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Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery

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Objective: Development of a core outcome set (COS) for clinical effectiveness trials in esophageal cancer resection surgery.

Background: Inconsistency and heterogeneity in outcome reporting after esophageal cancer resection surgery hampers comparison of trial results and undermines evidence synthesis. COSs provide an evidence-based approach to these challenges.

Methods: A long list of clinical and patient-reported outcomes was identified and categorized into outcome domains. Domains were operationalized into a questionnaire and patients and health professionals rated the importance of items from 1 (not important) to 9 (extremely important) in 2 Delphi survey rounds. Retained items were discussed at a consensus meeting and a final COS proposed. Professionals were surveyed to request endorsement of the COS.

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Results: A total of 68 outcome domains were identified and operationalized into a questionnaire; 116 (91%) of consenting patients and 72 (77%) of health professionals completed round 1. Round 2 response rates remained high (87% patients, 93% professionals). Rounds 1 and 2 prioritized 43 and 19 items, respectively. Retained items were discussed at a patient consensus meeting and a final 10-item COS proposed, endorsed by 61/67 (91%) professionals and including: overall survival; in-hospital mortality; inoperability; need for another operation; respiratory complications; conduit necrosis and anastomotic leak; severe nutritional problems; ability to eat/drink; problems with acid indigestion or heartburn; and overall quality of life.

Conclusions: The COS is recommended for all pragmatic clinical effectiveness trials in esophageal cancer resection surgery. Further work is needed to delineate the definitions and parameters and explore best methods for measuring the individual outcomes.

Keywords: Delphi technique, esophageal neoplasms, operative, outcome assessment, randomized controlled trial, surgical procedures

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Clinical effectiveness trials are designed to evaluate the performance of an intervention under pragmatic or real-world conditions, rather than the ideal and controlled circumstances often observed in efficacy trials.[1] The results of clinical effectiveness trials may therefore be more readily applied to everyday practice and are likely to influence clinical decision making and health policy.[2,3] Integral to the design and applicability of effectiveness trials is the selection, measurement and reporting of outcomes, which are required to evaluate clinical benefit from the view point of the patient and health provider in addition to assessing risks and harms (often the focus of the surgeon).[3] Systematic reviews have shown, however, that there are often inconsistencies in the way in which outcomes are defined, selected, measured, and reported in trials of esophageal cancer surgery.[4,5] This makes the robust evaluation of esophageal cancer surgery difficult.[4]

Outcomes that may be relevant to effectiveness trials of esophageal cancer surgery include long-term morbidity, disease recurrence, symptom alleviation and quality of life.[6,7] However, the heterogeneity of outcomes measured and reported across such trials hampers comparison of centers and trial results, thereby compromising evidence synthesis.[8] It also means that outcome reporting bias (the selective reporting of some outcomes but not others) may occur.[8] Core outcome sets (COSs), which define a minimum set of key outcomes to be measured and reported in all trials of specific conditions, provide an evidence-based approach to standardize outcome selection and reporting.[9,10] Their development and application has the potential to increase the quality of usable data generated by clinical effectiveness trials, thereby reducing research waste.[11] These sets of standardized outcomes do not preclude the measurement of additional outcomes of specific interest to investigators or studies. Instead, they outline the core set of outcomes that should be routinely measured and reported as a minimum.[10]

A COS for effectiveness trials of esophageal cancer surgery that includes both clinical and patient-centered outcomes has the potential to reduce reporting bias, increase homogeneity in outcome reporting and improve the value of research in this area.[8,11–13] This article describes the development of a COS for esophageal cancer resection surgery.

METHODS

Details of the COS development process are reported in accordance with recommendations of the Core Outcome Set-STAndards for Reporting (COS-STAR) checklist.[14] The COS was developed in 3 phases: (i) Phase 1—identification of a 'long list' of outcomes and development of survey questionnaire; (ii) Phase 2—prioritization of outcomes using Delphi survey; and (iii) Phase 3—consensus meeting to finalize COS.

Phase 1: Identification of Long List of Outcomes and Development of Survey Questionnaire

The identification of an exhaustive long list of outcomes of esophageal cancer resection surgery has been previously reported[4,5,15,16] and included systematic reviews, a national register/audit of outcomes and patient interviews (Fig. 1). Overlapping outcomes were merged and outcomes categorized independently by 2 study researchers into broader health domains, defined as areas of health within the same theme (eg, 30- and 90-day mortality were grouped into a ''mortality'' domain) and, in the absence of established definitions,[4] agreed after discussion between the study team. A patient representative assisted in the process of categorizing the patient-reported outcomes.[5] Domains were formulated as items for a survey questionnaire. Each item was written in lay language with the clinical terminology included in parentheses. The draft survey was piloted by four lay people and one patient representative to examine face validity, comprehension, and acceptability.

Phase 2: Prioritization of Outcomes

Stakeholders

Professionals from relevant disciplines and clinical backgrounds (esophagogastric surgeons and clinical nurse specialists) were identified from the membership of the Association of Upper Gastro Intestinal Surgeons of Great Britain and Ireland. Consecutive patients who had undergone primary esophagectomy or esophagectomy after neoadjuvant chemotherapy or chemoradiotherapy between 1 month and 5 years previously (January 2015 to January 2009) were sampled in descending chronological order from lists of patients at 2 United Kingdom hospital trusts with which the research team was collaborating (University Hospitals Bristol NHS Foundation Trust and Plymouth Hospitals NHS Trust). Professionals and patients were asked to complete 2 rounds of questionnaires.

Round 1

Professionals were contacted by email about the study and notified that they would receive the first questionnaire through the post with a prepaid return envelope. One postal reminder was sent if necessary. Patients were posted an invitation letter and information leaflet, asking them to return a completed consent form. Patients who returned consent were posted the round 1 survey questionnaire with a pre-paid return envelope. Patients who did not return their consent forms within four weeks were sent a reminder (Bristol patients only). Respondents were asked to rate the importance of retaining each item in the COS on a 9-point Likert-type scale ranging from 1 (not important) to 9 (extremely important).[17–20] The round 1 item scores were summarized and items to retain for round 2 identified using prespecified criteria (see analyses section). The team reviewed retained items to see if any could be further merged because of overlapping content. The participants were not made aware of the prespecified cutoff criteria when completing the questionnaire.

