The Development of a Core Outcome Set for Surgical Trials in Gastric Cancer

A thesis submitted to the University of Manchester for the degree of

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i. Tables

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iii. Abbreviations

AAOS – American Association of Orthopaedic Surgeons

AJCC – American Joint Commission of Cancer

COMET – Core Outcome Measures in Effectiveness Trials

COS – Core Outcome Set

COSMIN – **CO**nsensus-based **S**tandards for the selection of health **M**easurement **I**nstruments

COS-STAD – Core outcome set standards for development

COS-STAR – Core Outcome Set-STAndards for Reporting

CROWN – Core Outcomes in Women's Health

CT – Computerised Tomography

CI – Chief Investigator

DRF – Doctoral Research Fellowship

EMR – Endoscopic Mucosal Resection

ESD – Endoscopic Sub-mucosal Dissection

EUS – Endoscopic Ultrasound

FDG – 2-[fluorine 18] fluoro-2-deoxy-D-glucose

GASTROS – GAstric cancer Surgery Trials Reported Outcomes Standardisation

GCCG – Gastrectomy Complications Consensus Group

GI – Gastro-Intestinal

GIST – Gastro-Intestinal Stromal Tumours

HCP – Healthcare Professionals

HIC – High Income Country

HOG – Health Outcomes Group

HUInc – Health Utilities Inc.

IQOLA – International Quality of Life Assessment

ISPOR-TCA – The Professional Society for Health Economics and Outcomes Research – Translation and Cultural Adaptation group

IWG – International Working Group

KDQOL – Kidney Disease Quality of Life

LMIC – Low- to Middle-Income Country

MDT – Multi-Disciplinary Team

MOT – Medical Outcomes Trust

MRC – Medical Research Council

NET – Neuro-Endocrine Tumours

NICE – National Institute for Health and Care Excellence

NIHR – National Institute for Health Research

NOGCA – National Oesophago-Gastric Cancer Audit

OMERACT – Outcome Measures in Rheumatology

OMERACT – Outcome Measures in Rheumatology Clinical Trials

OMI – Outcome Measurement Instrument

OS – Overall Survival

PET – Positron Emission Tomography

PRO – Patient-reported Outcome

PROM – Patient Reported Outcome Measurement

RCT – Randomised Controlled Trials

SAG – Study Advisory Group

SCC – Squamous Cell Carcinoma

SMG – Study Management Group

SRC – The Survey Research Centre

StEP – Standardised Endpoints in Perioperative Medicine

StEP-COMPAC – Standardised Endpoints in Perioperative Medicine-Core Outcome Measures in Perioperative and Anaesthetic Care

iv. Abstract

The Development of a Core Outcome Set for Surgical Trials in Gastric Cancer

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A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health; September 2020

Background: Gastric cancer is a leading cause of cancer-related deaths worldwide. Whilst surgery is the mainstay of curative treatment, it is associated with significant risks. Identifying optimal surgical strategies for gastric cancer should be based on evidence from well-designed trials. However, inconsistencies in the reporting of outcomes from these trials makes evidence synthesis unreliable. This PhD study aims to address these challenges by developing a core outcome set (COS) – a standardised group of important outcomes – which should be reported as a minimum by future trials in this field.

Methods: The COS was developed over two stages employing methodological principles based on established guidelines from the field of COS development. Stage 1 involved identifying potentially important outcomes from previous trials and a series of patient interviews. In stage 2, potentially important outcomes were prioritised using a Delphi survey which informed a consensus meeting at which the COS was finalised.

Results: 498 outcomes were identified from previously reported trials (n=454) and patient interviews (n=70) and rationalised into 56 items presented in the Delphi survey. International stakeholder participation was facilitated through the establishment of collaborative networks and translation of the surveys using an approach adapted from international guidelines. 952 patients (n=268), surgeons (n=445) and nurses (n=239) from 6 continents enrolled into round 1 of the survey and 662 completed round 2. Demographic and regional differences did not impact on how participants prioritised outcomes in the survey. Following the consensus meeting, 8 outcomes were included in the COS - disease-free survival, disease-specific survival, surgery-related death, recurrence, completeness of tumour removal, overall quality of life, nutritional effects, and complications.

Conclusion: A COS for surgical trials in gastric cancer has been developed with international patients and healthcare professionals. This PhD study has also described key methodological considerations for COS development.

v. Thesis Chapters

Below is an overview of this thesis with an explanation how each section contributes to its stated aims.

Chapter 1. Introduction

Chapter one seeks to provide an overview of gastric cancer, in particular its epidemiology, staging, prognosis and management of potentially curative disease. It describes the current variation in its management and the reasons behind this. It proposes an approach to tackle these problems which forms the basis of the research described in this thesis.

Chapter 2. Standardising the reporting of outcomes in gastric cancer surgery trials: protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study)

Chapter two details the methods used to undertake this study. This is broadly based on guidance developed by the COMET initiative, but also acknowledges methodological contributions from implemented COS in other clinical specialties.

Chapter 3. Reporting of outcomes in gastric cancer surgery trials: a systematic review

The third chapter highlights the current state of outcome reporting in trials examining therapeutic surgical interventions for gastric cancer. It demonstrates the degree of inconsistency in this field and augments the findings of the 'rapid review' undertaken on trials published between January 2014 and January 2016 (described above). The systematic review also served to formulate a long-list of outcomes which were considered for prioritisation later in the study.

Chapter 4. Patient priorities in relation to surgery for gastric cancer: qualitative interviews with gastric cancer surgery patients to inform the development of a core outcome set

This qualitative research piece aimed to understand the priorities set by patients when reporting outcomes and appreciate how these may be different to the views of clinicians and researchers. During this stage, outcomes not identified from the systematic review were supplemented to the long-list to be considered for prioritisation.

Chapter 5. Methods for conducting international Delphi surveys to optimise global participation in Core Outcome Set development: a case study in gastric cancer informed by a comprehensive literature review

Chapter 5 describes a methodological approach to translating Delphi surveys for use in international COS development. It explores variations in current approaches amongst COS developers and describes key considerations aimed at maximising international recruitment to Delphi surveys in this field.

Chapter 6. Exploring the impact of regional variation on outcome prioritisation in core outcome set development: a case study in the field of gastric cancer surgery.

This chapter examines which factors, including regional variations, may influence how stakeholders prioritise outcomes during a Delphi survey. This work aims to highlight the importance of carefully selecting representative stakeholders by study teams developing COS.

Chapter 7. “Vicarious thinking” is a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results.

This chapter explores why Delphi survey participants change scores between rounds. It examines the importance of adopting a Delphi approach rather than a single survey to seek consensus in the development of a COS. This work was the result of a collaboration with two other COS studies.

Chapter 8. A Core Outcome Set for Surgical Trials in Gastric Cancer (GASTROS): International patient and healthcare professional consensus.

Chapter eight reports the final COS as recommended by a consensus meeting of international stakeholders and highlights areas which require further development.

Chapter 9. Discussion

The final chapter consolidates previous discussions from each chapter, focusing on the study’s main findings, significant contributions to research methodology, limitations and future plans for development.

vi. Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

vii. Copyright statement

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viii. Contributions

Author Contribution

All work contained in this thesis is the product of research which I have undertaken to develop a COS for surgical trials in gastric cancer. Chapter 7 is a collaboration with two other COS developers. My contribution to this research is stated in the respective chapter.

All chapters comply with the International Committee of Medical Journal Editors recommendations for authorship and fulfil each of the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Study Management Group

The Study Management Group (SMG) oversaw the day-to-day running of the study and the supervision of my PhD programme. Membership of the SMG included Professors Iain Bruce, Paula Williamson, Anne-Marie Glenny and Jane Blazeby, and Dr Aleksandra Metryka.

