special articles

Linking the European Organisation for Research and Treatment of Cancer Item Library to the Common Terminology Criteria for Adverse Events

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abstract

PURPOSE The European Organisation for Research and Treatment of Cancer (EORTC) Item Library is an interactive online platform currently composed of 950 unique items (questions) derived from 67 patient-reported outcome (PRO) questionnaires. PROs complement clinician adverse event (AE) reporting classifications like the Common Terminology Criteria for Adverse Events (CTCAE). This work aims to create a standardized framework using the CTCAE to systematically classify symptomatic AEs from the EORTC Item Library through linking individual items to corresponding AEs.

METHODS The EORTC Item Library items were searched for within the CTCAE (v5.0) and linked to an AE if they were described within the AE's title, description, or grading. Symptoms described in EORTC items but not located in the CTCAE were coded as missing symptoms. Other nonsymptom EORTC items, not described within the CTCAE were assigned a non-CTCAE descriptive classification. Further descriptive codes (eg, multiple issues) were allocated to enable descriptive analysis. Two raters independently coded 26.2% (n = 249) of the items. The remaining 701 items were coded by one rater and verified by the second, followed by discussion with two additional raters to reach consensus.

RESULTS Overall, 625 (65.8%) EORTC items were linked to 208 different AEs. Three hundred sixty-nine items provide information about non-CTCAE cancer–related issues and were categorized into seven descriptive classifications, including body image; emotional impact of a symptom, diagnosis, or treatment; global health and quality of life; and impact on life and daily activities. Inter-rater agreement for independent coding was 79.1%. Bowel urgency and tenesmus were identified as missing symptoms in CTCAEv5.0.

CONCLUSION The EORTC Item Library provides considerable coverage of CTCAE toxicities, along with other complementary issues important to patients with cancer. Using the CTCAE clinical framework to classify symptomatic PRO items may facilitate PRO selection and use in clinical trials and routine care.

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BACKGROUND

Regulatory authorities are increasingly aware of the need to develop and advance novel cancer therapies with a patient-centered approach.[1] The complexity of novel cancer treatment, including prolonged treatment duration and multimodal therapies, while improving overall survival, has led to the need to consider the burden of long-term adverse events (AEs) and impact on quality of life (QOL).[2]

The gold standard for AE reporting in cancer clinical trials is the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).[3] This descriptive terminology catalog of 838 different AEs is a clinician-developed instrument, maintained and regularly revised by the US National Cancer Institute. It measures symptomatic AEs (eg, pain), observable AEs (eg, rash), and laboratory and radiographic findings. Clinicians interpret, diagnose, and grade AEs using a scale from 1-5 over the duration of the trial. However, increasingly, regulators, including the US Food and Drug Administration and the European Medicines Agency, have recognized the importance of inclusion of patient-reported outcomes (PROs), alongside other clinical outcome assessments, to support decisions around safety, tolerability, and efficacy within trials.[2,4] By providing unique insights into domains that are difficult to assess through biomedical outcomes and clinician ratings alone (eg,, fatigue and pain), PROs provide a more complete, patient-centered picture of the impact of disease and treatment.[5]

PROs are included in cancer clinical trials to complement clinician reporting and to capture the patient perspective, including the measurement of symptomatic AEs, function, and QOL. The European Organisation

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Patient-reported outcomes (PROs) are included in clinical trials to capture the patients' perspective. This work descriptively maps the contents of the European Organisation for Research and Treatment of Cancer (EORTC) Item Library onto the Common Terminology Criteria for Adverse Events (CTCAE) at the individual PRO item level to facilitate identification of relevant adverse event (AE) items and provide a common clinical framework. To our knowledge, this is the first example to date of a distinct PRO measurement system classifying its contents according to CTCAE terminology.

Knowledge Generated

Two hundred eight different AEs were linked to the EORTC items, and more than 65% of items (n = 625) were qualified for a CTCAE classification. The Item Library also contains 369 items that capture non-AE–related issues (eg, body image) and two symptomatic AEs missing from the CTCAE.

Relevance

This framework will be integrated into the Item Library searchable database to harmonize selection of additional EORTC items when supplementing an existing questionnaire for use within clinical trials and practice.

for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires (QLQ) are some of the most commonly used PROs in cancer clinical trials.[6] Since the initial development of the core questionnaire (QLQ-C30) in 1993, the EORTC Quality of Life Group (QLG) has published 66 different PROs measures tailored to different disease types, treatments, and populations, with more than 110 different language versions available for some questionnaires.[7] The development of each questionnaire follows a rigorous, well-defined process designed to capture patient experience across a disease and treatment spectrum, using the literature, along with patient and health care provider interviews to generate issues before psychometric testing.[8] One of the most recent additions to the QLQ measurement system is the release of the EORTC Item library.[9] This online, interactive platform is currently composed of 950 unique items from the EORTC QLG's portfolio of questionnaires.[10,11] It enables more flexible usage of the static questionnaires by allowing users to create customized item lists, thereby increasing flexibility to cover different disease and treatment contexts.[12] The PRO-CTCAE and FACIT Searchable Library provide similar approaches.[13,14]

Given that both the EORTC Item Library and CTCAE v5.0 are extensive measurement systems (with nearly 2,000 different items or AEs together), it is important to create a comprehensive framework linking the Item Library with the CTCAE. This research aims to map the EORTC Item Library, one of the most widely used PRO systems in cancer clinical trials, onto the clinician-reported CTCAE to facilitate the identification of items and provide a common clinical framework. Such a framework may support the quality of integration, analysis, and application of PROs within future clinical trials by harmonizing the selection of additional items between trials when specific AEs or issues associated with novel treatments or techniques are not present within the validated questionnaires.[12] This framework will be integrated into the Item Library searchable database to provide researchers and clinicians with information on which PRO items are most relevant for specific AEs as classified by the CTCAE system.[12,15,16]

METHODS

A descriptive mapping exercise was undertaken with the primary aim of comparing and contrasting the EORTC Item Library content (accessed July 2020) with the current CTCAE framework (v5.0).[3,9] A typical EORTC symptom item may capture the presence of a symptom (eg, "Did you have pain?") and the impact of a symptom (eg, "Did pain interfere with your daily activities?") and sometimes capture several aspects of a symptom in one item ("Have you had skin problems [eg, itchy, dry]?"). The EORTC Item Library also contains items covering the impact of cancer and treatment on QOL and function (eg, physical, emotional, and social aspects) and, for example, satisfaction with care. Generally, EORTC item responses are graded by presence/severity (not at all/a little/quite a bit/very much). The CTCAE framework is organized by System Organ Class (SOC; eg, GI disorders), the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) terminology hierarchy, and further subcategorized by AE (eg, diarrhea), a MedDRA lowest level term, and accompanied by a definition. Ascribed to each AE is a severity grade description ranging from 1 (mild symptoms) to 5 (death; Tables 1 and 2).

All 950 items from the EORTC Item Library were exported into a database (QLQ-C30/modules/standalone questionnaires/computerized adaptive testing item banks).[10,11] Some items are used in multiple questionnaires, and some domains are measured by several different items (eg, QLQ-C30 and corresponding computerized adaptive testing item banks).