Round 2

All participants who returned a round 1 questionnaire and were still contactable were mailed a round 2 questionnaire with a

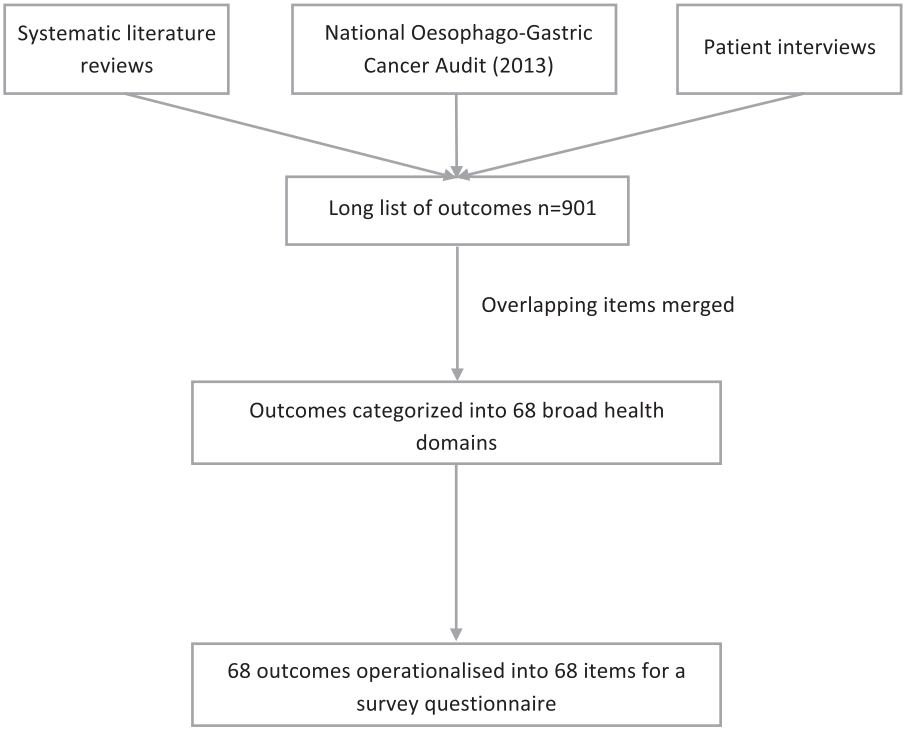

FIGURE 1. Data sources and steps involved in the development of the core outcome set.

prepaid return envelope. The round 2 questionnaire contained all items retained from round 1. All participants received anonymized feedback for each item, from each stakeholder group (patients, surgeons, nurses).[21] Feedback consisted of median round 1 scores calculated separately for each stakeholder group. Participants were asked to rerate the items' importance on the same 9-point scale. In a further attempt to encourage prioritization, the survey instructions in round 2 requested that respondents prioritize and rate highly only the items that they believed to be essential, intended to be "about 10 items." Round 2 questionnaire responses were summarized to identify a list of items that should be retained and discussed at the consensus meetings using pre-specified criteria.

Phase 3: Consensus Meetings

All participants who responded to the round 2 questionnaire were invited to a consensus meeting where the results of the Delphi survey were summarized. At the meeting, participants were asked to vote on the list of items carried forward from round 2 using an anonymized system (TurningPoint software[22]) with 3 keypad options: "in" (the item should be included in the COS), "out" (the item should not be included in the COS) or "unsure." Items for which consensus was not reached (see "Statistical analyses" section) were discussed further and additional voting conducted until the final list of items was agreed.

Statistical Analyses

Items in round 1 were categorized as "essential" and eligible to be retained for round 2 if they met the following cutoff criteria defined a priori: (i) rated 7–9 by $\geq$70% and 1–3 by $<$ 15% of either patients or professionals (surgeons and nurses combined). The same criteria were specified for identifying items to retain from round 2 for the consensus meetings. In both rounds, items were discarded if they did not meet these criteria. There are no universally agreed consensus criteria in Delphi surveys and examples vary widely; the criteria used here follow published recommendations.[9]

Prespecified criteria for the consensus meetings were that items voted "in" by $\geq$70% of participants would be included in the COS. Items voted "in" by $<$60% and "out" by $\geq$15% of participants would be discarded. Any other items were discussed further and revoted on until consensus was reached.

Sample Size

There are currently no agreed sample size guidelines for the number of participants necessary for consensus methods when developing a COS,[17] though the numbers of participants sampled for this study is in keeping with that of similar studies.[23,24] An opportunistic approach was used with the intention of recruiting 200 patients with experience of esophageal cancer resection surgery across two different hospital trusts and a range of 100 professionals involved in the care of esophageal cancer surgery patients. All patients who responded to the round 2 survey were invited to the consensus meeting to encompass a range of patients' experiences.

Ethical approval for this study was granted by the South-West Frenchay Research Ethics Committee (12/SW/0161).

RESULTS

Phase 1: Identification of Long List of Outcomes and Development of Survey Questionnaire

The systematic reviews, audit, and patient interviews[4,5,15,16] identified 901 outcomes, which were categorized into 68 health domains and 68 items for the survey (Table 1).

Phase 2: Prioritization of Outcomes

Stakeholders

A total of 94 professionals [esophagagastric surgeons (n = 72) and clinical nurse specialists (n = 22)] from 38 different United

TABLE 1. Domains Identified From Initial Long List (Survey Questionnaire Items)

