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Development of an EORTC Item Bank for Computer-Adaptive Testing of Nausea and Vomiting

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ABSTRACT

Objectives: Nausea and vomiting (NV) remain common cancer symptoms and frequent side effects of anticancer therapies despite available antiemetics. They can lead to treatment disruption and discontinuation. NV is an important patient reported outcome in oncology. This study aimed to build an item bank for computer-adaptive testing (CAT) based on NV questions in the European Organisation for Research for Treatment of Cancer, Quality of Life for Cancer Patients (EORTC QLQ-C30) questionnaire and complete the first three phases of development as described in the EORTC Quality of Life Group guidelines.
Data Sources: The development followed a standard procedure. The three phases include conceptualization and literature search (phase 1); item classification, selection, formulation and rating, and expert evaluations (phase 2); and patient pretesting (phase 3). The literature search resulted in a preliminary list of 115 items. Following classification, formulation, and rating, 21 candidate items adhered to the QLQ-C30 format. Evaluation by experts (n = 11) from five countries and patients (n = 31) pretesting in Denmark, Poland, and the UK lead to a final list of 20 items.
Conclusion: The selection, development, and refining of NV items have been described. The nature of this testing ensures an initial CAT item bank that after field testing (phase 4) and psychometric analysis is expected to provide a precise and efficient NV measurement while still being comparable to the original QLQ-C30 scale.
Implications for Nursing Practice: Access to reliable tools that facilitate NV comprehensive assessment is an important issue for nurses caring for patients with cancer. This CAT item bank is meant to support clinical decisions when all phases of testing are completed.

Introduction

Nausea and vomiting (NV) are symptoms often experienced by oncological patients, both as a result of the disease itself and as a consequence of treatment. Proper NV assessment helps to evaluate the effectiveness of medical intervention to improve patients well-being or minimize the risk of treatment interruption or termination due to NV. They can be captured as patient reported outcomes (PROs) or assessed by health care professionals, usually with a usage of Common Terminology Criteria for Adverse events (current version 5.0).[1] The Food and Drug Administration PRO guidance document clarifies that PRO measuring tools are needed and should be conceptually valid. They refer to the medical intervention and condition under study and should be relevant to patients.[2] Numerous tools are available for NV assessment—minority underwent psychometric validation or proper translation and cultural adaptation in patients with cancer—that would make them reliable for comprehensive assessment of NV in this population.[3-5]

NV symptoms may accompany each other or occur separately. Nausea is an unpleasant and subjective symptom described as an

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uneasiness of the stomach, often with an urge to vomit, and may occur in varying degrees.[6] Nausea typically precedes vomiting. Vomiting is the forceful expulsion of gastrointestinal contents through the mouth.[7]

There are numerous reasons for NV in patients with cancer. A majority of chemotherapy patients experience some degree of chemotherapy-induced NV. Targeted therapies or immunotherapies are also not free of this side effect.[8-10] Before the era of modern antiemetic drugs as described by Lindley et al,[11] 50% of patients experienced nausea on the day of chemotherapy administration. Approximately half of these patients had accompanying vomiting. Currently, with the usage of effective drugs, the problem of NV including chemotherapy-induced NV, in patients with cancer, is still an emerging issue[9,12]

