability based on the instructions provided.

After completing the questionnaire, the interviewer conducted the semi-scripted interview in Spanish. The scripts and standardized interviewing approaches were based on established standards [15] and were similar to those previously employed in the English PRO-CTCAE cognitive interviewing study [5]. First, a series of questions was asked about the patient's socio-demographic characteristics, followed by probes to evaluate common components of PRO-CTCAE item stems (e.g., recall period of the "past 7 days"; item attributes of frequency, severity, and interference with usual activities; and response options). Probes about prespecified, commonly occurring PRO-CTCAE symptoms terms were included (e.g., fatigue, nausea, pain) [13],

followed by in-depth probing of all items marked as difficult by patients. For example, "Let's consider this next question, '*In the last 7 days*, *how much did fatigue*, *tiredness*, *or lack of energy interfere with your usual or daily activities*?' What does the word 'interfere' mean in this question?"

Interviewers queried participants regarding comprehension, relevance, inclusiveness, cultural appropriateness, and cognitive processes used to generate responses [15]. Probes elicited the respondent's interpretations of terminology, response choices, and phrasing, to allow subsequent analysis of equivalence of the Spanish to the English language items. Interviewers probed any spontaneous patient comments about the questions or response choices, as well as hesitations and/or body language or facial expressions that might indicate reactions to the items. Respondents were also asked an open-ended question about whether they felt that there was anything else that should be added or changed in the questionnaire. The interviewers kept field notes on patient responses and interviews were audio recorded.

Analysis and retesting

For analysis of the individual PRO-CTCAE items, interview field notes and audio recordings were compiled, abstracted, and summarized on an item-by-item basis using established methods [12, 15, 16]. Participants' responses were categorized into linguistic themes (comprehension, relevance, inclusiveness, cultural appropriateness, cognitive processes), and were examined for semantic, content, and conceptual equivalence with the English versions of items and terminology. Interview data pertaining to item stem and response option components were analyzed and summarized across patients. The multidisciplinary PRO-CTCAE Spanish Translation Study Group reviewed the data analysis. The proportion of patients exhibiting any level of difficulty or hesitation with an item or with an item stem or response option component was tabulated.

Items which exhibited difficulties in ≥20 % of participants in Round 1 of interviews were flagged for study team review and considered for revision and retesting in Round 2. Item revision was considered by the study team using detailed review of participants' responses and the characteristics of those participants to assure comprehension across the spectrum of included patients (e.g., age, country of origin, acculturation, education level). Any item with difficulties reported by <20 % of participants was similarly reviewed, with revision and retesting at the discretion of the study team, depending on whether a revision was feasible (i.e., if alternative terms were available) or would potentially improve performance of the item.

Round 2 included testing of revised items using a similar methodology to Round 1. The study protocol prespecified an optional Round 3 of interviewing if comprehension difficulties with an item persisted during Round 2 testing.

Sample size

The sampling plan prespecified a minimum quota in each round of interviews of 10 patients with a high school education or less, 10 patients with low English language acculturation [14], and representation from across four regions of origin (Mexico, Central America, South America, Caribbean). Moreover, a sufficient number of participants were required to assure that multiple participants completed each item (minimum of 9 respondents per item in Round 1) and that male and female participants were included to evaluate the gender-specific items. Flexible accrual goals were necessary to enable continued accrual until conceptual saturation for each item was reached, as determined based on continuous review of results by the investigators. These approaches were based on accepted standards for cognitive interviews [15] and a prior similar study of the English PRO-CTCAE [5]. Based on these criteria, it was estimated that 60–80 interviews would be necessary in Round 1. The sample size for subsequent rounds was not prespecified as it would depend on the number of items requiring reassessment.

Results

Between February 2012 and May 2014, 109 participants were enrolled (77 in Round 1 and 32 in Round 2) with a range of cancer types, ages, and balance between genders (Table 1). Participants had diverse and well-distributed regions of national origin. Approximately half (56 %) had less than a high school education, and most (93 %) reported low levels of acculturation [14]. There were 64/109 (59 %) who were unable or preferred not to read items and requested that items be read to them verbatim by the interviewer.