Broad Health Domain	Domain
Quality of life after discharge from hospital (n = 38 items)	
Activities of daily living and work/employment	1 Able to carry out usual activities
	2 Able to participate/enjoy physical activities
Eating and drinking	3 Able to eat/drink more easily (dysphagia)
	4 Able to swallow without pain (odynophagia)
	5 Able to enjoy healthy/balanced eating pattern
	6 Problems with acid indigestion/heartburn including at night (reflux)
	7 Problems eating socially
	8 Problems with regurgitation and/or vomiting
	9 Belching, bloating or gas (flatulence)
	10 Feeling out of breath/difficulties breathing (dyspnea)
	11 Problems choking when eating/drinking
	12 Problems with appetite loss
	13 Problems with sense of taste
	14 Sudden dizziness, sweating and/or feeling drained after eating (dumping)
Physical health	15 Problems with feeling sick (nausea)
	16 Problems with diarrhoea, including frequent bowel movements
	17 Having good general health
	18 Problems with general pain/discomfort
	19 Problems with weak voice/hoarseness
	20 Problems with constipation
	21 Problems with coughing
	22 Problems with a dry mouth
	23 Problems with sleeping
	24 Problems with tiredness (fatigue)
Physical appearance	25 Problems with weight
	26 Feeling in control of weight and appearance
	27 Feeling satisfied/confident with one's body
	28 Problems with hair loss
Social life and relationships	29 Interested in and able to enjoy sex
	30 Able to have relationships with friends
	31 Able to have relationships with family members
Mental health	32 Problems with concentration and memory (cognitive function)
	33 Problems with anxiety
	34 Problems with depression
	35 Problems with changes in general mood
Overall health, wellbeing and life	36 Money worries due to loss of earnings (finances)
	37 Overall quality of life
	38 Spiritual or faith issues
Benefits of esophageal cancer surgery (n = 4 items)	
Improving problems of esophageal cancer	39 Improving patient's ability to eat and drink (dysphagia)
Survival and controlling cancer	40 How long a patient will live (overall survival)
	41 How long a patient may live free of esophageal cancer (Cancer-specific survival)
	42 The chances that the cancer will come back (recurrence)
In-hospital events (n = 18 items)	
Events during surgery	43 Inoperability
	44 Organ injury
	45 Hemorrhage
Post-operative events related to esophagectomy	46 Chyle/pleural leak
	47 Anastomotic leak
	48 Conduit necrosis
	49 Re-insertion of chest/abdominal/stomach drain
	50 Laryngeal nerve palsy
Other postoperative events	51 Wound infection or dehiscence
	52 Cardiac complications
	53 Renal complications
	54 Severe urine infection (septicaemia)
	55 Cerebral complications
	56 Liver failure
	57 Respiratory complications
	58 Blood clots in the legs or lungs (deep vein thrombosis; pulmonary embolism)
	59 Reventilation
	60 Inhospital mortality
Events after discharge (n = 8 items)	
Events related to eating and drinking	61 Esophageal stricture
	62 Pyloric dilatation
	63 Total parenteral nutrition

TABLE 1. (*Continued*)

Broad Health Domain	Domain
Complications needing reoperation or reintervention	64 Need for further surgery for a build-up of fluid around the lung (empyema)
	65 Need for further stomach surgery due to abdominal hernia
	66 Colonic interposition
	67 Diaphragmatic hernia repair
	68 Need for another operation

Kingdom hospital trusts and 200 patients from 2 United Kingdom hospital trusts participated in round 1.

Round 1

In this study, 128/200 (64%) patients consented to participate, and 116/128 (91%) patients and 72/94 (77%) health professionals completed the questionnaire. Participants' demographics are provided in Table 2.

Health professionals and patients all rated the same 28 items as essential with patients also rating another 25 items as essential (Table 3). Therefore, 53 items were retained for round 2. Ten of these were identified as overlapping with each other [eg, ''choking when eating'' (item 11) was covered by ''able to eat and drink more easily'' (item 3)] so they were combined and merged, meaning that 43 items were taken forward to round 2 (Table 3).

Because of the high percentage of items rated essential by patients in round 1, more stringent criteria were agreed by the study team (J.B., S.B., N.B., K.A., K.C.) for round 2. These more rigorous pre-defined criteria were: items to retain would be rated 8–9 (rather than 7–9) by $\geq$70% and 1–3 by $<$15% of patients or professionals.

Round 2

Response rates were high with 108/116 (93%) patients who completed round 1 contactable, of whom 94/108 (87%) returned the questionnaire in addition to 67/72 (93%) professionals. Using the more rigorous (8–9 by $\geq$70%) criteria, 34 items (79%) were rated essential by patients with 12 (28%) of these also rated essential by professionals. There was concern that 34 items would be an unfeasible number to discuss at the consensus meetings. As further survey rounds were not possible, a post hoc decision was made to further restrict the criteria. Items were taken forward for the consensus meetings if: (i) rated 8–9 by $\geq$70% and 1–3 by $<$15% of patients, and (ii) rated 8–9 by $>$50% (a majority) and 1–3 by $<$15% of health professionals. This identified 19 items rated 8–9 by $>$50% professionals, all of which were rated 8–9 by $\geq$70% patients and taken to the consensus meeting (Table 4). As these were post-hoc criteria, the study team gave further consideration to the 15 discordant items. Many were related to less common adverse events that might require a reoperation (thus captured in that item) or were generic surgical complications that may not be considered as appropriate for a COS specific to esophageal cancer surgery. Other discordant items were covered by retained items (eg, relationships with family/friends overlapped with overall quality of life). Round 2 Delphi results showed that 5 of the 19 items were considered by both patients and professionals to be of very high priority, with $>$90% of both patients and professionals rating these items 8–9 (Table 5). The study team agreed that these items (overall survival, in-hospital mortality, overall quality of life, conduit necrosis, and anastomotic leak) should be presented at the consensus meetings as being in the final COS.

Phase 3: Consensus Meetings

The patient consensus meeting was held in Bristol, United Kingdom (September 2015) and attended by 20 (21%) patients from the South-West United Kingdom (Table 2). There were no objections to the five highly rated items presented as being in the COS.

Results from voting on the remaining 14 items are shown in Table 5. Nine of the 14 items were voted ''in' and 3 ''out.'' One of these (''reventilation'') was voted ''out'' on the basis that it could be incorporated into ''respiratory complications.'' Two items were voted ''unsure'' (''colonic interposition'' and ''chyle/pleural leak'') and were discussed in further detail during the meeting. It was agreed that, as both of these events commonly lead to the need for another operation, they could be incorporated into ''need for another operation, any cause'' and so were subsequently voted ''out'' as additional items. Further indepth discussion during the patient consensus meeting led to the merging of ''conduit necrosis'' and ''anastomotic leak'' into a single item, ''being able to eat/drink more easily'' and ''being able to swallow without pain'' were merged to become ''the ability to eat and drink,'' and ''being able to carry out usual activities and participate/enjoy physical activities'' and ''having good general health'' were incorporated into ''quality of life.'' This resulted in a proposed COS of 10 items (Table 6).