Health-related quality of life (HRQoL) data is frequently gathered through self-report questionnaires. Beginning in 1986, the European Organisation for Research and Treatment of Cancer (EORTC) developed the Quality of Life Questionnaire of Cancer Patients (QLQ-C30) for assessing the quality of life (QoL) of patients with cancer, which has been widely used to date.[13,14] The EORTC Quality of Life Group has since been developing a computer-adaptive testing (CAT) version of the QLQ-C30 questionnaire.[15-19] CAT is a form of self-modifying questionnaire, which adjusts the choice of future questions accounting for previous answers.[20-22] This approach allows optimization of measurement and flexibility of the basic EORTC tool. On one hand it allows adaptation to studies or patients themselves, and on the other, it still allows comparability of results between individuals or the studies.[23,24] The statistical basis used in CAT measurement is item response theory that permits the uniform comparison of questionnaires between patients.[20,21] The CAT version of the QLQ-C30 contains the same dimensions as the original questionnaire; thus, data will be comparable to studies based on the original EORTC QLQ-C30. The CAT selects necessary questions from an item bank to fulfill each of the required dimensions in a pattern most relevant to each patient.[20] The strategy consists of a few steps, including the literature search, formulating new items matching the QLQ-C30 items, and 10 evaluations by experts and patients.[23,24] Cross-cultural application is the foundation of EORTC development strategy, and evaluation of items for the item bank are assessed simultaneously in multiple languages.[20] Together, almost 10,000 patients were recruited for the field testing to develop 14 domains, each consisting of 7-34 questions that resulted in generation of 260 new items in total. One of the main advantage of CAT application is maintaining similar power with a group reduction by up to 25%.[23,24]

The aim of this article is to present the development and selection process for the NV item bank for CAT based on NV questions in the EORTC QLQ-C30 questionnaire and complete the first three phases of development following EORTC Quality of Life Group guidelines.

Materials and Methods

The EORTC Quality of Life Group development of item banks for CAT is comprised of four phases:

1 Conceptualization and literature search to create a comprehensive list of potential candidate issues for the NV item bank.
2 Operationalization: Constructing relevant items based on (a selected set of) issues from phase 1 and evaluations of these new items by international experts (professionals with expertise in oncology, HRQoL measurement, and specific knowledge in measuring NV).
3 Cross-cultural item pretesting in oncological patients.
4 International field testing, psychometric analysis, and final selection of items.

The current article focuses on the first three phases of development and is based on work conducted in two stages: phases 1 and 2 were originally conducted in 2008. Because of a lack of time and other practical reasons, the work was paused and first resumed in 2012. Additional steps were performed to add new items that might have been created during this 4-year gap. The process followed the EORTC Quality of Life Group guidelines.[25]

Phase 1: Conceptualization and Literature Search

Before commencing the process of creating items for the item bank, a conceptualization was performed to determine the relevant aspects for EORTC measurement of NV. The new items being developed for the CAT instrument should assess the same aspects as the original items from the EORTC QLQ-C30.

The literature was searched to collect existing items measuring NV to serve as the basis for the creation of new items. The original literature search in 2008 was conducted in PubMed using combinations of various MeSH terms. The strategy included searching for: “neoplasms” AND (“vomiting” OR “nausea”) AND (“questionnaire” OR “severity of symptoms index”). Two instrument databases, QOL/PRO Resources (http://www.qolpro.org) and PROQOLID were used to search for instruments with items relating to NV. The equation for PROQOLID consisted of the same searching terms.

When the work was resumed in 2012, a supplemental search in the questionnaire database PROQOLID was conducted to assess whether new NV items had been published since the 2008 search. In 2012 the same equation was used with different filter in terms of dates. The process was performed by the same reviewers in 2008 and in 2012. They were experienced researchers working previously with other EORTC projects.

The two original NV items from the QLQ-C30 NV scale were: During the past week, “Have you felt nauseated” and “Have you vomited?” Both items have the response options “not at all,” “a little,” “quite a bit,” and “very much.” The first question on nausea does not quantify the level of nausea, so it is a relatively subjective question; the patient has to determine what qualifies as being nausea. The second question permits for less interpretation because there is less uncertainty about what is understood by vomiting. The item bank should reflect the relatively straightforward nature of the vomiting question, as well as the complexity of the existence, quality, and subjective nature of nausea. Neither of the items mentions severity, frequency, or duration directly though these are all inferred and are collectively referred to as intensity. Based on this conceptualization, we included items on NV intensity. NV interference/distress items (ie, items on whether NV have led to distress or affected different aspects of the patient’s life) may also provide (indirect) information on the intensity of NV. Therefore, generally formulated items on NV interference and distress were also included.