In Round 1, two Spanish PRO-CTCAE items presented difficulties among ≥20 participants: "Hot Flashes" (difficulty in 7/16 [44 %] of participants) and "Skin cracking at the corners of your mouth" (difficulty in 5/21 [23 %] of participants) (Table 2). Per the study protocol, these items were reviewed and were considered for revision and retesting in Round 2. "Hot flashes," originally translated as "sofocos o bochornos, " was revised to "calores o sofocos," and "corners of your mouth," originally translated as "comisuras de la boca," was revised to "lados de la boca." When the revised terms were retested in Round 2, no further difficulties were reported by any participants.

Three item terms presented difficulties in <20 patients but were felt by the study team to warrant revision and retesting (Table 3). Two of these items ("Sweating" and "Watery Stools") presented difficulty for 9 % of participants, with prominent comprehension difficulties experienced by some participants and availability of alternative terminologies. When revised phrasings were retested, no further difficulties were reported. A

Table 1 Patient characteristics

Characteristics	Pooled ($N=109$)	Round 1 ($N=77$)	Round 2 ($N=32$)
Age in years (SD) (range)	58 (±13) (23–82)	55 (±12) (29–79)	64 (±12) (23–82)
	n (%)	*n* (%)	*n* (%)
Gender	51 (47 %)	34 (44 %)	17 (53 %)
Male			
Education			
<High school	61 (56 %)	39 (51 %)	22 (69 %)
≥High school	48 (44 %)	38 (49 %)	10 (31 %)
Acculturation[a]			
Less acculturated	101 (93 %)	71 (92 %)	30 (94 %)
More acculturated	8 (7 %)	6 (8 %)	2 (6 %)
Region of birth			
Mexico and USA	42 (39 %)	34 (44 %)	8 (25 %)
Central and South America[b]	36 (33 %)	19 (25 %)	17 (53 %)
Cuba, Dominican Republic, and Puerto Rico	30 (27 %)	24 (31 %)	6 (19 %)
Spain	1 (1 %)	0 (0 %)	1 (3 %)
Cancer site			
Breast	28 (25 %)	23 (30 %)	5 (16 %)
Lung/thyroid	14 (13 %)	7 (9 %)	7 (22 %)
Prostate	11 (10 %)	7 (9 %)	4 (12 %)
Colorectal	8 (8 %)	7 (9 %)	1 (3 %)
Lymphoma	7 (6 %)	6 (8 %)	1 (3 %)
Head and neck	6 (6 %)	6 (8 %)	0 (0 %)
Other	35 (32 %)	21 (27 %)	14 (44 %)

[a] Acculturation level based on *Wallen GR, Feldman RH, Anliker J. Measuring acculturation among Central American women with the use of a brief language scale. J Immigr Health. 2002 Apr; 4(2):95-102*, using the a recommended cut score of 2.99 or lower to categorize respondents as less vs. more acculturated

[b] Central and South America includes Costa Rica, El Salvador, Honduras, Nicaragua, Argentina, Colombia, Ecuador, Peru, Uruguay, Venezuela

third item, "Sad or unhappy feelings," presented no difficulties for virtually all (99 %) participants, but based on review by bilingual translation experts on the study team, it was decided to test alternative phrasing in Round 2 to further clarify the symptom term. Participants in Round 2 preferred the alternate phrasing and reported no difficulties with comprehension.

Table 2 PRO-CTCAE items presenting difficulties to participants in Round 1 testing, resulting actions, and retesting in Round 2: Items for which a change was made based on Round 1 and additional cognitive interviewing was conducted in Round 2

Item content in English	Original item content in Spanish (as tested in Round 1)	Participants with difficulty in Round 1 *N* (%)	Revised item content in Spanish (as tested in Round 2)	Participants with difficulty in Round 2 *N* (%)
≥20 % of participants had difficulties in Round 1				
Hot flashes	Sofocos o bochornos	7/16 (44 %)	Calores o sofocos	0/11 (0 %)
Skin cracking at the corners of your mouth	Comisuras de la boca	5/21 (23 %)	Lados de la boca	0/10 (0 %)
<20 % of participants had difficulties in Round 1				
Sweating	Sudoración	2/21 (9 %)	Sudor	0/10 (0 %)
Loose or watery stools (diarrhea)	Heces o excrementos sueltos o acuosos (diarrea)	7/77 (9 %)	Heces o excrementos sueltos o líquidos (diarrea)	0/32 (0 %)
Sad or unhappy feelings	Sentimientos de tristeza o infelicidad	1/77 (1 %)	Sentimientos de tristeza o de no estar feliz	0/32 (0 %)