Although a professional consensus meeting was planned, it was agreed to be of little value as all items rated 8–9 by the majority of professionals ($>$50%) in round 2 were incorporated into the proposed final COS. It was agreed that it would be more informative to validate the final COS identified by the Delphi and the patient consensus meeting. Professionals responding to round 2 were therefore emailed information about the proposed COS, and asked to comment on its content and whether or not they would endorse it. Those who did not respond after 6 weeks were sent an email reminder. In total, 61/67 (91%) responded and endorsed the COS with some comments about how the outcome should be measured rather than questioning the outcomes themselves.

DISCUSSION

This study has established a COS for use in effectiveness trials of esophageal cancer resection surgery. A comprehensive list of 68 relevant clinical outcomes and patient-reported outcomes was generated from multiple and varied information sources as part of earlier work. In this study, robust survey methods using the Delphi technique were used to gain consensus among key stakeholders, including patients and health professionals, on the most important outcomes to include in a COS. Consensus was reached on a final core set comprising 10 items. The COS comprises health outcome domains related to overall survival; in-hospital mortality; inoperability; the need for another operation at any time; respiratory complications; conduit necrosis and anastomotic leak; severe nutritional problems; the ability to eat and drink; problems with acid indigestion or heartburn; and overall quality of life. It is recommended that future trials include measures of these outcomes and additional outcomes as particularly relevant to the research question.

Recently, a system for defining and recording in-hospital outcomes of esophageal cancer surgery has been developed.[25] This is incredibly valuable and will go some way to address the current problem with outcome reporting. However, this system focuses on

TABLE 2. Demographics of Participants

Patients	**Round 1 Survey N = 116**	**Round 2 Survey N = 94**	**Consensus Meeting N = 20**
Center, N (%)	116 (90.6)	94 (87.0)	–
Bristol	72 (90.0)	56 (83.6)	17 (85.0)
Plymouth	44 (91.7)	38 (92.6)	3 (15.0)
Male, N (%)	94 (81.0)	74 (78.7)	18 (90)
Age in years, mean (SD)	66.1 (8.1)	65.9 (7.9)	65.6 (8.9)
Educational background N* (%)			
GCSE (or equivalent)	37 (33.3)	31 (34.4)	6 (30.0)
A level (or equivalent)	19 (17.1)	15 (16.7)	5 (25.0)
University degree	6 (5.4)	5 (5.6)	1 (5.0)
Vocational qualification	18 (16.2)	15 (16.7)	3 (15.0)
Higher degree	2 (1.8)	2 (2.2)	1 (5.0)
No qualifications	9 (8.1)	3 (3.3)	1 (5.0)
Other	20 (18.0)	16 (17.8)	3 (15.0)
Marital status†, N (%)			
Single	9 (7.8)	7 (7.5)	1 (5.0)
Married	85 (73.9)	66 (71.0)	15 (75.0)
Cohabiting	5 (4.3)	5 (5.4)	1 (5.0)
Separated	2 (1.7)	2 (2.2)	0 (0.0)
Divorced	8 (7.0)	8 (8.6)	2 (10.0)
Widowed	6 (5.2)	5 (5.4)	1 (5.0)
Employment status, N (%)			
Working full time	18 (15.5)	14 (14.9)	5 (25.0)
Retired	76 (65.5)	61 (64.9)	11 (55.5)
Housewife/husband	1 (0.9)	1 (1.1)	0 (0.0)
Doing voluntary work	2 (1.7)	2 (2.1)	1 (5.0)
Unemployed sickness/disability	6 (5.2)	5 (5.3)	0 (0.0)
Unemployed and seeking work	1 (0.9)	1 (1.1)	0 (0.0)
Other	12 (10.3)	10 (10.6)	3 (15.0)
Time since surgery, months, mean (SD)	20.3 (14.9)	19.8 (15.0)	17.4 (12.1)
Second operation needed†, N (%)			
No	92 (80)	74 (79.6)	12 (66.7)
Duration of hospital stay‡, N (%)			
< 14 days	72 (63.7)	59 (64.1)	10 (55.6)
2–3 weeks	21 (18.6)	16 (17.4)	4 (22.2)
3–4 weeks	10 (8.8)	9 (9.8)	1 (5.6)
More than 4 weeks	10 (8.8)	8 (8.7)	3 (16.7)
Treatment before surgery§			
Chemotherapy	87 (100)	72 (90.0)	15 (83.3)
Radiotherapy	0 (0)	0 (0)	0 (0)
Other	13 (13.0)	8 (10.0)	3 (16.7)
Health Professionals	**Round 1 Survey N = 72**	**Round 2 Survey N = 67**	**COS Endorsement N = 61**
COS endorsement, N (%)	–	–	61 (100.0)
Male, N (%)	54 (75.0)	49 (73.1)	47 (77.1)
Age range in years, N (%)			
≤40	10 (13.9)	10 (14.9)	7 (11.5)
41–59	33 (45.8)	28 (41.8)	26 (42.6)
51–60	24 (33.3)	24 (35.8)	23 (37.7)
> 60	5 (6.9)	5 (7.5)	5 (8.2)
Job role, N (%)			
Consultant surgeon	53 (73.6)	50 (74.6)	47 (77.1)
Surgical registrar	2 (2.8)	1 (1.5)	1 (1.6)
Clinical specialist nurse	17 (23.6)	16 (23.9)	13 (21.3)
Length of consultant experience¶, years, N (%)			
<5	5 (9.6)	3 (6.1)	2 (4.3)
5–10	11 (21.2)	11 (22.4)	10 (21.7)
>10	36 (69.2)	35 (71.4)	34 (73.9)

COS indicates core outcome set; SD, standard deviation.
*Data missing for 5 patients in round 1 and 4 patients in round 2.
†Data missing for 1 patient in both round 1 and round 2.
‡Data missing for 3 patients in round 1 and 2 patients in round 2.
§Data missing for 16 patients in round 1, 14 patients in round 2 and 2 patients at the consensus meeting.
¶Data missing for one consultant each at round 1, round 2 and COS endorsement.