A patient experiencing only nausea would answer “not at all” to an interference item relating only to vomiting (“Has vomiting interfered with . . . ?”) even though nausea may have interfered significantly with their quality of life. In a unidimensional item bank covering both NV, this would be problematic because a fundamental requirement is that the items in the bank can be ranked according to severity. Given an estimate of a patient’s level of NV, the CAT procedure should be able select the next most relevant item for that patient. But if the items relate only to either nausea or vomiting, this would not be feasible (based on the level of NV, the vomiting item may seem relevant even though it is not). Therefore, to ensure that items are also generally relevant for patients who have only had nausea or who have only vomited and to enhance the unidimensionality of the item bank, it was decided that all new candidate items should refer to both NV.

Phase 2: Operationalization

This phase has been completed in four steps: item classification and selection, new item selection, formulating and rating of items, and expert evaluation.

Each of steps 1-3 was conducted independently by two reviewers. After each step, their individual evaluations were compared, disagreements were discussed, and a consensus about each item was attained. In the cases when an agreement could not be achieved, a consensus was reached by involving a third reviewer.

Step 1: Item Classification and Selection

Items were sorted and reviewed for relevance and redundancy. The relevance of items for EORTC measurement of NV were judged based on the results of the conceptualization in phase 1. Items were considered redundant/duplicates if they had identical wording, or if they were conceptually or semantically similar. The item to be retained was independently selected by the two reviewers. In case of disagreements between the two reviewers on what to retain or delete the issues were discussed with a third reviewer, resulting in consensus when all parties were in agreement.

Step 2: Supplemental Item Selection

Results of the supplemental search in PROQOLID in 2012 were evaluated individually by two reviewers for relevance and redundancy. Evaluations were compared, and when different, a consensus was achieved. Relevant items were added to the existing list of items, and the entire item pool was re-reviewed for relevance and redundancy.

Step 3: Formulating and Rating of New Items

Items were reformulated to fit the standard EORTC format, a question with a 4-point Likert response (not at all, a little, quite a bit, or very much) and rated with regard to relevance: Did the item seem most relevant for patients with mild, moderate, or severe NV?

Step 4: Expert Evaluations

The remaining items were evaluated by an international sample of experts. They were experienced practitioners: oncologists, surgical oncologists, and psychologists working with patients with cancer. The experts were asked to evaluate what the items measure, their relevance for measuring NV, whether they were appropriate, and whether they were clear and well formulated. The responses were provided as written comment on a predetermined sheet. All experts answered fully independently having no contact with each other. Revisions based on experts' comments were primarily focused on items for which more than two experts had made a comment. Comments might also give rise to new items.

Phase 3: Pretesting

To pretest the item wording, the items were evaluated by oncological patients from three different countries: Denmark, Poland, and the UK. The interviews followed the EORTC Quality of Life Group guidelines for patient interviews.[25] The patients were asked to answer the questions and were then interviewed about whether the items were difficult to answer, confusing, annoying, upsetting, or intrusive, or whether they had any other comments to the questions. Prior to pretesting, the items were translated from English into Polish and Danish using the well-established EORTC Quality of Life Group forward backward translation procedures.[26] Ethical approval was obtained at local ethical committees. All participating patients provided written informed consent before entering the study.

Results

Phase 1: Conceptualization and Literature Search

Questionnaires were identified in the literature search and pulled from various journals. The 2008 search resulted in 31 items from 10 instruments identified in the PROQOLID database, 70 items in the QOL/PRO Resources search, and 14 items in the PubMed search. A total of 115 items related to NV were obtained in total.

Phase 2: Operationalization

Step 1: Item Classification and Selection

Items were inspected for relevance for EORTC measurement of NV and compared for redundancy or conceptual similarity. To ease the search for redundant items, the items were grouped in themes (eg, items on being bothered by NV, frequency of NV, timing of NV). For this stage, the two reviewers attained 75% (86 out of 115) agreement in selection of items to retain or delete. If duplicated items were noticed, they were removed in that step as well. Discussion of item deletion with the third reviewer resulted in consensus that 65 items should be deleted. The item bank now contained 50 items.