Study Advisory Group

The Study Advisory Group (SAG) formed part of the management structure of the wider GASTROS study. The SAG was made up of key stakeholder representatives including patients, oncology nurses and surgeons. The group provided advice on the methodology of the study, general delivery of the study against its stated objectives and ensured that the viewpoints of all stakeholder groups were considered. The SAG included 3 surgeons, 3 nurses and 3 patients.

International Working Group

Research-active collaborators from countries with a significant incidence of gastric cancer were approached to form an International Working Group (IWG). Their responsibilities included local recruitment of Delphi survey participants, seeking regulatory approvals and translating the Delphi survey. Membership of the IWG is described in greater detail in Chapter 5.

ix. Acknowledgements

I would like to acknowledge the support and mentorship of my supervisory team; Professors Iain Bruce, Paula Williamson, Anne-Marie Glenny and Jane Blazeby. Their expertise and pastoral guidance have been vital during my five years of study. I am certain their support will continue and the experience I have gained from them will form the basis of my approach to future research. I would also like to thank Dr Aleksandra Metryka for her coordination of this study; this has been particularly important during periods where my clinical work has taken priority. I would like to thank Dr Rebecca Morris whose guidance during the patient interviews was instrumental. Professor Kevin O'Brien agreed to take on a role as 'Advisor' despite his plans to reduce academic activity. I thank him for his wise words and guidance.

My PhD study has resulted in the development of a large network of supportive colleagues across six continents, without whom this work would not have been possible. Many of these colleagues have become friends who I have collaborated with on several other projects. I would also like to acknowledge the significant contribution of our patients and nurses. These relationships will be vital in ensuring that future research remains relevant to those who stand to gain the most from it.

Finally, I would like to recognise the unending support of my long-suffering wife, Dina, and my children Omar, Safa and Ayah. In addition to her busy position as a highly respected consultant radiologist, Dina has provided the necessary stability at home that has enabled me to undertake my research which has included extensive travel to meetings both nationally and internationally. As a result of the combined pressures of this study and a busy clinical job, my family have had to endure lost weekends, evenings, and school holidays. Without their sacrifice and support, I would not have been able to complete this work.

x. Preface

I undertook my undergraduate medical studies at the University of Manchester graduating in 2003. Having been exposed from an early age to the excitement and challenges of surgery (my father is a vascular surgeon) I knew that this was a path that I wanted to follow. As a result of guidance and mentorship from several surgeons in the region, I pursued a career in oesophago-gastric surgery and gained entry onto the specialist register in September 2013.

In October 2013, I was appointed as a consultant oesophago-gastric (OG) surgeon at Manchester University NHS Foundation Trust. At around the same time, I had been heavily involved in gathering and analysing outcome data related to oesophageal and gastric cancer surgery at the centre. This work was the basis of our unit's submission to a publicly reported national audit and informed the reconfiguration of OG cancer services in Manchester.

One of the significant challenges I came across during this exercise was understanding which outcomes to collect and report. It was clear that publicly available outcomes data may not necessarily be relevant to or easily understood by patients. In addition, data which may provide further context to how well a centre was performing was not routinely collected. As my interest in outcomes reporting grew, it became apparent that these issues were not confined to national audit and service reviews but extended to the field of clinical trials. These challenges would impact on the evidence produced by trials and ultimately our daily practice.

To support my educational development in this area, I attended the 4th meeting of the Core Outcome Measures in Effectiveness Trials (COMET) Initiative in Rome during November 2014. On the flight out, I was fortuitously seated next to Professor Iain Bruce, Consultant Paediatric Ear, Nose and Throat Surgeon who was delivering a lecture at the meeting. We began talking about his work on core outcome sets (COS) and how it could be applied to OG surgery. I was already aware that there was work being undertaken by Professor Jane Blazeby (Bristol) to develop a COS in oesophageal cancer surgery, but also knew that a gap in the field of gastric cancer surgery existed. At the meeting I had the opportunity to talk to Professor Blazeby about supporting a gastric surgery COS. She agreed and introduced me to Professor Paula Williamson from COMET.

Within 8 weeks of the Rome meeting, a supervisory team had been assembled and an application was submitted for a National Institute for Health Research Doctoral Research Fellowship grant to support this work. The application was successful, and I was able to begin my PhD research at the University of Manchester in October 2015, on a part-time basis alongside a busy clinical job.

xi. Thesis Format

I have been granted permission to submit this Ph.D. thesis in a 'journal format' by my supervisors Professors Iain Bruce, Paula Williamson and Anne-Marie Glenny. The thesis conforms to the guidelines described in the University of Manchester's 'Presentation of Theses Policy' (July 2020).

The following chapters in this thesis have been published or submitted for publication:

Chapter	Status
Chapter 1. Introduction	Submitted as a book chapter.
Chapter 2. Standardising the reporting of outcomes in gastric cancer surgery trials: protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study). Alkhaffaf B, Glenny AM, Blazeby JM, Williamson PR, Bruce IA. Trials. 2017 Aug 9;18(1):370. doi: 10.1186/s13063-017-2100-7.	Published
Chapter 3. Reporting of outcomes in gastric cancer surgery trials: a systematic review. Alkhaffaf B, Blazeby JM, Williamson PR, Bruce IA, Glenny AM. BMJ Open 2018;8:e021796. doi: 10.1136/bmjopen-2018-021796	Published
Chapter 4. Patient priorities in relation to surgery for gastric cancer: qualitative interviews with gastric cancer surgery patients to inform the development of a core outcome set. Alkhaffaf B, Blazeby JM, Bruce IA, Morris R BMJ Open 2020;10:e034782. doi: 10.1136/bmjopen-2019-034782	Published
Chapter 5. Methods for conducting international Delphi surveys to optimise global participation in Core Outcome Set development: a case study in gastric cancer informed by a comprehensive literature review	Unpublished

Chapter	Status
Chapter 6. Exploring the impact of regional variation on outcome prioritisation in core outcome set development: a case study in the field of gastric cancer surgery.	Unpublished
Chapter 7. "Vicarious thinking" is a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results. Fish R, MacLennan S, Alkhaffaf B, Williamson PR J Clin Epidemiol. 2020 Dec;128:118-129. doi: 10.1016/j.jclinepi.2020.09.028. Epub 2020 Oct 1.	Published
Chapter 8. A Core Outcome Set for Surgical Trials in Gastric Cancer (GASTROS): International patient and healthcare professional consensus.	Unpublished

xii. Publications

The following publications have resulted from work undertaken for this doctoral thesis.

1. **Standardising the reporting of outcomes in gastric cancer surgery trials: protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study).**
   Alkhaffaf B, Glenny AM, Blazeby JM, Williamson PR, Bruce IA.
   Trials. 2017 Aug 9;18(1):370. doi: 10.1186/s13063-017-2100-7.

2. **Reporting of outcomes in gastric cancer surgery trials: a systematic review.**
   Alkhaffaf B, Blazeby JM, Williamson PR, Bruce IA, Glenny AM.
   BMJ Open 2018;8:e021796. doi: 10.1136/bmjopen-2018-021796

3. **Patient priorities in relation to surgery for gastric cancer: qualitative interviews with gastric cancer surgery patients to inform the development of a core outcome set.**
   Alkhaffaf B, Blazeby JM, Bruce IA, Morris R
   BMJ Open 2020;10:e034782. doi: 10.1136/bmjopen-2019-034782

4. **"Vicarious thinking" is a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results.**
   Fish R, MacLennan S, Alkhaffaf B, Williamson PR
   J Clin Epidemiol. 2020 Dec;128:118-129. doi: 10.1016/j.jclinepi.2020.09.028. Epub 2020 Oct 1.

xiii. Funding

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Disclaimer

This thesis presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

xiv. Study Logo & Online Information

Logo

GASTROS

Standardising Outcome Reporting in Gastric Cancer Surgery Research

Website

www.GASTROSstudy.org

Twitter Handle

www.twitter.com/GASTROSstudy

xv. Ethical Approvals & NIHR Portfolio adoption

The necessary ethical approvals were obtained for this study.