Table 3 PRO-CTCAE items presenting difficulties to participants in Round 1 testing: Items for which no change was made due to lack of alternatives (these items were retested in Round 2 to provide additional assessment)

Item content in English	Original item content in Spanish (as tested in Round 1)	Participants with difficulty in Round 1 *N* (%)	Participants with difficulty in Round 2 *N* (%)
Loss of control of bowel movements	Pérdida de la capacidad para contener las evacuaciones intestinales	4/21 (19 %)	0/10 (0 %)
Anxiety	Ansiedad	9/77 (12 %)	2/32 (6 %)

An additional two items that presented difficulties in <20 patients in Round 1 were considered for possible revision; however, no suitable alternative phrasing that might improve clarity or comprehension was identified. Further testing of these unaltered items was conducted in Round 2 for confirmation. These terms were "Loss of control of bowel movements" and "Anxiety", which in Round 1 presented difficulties in 19 % and 12 % of participants, respectively. In Round 2 retesting, these proportions declined to 0 % and 6 %, respectively. The study team again reviewed options for "Anxiety," which was translated as "ansiedad" and concluded that this is generally a challenging concept with no better phrasing options available. An additional 16 items that presented difficulties for 2–12 % of respondents were reviewed (Table 4), and felt not to warrant change or retesting due to a dearth of alternative phrasing and because difficulties with comprehension were minimal in the initial round of interviews.

No participants in either round of testing experienced difficulties with generic components of item stems (Table 5) including phrasing related to recall period, symptom attributes (e.g., severity, frequency, interference) or item response options, and no changes to these elements were deemed necessary.

Following Round 2, it was felt that no further testing was required for any of the translated items due to favorable results for retested items and lack of alternative approaches for those items that presented minor difficulties to participants.

Discussion

This study provides evidence that items in the Spanish language version of the PRO-CTCAE are generally well understood by native Spanish-speaking patients with cancer in the USA, including those with low levels of educational attainment and acculturation, and from diverse countries of origin. These results build on prior qualitative and quantitative studies of the U.S. English PRO-CTCAE, which demonstrated that the PRO-CTCAE items are acceptable and meaningful to individuals receiving cancer treatment, reflect symptomatic AEs contained in the CTCAE, and are valid, reliable, and responsive [4, 5, 6].

This study also demonstrates that it is feasible to include patients of diverse Spanish-speaking backgrounds in U.S.-based qualitative research, particularly those with lower education and acculturation. A particular strength of this study is inclusion of these individuals, which was prioritized by the NCI for

Table 4 Items for which no changes were necessary based on interview results of Round 1, with no further cognitive interviewing in Round 2

Item content in English	Original item content in Spanish (as tested in Round 1)	Participants with difficulty in Round 1 *N* (%)
Acne or pimples on the face or chest	Acné o los granos en el rostro o en el pecho	2/23 (8 %)
Decreased appetite	Disminución del apetito	2/109 (2 %)
Ejaculation problems	Problemas de eyaculación	1/13 (8 %)
Hand-foot syndrome	Síndrome de mano-pie	1/31 (3 %)
Hives (itchy red bumps on the skin):	Urticaria (ronchas rojas en la piel que pican)	1/31 (3 %)
Hoarse voice	Ronquera	2/31 (6 %)
Increased passing of gas (flatulence)	Mayor expulsión de gases intestinales (flatulencia)	2/31 (6 %)
Mouth or throat sores	Llagas (úlceras) en la boca o en la garganta	2/109 (2 %)
Nausea	Náuseas	3/109 (3 %)
Pain in the abdomen (belly area)	Dolor en el abdomen (el vientre)	1/23 (4 %)
Ridges or bumps on your fingernails or toenails	Líneas elevadas o pequeños bultos en las uñas de las manos o de los pies	2/27 (7 %)
Shivering or shaking chills	Escalofríos (tiritó o tembló de frío)	2/23 (4 %)
Unable to have an orgasm or climax	Le fue imposible llegar al orgasmo o al clímax	1/28 (4 %)
Unusual darkening of the skin	Oscurecimiento inusual de la piel	1/28 (4 %)
Unusual vaginal discharge	Secreción vaginal inusual	2/17 (12 %)
Wheezing	Sibilancias (silbidos en el pecho al respirar)	2/28 (4 %)