The following is an example of conceptually similar items:

- "Have you been bothered during the past week by nausea?" Not at all; a little; quite a bit; very much
- "Please circle the number on the line to indicate how you felt relating to each statement in the past week—I am bothered by nausea." (Not at all) 0; 1;2;3; 4; 5; 6; 7; 8; 9; 10 (very much so)

Based on simplicity and proximity to EORTC item style, the two reviewers agreed to keep the first item and delete the second.

Step 2: Supplemental Item Selection

The 2012 supplemental search in PROQOLID resulted in 28 additional NV items. These were reviewed for relevance and redundancy (mutually and with the 50 items selected in step 1). After reaching a consensus, 21 items were deleted because of redundancy or lack of relevance. The remaining seven items were added to the item list from step 1.

In the original item selection in step 1 items referring to either nausea or vomiting but otherwise similar in content had been kept (eg, items on severity of nausea and on severity of vomiting, respectively). Further, the selection in step 1 had been more "inclusive" than "exclusive" in the sense that items with a potentially relevant content had generally been included, even though they might not fit with the general item style of the QLQ-C30 (ie, be generally applicable and fit the time frame and response options). As the intention was to construct items fitting the QLQ-C30 item style and covering both NV, the 57 items were reassessed for redundancy and relevance. Using these more "strict" criteria, 46 items were deleted: nine because of redundancy, eight because they did not fit the response options (eg, if asking about the number of days having had NV), 14 for being too specific (eg, if referring to treatment related NV), and 15 because the content did not seem relevant for EORTC measurement of NV (eg, did not measure intensity of NV). Thus, after this step, the two reviewers agreed to keep 11 items in addition to the two original QLQ-C30 items.

Step 3: Formulating and Rating of Items

Using the 11 items from step 2 as inspiration, a total of 19 new items fitting the QLQ-C30 item style were formulated. Hence, together with the two QLQ-C30 items, the list consisted of 21 candidate items. The 21 items were rated with regard to relevance: Did the item seem most relevant for patients with mild, moderate, or severe NV. All items except the original QLQ-C30 nausea question

were rated as mostly relevant for patients with either moderate or severe NV (eight mostly relevant for moderate NV, three for moderate/severe, and nine for severe NV). Hence, the list of items seems to cover moderate and severe levels of NV well but may lack items for mild degrees of NV.

Step 4: Expert Evaluation

The 21 items from step 3 were evaluated by 11 experts from Australia (four), Canada (one), Denmark (two), the Netherlands (two), and Spain (two). Based on these evaluations, two items were deleted, and six were reformulated. The commentary gave rise to three additional items, resulting in a total of 22 items including the two original QLQ-C30 questions.

The two items deleted were:

- "Have you had so much nausea or vomited so much that you could not concentrate on anything else?" Three experts preferring a variant version of the item ("Have you felt so nauseous or . . .)."
- "Have there been days when you had nausea or vomited all day?" Experts felt the question was ambiguous (what is meant by "vomiting all day") and that it fitted better with yes/no responses.

The three additional items added following the experts' commentary were:

- "Has nausea or vomiting interfered with your appetite?"
- "Has nausea or vomiting interfered with your sleep?"
- "Has nausea or vomiting interfered with your physical activities like taking a walk?"

Phase 3: Pretesting

The 22 candidate items following step 4 of phase 2 were evaluated by 31 patients from Denmark, Poland, and the UK. Patient characteristics are summarized in Table 1.

Following this evaluation, patients generally had few comments with respect to each of the questions. There were also a few general remarks, mainly that some questions seemed repetitive. However, as there were no suggestions for which items to delete because of redundancy, these remarks did not lead to deletion of items at this point. Overall, the item evaluation by patients resulted in the deletion of two items:

- "Has nausea or vomiting interfered with your enjoyment of food?" Five patients found the item confusing/difficult to answer. Enjoyment may also depend on other factors than NV (eg, quality of food). Hence, it may be a poor measurement of NV levels.
- "Have you had nausea or vomiting you could not ignore?" Six patients found the item problematic. Several commented "How can you ignore vomiting?" As the essence of the item is covered by other items it was deleted.

Table 1
Summary of Phase III Patient Characteristics (n = 31).

