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## **Development of the EORTC QLQ-CAX24, a questionnaire for cancer patients with cachexia**

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## **Abstract**

### **Context**

Cachexia is commonly found in cancer patients and has profound consequences yet there is only one questionnaire that examines the patient's perspective.

### **Objective**

To report a rigorously developed module for patient self-reported impact of cancer cachexia.

### **Methods**

Module development followed published guidelines. Patients from across the cancer cachexia trajectory were included. In Phase 1, HRQOL issues were generated from a literature review and interviews with patients in four countries. The issues were revised based on patient and health care professional (HCP) input. In Phase 2, questionnaire items were formulated and translated into the languages required for Phase 3, the pilot phase, in which patients from eight countries scored the relevance and importance of each item, and provided qualitative feedback.

### **Results**

A total of 39 patients and 12 HCPs took part in Phase 1. The literature review produced 68 HRQOL issues, with 22 new issues arising from the patient interviews. Following patient and HCP input, 44 issues were formulated into questionnaire items in Phase 2. 110 patients took part in Phase 3. One item was reworded and 20 items were deleted as a consequence of patient feedback.

### **Conclusions**

The QLQ-CAX24 is a cancer cachexia-specific questionnaire, comprising 24 items, for HRQOL assessment in clinical trials and in practice. It contains five multi-item scales (food aversion, eating and weight-loss worry, eating difficulties, loss of control and physical decline) and four single items.

### **Keywords**

Cachexia; quality of life; palliative care; patient outcome assessment

### **Running title**

Development of the EORTC QLQ-CAX24

## Background

Cancer cachexia is a multidimensional syndrome characterised by involuntary weight loss, at least partly attributable to muscle atrophy, which leads to progressive functional impairment (1) (see Figure 1). It has a profound negative outcome on treatment, survival, clinical burden and psychosocial factors yet there are currently no standard of care or approved drug treatments. The incidence of cachexia among cancer patients is approximately 50-80% and cachexia accounts for up to 20% of cancer deaths (2). Cachexia is therefore a common problem for cancer patients which has serious consequences.

*Insert Fig 1 about here*

Patient reported outcome (PRO) measures, which provide a measure of patients' health from the perspective of the patient, can improve routine clinical practice (3). Health-related quality of life (HRQOL) is a PRO concerned with those aspects of quality of life which patients consider are affected by disease and treatment (4). Evaluating HRQOL is particularly important in conditions like cancer cachexia when disease outcome measures, such as survival, are an inappropriate assessment of treatment success. A validated HRQOL assessment tool is vital for the assessment of new treatments.

Where a patient lies on the cachexia continuum and the extent of primary and secondary cachexia are crucial clinical considerations and it is important that an HRQOL instrument is applicable to the full range of cancer patients with cachexia (5). Primary cachexia refers to the tumour-induced metabolic component of the condition and in secondary cachexia, secondary nutritional impact symptoms (S-NIS) contribute to the progression of the primary cachexia (6, 7). S-NIS are factors which interfere with nutritional intake, some of which are treatable using supportive care measures (8-10).

HRQOL is an essential component in the evaluation of therapeutic interventions for cachexia because patients must perceive a benefit if a treatment is to be considered successful (7). Clinical decisions should partly be based on the impact of treatment on HRQOL (11). Therefore an instrument is required to measure the HRQOL effects of cachexia from diagnosis, through treatment and beyond. The only currently available cancer cachexia specific instrument, the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) (12-15), is part of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system. The European Organisation for the Research and Treatment of Cancer (EORTC) provides an alternative measurement system with the core instrument, the QLQ-C30, widely used to measure HRQOL in patients with cancer (16, 17). This paper

describes the development of a questionnaire module to supplement the EORTC QLQ-C30 to provide a comprehensive assessment of HRQOL in patients with cancer cachexia.

## **Methods**

The development of EORTC Quality of Life Group modules follows four phases (18). In Phase 1, HRQOL issues are generated through interviews with patients and health care professionals (HCPs), and a literature search. These HRQOL issues are reviewed and revised in Phase 2 and questionnaire items are formulated. In Phase 3, the questionnaire items are pilot tested and a provisional version of the module is developed. In Phase 4 the new module is field tested. The work reported here describes Phases 1-3. The study protocol was approved by the EORTC Quality of Life Group. Ethical and research governance approvals were obtained at each centre in accordance with local requirements and all patients provided written informed consent. The study was coordinated from Southampton, UK with additional centres in France, Germany, Greece, Italy, Norway, Poland, Sweden and Switzerland. Collaborator meetings were held every six months, with regular email discussion and teleconferences between these times.