Table 5 Spanish translations of generic PRO-CTCAE item components

Category	Content in English	Content in Spanish
Recall period	Past 7 days	En los últimos 7 días
Attribute terminology	Severity	Intensidad
	Often	Frecuencia
	Interfere	Interfirió
Response options	None	Ninguna
	Mild	Leve
	Moderate	Moderada
	Severe	Intensa
	Very severe	Muy intensa
	Never	Nunca
	Rarely	Rara vez
	Occasionally	A veces
	Frequently	A menudo
	Almost constantly	Casi siempre
	Not at all	Nada
	A little bit	Un poco
	Somewhat	Algo
	Quite a bit	Mucho
	Very much	Muchísimo

evaluation of the Spanish PRO-CTCAE. Many participants requested that items be read to them, suggesting low literacy. It is important to recognize that for such individuals in clinical trials, it is necessary to provide an option for PRO questionnaires to be read to them either via an automated telephone "interactive voice response system" (IVRS) or a human interviewer. The NCI's PRO-CTCAE software includes an IVRS functionality.

Limitations of this study include a low number of participants from Spain, and future evaluations may test the items in this population and in other Spanish-speaking countries. Notably, the translation and analysis study team included native Spanish speakers from Spain who evaluated the items from this linguistic and cultural perspective. Spaniards represent less than 1 % of the U.S. population [17] but may be included in multinational clinical trials. The items were tested using paper questionnaires, whereas administration of PRO-CTCAE may be electronic in some trials. Measurement equivalence between paper, web, and automated telephone administration of English PRO-CTCAE items has been established in a separate study [4, 18] Finally, there were a number of items for which some comprehension problems persisted in a small proportion of participants. Overall, these problems were deemed as minor and unlikely to substantially impair respondents' comprehension of the PRO-CTCAE items.

There is mounting interest to integrate PROs into cancer clinical research [19, 20]. The availability of a library of items to facilitate patient-reporting of symptomatic AEs will allow trials to represent the tolerability of cancer treatments from the patient perspective. Availability of this library in languages spoken by clinical trial participants will allow the PRO data gathered in trials to reflect the experiences of a diverse population. For more information about PRO-CTCAE and permission to use the Spanish PRO-CTCAE, please visit: http://healthcaredelivery.cancer.gov/pro-ctcae.

Conclusions

A Spanish language version of the PRO-CTCAE has been developed and refined for use in cancer clinical trials. Cognitive interviews were conducted among cancer patients representing a diverse spectrum of countries of origin, educational attainment, and acculturation of native Spanish speakers. The finalized items exhibited high levels of comprehension, meaningfulness, and content equivalence to the U.S. English PRO-CTCAE items. The Spanish version of the PRO-CTCAE has been integrated into several prospective cancer clinical trials as a part of the NCI's ongoing development work for the PRO-CTCAE. This work is focused on assessing approaches for optimally integrating the PRO-CTCAE into clinical trials and for analyzing and reporting PRO-CTCAE data. The ultimate goal of the PRO-CTCAE is to improve our understanding of the patient experience of symptomatic toxicity so as to inform better decisions by patients, clinicians, and policy makers. To this end, the Spanish PRO-CTCAE will broaden the population of clinical trial participants who can directly report their symptomatic adverse events.

PRO-CTCAE Patient-Reported outcomes version of the common terminology criteria for adverse events, *AEs* adverse events, *CTCAE* Common Terminology Criteria for Adverse Events, *NCI* National Cancer Institute, *PRO* Patient-Reported outcome, *IRB* Institutional Review Board, *IVRS* Interactive voice response system

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FJP, JH, and EB) have given final approval of the version to be published. All authors (BA, SAM, LL, TRM, LJR, NB, GW, MM, SL, FJP, JH, and EB) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Competing interests All of the co-authors of this manuscript declare no financial competing interests nor any non-financial competing interests. We declare no relevant conflicts of interest associated with this work.

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