



Avery, K. N. L., Chalmers, K. A., Brookes, S. T., Blencowe, N. S., Coulman, K., Whale, K., ... the ROMIO Study Group (2018). Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. *Annals of Surgery*, 267(4), 700-710.  
<https://doi.org/10.1097/SLA.0000000000002204>

Peer reviewed version

Link to published version (if available):  
[10.1097/SLA.0000000000002204](https://doi.org/10.1097/SLA.0000000000002204)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Wolters Kluwer at [http://journals.lww.com/annalsofsurgery/Abstract/publishahead/Development\\_of\\_a\\_Core\\_Outcome\\_Set\\_for\\_Clinical.96178.aspx](http://journals.lww.com/annalsofsurgery/Abstract/publishahead/Development_of_a_Core_Outcome_Set_for_Clinical.96178.aspx). Please refer to any applicable terms of use of the publisher.

## **University of Bristol - Explore Bristol Research**

### **General rights**

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/pure/about/ebr-terms>

## **Development of a core outcome set for clinical effectiveness trials in esophageal cancer resection surgery**

Kerry N. L. Avery PhD<sup>1\*</sup>, Katy A. Chalmers PhD<sup>1</sup>, Sara T. Brookes PhD<sup>1</sup>, Natalie S. Blencowe PhD<sup>1</sup>, Karen Coulman PhD<sup>1</sup>, Katie Whale DHealthPsy<sup>1</sup>, Chris Metcalfe PhD<sup>1,2</sup>, Jane M. Blazeby MD<sup>1,3</sup> on behalf of the ROMIO study group<sup>4</sup> and the CONSENSUS (Core Outcomes and iNformation SEts iN SURgical Studies) Esophageal Cancer working group<sup>5</sup>

<sup>1</sup>Centre for Surgical Research, School of Social and Community Medicine, University of Bristol, United Kingdom;

<sup>2</sup>Bristol Randomised Trials Collaboration, University of Bristol, Bristol, United Kingdom.

<sup>3</sup>Division of Surgery, Head and Neck, University Hospitals Bristol NHS Foundation Trust, Bristol, UK;

<sup>4</sup>The ROMIO study group comprises co-applicants on the ROMIO feasibility study (funded by the National Institute for Health Research Health Technology Assessment Programme, project number 10/50/65) who contributed to the conception and design of the study and assisted in the acquisition and interpretation of data and who are listed here in alphabetical order: C Paul Barham (University Hospitals Bristol NHS Foundation Trust, UK), Richard Berrisford (Plymouth Hospitals NHS Trust, UK), Jenny Donovan (University of Bristol, UK), Jackie Elliott (Bristol Gastro-Oesophageal Support and Help Group, UK), Stephen Falk (University Hospitals Bristol NHS Foundation Trust, UK), Robert Goldin (Imperial College London, UK), George Hanna (Imperial College London, UK), Andrew Hollowood (University Hospitals Bristol NHS Foundation Trust, UK), Sian Noble (University of Bristol, UK), Grant Sanders (Plymouth Hospitals NHS Trust, UK), Tim Wheatley (Plymouth Hospitals NHS Trust, UK);

<sup>5</sup>The CONSENSUS (Core Outcomes and iNformation SEts iN SURgical Studies) Esophageal Cancer working group comprises health professionals who contributed to the design of the study, assisted in the acquisition of data (including participating in at least one round of the Delphi survey) and interpretation of data and are listed here in alphabetical order: Derek Alderson (University Hospitals