We used an item-level content analysis approach adapted from previous work.[17-20] Primary fields included item wording and a numeric identifier assigned to each unique EORTC

TABLE 1. Decision Rules (adapted from the study by Cieza et al[17])

No.	Rule	Example
1	Each item of the PRO should be linked to the single most precise CTCAE category	eg, "Were you short of breath?" coded with a single symptomatic *CTCAE AE code* dyspnea and SOC respiratory, thoracic, and mediastinal disorders. If more than one option exists, the most accurate single CTCAE AE code is selected
2	If a single item encompasses different constructs, the information in each construct should be linked to all relevant AEs and items may qualify for several AEs from the same or different SOCs	eg, "Have you had skin problems (eg, itchy, dry)?" coded with two CTCAE AE codes dry skin and pruritus from SOC skin and subcutaneous tissue disorders
3	All constructs of the item to be linked have to be highlighted (ie, multiple distinct issues)	eg, "Have you had other problems with your nose, like sense of smell, runny or blocked nose, sneezing, sore or dry nose?" was coded as being linked to multiple issues and CTCAE AE sneezing and allergic rhinitis and SOC respiratory, thoracic, and mediastinal disorders
4	If the content of an item is not explicitly named an AE but could be described using an CTCAE diagnostic AE, this was linked	eg, "Have your skin or eyes been yellow (jaundiced)?" coded with CTCAE AE blood bilirubin increased and SOC investigations, accepting the limitation that although a PRO assessment would not provide sufficient information to perform a diagnosis, it could be informative
5	Items not found in the CTCAE are classified as either missing symptoms or not covered by CTCAE (non-CTCAE)	Symptomatic toxicity items captured within the EORTC Item Library and not located within the CTCAE v5.0 coded as missing symptoms, with the specific symptom described. Items not captured in the CTCAE and not linked to specific symptoms are assigned a non-CTCAE classification, eg, impact on life and daily activities
6	Item content not adequately described by a single CTCAE code should have a non-CTCAE code added (dual coding)	eg, "Did you take any medicine for pain?" was coded as a pain AE and a non-CTCAE code medication/medical device use
7	After unblinding to source questionnaire, CTCAE secondary AE codes should be linked	eg, "Have you had pain in your genital area?" is from the vulval cancer module (VU34). When blind to the source questionnaire, genitalia is not ascribed to sex. After unblinding, the primary AE is coded as vaginal pain and the secondary AE codes are coded as penile pain, scrotal pain, and testicular pain, all from SOC reproductive system and breast disorders

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; SOC, System Organ Class.

item. In the initial phases of coding (phase I and II), the EORTC source questionnaires (eg, QLQ-C30) from which each item originated were deliberately not included to blind the coders. This blinded approach had the secondary aim of assessing the face validity and potential versatility of items for use outside of the setting that it was developed for. The coding took place in several phases (Fig 1 and Table 1). Items were deductively searched for within the CTCAE (v5.0) and coded with a *CTCAE AE code* if they were described within the CTCAE term, definition, or grade description of an AE. Not all items from the CTCAE could be considered as appropriate for symptomatic item coding.[21] Many items (approximately n = 85) are analytic AEs (eg, laboratory findings), and many others (approximately n = 547) are diagnostic AEs (eg, mitral valve disease), which limited the total number of AEs from the CTCAE relevant to this exercise. However, the use of a deductive searching technique enabled laboratory findings and diagnostic AE codes to be used if they were deemed sufficiently descriptive (Table 2, examples 4/5). Once an appropriate AE was identified, the raters assigned an SOC and AE code to each item. During phase I, both raters independently assigned codes to 249 items, derived from a set of randomly selected questionnaires (C30/BM22/BN20/BR23/CR29/CX24/EN24/GI.NET21/HCC18/H&N35/LC13/LMC21/MY20/OES18/OG25/OV28/PR25/PR23/STO22), aiming for a coverage of approximately 25% of the Item Library content. Following phase I, the coding framework (Table 1) underwent minor modifications to clarify the decision rules and reduce future discrepancies. In phase II, the remaining 701 items were coded by one rater (C.P.) and reviewed by the second (A.G.) to reach agreement, highlighting ambiguous items for further review. In phase III, all 950 items were unblinded (revealing the source questionnaire(s) and scale structure) and reverified by both raters (A.G./C.P.) and a third rater (G.V.) to discuss areas of coding ambiguity. In phase IV, final coding decisions were taken including a fourth rater (M.G.) to reach final consensus and finalize the decision rules.

The coding framework is shown in Table 1 with examples in Table 2. Items (eg, "Were you short of breath?") were coded with a single symptomatic *CTCAE AE code* (eg, dyspnea) if

they were sufficiently described within the CTCAE v5.0 (Table 2; examples 1 and 2). Items were linked to all relevant AEs, therefore some qualified for several AEs from the same or different SOCs (examples 3, 5, and 6). For some items, multiple potential AE diagnoses were included (example 5). If an item was clearly linked to several different underlying issues (eg, used in different source questionnaires to evaluate different issues, or the item itself included multiple distinct issues) it was coded as linked to *multiple issues* (example 3). Items linked to a CTCAE *diagnosis only* code were coded as such, accepting the limitation that although a PRO assessment would not provide sufficient information to carry out a diagnosis, it could be informative (eg, jaundice; example 4). Items that were linked to both a diagnostic AE and a symptomatic toxicity were coded as *diagnostic + symptomatic toxicity* items (example 9). Symptomatic toxicity items captured within the EORTC Item Library but not located within the CTCAE v5.0 were coded as *missing symptoms*, with the specific symptom described. After unblinding the source questionnaires, the scale structure could be reviewed, which provided additional insight into the underlying issues that the items were developed to capture, to improve coding quality. If an alternative clinical application for an item was recognized (pending testing), a *secondary AE* code was ascribed (example 6).[22] Items not captured in the CTCAE and that could not be linked to a specific symptomatic AE were inductively assigned a *non-CTCAE classification* (eg, body image, example 7; medication/medical device use, example 8), defined using a bottom-up approach. During phase I, one rater (A.G.) devised a provisional list of *non-CTCAE* classification codes, which was later agreed upon with all raters (Table 3). These codes were also used in addition to an AE code if the content of an item was not sufficiently captured within the CTCAE grading (*non-CTCAE + AE code*; example 8).

In total, the coding database underwent 17 different iterations (Appendix Table A1, online only). Descriptive analyses were performed on the full group of items (n = 950) to evaluate the full number and range of CTCAE SOCs and AEs captured by EORTC items, the number of non-CTCAE classification codes, missing symptoms, multiple issue, diagnosis only, and diagnosis plus symptomatic AE codes. Results were also stratified by CTCAE SOC to highlight the items and linked AEs within each SOC. The resulting framework will be made available as part of the Item Library online search strategy.

RESULTS

For phase I, independent coding of the initial 249 items led to a 79.1% agreement rate between raters; 145 items had at least one overlapping AE, and 52 items were considered not suitable for CTCAE coding by both raters. For the 52 items where there was disagreement, this was mainly due to one rater deeming the item to be ineligible for CTCAE coding and the other assigning a *CTCAE AE* code (59.2%; Table 2, example 10—*non-CTCAE* item codes were agreed after phase I leading to this discrepancy), items describing a complex movement pattern involving different anatomic areas (12.2%, example 9), items where the item content led to ambiguity in coding (8.2%, examples 6 and 9), and simple disagreements related to *CTCAE AE* codes assigned (20.4%). These issues were resolved through minor modifications to the coding framework before phase II, unblinding of items to reveal the source questionnaire(s), and consensus discussion. Ascribing coding for items that were not simply *symptomatic AEs* or *non-CTCAE* issues encouraged significant debate, and additional raters (G.V./M.G.) were consulted to reach consensus.