## **Participants**

Eligible patients had a confirmed cancer diagnosis and met the consensus definition of cancer cachexia (1). A 2x2 recruitment matrix was used for Phase 1 with patients categorised according to cachexia stage (syndrome vs. refractory cachexia) and many or few S-NIS, as assessed by the local researcher (Table 1). Patients with many S-NIS were required to have been treated for these symptoms for at least two weeks.

For the Phase 3 interviews, the recruitment matrix became 3x2. Patients with an ECOG performance status (19) of 3 or 4 were classified as refractory cachexia. The remaining patients were divided into those with a relatively recent cancer diagnosis (within the first 100 days) and those who had been diagnosed more than 100 days prior to the interview. Scores on the Symptom Checklist (see section Phase 3: Testing the questionnaire for relevance and acceptability) were used to categorise patients into those with fewer S-NIS symptoms (Group A) and more S-NIS symptoms (Group B).

All participants were 18 years or over. Patients unable to take part in interviews and complete self-report questionnaires were excluded.

### **Phase 1: Generation of relevant HRQOL issues**

A comprehensive systematic review of the literature review was carried out to generate an initial list of HRQOL issues (20). Semi-structured interviews (Phase 1a interviews), in which patients were asked to describe their experience of weight loss, were conducted in four countries (Italy, Norway, Switzerland, UK) to identify novel issues. Interviews were carried out until data saturation was achieved, defined as when three consecutive interviews produced no new issues (21). The issues generated in the patient interviews were added to those already collected in the literature review.

The list of issues was distributed to the project collaborators for feedback and to check for missing issues. This led to the combination of some issues, modifications, and removal of issues with obvious overlap with the EORTC QLQ-C30. The revised list was used in a second round of patient interviews (Phase 1b interviews) and also interviews with HCPs who were all experienced in cancer cachexia. Interviewees rated the importance of each issue on a four point scale ranging from not at all (1 point) to very much (4 points) and identified any issues that should not be included. Finally, participants were asked to consider whether any issues were missing.

### **Phase 2: Construction of the provisional questionnaire**

EORTC guidelines were followed to determine which issues should be removed and whether any new issues should be added to the list (18). Issues were operationalised into items with a response format and time frame compatible with the EORTC QLQ-C30. The EORTC QLG item bank, an unpublished weight loss and eating habits questionnaire which had been used in several Macmillan trials and the FAACT were consulted to help create the items. Items were then translated into all the languages required for Phase 3, following the EORTC translation procedure guidelines(22).

### **Phase 3: Testing the questionnaire for relevance and acceptability**

The provisional questionnaire was piloted with patients in eight European countries: France, Germany, Greece, Italy, Norway, Poland, Sweden and the UK. After providing informed consent, patients completed the EORTC QLQ-C30 followed by the provisional questionnaire. For each item on the provisional questionnaire, patients were asked to indicate relevance (yes or no) and importance (not at all, a little, quite a bit, very much). They were encouraged to “think aloud” during this process, to indicate if they found any question difficult, annoying, confusing, upsetting or intrusive, and to make any other comment. Sociodemographic and clinical data were recorded, along with the Charlson Comorbidity Index(23), Eastern Cooperative Oncology Group (ECOG) Common Toxicity Criteria and ECOG Performance Status (19). Finally, the patients completed the Symptom Checklist, a measure of S-NIS. This checklist combines items from the Patient-Generated Subjective Global

Assessment (24) and the Nutrition Impact Symptoms Checklist (10) to produce a checklist of 17 items which is applicable to patients with any type of cancer (Figure 2). Patients with a scaled score of below 25 on the Symptom Checklist were assigned to Group A (few S-NIS symptoms) whereas patients scoring above 25 were assigned to Group B (more S-NIS symptoms).

*Insert Fig 2 about here*

The number of items in the questionnaire was reduced by application of decision rules from the module development guidelines (18).

The HRQOL review (20) informed the scales for the new module and multitrait scaling was used to examine whether the hypothesised scales demonstrated convergent validity i.e. whether each item within the scale correlated  $\geq 0.4$  (corrected for overlap) with its own hypothesised scale (25). The internal consistency of the scales was tested using Cronbach's alpha. A Cronbach's alpha of  $\geq 0.70$  is often considered to provide evidence of adequate internal consistency (25). Analyses were carried out using Stata Statistical Software, release 13 (26).

## **Results**

Module development is summarised in Figure 3.

*Insert Fig 3 about here*

### **Phase 1**

The systematic literature review (20) identified 18 relevant papers, from which 68 HRQOL issues were extracted. Twenty one patient interviews were required to achieve data saturation. Analysis of these interviews identified 22 new issues, resulting in a total of 90 issues. The characteristics of the patients who participated in Phase 1a are shown in Table 1.