Parameter		No (%)
Sex	Men	14 (45%)
	Women	17 (55%)
Countries	Denmark	10 (32%)
	Poland	10 (32%)
	UK	11 (36%)
Age (mean, n = 29)		65 Years
Cancer Stage	I-II	14 (45%)
	III-IV	15 (48%)
	Unknown	2 (7%)
Diagnosis	Breast	3 (10%)
	Gastrointestinal	10 (32%)
	Genitourinary	2 (6%)
	Gynecologic	7 (23%)
	Hematologic	2 (6%)
	Head and Neck	2 (6%)
	Lung	2 (6%)
	Other	3 (10%)

Phase 3 culminated in a candidate item list of 20 questions. The 20 items moving forward into phase 4 are detailed in Table 2. The results of phases 1-3 are summarized in Fig 1.

Discussion

NV are common symptoms experienced by patients with cancer. Developing a proper item list is important for future evaluation of oncological patients. Following the guidelines on item development for CAT, a rigorous and thoroughly tested list has been created. The literature search provided a reasonable yet small number of instruments and items but brought about other questions about the intertwined nature of NV. For our tool, the small number of items supports the notion that NV are concepts that are difficult to define by parameters other than NV itself, but at the same time, the limited number of questions can result from chosen selection criteria (eg, phase 2, step 2 we deleted 14 items for being too specific).

Several synonyms and related words were included to probe the databases for any possible references that included questionnaires on NV. Overall, the literature search revealed a larger number of items than that seen with a similar literature search when developing an item bank for loss of appetite but still far less than seen with fatigue.[15,20] Several items were redundant in wording or concept that led to the deletion of more than half of the original item list in the first stage. When taking the response options and the time frame of the QLQ-C30 into consideration, the item list was further reduced, leaving less than 10% of the retrieved items. The remaining items served as inspiration to form new items in the desired format.

Table 2
Item List for Field Testing in Phase IV.

Number	Item Text
Item 01	Have you felt nauseated?*
Item 02	Have you vomited?*
Item 03	Has nausea or vomiting interfered with your work or other daily activities?
Item 04	Have you had severe nausea or vomiting?
Item 05	Has nausea or vomiting interfered with your ability to enjoy life?
Item 06	Have you eaten less because of nausea or vomiting?
Item 07	Has nausea or vomiting been a problem for you?
Item 08	Has nausea or vomiting interfered with your physical activities like taking a walk?
Item 09	Have you had such severe nausea or vomiting that it was almost unbearable?
Item 10	Has nausea or vomiting interfered with your family life?
Item 11	Have you been distressed by nausea or vomiting?
Item 12	Has nausea or vomiting interfered with your sleep?
Item 13	Have you felt so nauseous or vomited so much that you could not concentrate on anything else?
Item 14	Has nausea or vomiting interfered with your hobbies or other leisure time activities?
Item 15	Has nausea or vomiting interfered with your appetite?
Item 16	Have you had nausea or vomited day and night?
Item 17	Have you been unable to eat because of nausea or vomiting?
Item 18	Has nausea or vomiting interfered with your social activities?
Item 19	Have you been drinking less fluid because of nausea or vomiting?
Item 20	Have you felt so nauseous or vomited so much that you were unable to eat or keep anything in your stomach?

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer, Quality of Life of Cancer Patients
* Item from the original EORTC QLQ-C30