After phase IV, 625 items (65.8%) were linked to 208 different AEs from 20 different SOCs (Table 4; Appendix Table A2, online only). The majority of linked PRO items were associated with one (65.6%) or two (23.5%) different *CTCAE AE* codes, with a smaller proportion associated with three or more (10.9%; range 3-7 AEs; Table 5). Fatigue was the most commonly linked AE, representing 4.9% of all linked AEs followed by *general disorders and administration site conditions, other specify* (used to describe AEs affecting activities of daily living; 4.1%), pain (4.1%), and dyspnea (3.8%; Appendix Table A3, online only). SOC GI disorders had the largest number of different AEs coded (n = 37; 17.8%) followed by nervous system disorders (n = 23; 11.1%) and reproductive system and breast disorders (n = 21; 10.1%; Table 4).

For the 625 items linked to a CTCAE code, 19 items (3.0%) were coded as being linked to *multiple issues* (Table 2, examples 3, 6, and 9), 42 (6.7%) were linked to both a *CTCAE symptomatic AE* and a *diagnosis* code, and an additional 42 (6.7%) were linked to a CTCAE *diagnosis* alone (Table 2, example 4; Table 5). Twelve items (1.9%) were eligible for a *secondary AE* code, denoting a PRO item developed for a particular (sub)population, whose content meant that it could be relevant in a different patient (sub) population if validated (Table 2, example 6). Only two symptoms, linked to six different EORTC items, were coded as *missing symptoms* not captured within the CTCAE: tenesmus and bowel urgency (Table 3).

Although the majority of items (73.9%) have only one source questionnaire (eg, QLQ-C30), a smaller proportion of PRO items appear in multiple different questionnaires: two (12.4%), three (4.8%), and four or more (8.9%; Table 2, example 9; Table 4). The item included in the greatest number of different questionnaires is "Were you worried about your health in the future?" included in 24 modules.

For the items not eligible for CTCAE classification, seven *non-CTCAE* codes were developed: body image; emotional impact of a symptom, diagnosis, or treatment; global health and QOL; impact on life and daily activities; information/

TABLE 2. Worked Examples of EORTC QLQ/CTCAE Coding

			Primary CTCAE Codes						Secondary CTCAE Codes							
No.	Item	Non-CTCAE Classification	SOC 1	AE 1	AE 2	AE 3	AE 4	AE 5	SOC 1	AE 1	AE 2	AE 3	Multiple Issues	Diagnosis Only CTCAE Code	Diagnosis + Symptomatic Toxicity Code	Rationale
1	Were you short of breath?	NA	Respiratory, thoracic, and mediastinal disorders	Dyspnea	NA	NA	NA		NA	NA	NA	NA	No	No	No	Simple PRO item to AE match
2	Have you had tingling in your fingers or toes?	NA	Nervous system disorders	Paresthesia	NA	NA	NA		NA	NA	NA	NA	No	No	No	Additional diagnostic code peripheral sensory neuropathy omitted since the symptomatic toxicity code paresthesia adequately describes the issue
3	Have you had skin problems (eg, itchy, dry)?	NA	Skin and subcutaneous tissue disorders	Dry skin	Pruritus	NA	NA		NA	NA	NA	NA	Yes	No	No	Wording of item captures two distinct issues
4	Have your skin or eyes been yellow (jaundiced)?	NA	Investigations	Blood bilirubin increased	NA	NA	NA		NA	NA	NA	NA	No	Yes	No	The only relevant code for this item is diagnostic
5	Have you had blood in your stools (motions)?	NA	GI disorders	Colitis	Proctitis	Anal hemorrhage	Rectal hemorrhage		NA	NA	NA	NA	No	Yes	No	Multiple relevant diagnostic codes to describe per rectal bleeding symptom
6	Have you had pain in your genital area?	NA	Reproductive system and breast disorders	Vaginal pain	NA	NA	NA		Reproductive system and breast disorders	Penile Pain	Scrotal pain	Testicular pain	No	No	No	Primary code assigned is vaginal pain as this item was developed and tested to measure genital pain in vulvar cancer, but the item (pending testing) could also be applied to other types of genital pain and hence the secondary codes
7	Have you felt less feminine as a result of your disease or treatment?	Body image	NA	NA	NA	NA	NA		NA	NA	NA	NA	No	No	No	This item is not eligible for a CTCAE code as it covers a broader QOL issue (body image) not captured within the scope of the CTCAE
8	Did you frequently have to change your urostomy bag?	Medication/ medical device use	Renal and urinary disorders	Urinary frequency	NA	NA	NA		NA	NA	NA	NA	No	No	No	Given that the urinary frequency code in the CTCAE does not capture the use of a urinary stoma, the additional non-CTCAE classification is also used

(continued on following page)

TABLE 2. Worked Examples of EORTC QLQ/CTCAE Coding (continued)

No.	Item	Non-CTCAE Classification	Primary CTCAE Codes						Secondary CTCAE Codes				Multiple Issues	Diagnosis Only CTCAE Code	Diagnosis + Symptomatic Toxicity Code	Rationale
			SOC 1	AE 1	AE 2	AE 3	AE 4	AE 5	SOC 1	AE 1	AE 2	AE 3				
9	Have you had trouble with eating?	NA	GI disorders	Mucositis oral	Oral pain	Dysphagia	Sore throat	Gastrointestinal pain	NA	NA	NA	NA	Yes	No	Yes	Unblinding to source questionnaires (H&N43, H&N35, BIL21, LMC21, OES18, GI.NET21, and OG25) increased the number of AE codes allocated—reflecting the AE arising from different underlying issues, both anatomical (eg, because of oral, throat, or bowel problems) and toxicity/disease-related (eg, inflammatory, anorexia, or because of a stricture); mucositis oral is a diagnosis, whereas the other codes are symptomatic toxicities and hence the diagnostic + symptomatic toxicity code
10	To what extent have you been troubled with side effects from your treatment?	NA	Injury, poisoning, and procedural complications	Injury, poisoning, and procedural complications—others, specify									NA	No	No	Generic CTCAE code assigned to capture treatment burden, as the item itself is nonspecific

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; NA, not available; PRO, patient-reported outcome; QLQ, Quality of Life questionnaires; QOL, quality of life; SOC, System Organ Class.