The original 90 issues were reduced to 50 following review for repetition and overlap with the EORTC QLQ-C30. These issues were reviewed by eighteen patients from three countries (UK, Norway and Italy) and 12 HCPs (including palliative care doctors and nurses, dietitians and oncologists) from Norway, Italy, Switzerland and the UK.

### **Phase 2**

Comments from patients and HCPs led to the inclusion of items being too tired to eat and being in too much pain to eat. Thirteen issues were removed as a result of the decision rules ( $n=9$ ), because it was not clear whether these were positive or negative in terms of HRQOL ( $n=2$ ) or because they

were not patient reported outcomes (n=2). One issue, 'strong negative reaction to food' became three items to distinguish whether the negative reaction was due to the thought, smell or sight of food. 'Embarrassed by eating or weight loss' became two items to differentiate the two sources of embarrassment. As a result of all these modifications, the questionnaire for Phase 3 comprised a total of 44 items.

### **Phase 3**

A total of 110 patients was recruited (Table 2).

*Insert Table 2 about here*

The characteristics of the patients taking part in this phase are shown in Table 3. Group A (low Symptom Checklist score) and Group B (high Symptom Checklist score) were similar across most variables.

*Insert Table 3 about here*

Application of the item decision rules resulted in the removal of 25 items leaving 19 items. Collaborator review of these items raised the concern that many of the items related to function had been lost. The item decision rules were therefore applied to Group A and Group B separately resulting in one additional item to consider from Group A and ten from Group B (Table 4). Any patient comments for each of the 30 surviving items were carefully reviewed which led to the removal of five items (marked as 'removed' in the final column of Table 4). The wording of one item (issue 39) was changed from 'Have you worried that you might lose your independence?' to 'Have you worried about becoming more dependent on others?' as some patients pointed out that they were already somewhat dependent on others. The collaborators at each centre translated this item into their own language and then checked with 5-10 patients that the new version was acceptable. Item 31, 'Have you felt hungry?' (issue 1) was also removed because it is ambiguous whether this is positive or negative with respect to HRQOL. Appetite loss is covered by the QLQ-C30.

*Insert Table 4 about here*

The provisional module therefore has 24 items and is called the EORTC QLQ-CAX24. Five multi-item scales are proposed – food aversion, eating and weight-loss worry, eating difficulties, loss of control and physical decline and four – and four single items (Table 5). Adequate internal consistency and



convergent validity was demonstrated for three of the five scales. For the other two scales, eating difficulties and physical decline, the values fell slightly below the desired levels.

*Insert Table 5 about here*

## **Discussion**

Cachexia is a common condition in cancer patients with profound consequences. The EORTC QLQ-CAX24 has been developed to be used in conjunction with the EORTC QLQ-C30 to assess HRQOL in this patient group. The development process followed a predefined set of guidelines and decision rules for inclusion of relevant issues. The module was developed with the help of cancer patients from nine countries at different stages of the cancer disease trajectory, from relatively soon after diagnosis to those approaching the end of life, and with differing numbers of S-NIS. Item selection was primarily based on the results and feedback from the patient participants. This study has shown that the QLQ-CAX24 is relevant, acceptable and applicable to patients with cancer cachexia.

The issues included in the QLQ-CAX24 are consistent with the conceptual model we developed (20) from our review of the literature. The provisional module contains five scales and four single items. Further assessment of scale structure, using multi-trait scaling and factor analyses, along with possible modification, will occur in Phase 4 (international validation study). The Phase 4 study will also be used to explore differences in the HRQOL of patients with many and few S-NIS and it may be that the module is shortened if some items are not applicable across all patients. Information about the progress of Phase 4, and copies of the QLQ-CAX24 can be obtained from the EORTC Quality of Life Group website, <http://groups.eortc.be/qol>.

Although there may be some modification to the QLQ-CAX24 after Phase 4, through a reduction in length and adjustment to the scale structure, it is now available for use in clinical trials. Whether clinicians and researchers should choose to use the QLQ-CAX24 or the FAACT, the only other instrument for the assessment of HRQOL in patients with cancer cachexia, will partly be determined by which of the core questionnaires from the EORTC and FACIT measurement systems is most applicable to their requirements (16, 27). An additional consideration is that the FAACT is a single scale whereas the QLQ-CAX24 comprises scales allowing more precise hypothesis testing.

Although the QLQ-CAX24 has been developed with and for patients with cancer cachexia, cachexia is a condition found in a number of other diseases, both chronic and acute (28). The items included in the QLQ-CAX24 may be applicable to patients with cachexia regardless of the underlying disease. With a relatively small amount of further development and testing, the QLQ-CAX24 may prove useful with patients who have cachexia as a result of a disease other than cancer.