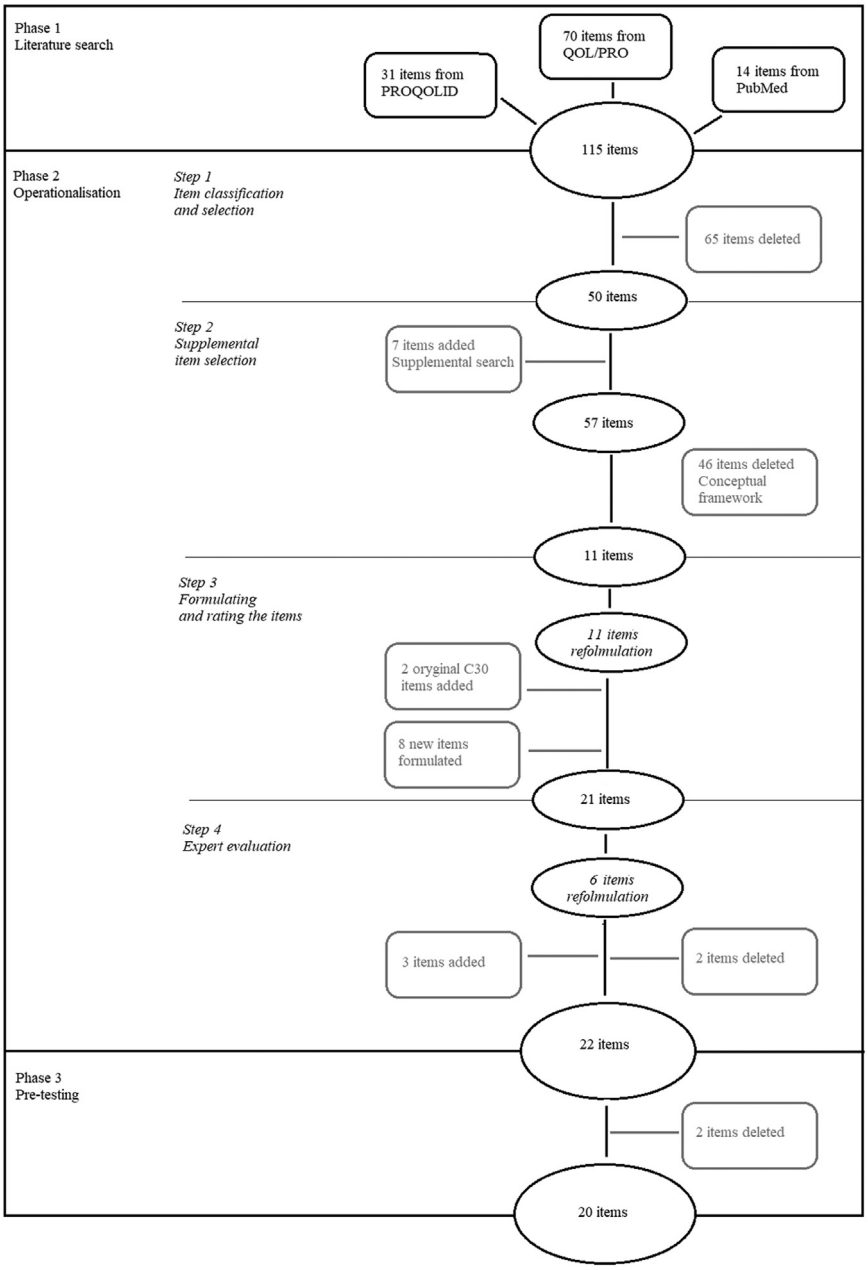

FIG 1. Flowchart of the item selection procedure.

This process ended with a list of 20 candidate items including the two original OLQ-C30 items. These 20 NV items are currently available in three languages (English, Polish, Danish), and their psychometric properties will be further evaluated in phase 4 of the EORTC CAT development process.

It was agreed that both NV should be presented together in each question rather than individually. The basis for this decision was to create a more homogenous set of items that would be applicable to all patients regardless of having only nausea, only vomiting, or NV together. Because an item on vomiting would not be relevant for patient feeling nausea only and vice versa, it would be difficult to combine separate NV items into a unidimensional item bank; it may result in response combinations that contradict the logic of a unidimensional item bank, where items can be ordered from "easy" to "difficult." However, when both terms are included in each item if a patient answer that nausea or vomiting has been quite a bit of a problem for them, we do not know from this response whether it is nausea or vomiting, which has been the problem. Such distinction is lost in these combined items. The QLQ-C30 scoring guidelines recommend summing the two items into one measure giving the combined/"average" level of NV. The new items are well in line with such NV measurement. Further, as the new item bank will include the QLQ-C30 nausea item and the vomiting item, we can still obtain measures of the separate levels of NV when this is of relevance.