TABLE 3. Rating of items in Round 1*

Item	Item Description (n = 68)	Median (Range)	% of Patients Rating Item (n = 116) 7–9†	1–3†	Outcome	Median (Range)	% of Professionals Rating Item (n = 72) 7–9†	1–3†	Outcome	Eligible to be Taken Forward to Round 2
1	*Able to carry out usual activities*	9 (3–9)	91.2	0.9	essential	8 (3–9)	87.5	1.6	essential	yes
2	*Able to participate/enjoy physical activities*	9 (3–9)	86.0	1.8	essential	8 (3–9)	87.5	1.6	essential	yes
3	Able to eat/drink more easily	9 (3–9)	87.8	1.7	essential	8 (5–9)	89.1	0.0	essential	yes
4	Able to swallow without pain	9 (3–9)	91.3	0.9	essential	8 (3–9)	82.8	1.6	essential	yes
5	Able to enjoy healthy/balanced eating pattern	9 (3–9)	86.8	1.8	essential	7 (3–9)	60.9	1.6	not essential	yes
6	Problems with acid indigestion/ heartburn including at night (reflux)	8 (2–9)	78.8	4.4	essential	7 (4–9)	60.9	0.0	not essential	yes
7	Problems eating socially	8 (1–9)	72.6	7.1	essential	7 (3–9)	59.4	3.1	not essential	yes
8	Problems with regurgitation and/or vomiting	8 (1–9)	75.9	5.4	essential	7 (3–9)	76.6	1.6	essential	yes
9	Flatulence	7 (1–9)	69.3	6.1	not essential	6 (3–9)	43.8	1.6	not essential	no
10	Difficulties breathing	8 (1–9)	78.9	6.1	essential	7 (3–9)	54.7	1.6	not essential	yes
11	Problems with choking when eating‡	8 (1–9)	79.5	5.4	essential	8 (3–9)	79.7	1.6	essential	yes
12	Problems with appetite loss	8 (1–9)	73.2	7.1	essential	7 (3–9)	64.1	3.1	not essential	yes
13	Problems with sense of taste	7 (1–9)	59.5	11.7	not essential	6 (1–9)	39.1	12.5	not essential	no
14	Sudden dizziness, sweating and/or feeling drained after eating (dumping)	8 (1–9)	76.4	4.5	essential	7 (3–9)	62.5	1.6	not essential	yes
15	Nausea	7 (1–9)	69.6	7.1	not essential	7 (3–9)	67.2	3.1	not essential	no
16	Diarrhoea	8 (2–9)	73.0	1.8	essential	7 (3–9)	60.9	4.7	not essential	yes
17	Having good general health	9 (3–9)	89.4	1.8	essential	7 (2–9)	73.4	1.6	essential	yes
18	Problems with general pain	7 (1–9)	75.0	5.4	essential	7 (2–9)	68.8	4.7	not essential	yes
19	Problems with weak voice/ hoarseness	7 (1–9)	60.0	12.7	not essential	7 (2–9)	50.0	9.4	not essential	no
20	Constipation	7 (1–9)	57.5	9.7	not essential	6 (2–9)	32.8	7.8	not essential	no
21	Coughing	7 (1–9)	64.9	12.6	not essential	6 (2–9)	46.9	3.1	not essential	no
22	Dry mouth	7 (1–9)	56.8	13.5	not essential	6 (1–9)	26.6	15.6	not essential	no
23	Problems with sleeping§	8 (1–9)	74.1	5.4	essential	7 (2–9)	62.5	6.3	not essential	yes
24	Fatigue	8 (1–9)	77.3	6.4	essential	7 (2–9)	56.3	4.7	not essential	yes
25	Problems with weight	7 (1–9)	63.7	8.0	not essential	6 (3–9)	48.4	4.7	not essential	no
26	Feeling in control of weight and appearance	8 (2–9)	74.3	4.4	essential	6 (2–9)	43.8	12.5	not essential	yes
27	Feeling satisfied/confident with one's body	8 (2–9)	72.3	3.6	essential	6 (2–9)	50.0	9.4	not essential	yes
28	Hair loss	5.5 (1–9)	40.7	23.9	not essential	6 (1–9)	28.1	17.2	not essential	no
29	Interested in/able to enjoy sex	7 (1–9)	53.6	17.9	not essential	6 (2–9)	48.4	7.8	not essential	no
30	*Relationships with friends*	8 (2–9)	77.0	1.8	essential	7 (2–9)	65.6	6.3	not essential	yes
31	*Relationships with family*	9 (1–9)	84.8	1.8	essential	7 (2–9)	76.6	4.7	essential	yes
32	Cognitive function	8 (1–9)	72.6	6.2	essential	7 (2–9)	56.3	6.3	not essential	yes
33	Anxiety	7 (1–9)	61.1	10.6	not essential	7 (2–9)	59.4	4.7	not essential	no
34	Depression	8 (1–9)	68.1	13.3	not essential	7 (2–9)	68.8	3.1	not essential	no
35	Problems with changes in general mood	7 (1–9)	67.0	13.4	not essential	7 (2–9)	65.6	4.7	not essential	no
36	Money worries due to loss of earnings	7 (1–9)	52.2	18.6	not essential	7 (1–9)	67.2	4.7	not essential	no
37	Overall quality of life	9 (1–9)	85.8	1.8	essential	8 (2–9)	93.8	1.6	essential	yes
38	Spiritual or faith issues	5 (1–9)	34.5	38.1	not essential	6 (1–9)	42.2	20.3	not essential	no
39	Improving patient's ability to eat and drink‡	9 (3–9)	94.7	0.9	essential	7 (2–9)	73.0	1.6	essential	yes
40	Overall survival	9 (5–9)	93.8	0.0	essential	9 (5–9)	98.4	0.0	essential	yes
41	Cancer-specific survival¶	9 (5–9)	95.5	0.0	essential	9 (5–9)	95.3	0.0	essential	yes
42	Chance of cancer returning¶	9 (1–9)	87.5	1.8	essential	9 (6–9)	92.2	0.0	essential	yes
43	Inoperability	9 (1–9)	85.6	2.7	essential	8 (3–9)	89.1	3.1	essential	yes
44	Organ injury	9 (3–9)	82.1	0.9	essential	7 (3–9)	73.4	3.1	essential	yes
45	Hemorrhage	8 (1–9)	79.6	4.4	essential	7 (4–9)	76.6	0.0	essential	yes
46	Chyle/pleural leak	8 (1–9)	80.7	4.4	essential	8 (4–9)	84.4	0.0	essential	yes
47	Anastomotic leak	8 (1–9)	89.3	1.8	essential	9 (5–9)	95.3	0.0	essential	yes
48	Conduit necrosis	9 (1–9)	89.3	0.9	essential	9 (5–9)	95.3	0.0	essential	yes
49	Need for insertion of further tubes	8 (1–9)	75.0	4.5	essential	6 (1–9)	48.4	12.5	not essential	yes
50	Laryngeal nerve palsy	9 (1–9)	82.7	1.8	essential	7 (2–9)	68.8	4.7	not essential	yes
51	Wound infection or dehiscence	8 (1–9)	82.1	4.5	essential	7 (2–9)	51.6	4.7	not essential	yes
52	Cardiac complications	9 (1–9)	77.7	3.6	essential	7 (3–9)	64.1	1.6	not essential	yes
53	*Renal complications*	9 (1–9)	76.8	3.6	essential	7 (3–9)	50.0	3.1	not essential	yes
54	*Severe urine infection (septicaemia)*	8 (1–9)	80.2	3.6	essential	6 (2–9)	37.5	6.3	not essential	yes
55	Cerebral complications	9 (1–9)	77.5	2.7	essential	7 (2–9)	53.1	6.3	not essential	yes
56	Liver failure	9 (1–9)	80.4	3.6	essential	6 (1–9)	46.9	12.5	not essential	yes
57	Respiratory complications	9 (1–9)	85.8	2.7	essential	7 (3–9)	71.9	0.0	essential	yes
58	Deep vein thrombosis; Pulmonary embolism	9 (1–9)	80.4	3.6	essential	7 (3–9)	71.9	1.6	essential	yes
59	Re-ventilation	9 (1–9)	84.1	1.8	essential	8 (4–9)	89.1	0.0	essential	yes