### **Limitations**

The limitations of the study include possible participation bias. As a formal cachexia assessment instrument is not currently available (29), patients were selected based on clinical judgement and because they met the consensus definition of cancer cachexia (1). However, use of a recruitment matrix ensured that the views of patients at different stages of cachexia, some of whom were nearing the end of life, were included. Patients with pre-cachexia were not included because of the difficulty in identifying this group clinically (30).

Only European centres have contributed to the development of the QLQ-CAX24 so far. Non-European centres, including North and South America, Japan and India, will be included in the Phase 4 validation study.

### **Conclusion**

In conclusion, the QLQ-CAX24 is a new cachexia-specific HRQOL questionnaire which has been developed for use with cancer patients in research and clinical practice. The questionnaire has been pilot tested and a provisional scale structure has been proposed. Full validation will be carried out in the final phase of development, when the provisional questionnaire is tested with a large number of patients in an international field study. This will allow the reliability and validity, the cross-cultural applicability and the psychometric properties of module to be assessed.

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**Table 1: Characteristics of patients participating in Phase 1**

	<b>Phase 1a participants</b>	<b>Phase 1b participants</b>
<b>Age (years)</b>		
Mean (SD)	63.5 (11.2)	60.7 (11.9)
Range	43-87	31-82
<b>Number of males</b>	12 (57.1)	9 (50.0)
<b>Country</b>		
Italy	6 (28.6)	6 (33.3)
Norway	3 (14.3)	6 (33.3)
Switzerland	7 (33.3)	-
UK	5 (23.8)	6 (33.3)
<b>Primary tumour</b>		
lung	2 (9.5)	2 (11.1)
head & neck	1 (4.8)	2 (11.1)
upper GI	5 (23.8)	5 (27.8)
breast	4 (19.0)	1 (5.6)
colorectal	3 (14.3)	2 (11.1)
gynaecological	1 (4.8)	-
lymphoma	3 (14.3)	1 (5.6)
male cancer	-	1 (5.6)
melanoma	-	1 (5.6)
thyroid	2 (9.5)	-
unknown origin	-	2 (11.1)
brain	-	1 (5.6)
<b>Disease stage</b>		
local	1 (4.8)	2 (11.1)
local advanced	5 (23.8)	4 (22.2)
metastatic	15 (71.4)	12 (66.7)
<b>Cachexia type</b>		
syndrome, few S-NIS	5 (23.8)	5 (27.8)
refractory, few S-NIS	3 (14.3)	3 (16.7)
syndrome, many S-NIS	8 (38.1)	8 (44.4)
refractory, many S-NIS	5 (23.8)	2 (11.1)

Values in parentheses are percentages unless indicated otherwise. Abbreviations: SD, standard deviation; S-NIS, secondary nutrition impact symptoms

**Table 2: Number of patients in each cell of the Phase 3 sampling matrix<sup>a</sup>**

	Cachexia syndrome: Interview within 100 days of cancer diagnosis	Cachexia syndrome: Interview >100 days after cancer diagnosis	Refractory cachexia: ECOG performance status 3 or 4
Group A Symptom Checklist scaled score $\leq 25$	25	17	13
Group B Symptom Checklist scaled score $> 25$	12	20	22

Abbreviations: ECOG, Eastern Cooperative Oncology Group

<sup>a</sup>Total is less than 110 because one patient with cachexia syndrome, interviewed in the first 100 days after cancer diagnosis, did not complete a Symptom Checklist

**Table 3: Characteristics of patients participating in Phase 3<sup>b</sup>**

		<b>Whole Sample n=110</b>	<b>Group A (low symptom checklist score) n=55</b>	<b>Group B (high symptom checklist score) n=54</b>
<b>Age (years)</b>	Mean (SD)	62.9 (13.7)	62.5 (13.2)	63.4 (14.4)
	Range	20-93	40-93	20-84
<b>Number of males</b>		63 (57.3)	31 (56.4)	31 (56.4)
<b>Primary tumour</b>	lung	25 (22.7)	10 (18.2)	14 (25.9)
	head & neck	17 (15.5)	11 (20.0)	6 (10.9)
	upper GI	16 (14.5)	7 (12.7)	9 (16.4)
	breast	13 (11.8)	7 (12.7)	6 (10.9)
	colorectal	13 (11.8)	8 (14.5)	5 (9.1)
	gynaecological	8 (7.3)	5 (9.1)	3 (5.5)
	lymphoma	6 (5.5)	3 (5.5)	3 (5.5)
	male cancer	4 (3.6)	1 (1.8)	3 (5.5)
	kidney	3 (2.7)	1 (1.8)	2 (3.6)
	melanoma	3 (2.7)	1 (1.8)	2 (3.6)
	thyroid	1 (0.9)	0 (0.0)	1 (1.8)
	unknown origin	1 (0.9)	1 (1.8)	0 (0.0)
<b>One or more comorbidities</b>		32 (29.1)	17 (30.9)	15 (27.3)
<b>Symptom Checklist scaled score</b>	Mean (SD)	25.9 (15.4)	13.9 (7.5)	38.2 (10.9)
	Range	0-74.5	0-23.5	25.5-74.5
<b>BMI</b>	Mean (SD)	21.3 (3.9)	21.9 (3.9)	20.8 (3.8)
	Range	15.5-31.2	16.0-31.2	15.5-28.4
	n	109	55	53
<b>% WL in last 3 months</b>	Mean (SD)	7.7 (6.6)	8.0 (5.6)	7.4 (7.5)
	Range	-7.3-23.4	-6.7-22.1	-7.3-23.4
	n	96	46	50
<b>% WL in last 6 months</b>	Mean (SD)	12.9 (7.6)	12.8 (6.6)	12.7 (8.4)
	Range	-9.6-32.6	-9.6-25.7	-8.3-32.6
	n	102	51	50
<b>% WL from premorbidity</b>	Mean (SD)	18.2 (7.5)	17.4 (7.4)	18.7 (7.6)
	Range	-6.9-45	6.3-45.0	-6.9-37.6
	n	92	43	48