Birmingham NHS Foundation Trust, UK), Bilal Alkhaffaf (Central Manchester University Hospitals NHS Foundation Trust, UK), William Allum (The Royal Marsden NHS Foundation Trust, UK), Stephen Attwood (Northumbria Healthcare NHS Foundation Trust, UK), Hugh Barr (Gloucestershire Hospitals NHS Foundation Trust, UK), Issy Batiwalla (North Bristol NHS Trust, UK), Guy Blackshaw (University Hospital of Wales, UK), Marilyn Bolter (Plymouth Hospitals NHS Trust, UK), Abrie Botha (Guy and St Thomas' NHS Foundation Trust, UK), Jim Byrne (University Hospitals Southampton NHS Foundation Trust, UK), Joanne Callan (Heart of England NHS Foundation Trust, UK), Graeme Couper (NHS Lothian, UK), Khaled Dawas (University College London Hospitals, UK), Chris Deans (NHS Lothian, UK), Claire Goulding (Plymouth Hospitals NHS Trust, UK), Simon Galloway (South Manchester University Hospitals NHS Trust, UK), Michelle George (Maidstone and Tunbridge Wells NHS Trust, UK), Jay Gokhale (Bradford Teaching Hospitals NHS Foundation Trust, UK), Mike Goodman (The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, UK), Richard Hardwick (Cambridge University Hospitals NHS Foundation Trust, UK), Ahmed Hassn (Princess of Wales Hospital, UK), Mark Henwood (Glangwili General Hospital, UK), David Hewin (Gloucestershire Hospitals NHS Foundation Trust, UK), Simon Higgs (Gloucestershire Hospitals NHS Foundation Trust, UK), Jamie Kelly (University Hospitals Southampton NHS Foundation Trust, UK), Richard Kryzstopik (Royal United Hospitals Bath NHS Trust, UK), Michael Lewis (Norfolk and Norwich University Hospitals NHS Foundation Trust, UK), Colin MacKay (NHS Greater Glasgow and Clyde, UK), James Manson (Singleton Hospital, UK), Robert Mason (Guy and St Thomas' NHS Foundation Trust, UK), Ruth Moxon (Royal Berkshire NHS Foundation Trust, UK), Muntzer Mughal (University College London Hospitals, UK), Sue Osborne (Yeovil District Hospital NHS Foundation Trust, UK), Richard Page (Liverpool Heart and Chest Hospital NHS Foundation Trust, UK), Raj Parameswaran (Leeds Teaching Hospitals NHS Trust, UK), Simon Parsons (Nottingham University Hospitals NHS Trust, UK), Simon Paterson-Brown (NHS Lothian, UK), Anne Phillips (Oxford University Hospitals NHS Foundation Trust, UK), Shaun Preston (Royal Surrey County Hospital NHS Foundation Trust, UK), Kishore Pursnani (Lancashire Teaching Hospitals NHS Foundation Trust, UK), John Reynolds (St James' Hospital, Dublin, Ireland), Bruno Sgromo (Oxford University Hospitals NHS

Foundation Trust, UK), Mike Shackcloth (Liverpool Heart and Chest Hospital NHS Foundation Trust, UK), Jane Tallett (Norfolk and Norwich University Hospitals NHS Foundation Trust, UK), Dan Titcomb (University Hospitals Bristol NHS Foundation Trust, UK), Olga Tucker (Heart of England Birmingham NHS Foundation Trust, UK), Tim Underwood (University of Southampton, UK), Jon Vickers (Salford Royal NHS Foundation Trust, UK), Mark Vipond (Gloucestershire Hospitals NHS Foundation Trust, UK), Lyn Walker (University Hospitals of North Midlands NHS Trust, UK), Neil Welch (Nottingham University Hospitals NHS Trust, UK), John Whiting (University Hospitals Birmingham NHS Foundation Trust, UK), Jo Price (Royal United Hospitals Bath NHS Foundation Trust, UK), Peter Sedman (Hull and East Yorkshire Hospitals NHS Trust, UK), Thomas Walsh (Connolly Hospital, Dublin, Ireland), Jeremy Ward (Lancashire Teaching Hospitals NHS Foundation Trust, UK).

\*Corresponding author: Dr. Kerry N. L. Avery, School of Social and Community Medicine, University of Bristol, 39 Whatley Road, Clifton, Bristol, BS8 2PS, UK. Tel: 0044 (0)117 928 7233. Email: kerry.avery@bristol.ac.uk. Reprints available on request.

## **CONFLICTS OF INTEREST AND SOURCE OF FUNDING**

William Allum receives speaker honoraria from Lilly, Nestle and Taiho and honoraria for consulting/advising on trials for Lilly and Nestle.