TABLE 3. (*Continued*)

Item	Item Description (n = 68)	Median (Range)	% of Patients Rating Item (n = 116) 7–9†	1–3†	Outcome	Median (Range)	% of Professionals Rating Item (n = 72) 7–9†	1–3†	Outcome	Eligible to be Taken Forward to Round 2
60	In-hospital mortality	9 (1–9)	84.8	5.4	essential	9 (7–9)	100.0	0.0	essential	yes
61	Esophageal stricture‡	9 (1–9)	79.5	4.5	essential	7 (4–9)	78.1	0.0	essential	yes
62	Pyloric dilatation‡	8 (1–9)	79.5	4.5	essential	7 (4–9)	71.9	0.0	essential	yes
63	Severe problems related to nutrition	8 (1–9)	81.4	2.7	essential	7 (4–9)	81.3	0.0	essential	yes
64	Empyema	8 (1–9)	78.2	3.6	essential	7 (3–9)	67.2	3.1	not essential	yes
65	Additional surgery due to abdominal hernia	8 (1–9)	74.5	6.4	essential	6 (2–9)	40.6	7.8	not essential	yes
66	Colonic interposition	9 (1–9)	86.2	1.8	essential	8 (2–9)	75.0	7.8	essential	yes
67	Diaphragmatic hernia repair	9 (1–9)	81.8	2.7	essential	7 (2–9)	68.8	7.8	not essential	yes
68	Need for another operation	9 (1–9)	85.5	3.6	essential	8 (1–9)	78.1	6.3	essential	yes

*Items ordered as they appeared in the Round 1 questionnaire.

†Survey items in Round 1 were categorized as "essential" and retained for Round 2 if they met the following cutoff criteria: (i) rated between 7 and 9 by ≥70% of respondents, and; (ii) rated between 1 and 3 by <15% of respondents.

Items in *italics* were merged with the adjacent item in *italics* at the end of round 1.

‡excluded – after discussion it was concluded that these items were covered by item number 3 "being able to eat/drink more easily."

§excluded – after discussion it was concluded that this item was covered by item number 6 "Problems with acid indigestion/heartburn including at night (reflux)."

¶excluded – after discussion it was concluded that these items could be put under the generic survival term of item number 40 "overall survival."

short term complications (some of which are included in the proposed COS described here—eg, respiratory complications, conduit necrosis and anastomotic leak and nutritional problems) and there remains a need for a clinical effectiveness outcome set to use in pragmatic trials, which includes the views of patients about long term outcomes. To our knowledge, this is the first COS to be developed for esophageal cancer resection surgery. It is recommended that the outcome domains included in the COS are measured and reported in all clinical effectiveness trials of esophageal cancer resection surgery. This includes studies of primary esophagectomy or esophagectomy after neoadjuvant chemotherapy in patients with esophageal, esophagogastric junctional adenocarcinoma, squamous cell carcinoma, or high grade dysplasia (final pretreatment tumor stage between high grade dysplasia and T4aN1M0). The COS may also be suitable for other studies and audits of esophageal cancer resection surgery. There may be a place to develop a COS that can be used for other types of treatment for esophageal cancer (eg, chemotherapy or radiotherapy) or a generic core set with additional items for specific subsets of patients undergoing particular treatments. We would encourage further work in this area although the initial challenge is to promote the widespread use of the COS to improve data synthesis.