Patient interviews (chapter 4)

Ethical approval was obtained from the National Research Ethics Service North West—Cheshire (11/NW/0739) and governance approvals by Central Manchester University Hospital NHS Foundation Trust. The study was adopted by the National Institute for Health Research (NIHR) Clinical Research Network Portfolio (ID 33312).

International Delphi survey (chapters 5-7)

Ethical approval was obtained from the North West - Greater Manchester East Research Ethics Committee (18/NW/0347) and governance approvals by Manchester University Hospitals NHS Foundation Trust. The study was adopted by the National Institute for Health Research (NIHR) Clinical Research Network Portfolio (ID 38318).

1 Introduction

Author

Bilal Alkhaffaf

Publication status

Submitted as a book chapter in the ‘Oxford Textbook of Surgery’.

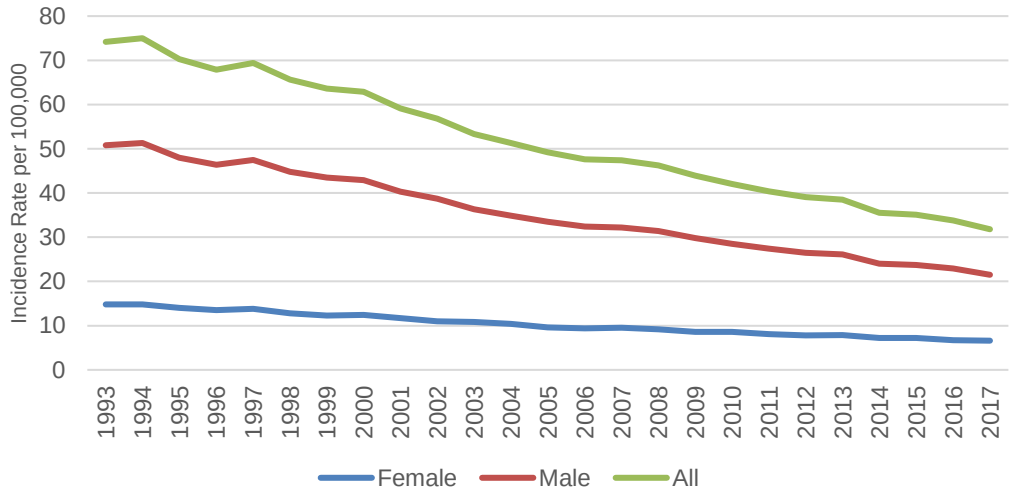
1.1 Defining Gastric Cancer

The term ‘gastric cancer’ is sometimes used to describe a number of potentially life-threatening neoplasia which arise in the stomach. These include adenocarcinoma, squamous cell carcinoma (SCC), lymphoma, gastro-intestinal stromal tumours (GIST) and neuro-endocrine tumours (NET)[1]. Adenocarcinoma, which makes up 95 per cent of all stomach neoplasia, is what is commonly referred to as ‘gastric cancer’ amongst healthcare professionals and researchers. Squamous cell carcinoma of the stomach is extremely rare (less than 0.1 per cent of all stomach neoplasia[2]), but as its treatment is broadly similar to adenocarcinoma, it is also encompassed by the term ‘gastric cancer’. Lymphomas, GISTs and NETs make up the remaining 5 per cent of neoplasia but as their treatment approaches differ significantly, they are usually considered as separate entities. For the purpose of this thesis, the term ‘gastric cancer’ refers to primarily adenocarcinoma but also includes the rarer SCC.

1.2 Overview of Gastric Cancer

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer related-deaths worldwide[3]. Over the last three decades, there has been a steady decline in its incidence in the United Kingdom (figure 1), most likely as a consequence of the recognition of important risk factors such as Helicobacter Pylori infection, smoking, high salt intake and other environmental factors[4]. Despite this, evidence suggests that the absolute number of new cases per year is beginning to increase in some parts of the world, primarily due to increasing and aging populations. Figure 2 illustrates an example of such trends in Japan[5]. As such, gastric cancer will continue to contribute significantly to cancer-related mortality for the foreseeable future.

Figure 1-1 Trends in the incidence of gastric cancer in the United Kingdom. Reproduced with permission from Cancer Research UK.



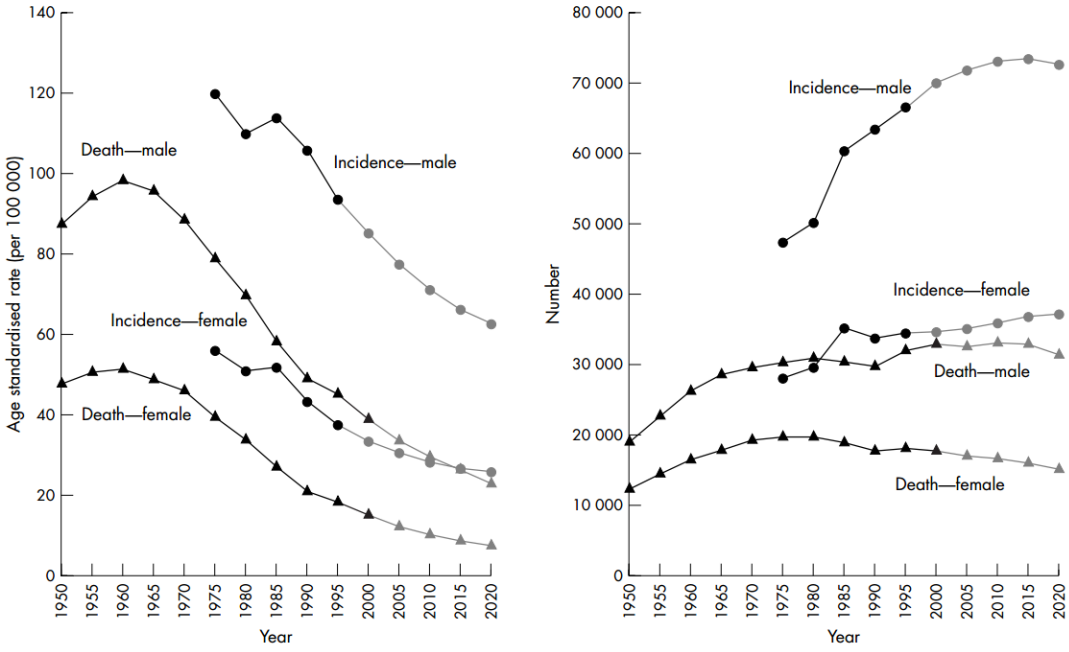


Figure 1-2 Trends in the incidence and death from gastric cancer diagnoses in Japan[5]. Reproduced by permission from Copyright Clearance Center on behalf of the Postgraduate Medical Journal, Epidemiology of gastric cancer in Japan, M Inoue,S Tsugane, Volume 81, Copyright 2005, with permission from BMJ Publishing Group Ltd.

1.3 Changes in tumour characteristics

Despite the recent period of decline in gastric cancer rates, there has been sharp and dramatic rise in the incidence of neoplasia of the proximal stomach[6]. One theory to explain this change proposes that carcinoma of the proximal stomach is a different entity than cancer of other parts of the stomach and has more in common with oesophageal adenocarcinoma, which has quickly become the fastest-growing cancer in the Western World[7]. In this respect, there are strong parallels in the male predominance and associated demographic and pathological risk factors such as obesity, proliferation of the 'Western diet' and the increasing incidence of chronic gastro-oesophageal reflux disease[6]. These changes in tumour characteristics will have a direct impact on the types of treatments available to patients which tends to be more radical when compared to treatment for distal gastric cancers (total gastrectomy versus partial gastrectomy), and as a consequence lead to greater post-therapy morbidity.