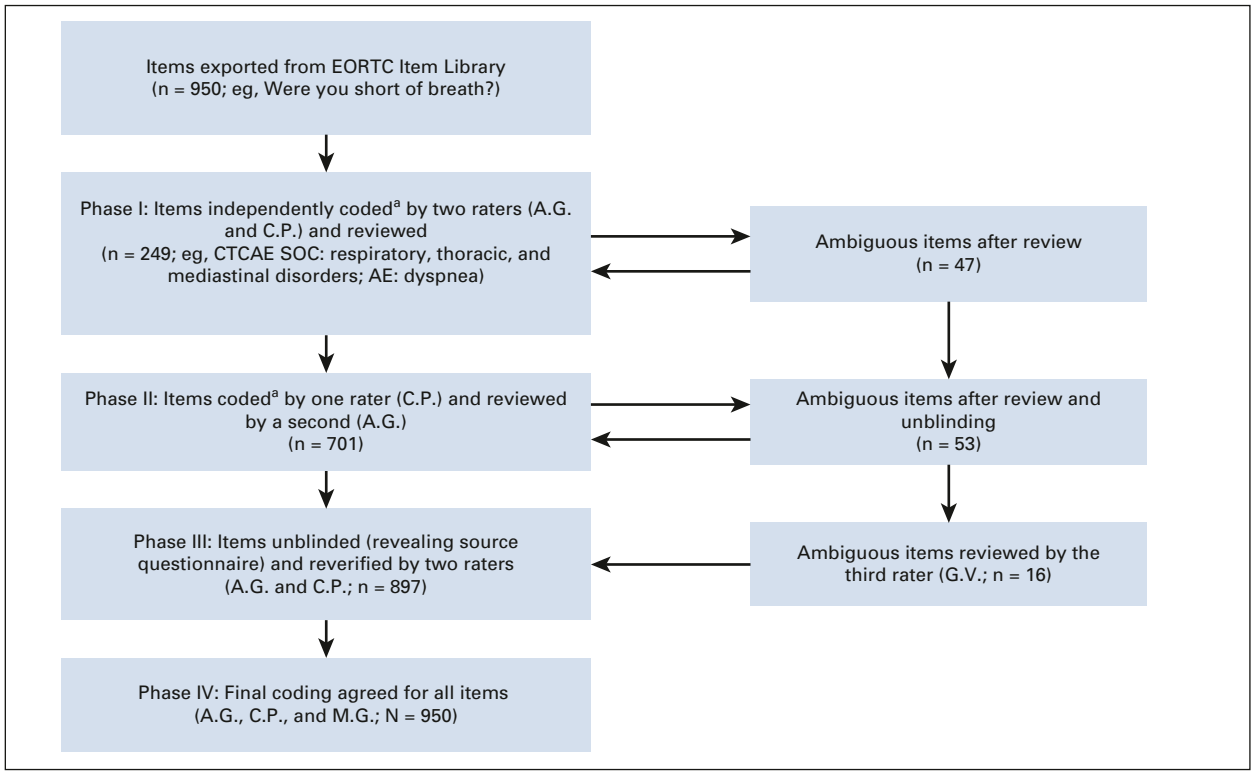

FIG 1. EORTC QLQ/CTCAE coding workflow. [a]Items coded as CTCAE SOC(s) and AE(s), missing symptom, or assigned a non-CTCAE classification. Description of process: phase I: two raters (A.G., UK English and C.P., North American English) independently coded 26.2% of the items from the Item Library taken from 19 questionnaires (26.2%; n = 249; QLQ-C30, BM22, BN20, BR23, CR29, CX24, EN24, GI.NET21, HCC18, H&N35, LC13, LMC21, MY20, OES18, OG25, OV28, PR25, PR23, and STO22). AE was defined as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure" as per the CTCAE (v5.0). If at least one common AE was selected by both raters or raters agreed that the item was not eligible for a CTCAE code, these were coded as agreement. Items for which there were any discrepancies (even those that had at least one overlapping AE) were discussed between both raters until an agreement was reached. Items where ambiguity remained were highlighted for later review. Phase II: the remaining 701 items were coded by one rater (C.P.) and then reviewed by the second (A.G.) to reach agreement, with ambiguous items highlighted for further review. Phase III: all 950 items were unblinded, revealing the source questionnaire, and reverified by both raters (A.G. and C.P.) to ensure that the primary coding accurately reflected the underlying issues for which the items were developed (on the basis of the scale structure[s] of their source questionnaires). A third rater was introduced (G.V.) to discuss the remaining ambiguous items to reach consensus. Phase IV: decisions about optimal higher-level coding choices (eg, coding of multiple AE for a single PRO item, and diagnostic AEs) were discussed between the two raters (A.G. and C.P.), and a fourth rater, M.G., was consulted to reach a final consensus. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; QLQ, Quality of Life questionnaires; SOC, System Organ Class.

satisfaction with care; medication/medical device use; and screening items (eg, "Do you have a stoma bag [colostomy/ileostomy]?"). Three hundred twenty items were coded with a *non-CTCAE* code only, with an additional 49 coded with both *CTCAE* and *non-CTCAE* codes (Table 2, example 8). The majority of descriptive classifications were assigned for items related to the emotional impact of symptom, diagnosis, or treatment (n = 124; 33.6%), followed by information/satisfaction with care (n = 117; 31.7%) and impact on life and daily activities (n = 84; 22.8%; Table 3).

DISCUSSION

To our knowledge, this is the first comprehensive analysis and mapping of EORTC-QLQ items to the CTCAE. This work was performed to provide a framework to systematically classify symptomatic AEs from the EORTC Item Library using the CTCAE and will be made available as part of a planned update of the Item Library online search strategy. Both within clinical trials and routine care, the selection of appropriate additional EORTC item(s) to supplement an existing questionnaire is crucial for the assessment of the impact of cancer and its treatment from the patient perspective. This is particularly relevant when the selected questionnaires may not adequately cover all relevant toxicities from novel treatments or their impact on a patients' QOL and function.[2] This work aimed to develop a framework to harmonize the selection of additional items for use within clinical trials and practice. The analysis

TABLE 3. Non-CTCAE Classification of EORTC Items and Missing Symptoms

Non-CTCAE Classification	EORTC Items	
	Total, No. (%)	CTCAE Code(s),[a] No. (%)
Descriptive/general		
Body image	22 (6.0)	—
Screening item	4 (1.1)	—
Emotional impact of symptom, diagnosis, or treatment	124 (33.6)	6 (12.2)
Global health and QOL	2 (0.5)	—
Impact on life and daily activities	84 (22.8)	39 (79.6)
Information/satisfaction with care	117 (31.7)	—
Medication/medical device use	16 (4.3)	4 (8.2)
Total	369 (100)	49 (100)
Missing symptoms		
Bowel urgency	4 (66.7)	
Tenesmus	2 (33.3)	
Total	6 (100)	

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; QOL, quality of life.

[a]Items that were eligible for both non-CTCAE classification and CTCAE code(s).

TABLE 4. Summary of SOC and CTCAE Coverage

SOC	Total No. of Different AEs Covered by an EORTC Item Within Each SOC, No. (%)
Cardiac disorders	2 (1.0)
Ear and labyrinth disorders	3 (1.4)
Endocrine disorders	2 (1.0)
Eye disorders	14 (6.7)
GI disorders	37 (17.8)
General disorders and administration site conditions	15 (7.2)
Immune system disorders	1 (0.5)
Infections and infestations	5 (2.4)
Injury, poisoning, and procedural complications	7 (3.4)
Investigations	3 (1.4)
Metabolism and nutrition disorders	1 (0.5)
Musculoskeletal and connective tissue disorders	17 (8.2)
Nervous system disorders	23 (11.1)
Psychiatric disorders	12 (5.8)
Renal and urinary disorders	9 (4.3)
Reproductive system and breast disorders	21 (10.1)
Respiratory, thoracic, and mediastinal disorders	16 (7.7)
Skin and subcutaneous tissue disorders	16 (7.7)
Surgical and medical procedures	1 (0.5)
Vascular disorders	3 (1.4)
Total SOC (n = 20)	Total AEs, n = 208 (100)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; SOC, System Organ Class

shows considerable overlap between the two systems, with the EORTC Item Library providing coverage of 208 different AEs from the CTCAE (v.5.0), noting that not all CTCAE AEs are relevant for patient-reporting.[14] Of the 950 EORTC Item Library items, 625 items were mapped to a *CTCAE AE* code. In addition, 369 EORTC-QLQ items provide information on issues not specifically related to AEs alone, in particular regarding the impact of disease, symptoms, and treatment on patients' function (n = 84) and emotional well-being (n = 124). The analysis also revealed two missing symptoms from the CTCAE: bowel urgency and tenesmus. Bowel urgency, specifically, has been highlighted as missing in previous work.[23] MedDRA terms for these missing symptoms (defecation urgency and rectal tenesmus) and other issues (eg, body image) can be found.