Although there is no universally agreed methodological approach to COS development, a recent review showed that studies are adopting a more structured approach, typically involving a systematic literature review and consensus methods (such as Delphi, nominal group) to assess and develop agreement among key stakeholders;[26] methods that were used in the current study. The Delphi technique is frequently used to achieve consensus, enabling participants to vote anonymously and without direct interaction, thereby avoiding situations where the group may be dominated by specific individuals, and enabling participants to change their ratings in light of others' opinions.[17] Patient involvement in COS development is key to ensuring that clinical effectiveness trials evaluate the benefits and harms of treatment from both a clinical and patient perspective but is often overlooked.[17] This may lead to the exclusion of important outcomes.[9,26] In this study, stakeholders were sampled to include participants with knowledge of the benefits and harms of esophageal cancer resection surgery, including patients and specialist professionals. Participants' characteristics reflected a typical broad range (eg, for patients: age, sex, educational background, marital status, length of hospital stay, experience of neoadjuvant treatment; and for professionals: age, sex, specialty/job title, experience). All participants had undergone primary esophagectomy or esophagectomy after neoadjuvant chemotherapy or chemoradiotherapy between 1 month and 5 years previously. It is likely that this sample would include participants with a range of experiences postoperatively, including participants who are healthy, those with varying types and severity of symptoms and those with recurrent disease, though it is possible that recruiting an even more diverse sample of participants (eg, patients' partners or close family) may have resulted in different outcomes being included in the COS. The number of participants in this study is in keeping with that of similar studies,[23,24] and response rates throughout the different phases of this study were high; a factor considered integral to maximizing the quality of studies that use the Delphi process to develop COSs.[17]

This study has some limitations. It did not involve international participants. However, a comprehensive long list of 901 possible outcomes that could be reported after esophageal cancer resection surgery was identified from multiple sources, including systematic reviews of clinical and patient-reported outcomes reported in the international literature.[4,5,20] At present, this study provides the best evidence on which to base recommendations, but should be repeated in other countries and settings to validate the COS more widely. The COS developed in the present study is intended to complement the core information set (CIS). Similar items included in the CIS were long-term survival, in-hospital death, chances of inoperability, information about major complications, impact on eating and drinking in the longer term, and long-term overall quality of life.

Participants demonstrated difficulty prioritizing items after 2 survey rounds and therefore more stringent cutoff criteria were applied in round 2. It is possible that the use of different criteria in Rounds 1 and 2 may have impacted on the content of the final COS, although it was important to ensure that the consensus meeting was not overwhelmed with too many items for discussion. Items rated highly by patients but not professionals (and that were

TABLE 4. Rating of Items in Round 2*

Item	Item Description (n = 43)	Median (Range)	% of Patients Rating Item (n = 94) 8–9†	1–3†	Outcome	Median (Range)	% of Professionals Rating Item (n = 67) 8–9†	1–3†	Outcome	Taken Forward to Patient Consensus Meeting
1	Usual activities and enjoy physical activities	9 (7–9)	96.7	0.0	essential	8 (7–9)	89.2	0.0	essential	yes
2	Eat and drink more easily	9 (7–9)	94.6	0.0	essential	8 (5–9)	84.6	0.0	essential	yes
3	Swallow without pain	9 (7–9)	94.6	0.0	essential	8 (2–9)	78.5	3.3	essential	yes
4	Enjoy healthy balanced eating pattern	9 (6–9)	88.2	0.0	essential	8 (2–9)	60.0	1.6	essential	yes
5	Reflux	8 (5–9)	89.2	0.0	essential	8 (2–9)	52.3	1.6	essential	yes
6	Problems eating socially	8 (1–9)	68.8	3.3	not essential	7 (4–9)	47.7	0.0	not essential	no
7	Regurgitation/vomiting‡	8 (1–9)	79.6	3.3	essential	8 (5–9)	49.2	0.0	not essential	no
8	Difficulties breathing‡	8 (4–9)	76.3	0.0	essential	7 (5–9)	39.1	0.0	not essential	no
9	Appetite loss	8 (1–9)	60.2	3.3	not essential	7 (2–9)	33.8	1.6	not essential	no
10	Dumping	8 (1–9)	67.4	3.4	not essential	7 (5–9)	43.1	0.0	not essential	no
11	Diarrhoea	8 (2–9)	68.8	2.2	not essential	7 (2–0)	40.0	1.6	not essential	no
12	Good general health	9 (5–9)	88.0	0.0	essential	8 (4–9)	75.4	0.0	essential	yes
13	General pain discomfort	8 (1–9)	67.7	1.1	not essential	7 (4–9)	30.8	0.0	not essential	no
14	Fatigue‡	8 (2–9)	73.1	1.1	essential	7 (4–9)	44.6	0.0	not essential	no
15	Feeling in control of weight/ appearance	8 (2–9)	67.0	1.1	not essential	7 (3–8)	29.2	3.3	not essential	no
16	Feeling satisfied and confident with one's body	8 (4–9)	59.6	0.0	not essential	7 (2–9)	29.2	3.3	not essential	no
17	Relationships with family/friends‡	8 (6–9)	80.9	0.0	essential	8 (4–9)	50.0	0.0	not essential	no
18	Cognitive function‡	8 (1–9)	75.3	4.4	essential	7 (5–9)	35.4	0.0	not essential	no
19	Overall quality of life	9 (5–9)	91.5	0.0	essential	9 (8–9)	100.0	0.0	essential	yes
20	Overall survival	9 (7–9)	97.8	0.0	essential	9 (7–9)	98.4	0.0	essential	yes
21	Inoperability	9 (1–9)	92.5	2.2	essential	9 (5–9)	89.2	0.0	essential	yes
22	Organ injury‡	8 (1–9)	83.9	1.1	essential	7 (4–9)	47.7	0.0	not essential	no
23	Hemorrhage‡	8 (1–9)	83.9	1.1	essential	7 (3–9)	47.7	1.6	not essential	no
24	Chyle/pleural leak	8 (4–9)	86.0	0.0	essential	8 (4–9)	78.5	0.0	essential	yes
25	Anastomotic leak	9 (1–9)	91.4	1.1	essential	9 (7–9)	98.5	0.0	essential	yes
26	Conduit necrosis	9 (1–9)	93.5	1.1	essential	9 (7–9)	96.9	0.0	essential	yes
27	Reinsertion of drains	8 (4–9)	62.4	0.0	not essential	7 (3–9)	18.5	1.6	not essential	no
28	Laryngeal nerve palsy‡	8 (1–9)	82.8	1.1	essential	7 (4–9)	47.7	0.0	not essential	no
29	Wound infection‡	8 (1–9)	71.0	2.2	essential	7 (3–8)	13.8	1.6	not essential	no
30	Cardiac complications‡	9 (1–9)	76.3	2.2	essential	7 (4–9)	43.1	0.0	not essential	no
31	Renal complications‡	8 (1–9)	72.0	2.2	essential	7 (4–9)	24.6	0.0	not essential	no
32	Cerebral complications‡	9 (1–9)	76.3	2.2	essential	7 (3–9)	35.4	1.6	not essential	no
33	Liver failure‡	9 (1–9)	77.4	2.2	essential	7 (3–9)	23.1	3.3	not essential	no
34	Respiratory complications	9 (1–9)	81.7	1.1	essential	8 (4–9)	55.4	0.0	essential	yes
35	Deep vein thrombosis; Pulmonary embolism	9 (1–9)	83.7	2.2	essential	8 (4–9)	56.9	0.0	essential	yes
36	Re-ventilation	9 (1–9)	90.3	1.1	essential	8 (4–9)	78.5	0.0	essential	yes
37	In-hospital mortality	9 (1–9)	96.8	2.2	essential	9 (7–9)	98.5	0.0	essential	yes
38	Severe problems related to nutrition	8 (3–9)	78.3	1.1	essential	8 (4–9)	60.9	0.0	essential	yes
39	Empyema‡	8 (1–9)	79.3	1.1	essential	7 (1–9)	46.9	3.3	not essential	no
40	Abdominal hernia	8 (1–9)	65.9	1.1	not essential	6 (1–9)	15.6	3.3	not essential	no
41	Colonic interposition	9 (1–9)	90.0	1.1	essential	8 (4–9)	79.7	0.0	essential	yes
42	Diaphragmatic hernia repair‡	9 (1–9)	89.1	1.1	essential	7 (3–9)	37.5	1.7	not essential	no
43	Need for another operation	9 (1–9)	90.2	1.1	essential	8 (–9)	64.1	0.0	essential	yes