<b>ECOG performance status</b>	0	7(6.4)	3 (5.5)	4 (7.3)
	1	25 (22.7)	13 (23.6)	12 (21.8)
	2	42 (38.2)	25 (45.5)	16 (29.1)
	3	29 (26.4)	11 (20.0)	18 (32.7)
	4	6 (5.5)	2 (3.6)	4 (7.3)
	Missing	1 (0.9)	1 (1.8)	0 (0.0)
<b>Toxicity level</b>	None	45 (40.9)	25 (45.5)	19 (34.5)
	Mild	36 (32.7)	20 (36.4)	16 (29.1)
	Severe	29 (26.4)	10 (18.2)	19 (34.5)
<b>Living alone</b>		21 (19.0)	13 (23.6)	8 (14.5)
<b>Carer easily available</b>		85 (77.3)	39 (70.9)	46 (83.6)
<b>Education beyond secondary school</b>		46 (41.8)	24 (43.6)	22 (40.0)
<b>Previous employment level</b>	Unskilled	23 (20.9)	7 (12.7)	15 (27.3)
	Skilled manual	45 (40.9)	26 (47.3)	19 (34.5)
	Administrative	22 (20.0)	8 (14.5)	14 (25.5)
	Professional	17 (15.5)	12 (21.8)	5 (9.1)
	Missing	3 (2.7)	1 (1.9)	1 (1.8)

Values in parentheses are percentages unless indicated otherwise. Abbreviations: SD, standard deviation; WL, weight loss; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group

<sup>b</sup>Number of patients in Group A and Group B added together is less than Whole Sample because one patient did not complete a Symptom Checklist and so could not be classified.

**Table 4: Results from Phase 3**

<b>Issue</b>	<b>Samples meeting relevance &amp; importance criteria</b>	<b>Samples meeting floor &amp; ceiling criteria</b>	<b>Samples meeting prevalence criterion</b>	<b>Deletion vs. Retention</b>
1. No hunger	All 3	All 3	All 3	Delete (scoring ambiguity)
2. Willing but not able to eat	All 3	All 3	Whole sample & Group B	Retain
3. Taste changes	All 3	All 3	Whole sample & Group B	Retain
4. Texture of food unpleasant	Whole sample & Group B	All 3	Whole sample & Group B	Retain
5. Put off eating by thought of food	None	All 3	Group B	Delete
6. Put off eating by food smells	Whole sample & Group B	All 3	Group B	Retain
7. Put off eating by quantity	Group B	All 3	All 3	Retain
8. Change in food preferences	None	All 3	Whole sample & Group B	Delete
9. Changeable appetite	None	All 3	All 3	Delete
10. Missing past experiences	Group B	All 3	Whole sample & Group B	Delete (patient comments)
11. Weight loss preventing usual activities	All 3	All 3	All 3	Retain
12. Too tired to eat	Whole sample & Group B	All 3	Group B	Retain
13. Unable to eat because in pain	All 3	All 3	Group B	Retain
14. Feeling too full to eat	All 3	All 3	All 3	Retain
15. Difficulty drinking	All 3	All 3	Group B	Retain
16. Dry mouth	All 3	All 3	All 3	Retain
17. Difficulties chewing	Whole sample & Group A	All 3	None	Delete
18. Difficulties swallowing	All 3	All 3	Group B	Retain
19. Indigestion/heart burn	All 3	All 3	Group B	Retain
20. Not eating as much	All 3	All 3	Whole sample & Group B	Retain
21. Worried about weight loss	All 3	All 3	All 3	Retain
22. Thinks a lot about food and eating	None	All 3	Whole sample & Group B	Delete