1.4 Tumour Sub-types

Recent research on human genomes has highlighted the degree of heterogeneity existing amongst gastric adenocarcinoma. It is now accepted that there are numerous, distinct sub-types of gastric cancer, sometimes occurring within the same lesion, but each with its own unique genetic expression, response to treatment and, ultimately, prognosis[8]. As research within this field develops, so will the possibility of being able to move away from a 'one-size

fits all' approach to treatment and more towards individualising treatments with the aim of improving prognosis.

1.5 Geographical variation

There are large regional variations in the incidence of gastric cancer (figure 3). By far the highest incidence occurs in the East Asian sub-continent with the leading countries being South Korea, Mongolia and Japan (age-standardised incidence rates of 42, 33 and 30 per 100,000 population, respectively). This incidence is higher still in men (age-standardised incidence rates of 62, 47 and 46 per 100,000 population, respectively). Although the incidence in the United Kingdom is significantly lower (age-standardised incidence of 12 per 100,000) its impact is no less significant on the 7,000 patients who are diagnosed annually[9]. Although, no single factor has been identified to account for these variations, there is a suggestion that environmental factors are significantly influential given that migrant populations from high-incidence regions such as Japan show a marked reduction in risk when they move to low-incidence regions such as the US. Furthermore, the risk of subsequent generations reduces to that of the regional population[10].

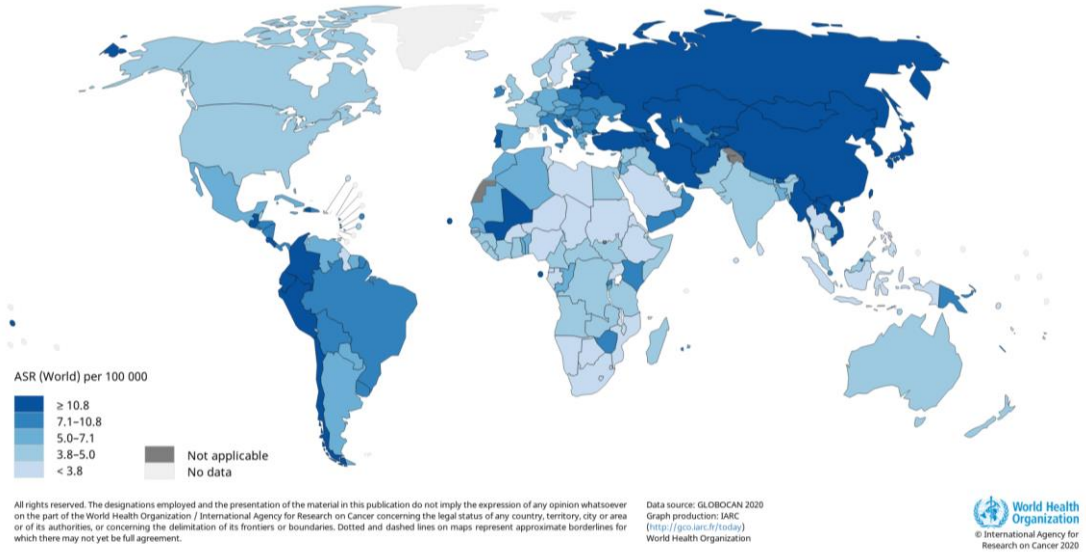


Figure 1-3 Global variations in gastric cancer incidence[3]. Reproduced from The Global Cancer Observatory - All Rights Reserved, December, 2020.

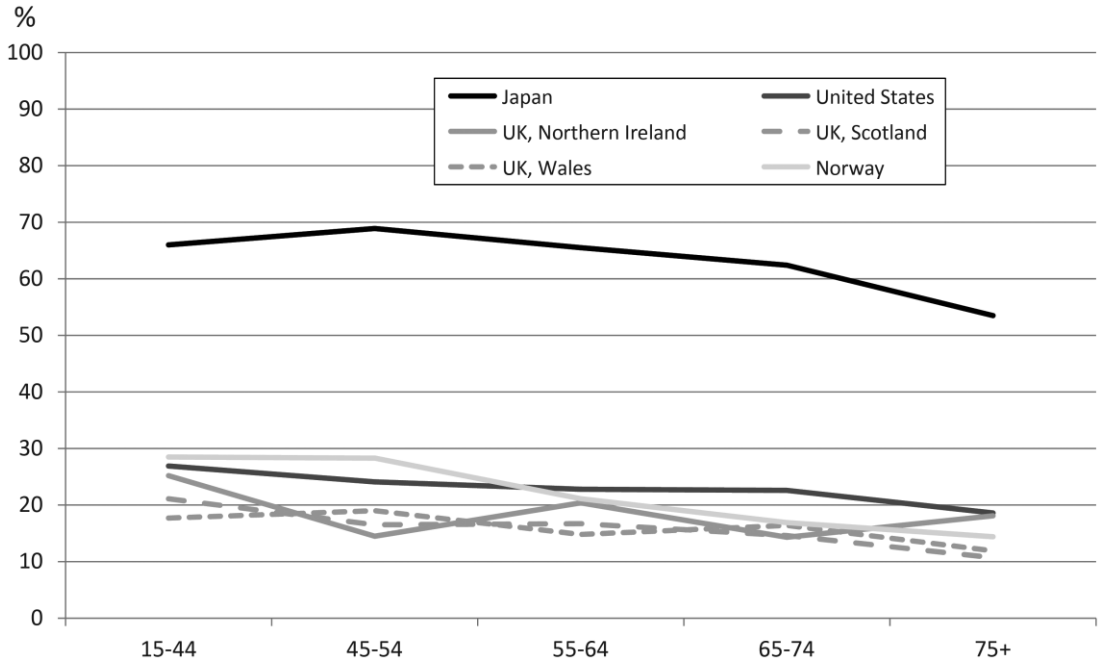
These geographical variations have important implications, particularly in high-risk populations, where strategies to detect early stage disease have been implemented to improve survival from gastric cancer. Both South Korea and Japan have been able to implement endoscopic population-screening programmes, although the overall impact of these policies has not been unequivocally established[11]. Nonetheless, there is evidence to suggest that screening has led to an increase in early stage diagnosis (table 1) and a subsequent improvement in survival rates in these populations (5-year survival in the UK 19% versus Japan 60% (figure 4)).

Endoscopic screening would not be a viable proposition in the UK given the significantly lower incidence of gastric cancer which would make it financially inhibitive. However, progress is being made on alternative, cheaper and readily available screening methods such as testing of serum-pepsinogen levels to target high-risk subgroups of patients[12].

Table 1.1 Comparison of disease location in patients screened and not screened for gastric cancer in Korea[13]. Adapted and reprinted by permission from Copyright Clearance Center on behalf of Cancer Research UK, Springer Nature, British Journal of Cancer, (Effect of endoscopy screening on stage at gastric cancer diagnosis: results of the National Cancer Screening Programme in Korea. Choi, K S; Jun, J K; Suh, M; Park, B; Noh, D K; Song, S H; Jung, K W; Lee, H-Y; Choi, I J; Park, E-C; Dr JK Jun), Copyright 2015.

Stage	Never screened	Screened
Localised	3264 (40.6)	4326 (53.8)
Regional	2372 (29.5)	1905 (23.7)
Distant	1134 (14.1)	660 (8.2)
Unknown	1274 (15.8)	1153 (14.3)

Figure 1-4 5-year survival rates for men with gastric cancer according to region[14]. Reprinted by permission from Copyright Clearance Center on behalf of the Japanese Journal of Clinical Oncology (The 5-Year Relative Survival Rate of Stomach Cancer in the USA, Europe and Japan, Tomohiro Matsuda, Kumiko Saika), Copyright 2013.