*Items ordered as they appeared in the Round 2 questionnaire.

†Items were categorized as "essential" and retained for the consensus meeting if they met the following cutoff criteria: (i) rated 8–9 by ≥70% and 1–3 by <15% of patients, and; (ii) rated 8–9 by >50% and 1–3 by <15% of health professionals.

‡Discordant items, rated as essential by patients but not professionals.

discarded when more stringent criteria were applied) were, however, predominantly related to outcomes that were covered by other retained items or to less common adverse events. Patients may have rated these items highly because they did not have the clinical knowledge that these items were less common. Items related to rarer adverse events were not considered to be of relevance to a COS intended for use as a minimum dataset for effectiveness trials of esophageal cancer resection surgery. One alternative to using more

TABLE 5. Final Outcome of 19 Items Taken Forward to Consensus Meeting (in Descending Order of the Percentage of Patients Voting the Item IN the Final COS)

Item Description	% Patients Voting Item IN, OUT, or UNSURE*			Decision After Voting	Final Decision Following Discussion and Second Vote
	IN	OUT	UNSURE		
Overall survival	n/a	n/a	n/a	n/a	IN
Inhospital mortality	n/a	n/a	n/a	n/a	IN
Overall quality of life	n/a	n/a	n/a	n/a	IN
Conduit necrosis	n/a	n/a	n/a	n/a	IN†
Anastomotic leak	n/a	n/a	n/a	n/a	IN†
Being able to carry out usual activities and participate /enjoy physical activities	95	5	0	IN	IN‡
Having good general health	75	0	25	IN	IN‡
Being able to eat/drink more easily	90	0	10	IN	IN§
Being able to swallow without pain	85	0	15	IN	IN§
Inoperability	85	0	15	IN	IN
Respiratory complications (infection, collapsed lung)	85	5	10	IN	IN
Need for another operation	85	5	10	IN	IN
Severe problems related to nutrition	80	10	10	IN	IN
Problems with acid indigestion/heartburn, including at night (reflux)	70	5	25	IN	IN
Reventilation (need to go to ITU on breathing machine)	65	15	20	UNSURE	OUT¶
Colonic interposition	60	5	35	UNSURE	OUT‖
Chyle/pleural leak	55	15	30	OUT	OUT‖
Deep vein thrombosis; Pulmonary embolism	45	20	35	OUT	OUT
Able to enjoy healthy/balanced eating pattern	45	30	25	OUT	OUT

COS, core outcome set; ITU, intensive treatment unit; n/a, 'Top 5' items rated 8–9 by >90% of patients and professionals in Round 2 and therefore not voted on at consensus meeting.

*IN: voted ''in'' by ≥70% of participants; OUT: voted ''in'' by <60% and ''out'' by ≥15% of participants; UNSURE: voted ''in'' by 60–69% of participants.

†Items combined to form a single item—conduit necrosis and anastomotic leak.

‡Items incorporated into overall quality of life.

§Items combined to form a single item—the ability to eat and drink.

¶Items incorporated into 'respiratory complications'.

‖Items incorporated in to 'the need for another operation, at any time.

stringent cutoff criteria would have been to conduct a third survey round but this was outside of the scope of this study and was considered unlikely to result in many more items being discarded as participants had already demonstrated difficulty prioritizing. Finally, a decision was made not to hold a professionals' consensus meeting because the patient meeting proposed a COS comprising 10 outcomes, which encompassed all items that >50% of professionals had rated highly (8–9). This is supported by the findings from the endorsement survey, in which all responding professionals indicated support for the content and use of the COS. Furthermore, seeking endorsement enabled a greater number of professionals to be surveyed than would have been possible to include in a consensus meeting.

TABLE 6. Final Core Outcome Set for Esophageal Cancer Resection Surgery

1. Overall survival
2. Inhospital mortality
3. Inoperability
4. The need for another operation related to their primary esophageal cancer resection surgery
5. Respiratory complications
6. Conduit necrosis and anastomotic leak
7. Severe nutritional problems
8. The ability to eat and drink
9. Problems with acid indigestion or heartburn
10. Overall quality of life

The development of this COS seeks to promote the standardized selection and reporting of outcomes and thereby facilitate the robust evaluation of esophageal cancer resection surgery, which is currently inconsistent and lacks standard methodology.[4] Further work is now needed to explore best methods for measuring the individual outcomes included in the COS, including work to delineate the definitions and parameters of the individual outcomes and to inform the selection of validated measurement instruments for the assessment of patient-reported outcomes. It will also be important in the future to evaluate the uptake and use of this COS in standardizing the selection and reporting of outcomes across clinical trials of esophageal cancer resection surgery.[27]

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