This work addresses one of the past criticisms of the EORTC-QLQ measurement system, which has been the inflexibility of the static measures to accurately measure symptomatic toxicities associated with novel agents, used in combination and alone, in a clinical trial setting.[12] Providing a framework to cover novel AEs and patient issues not covered by the existing questionnaires is essential in a fast-changing clinical world and to allow comparison between trials. Although the flexible use of the EORTC-QLQ items has long been practiced in trial settings where a disease-specific module was not available,[24] the lack of a platform with a well-developed classification system describing the scope of the items has limited wider application. Other commonly used PRO systems in cancer clinical trials have addressed the issue of flexible symptomatic toxicity measurement. The National Cancer Institute (NCI) PRO-CTCAE was developed from the CTCAE through a process of mapping symptomatic toxicities onto PRO items for self-report.[14] The PRO-CTCAE covers 78 symptomatic toxicities in 124 items. These items may be selected to create a trial-specific questionnaire. In comparison, the approach described by the FACIT Organization is similar to the EORTC Item Library.[13] The FACIT Searchable Library contains more than 700 items taken from the Functional Assessment of Cancer Therapy (FACT) static questionnaires and may be searched to find coverage of symptomatic AEs. The FACIT website reports that 55 of the 78 systematic AEs covered by the NCI PRO-CTCAE are included. The results of our analysis suggest that the EORTC-QLQ system has excellent symptomatic AE coverage. Further work is needed to address the

TABLE 5. Summarized Results of EORTC QLQ to CTCAE Mapping

QLQ Frequency	EORTC Item, No. (%)
Total No. of source questionnaires for an EORTC item	
1	702 (73.9)
2	118 (12.4)
3	46 (4.8)
4	33 (3.5)
5	18 (1.9)
6	9 (0.9)
7	8 (0.8)
8	2 (0.2)
9	3 (0.3)
10	3 (0.3)
11	2 (0.2)
12	2 (0.2)
13	1 (0.1)
15	1 (0.1)
21	1 (0.1)
24	1 (0.1)
Total items	950 (100)

AE Frequency	EORTC Item, No. (%)
Total No. of AEs linked to an EORTC item	
1	410 (65.6)
2	147 (23.5)
3	48 (7.7)
4	15 (2.4)
5	3 (0.5)
6	1 (0.2)
7	1 (0.2)
Total items	625 (100)

	Primary Classification, No. (%)	Secondary Classification, No. (%)
Total No. of AEs assigned to EORTC items	913 (100)	24 (100)

Proportions Calculated on the Basis of Total Linked Items (n = 625)	EORTC Item, No. (%)
Single EORTC items linked to multiple underlying AEs	19 (3.0)
Single EORTC items linked only to diagnostic AEs	42 (6.7)
Single EORTC items linked to both diagnostic and symptomatic AEs	42 (6.7)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; QLQ, Quality of Life questionnaires.

symptomatic AE coverage of the EORTC Item Library with respect to these two different PRO systems.[25]

This work provides a framework mapping the EORTC Item Library, containing all validated EORTC QLG questionnaires (accessed July 2020), onto the current version of the CTCAE (v5.0). These results will be integrated into the EORTC Item Library platform to facilitate identification of items using the CTCAE framework. The strengths of the methodological approach used include the following: independent researcher coding followed by code verification and consensus discussions; inclusion of multiple raters from different clinical, research, and language backgrounds; and blinding of the source questionnaires to enable decontextualized initial coding of the items. Regarding the limitations, the methodology used limits the ability to establish if there are CTCAE symptomatic toxicity items that are not covered by the EORTC Item Library insofar as the mapping used the Item Library as the initial framework, rather than vice versa. Although the process of PRO development used by the EORTC QLG aims to develop items that are relevant to capturing patient experience (including symptomatic AEs), future work mapping symptomatic AEs from the CTCAE onto the EORTC Item Library is necessary. This will ensure that the EORTC Item Library has comprehensive coverage of all symptomatic AEs. However, this work has identified that potentially, there are more symptomatic AEs than the 78 AEs identified by the NCI PRO-CTCAE team, which could be suitable for patient self-report.[14] Future work will compare the EORTC-QLQ system with other PRO systems, as well as MedDRA and WHO-ICF. The analysis also did not seek to select the best PRO item(s) to use for a specific AE; future work will aim to hone the specificity of this mapping, taking into account multiple issues such as content validity, cultural adaptability, translatability, psychometric properties, statistical performance, clinical relevance, and frequency of use within existing questionnaires, to improve the selection process, develop new items where needed, and potentially adapt or remove problematic items. The authors also acknowledge the limitation around the need to better understand the similarities and differences between clinician and patient-reported systems regarding AE severity grading. This complex issue, which requires a multiple methods approach, is an area of future work.[26-28]

The primary focus of this article is on improving the searchability and item selection for relevant symptomatic toxicities from the EORTC Item Library to assess in a trial from the patient perspective. However, this research has highlighted a need for future stakeholder work, including the regulatory perspective, to establish agreement on key issues related to PRO implementation within clinical trials, including (1) how to optimize use of PROs reporting within a trial AE database; (2) how to manage discrepancies and duplication of AE reporting to minimize clinician and patient burden (ie, are some AEs better reported with a PRO or vice versa); (3) how to manage PRO AE reporting, which may trigger clinical assessment, leading to hospitalization or modification of

treatment; and (4) what complementary measures (eg, QOL and function) are essential and best suited for patient-reporting.[29] Current guidance from US regulators encourages the use of PRO data to provide complementary information to support clinician assessment of tolerability and safety. However, there is no expectation to currently provide PRO data within safety reporting.[30]

In summary, this extensive descriptive analysis provides a comprehensive, clinical framework to facilitate selection of additional symptomatic AEs and cancer-related issues from the EORTC Item Library for use in clinical trials and practice. Future research will involve working with stakeholders to address issues around optimal PRO selection and application of the Item Library framework in clinical trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Linking the European Organisation for Research and Treatment of Cancer Item Library to the Common Terminology Criteria for Adverse Events