1.6 Diagnosis & Staging

Common symptoms associated with gastric cancer, such as nausea, dyspepsia, reflux, weight loss and lethargy (particularly secondary to iron-deficiency anaemia) can be attributable to a wide variety of other diseases. Consequently, these symptoms may remain un-investigated, leading to a delay in diagnosis. 'Red-flag' signs including vomiting from gastric-outlet obstruction, dysphagia and hematemesis generally indicate well-established disease, and as a consequence the majority of patients (66 per cent in the UK) have metastatic disease at the time of diagnosis[15].

The pathway for diagnosis usually begins with referral for upper gastro-intestinal endoscopy. In the UK, the National Institute for Health and Care Excellence (NICE) provides guidance for referral practice from primary care[16]. For example, urgent referral for upper-gastrointestinal endoscopy should be made for patients:

- with dysphagia **or**
- aged 55 and over with weight loss **and** any of the following:
    - upper abdominal pain
    - reflux
    - dyspepsia.

Once gastric cancer is suspected endoscopically and/or confirmed histologically, a Computerised Tomography (CT) scan is undertaken to assess the local tumour staging and detect distant metastatic spread. Staging of gastric cancer is based on the American Joint Commission of Cancer (AJCC) TNM system outlined in table 2[17]. Further investigations, such as magnetic resonance imaging (particularly of the liver), bones scan and fine-needle aspiration cytology under radiological or endoscopic ultrasound (EUS) guidance, may be required to further characterise equivocal lesions picked up on CT scan.

Consideration of all investigations and patient factors is undertaken in a specialist multi-disciplinary team (MDT) setting which involves surgeons, gastroenterologists, medical and clinical oncologists and several other clinical stakeholders. If the MDT decision is that the patient is suitable, fit and willing to undergo treatment with the intention of cure, a further procedure – staging laparoscopy – may be required to exclude metastatic disease undetected on CT-scan, which can occur in 13-57 per cent of cases[18].

Table 1.2 Staging of gastric cancer per prognostic group according to the 7th edition of the AJCC cancer staging manual[17]. Reprinted by permission from Copyright Clearance Center on behalf of the Springer, Annals of Surgical Oncology (7th Edition of the AJCC Cancer Staging Manual: Stomach, Kay Washington), Copyright 2010.

Stage 0	**Tis**	**N0**	**M0**
Stage IA	**T1**	**N0**	**M0**
Stage IB	**T2**	**N0**	**M0**
	T1	**N1**	**M0**
Stage IIA	**T3**	**N0**	**M0**
	T2	**N1**	**M0**
	T1	**N2**	**M0**
Stage IIB	**T4a**	**N0**	**M0**
	T3	**N1**	**M0**
	T2	**N2**	**M0**
	T1	**N3**	**M0**
Stage IIIA	**T4a**	**N1**	**M0**
	T3	**N2**	**M0**
	T2	**N3**	**M0**
Stage IIIB	**T4b**	**N0 or N1**	**M0**
	T4a	**N2**	**M0**
	T3	**N3**	**M0**
Stage IIIC	**T4b**	**N2 or N3**	**M0**
	T4a	**N3**	**M0**
Stage IV	**Any T**	**Any N**	**M1**

Accurate pre-operative staging is important for many reasons. Firstly, it ensures that patients do not undergo radical treatments associated with risk of complications that will have little impact on their disease or survival. It is also important as it can affect the treatment options available for consideration. For example, there is evidence that neo-adjuvant or adjuvant chemotherapy improves overall survival for patients with stage 2 or 3 disease, but little

evidence that it has the same impact on early-stage disease[19]. Again, unnecessarily subjecting patients to the significant side-effects of chemotherapy is a strategy that all clinicians involved in the treatment of gastric cancer strive to avoid. The accurate staging of metastatic disease also enables clinicians to manage the expectations of patients and their families, and facilitates the shared decision-making process related to palliative treatments[20].

There are some regional variations in staging practices. In addition to CT-scan and staging laparoscopy, countries such as Japan and South Korea routinely employ endoscopic-ultrasound (EUS) to more accurately assess the local tumour stage for gastric cancer[21,22]. In the UK, EUS is used routinely for oesophageal cancer staging and to characterise local staging for very proximal gastric tumours but not for lesions more distal to this. Gastric EUS is a highly skilled technique, which produces different results based on the operator's experience and ability[23], which may explain why it hasn't been accepted routinely outside of the Far East. Furthermore, the relatively large number of early cancer diagnoses in the Far East has facilitated the establishment of specialised non-surgical treatments such as endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD) as definitive treatments, which may also explain the endoscopic expertise in these regions.

Positron Emission Tomography (PET) scanning is another staging modality currently being considered for use in gastric cancer. PET is performed by injecting the patient with a radio-labelled tracer (2-[fluorine 18] fluoro-2-deoxy-D-glucose (FDG) labelled glucose) which is concentrated within certain metabolically active tissues. As radioactive decay occurs, emissions are measured with a scanner and appear as avid 'hot spots' on the scanned images. Routinely used for the staging of several other gastro-intestinal cancers, it gives additional information regarding lymph node and distant metastases. Its use is currently limited however as gastric tumours are not as 'avid' as other GI tumours[24]. Whilst PET may prove to be valuable in the future, more work is required to refine reporting protocols for PET in gastric cancer [24].

1.7 Survival

'Survival' following a diagnosis of cancer can be described in several ways[25]. The proportion of patients alive after diagnosis is commonly described at 1, 3, 5 and 10 years. The term 'overall survival' takes into account all causes of death whether or not they were related to the disease in question and regardless of the stage of disease. 'Disease-specific survival' is the time from treatment with curative intent (e.g. gastrectomy) to death related to the disease. 'Disease-free survival' is the time from treatment with curative intent to the time that recurrence of cancer is detected. Each term attempts to provide a different viewpoint on life after diagnosis or treatment and all can be important from the patient's perspective. Nonetheless, using several terms in the same context can be confusing, particularly if 'survival' is not clearly defined.

In the context of cancer, '5-year survival' is often used interchangeably with 'long-term survival'. This can be problematic, particularly with slow growing, less aggressive neoplasia such as prostate cancer[11]. For more aggressive cancers such as gastric adenocarcinoma, we can be more confident that by five years, survival curves have plateaued and do not decrease significantly afterwards. For the purpose of this thesis, 'survival' relates to '5-year overall survival' unless otherwise stated.

Survival from gastric cancer is amongst the poorest of any cancer group. However, just as there is variation in incidence, there exists variation in regional survival rates. Overall 5-year survival in the UK from gastric cancer currently stands at 19 per cent[9] compared to Japan which sees rates of between 60 and 70 per cent at 5 years[14]. As previously discussed, this is often linked to screening programmes being able to diagnose cancer at an earlier stage which naturally has a better prognosis (figures 5 and 6.).

Figure 1-5 Stage distribution of gastric cancer in Japan and the United States[5].