This study was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 10/50/65). This work was supported by the Medical Research Council ConDUCT-II (Collaboration and innovation for Difficult and Complex randomized controlled Trials In Invasive procedures) Hub for Trials Methodology Research (MR/K025643/1) (<http://www.bristol.ac.uk/social-community-medicine/centres/conduct2/>). JB is an NIHR Senior Investigator. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the MRC, the NIHR, the NHS or the Department of Health (UK).

**Running head:** Esophageal cancer resection surgery core outcome set

## **MINI-ABSTRACT**

This paper presents a minimum set of outcomes to be reported in all clinical effectiveness trials in esophageal cancer resection surgery – a core outcome set (COS). This evidence-based COS, agreed by patients and professionals, will allow more meaningful comparisons of surgery to be made, improving subsequent clinical decision making.

## STRUCTURED ABSTRACT

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

**Summary background data:** 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 two 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.

**Results:** 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:** Esophageal Neoplasms; Delphi Technique; Outcome Assessment; Randomized Controlled Trial; Surgical Procedures, Operative

## INTRODUCTION

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' (COS), 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 paper 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 three 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 (Figure 1). Overlapping outcomes were merged and outcomes categorized independently by two study researchers into broader health domains, defined as areas of health within the same theme (e.g. 30- and 90-day mortality were grouped into a 'mortality' domain) and, in the absence of established definitions[4], agreed following 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 following neo-adjuvant chemotherapy or chemoradiotherapy between one month and five years previously (01/2015 – 1/2009) were sampled in descending chronological order from lists of patients at two UK 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 two 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 pre-paid 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 pre-specified criteria (see analyses section). The team reviewed retained items to see if any could be further merged due to overlapping content. The participants were not made aware of the pre-specified cut-off 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 pre-paid 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 re-rate 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 prioritise 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 three 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' below) 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 cut-off 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].

Pre-specified 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 re-voted 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 in order 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***

94 professionals (esophagogastric surgeons (n=72) and clinical nurse specialists (n=22)) from 38 different UK hospital trusts and 200 patients from two UK hospital trusts participated in round 1.

### ***Round 1***

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 (for example, '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).

Due to the high percentage of items rated essential by patients in round 1, more stringent criteria were agreed by the study team (JB, SB, NB, KA, KC) 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 (93.1%) 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). Since 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 re-operation (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 (for example '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, UK (September 2015) and attended by 20 (21%) patients from the South-West UK (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 three 'out'. One of these ('re-ventilation') 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 since 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 in-depth 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 six 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 short term complications (some of which are included in the proposed COS described here, e.g. 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 following neo-adjuvant chemotherapy in patients with esophageal, esophago-gastric junctional adenocarcinoma, squamous cell carcinoma or high grade dysplasia (final pre-treatment tumour 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 (e.g. 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.

While 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 (e.g. for patients: age, sex, educational background, marital status, length of hospital stay, experience of neoadjuvant treatment; professionals: age, sex, specialty/job title, experience). All participants had undergone primary esophagectomy or esophagectomy following neo-adjuvant chemotherapy or chemoradiotherapy between one month and five years previously. It is likely that this sample would include participants with a range of experiences post-operatively, 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 (e.g. 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 maximising the quality of studies that use the Delphi process to develop COS[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 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 prioritising items after two survey rounds and therefore more stringent cut-off 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 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 stringent cut-off 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 prioritising. 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.

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].

#### **ACKNOWLEDGEMENTS**

The authors are grateful to all the health professionals and patients who gave up their time to participate in the Delphi surveys and the patient consensus meeting. The authors would also like to thank Claudette Blake and Steve Beech for their administrative support throughout the study.