23. Outlook on future worsened	Whole sample & Group A	All 3	All 3	Delete (patient comments)
24. Thinking about the ultimate result of weight loss	All 3	All 3	All 3	Retain
25. Mealtimes as social events	Group A	All 3	All 3	Delete (patient comments)
26. Feeling supported by others	All 3	Whole sample & Group B	None	Delete
27. Feeling pressured by others	Whole sample	All 3	Whole sample & Group B	Retain
28. Concern about being a burden	All 3	All 3	All 3	Retain
29. Problem eating with others	None	All 3	None	Delete
30. Embarrassed by eating	None	Whole sample & Group B	None	Delete
31. Embarrassed by weight loss	Whole sample	All 3	None	Delete
32. Change in self-identity upsetting	None	All 3	All 3	Delete
33. Bothered by appearance	All 3	All 3	All 3	Retain
34. Change in role in life upsetting	All 3	All 3	All 3	Delete (patient comments)
35. Feeling physically less attractive	Group B	All 3	Whole sample & Group B	Delete (patient comments)
36. Uncomfortable with sexual intimacy	None	All 3	None	Delete
37. No control over weight	All 3	All 3	All 3	Retain
38. Keeping things normal	All 3	All 3	All 3	Retain
39. Staying independent	All 3	All 3	Whole sample & Group B	Retain
40. Forcing self to eat	All 3	All 3	All 3	Retain
41. Avoiding thinking about weight loss	None	All 3	Whole sample & Group B	Delete
42. Acceptance of change in eating	Group B	All 3	None	Delete
43. Inadequate information	All 3	All 3	Group B	Retain
44. Lack of support from health care professionals	All 3	All 3	None	Delete



## **Legend**

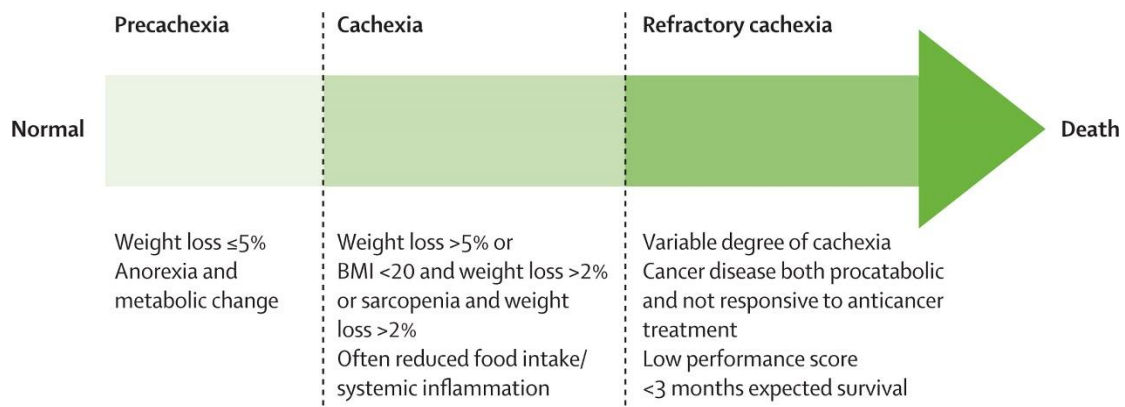
Samples: Group A - fewer secondary nutritional impact symptoms (S-NIS); Group B - more S-NIS symptoms; Whole sample - Group A and B combined. Relevance and importance criteria:  $\geq 60\%$  patients rated the item as relevant and important (quite a bit or very much); floor and ceiling criteria:  $\geq 10\%$  patient responses for both response options one or two and three or four; prevalence criteria  $\geq 50\%$  patients reported the issue applies quite a bit or very much

**Table 5: Issues included in the EORTC QLQ-CAX24 and hypothesised conceptual scales for QLQ-CAX24**

<b>Conceptual Scale</b>	<b>Issues</b>	<b>Cronbach's alpha</b>	<b>Item correlation with scale (range)<sup>a</sup></b>
Food aversion	Taste changes Texture of food unpleasant Put off eating by food smells Put off eating by quantity Feeling too full to eat	0.72	0.41 to 0.53
Eating and weight-loss worry	Worried about weight loss Worried not eating enough Worried about ultimate result of weight loss	0.74	0.52 to 0.60
Eating difficulties	Willing but not able to eat Difficulty drinking Difficulties swallowing	0.62	0.32 to 0.49
Loss of control	Feeling pressured by others Concern about being a burden Bothered by appearance No control over weight Keeping things normal Staying independent	0.79	0.43 to 0.66
Physical decline	Weight loss preventing usual activities Too tired to eat Unable to eat because in pain	0.62	0.39 to 0.52
4 single items	Dry mouth Indigestion/heartburn Forcing self to eat Inadequate information	N/A	N/A