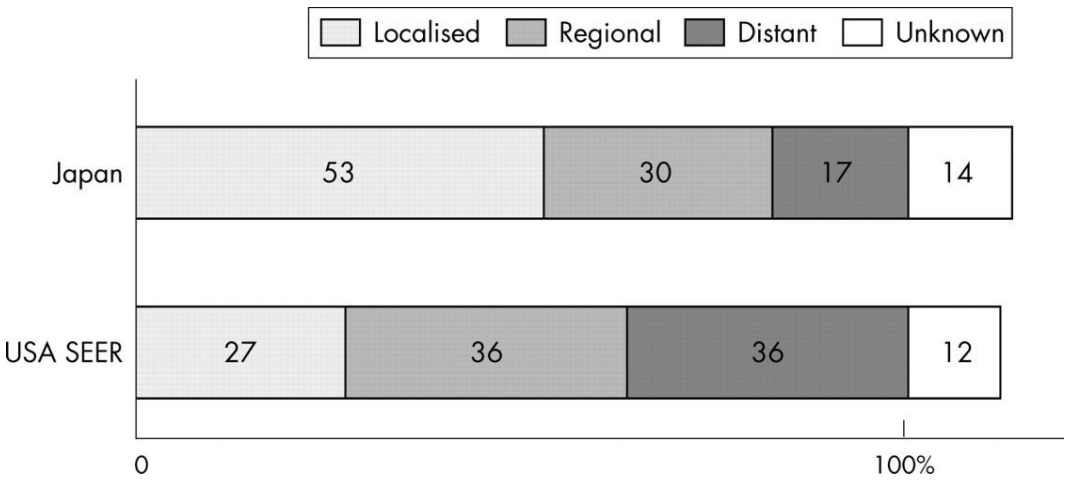
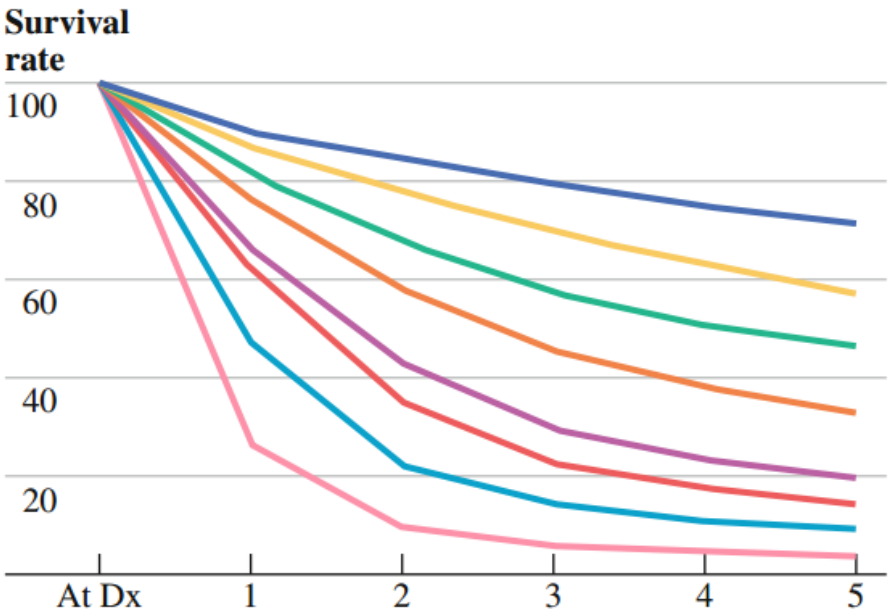


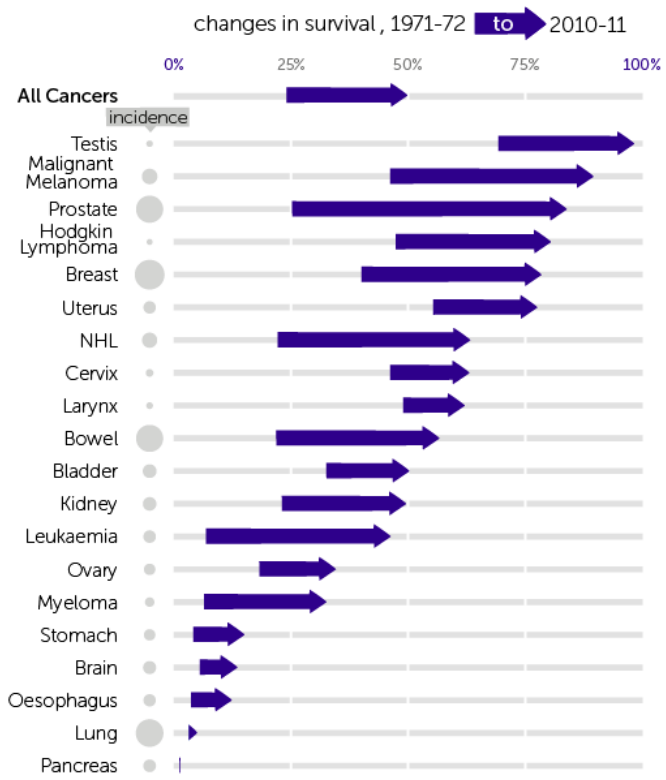
Figure 1-6 Observed 5-year survival rates per stage of gastric cancer according to the AJCC 7th edition cancer staging manual[17]. Reprinted by permission from Copyright Clearance Center on behalf of Springer, Annals of Surgical Oncology (7th Edition of the AJCC Cancer Staging Manual: Stomach, Kay Washington), Copyright 2010.



	At Dx	1	2	3	4	5
IA	100.0	90.2	84.8	79.8	74.8	70.8
IB	100.0	87.4	77.9	69.9	62.7	57.4
IIA	100.0	82.1	67.4	57.2	50.2	45.5
IIB	100.0	76.8	58.3	46.0	38.4	32.8
IIIA	100.0	66.5	42.4	29.9	23.5	19.8
IIIB	100.0	61.6	35.4	22.9	17.8	14.0
IIIC	100.0	47.4	21.8	14.2	11.0	9.2
IV	100.0	27.0	10.0	5.6	4.5	4.0

Further compounding poor survival rates in the ‘West’, there has been a concerning lack of improvement in survival over the last 40 years. Whilst other tumour groups such as prostate, breast and colon cancer have seen their survival rates increase dramatically, gastric cancer survival rates have stayed relatively static (figure 7). This data highlights the importance of maximising the research effort in the early diagnosis and treatment of gastric cancer in order to improve outcomes and survival for this patient group.

Figure 1-7 Changes in cancer survival from 1971 to 2011 in the UK[26].
Reproduced with permission from Cancer Research UK.



1.8 Management of Potentially Curative Cancer

There is no consensus on the optimal treatment for gastric cancer. Whilst in recent years there has been an acceptance that the 'gold standard' treatment for stage 2 and stage 3 cancers should incorporate a multi-modal approach, this can take many forms. For example, standard treatment in the UK would usually entail neo-adjuvant chemotherapy followed by gastrectomy followed by adjuvant chemotherapy[19,27]. In the Far East, the approach would be gastrectomy followed by adjuvant chemotherapy[22,28,29]. Some regions within Europe and North America prefer to follow surgery with chemo-radiotherapy[30–32].

1.8.1 Therapeutic Surgical Interventions for Gastric Cancer

This diversity is not restricted to the type and timing of different treatment modalities. Surgery is recognised as the mainstay of treatment with curative intent for all stages of gastric cancer, however there is great variation and ongoing debate as to how it should be undertaken. The aim of gastrectomy is to excise the primary malignant lesion in addition to loco-regional lymph glands where cancer may have metastasised. And whilst it can be extremely effective, particularly in earlier stage disease, gastrectomy carries with it significant risk of complications, both in the short and long-term. In the immediate post-operative period, the risks include death, cardio-pulmonary complications and anastomotic

leak[15,33]. In the longer-term, patients commonly face issues such as malnutrition, depression and reflux – all difficulties which significantly impact on quality of life and can take many months to adapt to[34].