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APPENDIX

TABLE A1. Coding Examples

Code	Wording	Source Questionnaire(s)			Total Source Questionnaires	Non-CTCAE Classification 1	Missing Symptom (not in CTCAE)	Total SOCs	Total AEs	Multiple Underlying Issues (on the basis of wording and source questionnaires)	Secondary AEs	Diagnosis-Only CTCAE Code	Diagnosis + Symptomatic Toxicity Codes	SOC 1	AE 1	AE 2	AE 3	AE 4	AE 5
Q1	Have you felt less masculine as a result of your disease or treatment?	PR25	SHQ-C22	TC26	3	Body image													
Q10	Were you limited in pursuing your hobbies or other leisure time activities?	C30	CAT Role Functioning		2	Impact on life and daily activities													
Q100	Have you been satisfied with your level of intimacy?	SHQ-C22			1	Emotional impact of symptom, diagnosis, or treatment													
Q101	Have you had problems eating in front of other people?	H&N43	H&N35	OES18	5	Emotional impact of symptom, diagnosis, or treatment													
Q102	Have you felt insecure regarding your ability to satisfy your partner?	SHQ-C22			1	Emotional impact of symptom, diagnosis, or treatment													
Q103	Have you had problems enjoying your meals?	H&N43	H&N35	OES18	5	Impact on life and daily activities													
Q104	Have you been satisfied with your sex life?	SHQ-C22			1	Emotional impact of symptom, diagnosis, or treatment													
Q105	To what extent did you feel sexual enjoyment?	SHQ-C22			1			1	2					Psychiatric disorders	Anorgasmia	Delayed orgasm			
Q106	Have you had problems talking to other people?	H&N43	H&N35		2			1	3					Nervous system disorders	Dysarthria	Dysphasia	Aphonia		

(continued on following page)

TABLE A1. Coding Examples (continued)

Code	Wording	Source Questionnaire(s)			Total Source Questionnaires	Non-CTCAE Classification 1	Missing Symptom (not in CTCAE)	Total SOCs	Total AEs	Multiple Underlying Issues (on the basis of wording and source questionnaires)	Secondary AEs	Diagnosis-Only CTCAE Code	Diagnosis + Symptomatic Toxicity Codes	SOC 1	AE 1	AE 2	AE 3	AE 4	AE 5
Q107	Were you confident about obtaining and maintaining an erection when you had sex?	SHQ-C22			1			1	1					Reproductive system and breast disorders	Erectile dysfunction				
Q109	Have you been feeling less feminine as a result of your disease or treatment?	BR45	BR23	CX24	6	Body image													
Q11	Were you short of breath?	C30	CAT Dyspnea	C-PAL15	4			1	1					Respiratory, thoracic, and mediastinal disorders	Dyspnea				
Q110	Have you had problems talking on the telephone?	H&N43	H&N35		2			1	3					Nervous system disorders	Dysarthria	Dysphasia	Aphonia		
Q111	Have you had trouble having social contact with your family?	H&N35			1	Impact on life and daily activities													
Q112	Have you had trouble having social contact with friends?	H&N35	LMC21		2	Impact on life and daily activities													
Q113	Have you had problems going out in public?	H&N43	H&N35		2	Impact on life and daily activities													
Q114	Did food and drink taste different than usual?	CAX24	SBQ74	BR45	11			1	1					Nervous system disorders	Dysgeusia				
Q115	Were your eyes painful, irritated, or watery?	BR45	BR23		2			1	2					Eye disorders	Eye pain	Watering eyes			

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SOC, System Organ Class.

TABLE A2. Fatigue Example

Wording	Source Questionnaire(s)									SOC 1	AE 1
Have you felt slowed down?	CAT Fatigue	FA12	LMC21	BIL21	CLL16					General disorders and administration site conditions	Fatigue
Have you lacked energy?	CAT Fatigue	FA12	SBQ74	CLL17	HL27	NHL-HG29	NHL-LG20	BIL21	LMC21	General disorders and administration site conditions	Fatigue
Did you have trouble getting things started?	FA12									General disorders and administration site conditions	Fatigue
Have you found it difficult to finish things you started?	HDC29	HCC18								General disorders and administration site conditions	Fatigue
Have you felt mentally exhausted?	THY34									General disorders and administration site conditions	Fatigue
Did you need to rest?	C30	CAT Fatigue								General disorders and administration site conditions	Fatigue
Were you tired?	C30	CAT Fatigue	C-PAL15	SBQ74						General disorders and administration site conditions	Fatigue
Did you feel drowsy during the daytime?	BN20									General disorders and administration site conditions	Fatigue
Have you been too tired to eat?	CAT Fatigue	CAX24								General disorders and administration site conditions	Fatigue
Have you felt exhausted?	CAT Fatigue	FA12								General disorders and administration site conditions	Fatigue
Did tiredness interfere with your daily activities?	FA12									General disorders and administration site conditions	Fatigue
Have you been so tired it was difficult keeping your eyes open during daytime?	CAT Fatigue									General disorders and administration site conditions	Fatigue
Have you woken up with a feeling of exhaustion?	CAT Fatigue									General disorders and administration site conditions	Fatigue
Have you lacked the energy to do things?	CAT Fatigue									General disorders and administration site conditions	Fatigue
Have you been too tired to do your usual activities?	CAT Fatigue									General disorders and administration site conditions	Fatigue
Have you felt drained?	CAT Fatigue									General disorders and administration site conditions	Fatigue
Have you been so exhausted it felt almost impossible to move your body?	CAT Fatigue									General disorders and administration site conditions	Fatigue
Have you had trouble starting things because you were tired?	CAT Fatigue									General disorders and administration site conditions	Fatigue

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TABLE A2. Fatigue Example (continued)

Wording	Source Questionnaire(s)		SOC 1	AE 1
Have you been too tired to do even simple things?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you found shopping and doing errands exhausting?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you felt physically exhausted?	CAT Fatigue	THY34	General disorders and administration site conditions	Fatigue
Have you found leisure and recreational activities exhausting?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you had to sleep for long periods during daytime?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you become easily tired?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you had trouble sitting up because you were tired?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you felt worn out?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you had a feeling of overwhelming and prolonged lack of energy?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you had trouble finishing things because you were tired?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you become tired from walking upstairs?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you required frequent or long periods of rest?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you become tired from carrying out your duties and responsibilities?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you had an extreme need for rest?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you become exhausted from dressing?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you felt tired for a long time after physical activity like taking a long walk?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Have you become exhausted from taking a shower?	CAT Fatigue		General disorders and administration site conditions	Fatigue
Has fatigue or a lack of energy affected your sex life?	SHQ-C22		General disorders and administration site conditions	Fatigue

Abbreviations: AE, adverse event; SOC, System Organ Class.

TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items

CTCAE		EORTC Items		
SOC	AE	Primary Classification, No. (%)	Secondary Classification, No. (%)	Total, No. (%)
Cardiac disorders	Chest pain—cardiac	1 (0.1)	1 (4.2)	2 (0.2)
	Palpitations	2 (0.2)	—	2 (0.2)
Ear and labyrinth disorders	Hearing impaired	1 (0.1)	—	1 (0.1)
	Vertigo	1 (0.1)	—	1 (0.1)
	Vestibular disorder	1 (0.1)	—	1 (0.1)
Endocrine disorders	Hyperthyroidism	1 (0.1)	—	1 (0.1)
	Hypothyroidism	1 (0.1)	—	1 (0.1)
Eye disorders	Blurred vision	4 (0.4)	—	4 (0.4)
	Conjunctivitis	3 (0.3)	—	3 (0.3)
	Dry eye	7 (0.8)	—	7 (0.7)
	Extraocular muscle paresis	3 (0.3)	—	3 (0.3)
	Eye pain	6 (0.7)	—	6 (0.6)
	Flashing lights	1 (0.1)	—	1 (0.1)
	Floaters	1 (0.1)	—	1 (0.1)
	Night blindness	1 (0.1)	—	1 (0.1)
	Periorbital edema	2 (0.2)	—	2 (0.2)
	Photophobia	2 (0.2)	—	2 (0.2)
	Retinal tear	2 (0.2)	—	2 (0.2)
	Uveitis	1 (0.1)	—	1 (0.1)
	Watering eyes	4 (0.4)	—	4 (0.4)
	Eye disorders—others, specify	13 (1.4)	—	13 (1.4)
GI disorders	Abdominal distension	2 (0.2)	—	2 (0.2)
	Abdominal pain	8 (0.9)	—	8 (0.9)
	Anal hemorrhage	2 (0.2)	—	2 (0.2)
	Anal pain	3 (0.3)	—	3 (0.3)
	Bloating	2 (0.2)	—	2 (0.2)
	Cecal hemorrhage	1 (0.1)	—	1 (0.1)
	Cheilitis	1 (0.1)	—	1 (0.1)
	Colitis	4 (0.4)	—	4 (0.4)
	Colonic hemorrhage	1 (0.1)	—	1 (0.1)
	Constipation	10 (1.1)	—	10 (1.1)
	Dental caries	2 (0.2)	—	2 (0.2)
	Diarrhea	18 (2.0)	—	18 (1.9)
	Dry mouth	3 (0.3)	—	3 (0.3)
	Dyspepsia	5 (0.5)	—	5 (0.5)
	Dysphagia	13 (1.4)	—	13 (1.4)
	Enterocolitis	2 (0.2)	—	2 (0.2)
	Fecal incontinence	11 (1.2)	—	11 (1.2)
	Flatulence	6 (0.7)	—	6 (0.6)
	Gastroesophageal reflux disease	1 (0.1)	—	1 (0.1)
	GI pain	10 (1.1)	—	10 (1.1)
	Gastroparesis	1 (0.1)	—	1 (0.1)

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TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items (continued)

CTCAE		EORTC Items		
SOC	AE	Primary Classification, No. (%)	Secondary Classification, No. (%)	Total, No. (%)
	Gingival pain	1 (0.1)	—	1 (0.1)
	Lip pain	1 (0.1)	—	1 (0.1)
	Mucositis oral	11 (1.2)	—	11 (1.2)
	Nausea	18 (2.0)	—	18 (1.9)
	Oral dysesthesia	1 (0.1)	—	1 (0.1)
	Oral hemorrhage	2 (0.2)	—	2 (0.2)
	Oral pain	8 (0.9)	—	8 (0.9)
	Periodontal disease	2 (0.2)	—	2 (0.2)
	Proctitis	4 (0.4)	—	4 (0.4)
	Rectal hemorrhage	2 (0.2)	—	2 (0.2)
	Rectal pain	3 (0.3)	—	3 (0.3)
	Salivary duct inflammation	2 (0.2)	—	2 (0.2)
	Stomach pain	8 (0.9)	—	8 (0.9)
	Toothache	1 (0.1)	—	1 (0.1)
	Vomiting	18 (2.0)	—	18 (1.9)
	GI disorders—others, specify	2 (0.2)	—	2 (0.2)
General disorders and administration site conditions	Chills	2 (0.2)	—	2 (0.2)
	Edema face	2 (0.2)	—	2 (0.2)
	Edema limbs	6 (0.7)	—	6 (0.6)
	Edema trunk	2 (0.2)	—	2 (0.2)
	Fatigue	46 (5.0)	—	46 (4.9)
	Fever	3 (0.3)	—	3 (0.3)
	Gait disturbance	13 (1.4)	2 (8.3)	15 (1.6)
	Generalized edema	1 (0.1)	—	1 (0.1)
	Injection site reaction	4 (0.4)	—	4 (0.4)
	Localized edema	8 (0.9)	—	8 (0.9)
	Malaise	2 (0.2)	—	2 (0.2)
	Neck edema	1 (0.1)	—	1 (0.1)
	Noncardiac chest pain	2 (0.2)	—	2 (0.2)
	Pain	37 (4.1)	1 (4.2)	38 (4.1)
	General disorders and administration site conditions—others, specify	36 (3.9)	2 (8.3)	38 (4.1)
Immune system disorders	Allergic reaction	1 (0.1)	—	1 (0.1)
Infections and infestations	Lip infection	1 (0.1)	—	1 (0.1)
	Stoma site infection	2 (0.2)	—	2 (0.2)
	Tooth infection	1 (0.1)	—	1 (0.1)
	Upper respiratory infection	1 (0.1)	—	1 (0.1)
	Infections and infestations—others, specify	2 (0.2)	—	2 (0.2)

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TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items (continued)

CTCAE		EORTC Items		
SOC	**AE**	**Primary Classification, No. (%)**	**Secondary Classification, No. (%)**	**Total, No. (%)**
Injury, poisoning, and procedural complications	Bruising	2 (0.2)	—	2 (0.2)
	Dermatitis radiation	4 (0.4)	—	4 (0.4)
	Intestinal stoma leak	1 (0.1)	—	1 (0.1)
	Postoperative thoracic procedure complication	1 (0.1)	—	1 (0.1)
	Urostomy leak	1 (0.1)	—	1 (0.1)
	Wound complication	1 (0.1)	—	1 (0.1)
	Injury, poisoning, and procedural complications—others, specify	2 (0.2)	—	2 (0.2)
Investigations	Blood bilirubin increased	3 (0.3)	—	3 (0.3)
	Weight gain	3 (0.3)	1 (4.2)	4 (0.4)
	Weight loss	10 (1.1)	—	10 (1.1)
Metabolism and nutrition disorders	Anorexia	9 (1.0)	—	9 (1.0)
Musculoskeletal and connective tissue disorders	Arthralgia	6 (0.7)	—	6 (0.6)
	Arthritis	1 (0.1)	—	1 (0.1)
	Back pain	4 (0.4)	—	4 (0.4)
	Bone pain	3 (0.3)	—	3 (0.3)
	Buttock pain	2 (0.2)	—	2 (0.2)
	Generalized muscle weakness	4 (0.4)	—	4 (0.4)
	Joint range of motion decreased	1 (0.1)	—	1 (0.1)
	Joint range of motion decreased lumbar spine	1 (0.1)	—	1 (0.1)
	Muscle weakness, left-sided	1 (0.1)	—	1 (0.1)
	Muscle weakness, lower limb	6 (0.7)	1 (4.2)	7 (0.7)
	Muscle weakness, right-sided	1 (0.1)	—	1 (0.1)
	Muscle weakness, upper limb	6 (0.7)	1 (4.2)	7 (0.7)
	Myalgia	6 (0.7)	2 (8.3)	8 (0.9)
	Neck pain	1 (0.1)	—	1 (0.1)
	Pain in extremity	2 (0.2)	—	2 (0.2)
	Superficial soft tissue fibrosis	3 (0.3)	—	3 (0.3)
	Trismus	2 (0.2)	—	2 (0.2)

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TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items (continued)