If NV were divided into separate questions, it would be necessary to have two separate item banks, a Nausea-CAT (NCAT) and a Vomiting-CAT (VCAT). An overall NV score should then be obtained as a combination of the NCAT and VCAT scores; however, how to best combine scores from different subscales into an overall score is not obvious. In summary, retaining the separation into NV items may induce several problems in the construction of a well-functioning, unidimensional item bank.

The close adherence to the EORTC guidelines and the format of the QLQ-C30 allows for the future comparison of studies using the new

CAT system and the QLQ-C30 and comparison of studies using the CAT with previous studies using the EORTC QLQ-C30. The applied guidelines for item development and format are strict, restricting questions that may be included. During the development, it became clear that only a limited number of distinct intensity items can be formulated regarding NV particularly with the requirements concerning response options. Items on NV interference/impact will probably also give information about NV intensity; the more NV affects a patient's life, the worse/more intense it has probably been. The example of such question can be: "Has nausea or vomiting interfered with your social activities?" or "Has nausea or vomiting interfered with your sleep?" Likewise, items about whether NV has caused distress, for example, "Have you been distressed by nausea or vomiting?", may indirectly give information about NV intensity. Therefore, we chose to include items on NV interference and distress as long as they seemed generally applicable and were judged to give knowledge about NV intensity. Whether the interference and distress items can be combined with the intensity items into a unidimensional item bank will be clarified in the phase 4 psychometric analyses. Information on the quality of patients' NV may provide further insight into the varying degrees of NV as a symptom. Detailed information on NV could also add to the understanding of how the symptoms affect lifestyle changes.

During the pretesting that was conducted in phase 3, the majority of comments about question content, other than being repetitive at times, were that the questions were difficult. With this being said, it needs to be ensured that questions are written clearly and concisely to prevent confusion. Some questions that were rated difficult involved emotional feelings, which are subjective and vary between individuals. Only occasionally did patients rate questions as annoying, confusing, upsetting, or intrusive; but these comments were generally so few that it did not warrant rating these items as problematic.

Nowadays PROs act as primary and secondary endpoints in clinical trials.[27-29] Building proper tools is a crucial step. The accurate assessment of NV by nurses and other health care professionals in oncological patients is also a vital tool to understanding how the symptoms impact their everyday lives. Development of a CAT form of the EORTC OLQ-C30 will allow for ease of patient answering while maintaining the ability to compare results both against studies in the past and those yet to come.

Study Limitations

The study has few limitations. An initial research that took place in 2008 was supplemented by search in PROQOLID after a 4-year gap only once in 2012. On one hand, all 260 items for 14 QLQ-C30 domains including NV were selected in similar period and their validation was completed. On the other hand, current supplemental search could reveal items covering new areas within this domain. The same strategy was approached for all other CAT forms of the EORTC OLQ-C30.[15-21] We also included minimum number of countries required by EORTC guidelines, but these were countries from three culturally different regions of Europe.

In phase 2, step 3 items (except the original questions) were rated as mostly relevant for patients with moderate or severe NV, lacking items for mild degrees of NV. However, measuring lower levels of nausea with high precision may be of less clinical significance. The sole presence of NV, even if mild, can be concluded from the original NV items from the QLQ-C30.

Conclusion

The primary objective of this study was to develop an item bank for the NV dimension of the CAT version of the EORTC QLQ-C30. The selection, development, and refining of NV items have been described in detail, resulting in a list of 20 candidate items. These will move forward into phase 4 of development, as described in the EORTC Quality of Life Group's guidelines for developing questionnaire modules and will be presented in detail in a future article. The new items have been tailored to ensure comparability and compatibility with the original NV items from the QLQ-C30, while offering the possibility of a more detailed assessment of NV in future questionnaire studies.

Nurses provide care for patients with cancer in outpatient and inpatient setting. Nursing assessment of NV is a regular and integral part of patients' care. The tool described in this research can be useful in NV assessment of nursing interventions within everyday practice and in clinical trials when all phases are completed.

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