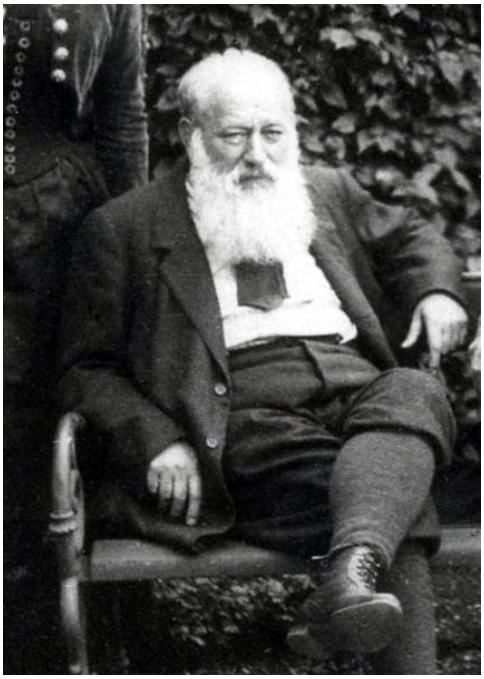
The variations in surgical interventions are an attempt not only to improve survival by ensuring radical excision of cancer but also to reduce the risks of serious complications. Surgical approaches can be broadly categorised into three groups:

1. Abdominal access
2. Extent of stomach excised
3. Extent of lymph node dissection

1.8.1.1 Abdominal Access

The first successful gastrectomy was performed by Christian Albert Theodore Billroth (1829-1894) (figure 8) on January the 29th, 1881 on Therese Heller – a 43-year-old mother of eight [35,36]. Billroth undertook a distal gastrectomy through a transverse abdominal incision for a malignant pre-pyloric ulcer which had caused gastric outlet obstruction.

Figure 1-8 Christian Albert Theodore Billroth (1829-1894)[37]. This image has been reproduced under the 'Public Domain' license and is not restricted by copyright.



Since 1881, there have been several modifications made to Billroth's operation, including methods to improve access to the stomach. It was reported that the size of Therese Heller's tumour made it difficult to deliver into the wound - a technical problem that is not uncommon to this day. However, whilst improving the surgeon's view, increasing the size or changing the orientation of the incision can increase post-operative pain and morbidity such as pulmonary complications and surgical site infection[38]. Laparoscopic gastrectomy, first undertaken by Seigo Kitano in 1991[39], has attempted to reduce post-operative pain and

shorten recovery time. Many argue that the magnified views achieved using the laparoscope enables the surgeon to undertake a safer, oncologically superior operation resulting in better outcomes from many perspectives[40]. In many regions such as the Far East it has now become the standard of care for early stage cancer and as skills and expertise develop, it is likely to become established practice for more advanced non-metastatic disease[22,29].

Nonetheless, laparoscopic surgery is not without its problems. It is an advanced and technically demanding procedure which takes significantly longer to perform than open surgery[41]. The skill required to undertake it is increased further in obese patients (more so a problem in Western regions as compared to the East) and where more radical lymphadenectomy is required (see below). It also exposes the patient to other, previously un-encountered complications such as laparoscopic port site complications and unrecognised perforations. Some also argue that the benefits seen in some series are only achievable in high-volume centres where there is a strong focus on laparoscopic surgery[42].

In an attempt to combat some of these issues, manufacturers of laparoscopic equipment have developed 3-dimensional laparoscopy to further aid the surgeon, however the evidence base is limited to significantly less complicated surgery such as laparoscopic cholecystectomy[43].

Proponents of robotic surgery claim that many of the technical demands of laparoscopic surgery can be reduced without compromising on incision size or the degree of lymph node dissection[44,45]. Robotic arms are able to articulate 720 degrees and provide better manipulation of tissues all whilst the surgeon is sat at a console. However robotic systems are expensive, not widely available and there is currently no randomized control trial evidence to suggest its superiority to laparoscopic surgery or indeed open surgery. Nonetheless, as cancer services continue to centralise into super-specialist centres, the availability of robots used routinely in cancer disciplines (such as prostate cancer) will see their use continue to develop.

1.8.1.2 Extent of Stomach Excised

The debate over how much of the stomach should be excised to treat gastric cancer seeks to balance preservation of organ function, minimising complications and ensuring sufficient oncological clearance. As an example, a total gastrectomy for mid-body or distal tumours, whilst oncologically radical, is associated with a higher incidence of long-term complications such as malnutrition, dumping syndrome and reflux-oesophagitis when compared to sub-total gastrectomy[46]. Conversely, in the context of proximal tumours, proximal gastrectomy, whilst enabling the preservation of the majority of the stomach, is associated with a higher rate of reflux oesophagitis and anastomotic strictures when compared to total gastrectomy. In addition, the number of lymph nodes excised with proximal gastrectomy are typically fewer when compared to total gastrectomy, calling into question its efficacy as an operation for more advanced cancers[47].

Table 1.3 Types of gastrectomy available for consideration related to position of primary lesion.

Location of Tumour	Surgical Options
Proximal stomach	Extended total gastrectomy, total gastrectomy, proximal gastrectomy
Mid-body of stomach	Total gastrectomy, sub-total gastrectomy
Distal stomach	Total gastrectomy, sub-total gastrectomy

In more recent years, the development of expertise in endoscopic therapies has opened the door to endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) being used to treat a select group of early stage gastric cancers. EMR and ESD in these patients offers the benefit of total tumour excision with excellent survival results without causing significant disruption to the stomach[48]. However, in the context of gastric cancer, these therapies are yet to become established in the West. This is partly due to the low volume of early stage tumours, in addition to the uncertainty as to whether the same oncological results can be produced when compared to gastrectomy.

1.8.1.3 Extent of Lymph Node Dissection

The stomach is supplied by a rich complex of blood vessels and an accompanying lymphatic drainage system which is a common site for metastatic spread (figure 9). Nodal metastases are strongly associated with poorer survival rates and as a consequence, excision of loco-regional lymph nodes (lymphadenectomy) is a vital component of gastric cancer surgery. In 1963, the Japanese Research Society published their categorization of gastric lymph nodes, grouping them into 16 stations (later translated into English in 1995)[49]. These stations are further organised into levels depending on their proximity to the stomach. The extent of lymphadenectomy is described by the number of nodal levels excised during surgery (table 4). For example, complete excision of level 1 nodes is described as a ‘D1 lymphadenectomy’ whilst a ‘D2 lymphadenectomy’ involved the excision of all the level 2 nodes and so on and so forth. The nodal stations incorporated in the lymphadenectomy differ according to the location of the tumour and type of gastrectomy.

Figure 1-9 Lymph node stations draining the stomach[50]. Reprinted by permission from Copyright Clearance Center on behalf of Springer Nature, Nature Clinical Practice Oncology (Perspectives in the treatment of gastric cancer, Dimitrios H Roukos et al), Copyright 1969.