CTCAE		EORTC Items		
SOC	AE	Primary Classification, No. (%)	Secondary Classification, No. (%)	Total, No. (%)
Nervous system disorders	Akathisia	1 (0.1)	—	1 (0.1)
	Amnesia	1 (0.1)	—	1 (0.1)
	Aphonia	4 (0.4)	1 (4.2)	5 (0.5)
	Ataxia	1 (0.1)	—	1 (0.1)
	Brachial plexopathy	1 (0.1)	—	1 (0.1)
	Cognitive disturbance	4 (0.4)	—	4 (0.4)
	Concentration impairment	13 (1.4)	—	13 (1.4)
	Dizziness	3 (0.3)	—	3 (0.3)
	Dysarthria	5 (0.5)	1 (4.2)	6 (0.6)
	Dysgeusia	5 (0.5)	—	5 (0.5)
	Dysphasia	6 (0.7)	1 (4.2)	7 (0.7)
	Headache	1 (0.1)	—	1 (0.1)
	Hypersomnia	7 (0.8)	—	7 (0.7)
	Lethargy	33 (3.6)	—	33 (3.5)
	Memory impairment	24 (2.6)	—	24 (2.6)
	Oculomotor nerve disorder	3 (0.3)	—	3 (0.3)
	Paresthesia	16 (1.8)	1 (4.2)	17 (1.8)
	Peripheral motor neuropathy	9 (1.0)	1 (4.2)	10 (1.1)
	Peripheral sensory neuropathy	8 (0.9)	1 (4.2)	9 (1.0)
	Seizure	1 (0.1)	—	1 (0.1)
	Somnolence	11 (1.2)	—	11 (1.2)
	Stroke	1 (0.1)	—	1 (0.1)
	Syncope	1 (0.1)	—	1 (0.1)
Psychiatric disorders	Agitation	5 (0.5)	—	5 (0.5)
	Anorgasmia	4 (0.4)	—	4 (0.4)
	Anxiety	6 (0.7)	—	6 (0.6)
	Confusion	1 (0.1)	—	1 (0.1)
	Delayed orgasm	3 (0.3)	—	3 (0.3)
	Depression	16 (1.8)	—	16 (1.7)
	Insomnia	12 (1.3)	—	12 (1.3)
	Irritability	1 (0.1)	—	1 (0.1)
	Libido decreased	4 (0.4)	—	4 (0.4)
	Libido increased	1 (0.1)	—	1 (0.1)
	Restlessness	2 (0.2)	—	2 (0.2)
	Psychiatric disorders—others, specify	5 (0.5)	—	5 (0.5)

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TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items (continued)

CTCAE		EORTC Items		
SOC	**AE**	**Primary Classification, No. (%)**	**Secondary Classification, No. (%)**	**Total, No. (%)**
Renal and urinary disorders	Bladder spasm	1 (0.1)	—	1 (0.1)
	Cystitis noninfective	2 (0.2)	—	2 (0.2)
	Urinary frequency	6 (0.7)	—	6 (0.6)
	Urinary incontinence	3 (0.3)	—	3 (0.3)
	Urinary retention	1 (0.1)	—	1 (0.1)
	Urinary tract obstruction	1 (0.1)	—	1 (0.1)
	Urinary tract pain	2 (0.2)	—	2 (0.2)
	Urinary urgency	1 (0.1)	—	1 (0.1)
	Renal and urinary disorders—others, specify	1 (0.1)	—	1 (0.1)
Reproductive system and breast disorders	Breast atrophy	4 (0.4)	—	4 (0.4)
	Breast pain	3 (0.3)	—	3 (0.3)
	Dyspareunia	5 (0.5)	—	5 (0.5)
	Ejaculation disorder	1 (0.1)	—	1 (0.1)
	Erectile dysfunction	2 (0.2)	—	2 (0.2)
	Genital edema	1 (0.1)	—	1 (0.1)
	Gynecomastia	1 (0.1)	—	1 (0.1)
	Irregular menstruation	1 (0.1)	—	1 (0.1)
	Menorrhagia	1 (0.1)	—	1 (0.1)
	Pelvic pain	1 (0.1)	—	1 (0.1)
	Penile pain	2 (0.2)	2 (8.3)	4 (0.4)
	Premature menopause	1 (0.1)	—	1 (0.1)
	Scrotal pain	.	2 (8.3)	2 (0.2)
	Testicular pain	.	2 (8.3)	2 (0.2)
	Vaginal discharge	2 (0.2)	—	2 (0.2)
	Vaginal dryness	3 (0.3)	—	3 (0.3)
	Vaginal hemorrhage	1 (0.1)	—	1 (0.1)
	Vaginal inflammation	3 (0.3)	—	3 (0.3)
	Vaginal pain	6 (0.7)	—	6 (0.6)
	Vaginal stricture	6 (0.7)	—	6 (0.6)
	Reproductive system and breast disorders—others, specify	4 (0.4)	—	4 (0.4)

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TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items (continued)

CTCAE		EORTC Items		
SOC	AE	Primary Classification, No. (%)	Secondary Classification, No. (%)	Total, No. (%)
Respiratory, thoracic, and mediastinal disorders	Allergic rhinitis	1 (0.1)	—	1 (0.1)
	Aspiration	1 (0.1)	—	1 (0.1)
	Bronchopulmonary hemorrhage	1 (0.1)	—	1 (0.1)
	Cough	3 (0.3)	—	3 (0.3)
	Dyspnea	36 (3.9)	—	36 (3.8)
	Epistaxis	1 (0.1)	—	1 (0.1)
	Hoarseness	5 (0.5)	—	5 (0.5)
	Laryngeal hemorrhage	1 (0.1)	—	1 (0.1)
	Laryngeal inflammation	2 (0.2)	—	2 (0.2)
	Pharyngitis	1 (0.1)	—	1 (0.1)
	Pleuritic pain	1 (0.1)	1 (4.2)	2 (0.2)
	Sneezing	1 (0.1)	—	1 (0.1)
	Sore throat	6 (0.7)	—	6 (0.6)
	Tracheal mucositis	1 (0.1)	—	1 (0.1)
	Voice alteration	3 (0.3)	—	3 (0.3)
	Wheezing	3 (0.3)	—	3 (0.3)
Skin and subcutaneous tissue disorders	Alopecia	5 (0.5)	—	5 (0.5)
	Dry skin	4 (0.4)	—	4 (0.4)
	Erythroderma	2 (0.2)	—	2 (0.2)
	Hair color changes	1 (0.1)	—	1 (0.1)
	Hyperhidrosis	1 (0.1)	—	1 (0.1)
	Nail loss	2 (0.2)	—	2 (0.2)
	Nail ridging	1 (0.1)	—	1 (0.1)
	Pain of skin	10 (1.1)	—	10 (1.1)
	Palmar-plantar erythrodysesthesia syndrome	2 (0.2)	—	2 (0.2)
	Photosensitivity	1 (0.1)	—	1 (0.1)
	Pruritus	7 (0.8)	—	7 (0.7)
	Skin hyperpigmentation	1 (0.1)	—	1 (0.1)
	Skin hypopigmentation	1 (0.1)	—	1 (0.1)
	Skin induration	1 (0.1)	—	1 (0.1)
	Skin ulceration	2 (0.2)	—	2 (0.2)
	Skin and subcutaneous tissue disorders—others, specify	2 (0.2)	—	2 (0.2)
Surgical and medical procedures	Surgical and medical procedures—others, specify	4 (0.4)	—	4 (0.4)
Vascular disorders	Flushing	1 (0.1)	—	1 (0.1)
	Hot flashes	4 (0.4)	—	4 (0.4)
	Peripheral ischemia	1 (0.1)	—	1 (0.1)
	Total AEs	913 (100)	24 (100)	937 (100)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; SOC, System Organ Class.