<sup>a</sup> corrected for overlap

Figure 1: Stages of cancer cachexia



Abbreviation: BMI Body-mass index

Figure 2: Symptom checklist

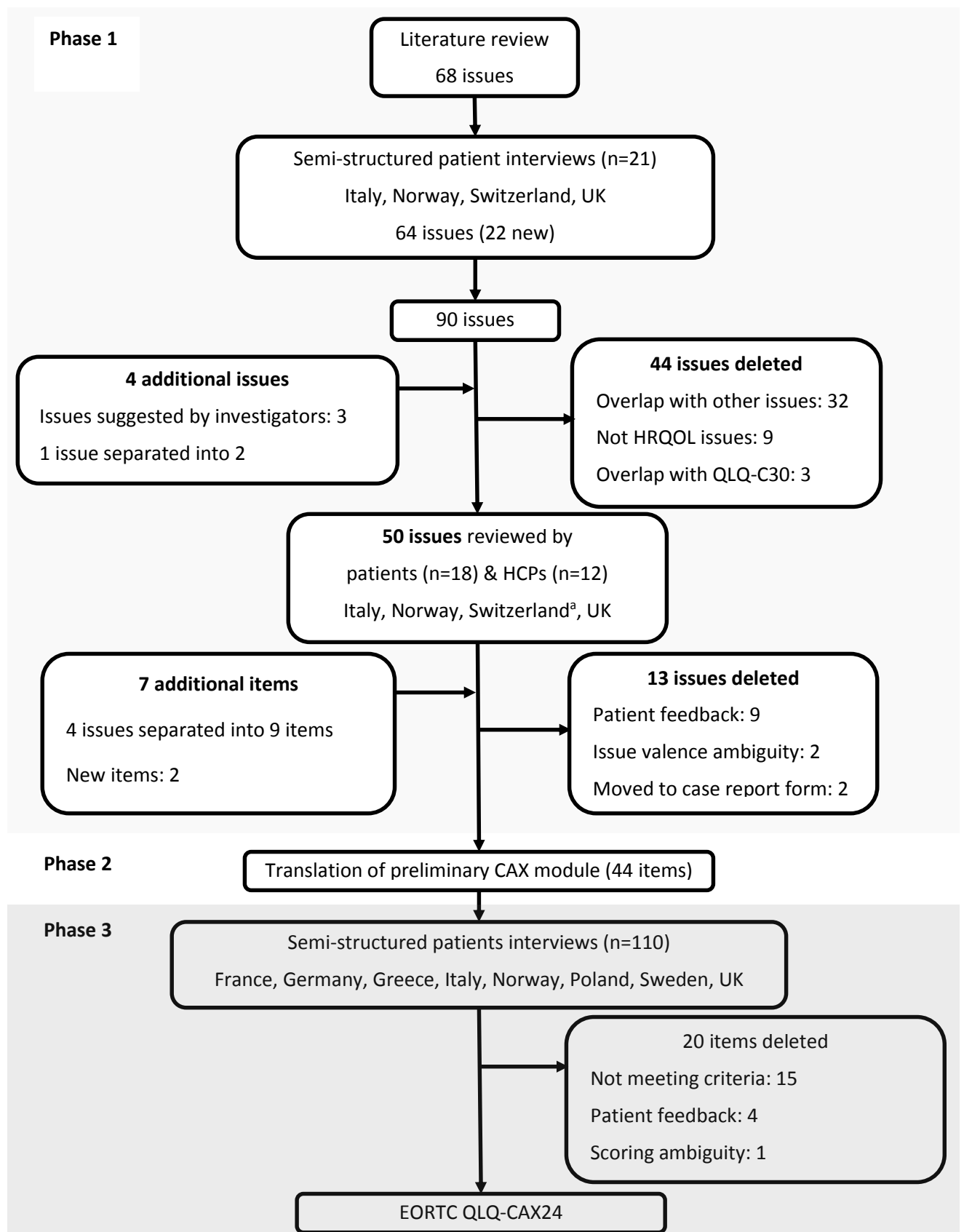
Based on abridged Patient-Generated Subjective Global Assessment and Nutrition Impact Symptoms Checklist