**REFERENCES**

1. Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world. Effectiveness versus efficacy studies. *Pharmacoeconomics*. 1999;15:423-434.
2. Singal AG, Higgins PDR, Waljee AK. A primer on effectiveness and efficacy trials. *Clin Transl Gastroenterol*. 2014;5:e45.
3. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. Criteria for distinguishing effectiveness from efficacy trials in systematic reviews. In: *Technical Review*. Agency for Healthcare Research and Quality; 2006.
4. Blencowe NS, Strong S, McNair AG, Brookes ST, Crosby T, Griffin SM, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. *Ann Surg*. 2012;255:658-666.
5. Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, et al. Developing core outcome sets: methods for identifying and including patient-reported outcomes (PROs). *Trials*. 2014;15:49.
6. Briez N, Piessen G, Bonnetain F, Brigland C, Carerre N, Collet D, et al. Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial - the MIRO trial. *BMC Cancer*. 2011;11:310-310.
7. Avery KNL, Metcalfe C, Berrisford R, Barham CP, Donovan JL, Elliott J, et al. The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer - the ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial. *Trials*. 2014;15:200-209.
8. Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews? A survey of the Co-ordinating Editors of Cochrane Review Groups. *Trials*. 2013;14:21-25.

9. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132.
10. Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials*. 2007;8:39.
11. Macleod MR, Michie S, Roberts I, Dimagl U, Chalmers I, Ioannidis JP, et al. Biomedical research: increasing value, reducing waste. *Lancet*. 2014;383:101-104.
12. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ*. 2010;340:c365.
13. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative. Available at: <http://www.comet-initiative.org/>. Accessed September 7, 2016.
14. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core outcome set-standards for reporting: the COS-STAR statement. *PLoS Med*. 2016;13:e1002148.
15. The Royal College of Surgeons of England. National Oesophago-Gastric Audit 2013 [NHS website]. 2013. Available at: <http://digital.nhs.uk/catalogue/PUB11093/clin-audi-supp-prog-oeso-gast-2013-rep.pdf>. Accessed September 7, 2016.
16. McNair AG, MacKichan F, Donovan JL, Brookes ST, Avery KNL, Griffin SM, et al. What surgeons tell patients and what patients want to know before major cancer surgery: a qualitative study. *BMC Cancer*. 2016;16:258-265.
17. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Med*. 2011;8:e1000393.
18. Gillies K, Entwistle V, Treweek SP, Fraser C, Williamson PR, Campbell MK. Evaluation of interventions for informed consent for randomised controlled trials (ELICIT): protocol for a

- systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials*. 2015;16:484-493.
19. Potter S, Holcombe C, Ward JA, Blazeby JM, the BRAVO Steering Group: Development of a core outcome set for research and audit studies in reconstructive breast surgery. *Br J Surg*. 2015;102:1360-1371.
  20. Blazeby JM, Macefield R, Blencowe NS, Jacobs M, McNair AGK, Sprangers M, et al. Core information set for oesophageal cancer surgery. *Br J Surg*. 2015;102:936-943.
  21. Brookes ST, Macefield RC, Williamson PR, McNair AG, Potter S, Blencowe NS, et al. Three nested randomized controlled trials of peer-only or multiple stakeholder group feedback within Delphi surveys during core outcome and information set development. *Trials*. 2016;17:409.
  22. *TurningPoint* [voting software]. Ohio: Turning Technologies.
  23. van 't Hooft J, Duffy JM, Daly M, Williamson PR, Meher S, Thom E, et al. A core outcome set for evaluation of interventions to prevent preterm birth. *Obstet Gynecol*. 2016;27:49-58.
  24. Gerritsen A, Jacobs M, Henselmans I, van Huttum J, Efficace F, Creemers GJ, et al. Developing a core set of patient-reported outcomes in pancreatic cancer: a Delphi survey. *Eur J Cancer* 2016;57:68-77.
  25. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy. *Ann Surg*. 2015;262:286-294.
  26. Gorst SL, Gargon E, Clarke M, Blazeby JM, Altman DG, Williamson PR. Choosing important health outcomes for comparative effectiveness research: an updated review and user survey. *PLoS One*. 2016;11:e0146444.

27. Copsey B, Hopewell S, Becker C, Cameron ID, Lamb SE: Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: a case study in fall injury prevention. *Trials*. 2016;17:131-141.

## **ABBREVIATIONS**

COS: core outcome set; DVT: Deep vein thrombosis; ITU: intensive treatment unit; PE: Pulmonary embolism