### Symptom Checklist

**I have had the following problems that have kept me from eating enough during the past two weeks:**

	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
1. No appetite, just did not feel like eating	1	2	3	4
2. Nausea	1	2	3	4
3. Constipation	1	2	3	4
4. Mouth sores (stomatitis)	1	2	3	4
5. Things taste funny or have no taste	1	2	3	4
6. Problems swallowing	1	2	3	4
7. Abdominal/stomach pain	1	2	3	4
8. Other pain: where? _____	1	2	3	4
9. Vomiting	1	2	3	4
10. Diarrhoea	1	2	3	4
11. Dry mouth	1	2	3	4
12. Smells bother me	1	2	3	4
13. Feels full quickly	1	2	3	4
14. Defecation after meals	1	2	3	4
15. Shortness of breath	1	2	3	4
16. Fatigue	1	2	3	4
17. Other reason: what? _____	1	2	3	4

Figure 3: Summary of EORTC QLQ-CAX24 Development



<sup>a</sup>HCP interviews only

## References

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncology* 2011;12:489-495.
2. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer* 2014;14:754-62.
3. Snyder CF, Herman JM, White SM, et al. When using patient-reported outcomes in clinical practice, the measure matters: A randomized controlled trial. *Journal of Oncology Practice* 2014;JOP. 2014.001413.
4. Aaronson NK. Quality of life research in cancer clinical trials: a need for common rules and language. *Oncology (Williston Park)* 1990;4:59-66; discussion 70.
5. Blum D, Omlin A, Fearon K, et al. Evolving classification systems for cancer cachexia: ready for clinical practice? *Supportive Care in Cancer* 2010;18:273-279.
6. Hopkinson JB. The emotional aspects of cancer anorexia. *Curr Opin Support Palliat Care* 2010;4:254-8.
7. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol* 2013;10:90-99.
8. Hopkinson JB, Wright DN, Foster C. Management of weight loss and anorexia. *Ann Oncol* 2008;19 Suppl 7:vii289-93.
9. Kubrak C, Olson K, Jha N, et al. Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck* 2010;32:290-300.
10. Omlin A, Blum D, Wierecky J, et al. Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case-control study. *J Cachexia Sarcopenia Muscle* 2013;4:55-61.
11. Fitzsimmons D, Johnson CD. What is quality of life? In: 2014.
12. Cella DF, Bonomi AE, Leslie WT, VonRoenn J, Tchekmedyian NS. Quality of life and nutritional well-being: Measurement and relationship. *Oncology* 1993;7:105-111.
13. Ribaldo JM, Cella D, Hahn EA, et al. Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. *Qual Life Res* 2000;9:1137-46.
14. LeBlanc T, Samsa G, Wolf S, et al. Validation and real-world assessment of the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) scale in patients with advanced non-small cell lung cancer and the cancer anorexia-cachexia syndrome (CACS). *Supportive Care in Cancer* 2015:1-7.
15. Wheelwright S, Darlington AS, Hopkinson JB, et al. A systematic review of health-related quality of life instruments in patients with cancer cachexia. *Support Care Cancer* 2013;21:2625-36.
16. Lockett T, King MT, Butow PN, et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. *Ann Oncol* 2011;22:2179-90.
17. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.
18. Johnson CD, Aaronson NK, Blazeby J, et al. EORTC Quality of Life Group: guidelines for developing questionnaire modules. In: 4th ed. 2011.
19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
20. Wheelwright SJ, Darlington AS, Hopkinson JB, et al. A systematic review to establish health-related quality-of-life domains for intervention targets in cancer cachexia. *BMJ Support Palliat Care* 2014.
21. Francis JJ, Johnston M, Robertson C, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychology & health* 2010;25:1229-45.

22. Dewolf L, Koller M, Velikova G, et al. EORTC Quality of Life Group Translation Procedure. In: 3rd ed. Brussels: 2009.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
24. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* 1996;12:S15-9.
25. Fayers P, Machin D. *Quality of Life: the Assessment, Analysis and Interpretation of Patient-reported Outcomes*, 2nd ed. Chichester: John Wiley & Sons, 2007.
26. StataCorp. *Stata Statistical Software: Release 13*. In: College Station, TX: StataCorp LP, 2013.
27. King MT, Bell ML, Costa D, Butow P, Oh B. The Quality of Life Questionnaire Core 30 (QLQ-C30) and Functional Assessment of Cancer-General (FACT-G) differ in responsiveness, relative efficiency, and therefore required sample size. *Journal of clinical epidemiology* 2014;67:100-107.
28. Farkas J, von Haehling S, Kalantar-Zadeh K, et al. Cachexia as a major public health problem: frequent, costly, and deadly. *Journal of Cachexia, Sarcopenia and Muscle* 2013;4:173-178.
29. Blum D, Strasser F. Cachexia assessment tools. *Curr Opin Support Palliat Care* 2011;5:350-5.
30. Blum D, Stene GB, Solheim TS, et al. Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model – A study based on data from an international multicentre project (EPCRC-CSA). *Annals of Oncology* 2014.