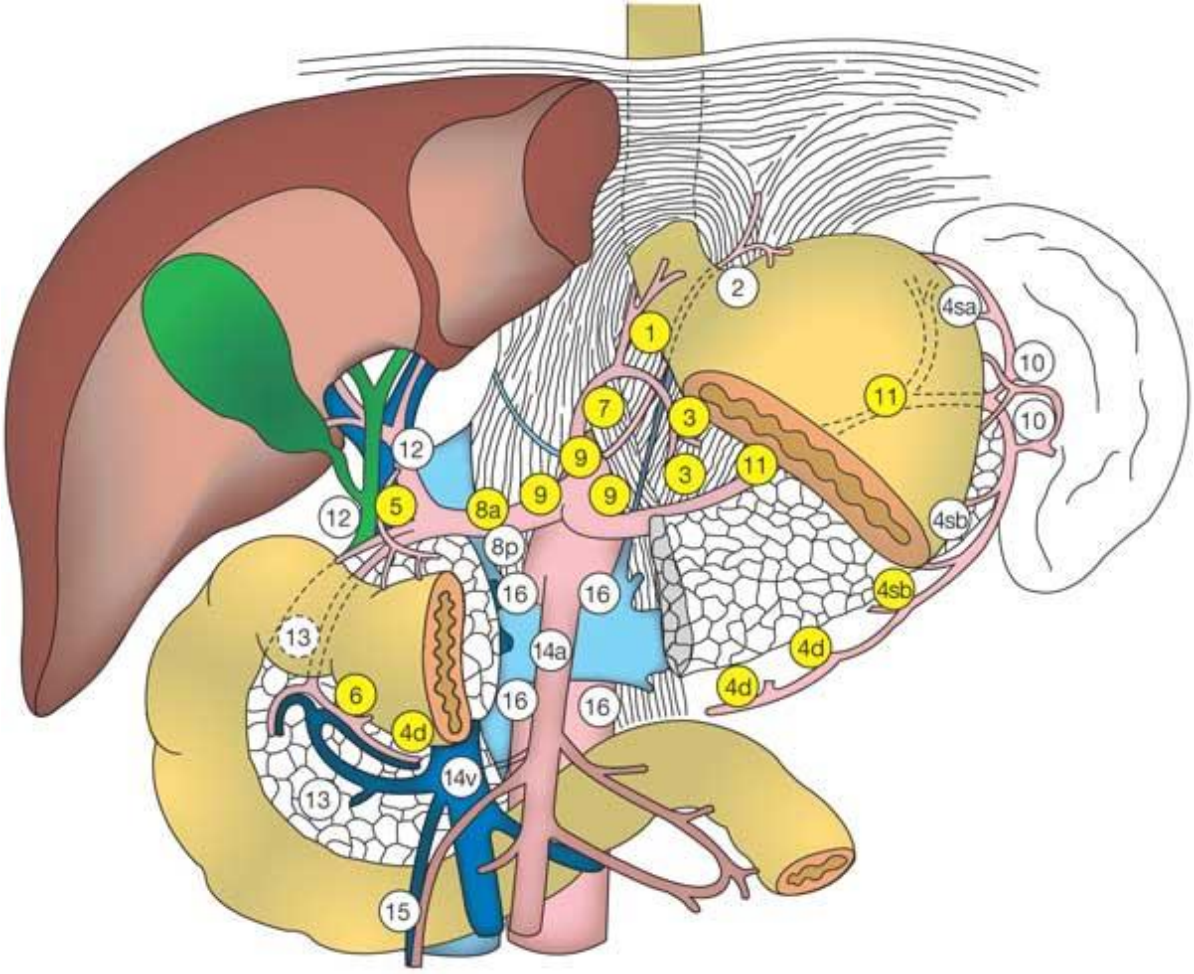


Table 1.4 Lymphadenectomy for total and sub-total gastrectomy[29]. Adapted by permission from Copyright Clearance Center on behalf of Springer Nature, Gastric Cancer (Japanese gastric cancer treatment guidelines 2010, Japanese Gastric Cancer Association), Copyright 2010.

Lymphadenectomy	Nodal level	Lymph Node Stations	
		Total Gastrectomy	Distal Gastrectomy
D0		No dissection or incomplete dissection of level 1 nodes	
D1	Level 1	Nos. 1–7	Nos. 1, 3, 4sb, 4d, 5, 6, 7
D1+		D1 plus Nos. 8a, 9, 11p	D1 plus Nos. 8a, 9
D2	Level 2	D1 plus Nos. 8a, 9, 10, 11p, 11d	D1 plus Nos. 8a, 9, 11p
D3	Level 3	D2 plus Nos. 12 - 14	D2 plus Nos. 12 - 14
D4	Level 4	D3 plus 15 and 16	D3 plus 15 and 16

The optimal extent of lymphadenectomy is a controversial topic which has been debated in the literature for decades. Up to a point, a more extensive lymphadenectomy results in improved survival, however this is often at the expense of increased post-operative morbidity[51] . Where the balance lies remains an uncertainty. Both the Japanese Gastric Cancer Association (figure 10) and the Korean Gastric Cancer Association guidelines state that for node positive disease, D2 lymphadenectomy should be the standard of care[22,29]. However, this is not standard practice in many regions outside of the Far East where other factors such as surgeon experience, obesity and pre-existing co-morbidities may influence decision making[27].

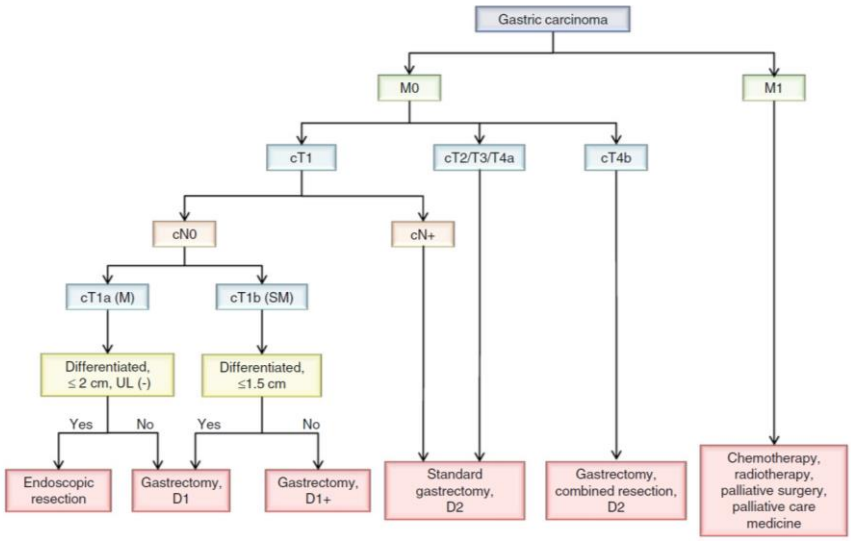


Figure 1-10 Management strategy for gastric cancer according to the Japanese Association of Gastric Cancer[29]. Adapted and reprinted by permission from Copyright Clearance Center on behalf of Springer Nature, Gastric Cancer (Japanese gastric cancer treatment guidelines 2010, Japanese Gastric Cancer Association), Copyright 2010.

'Super-extended' D3 and D4 lymphadenectomies do not seem to provide significant survival advantages over D2 and have fallen out of favour in the Far East[51]. Nonetheless, there are several planned and ongoing randomized trials examining this topic. Other areas of uncertainty include whether splenectomy for proximal gastric tumours is necessary in order to clear the station 10 (splenic hilar) lymph nodes and whether excising the omental bursa adds any benefit to survival[52,53].

1.9 Inadequacies Within the Evidence Base

The reasons for the variations in surgical approach are multi-factorial, but ultimately result from a lack of robust, well-designed trials and reproducible evidence. This is not surprising given the degree of 'waste' which is estimated to affect approximately 85 per cent of biomedical research[54,55]. Chalmers and Glasziou broke down this figure in the following manner:

- 50% of studies are never published
- 25% are not usable or replicable
- 12.5% have serious and avoidable design flaws

A systematic review and meta-analysis of randomized control trials constitutes the highest level of evidence on which to base changes in practice. However, systematic reviews persistently remark on the heterogeneity and low quality of available evidence in therapeutic

surgical interventional trials for gastric cancer[51,56]. As a result, they are unable to provide strong recommendations for, or against, the intervention in question.

A major contributing factor to this heterogeneity relates to the inconsistent reporting of outcomes in trials[57]. If trials do not report the same outcome measures using the same definitions and measurement instruments, their results cannot be combined and contrasted. Furthermore, if trials do not report outcomes which are relevant to major stakeholders such as patients, the value of the research diminishes significantly.

1.9.1 Rapid Review

A rapid review of RCTs (published between January 2014 and January 2016) examining therapeutic surgical interventions for gastric cancer was undertaken using a structured search strategy applied to MEDLINE via Ovid and EMBASE via Ovid. The review revealed large variations in the reporting of outcomes. In the six trials identified, a total of 102 outcomes were reported. Only fifteen per cent of these were defined. No single outcome was reported by every trial. One trial described patient-reported outcomes (defined as a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else[20]) and no trials measured quality of life after surgery.

Inconsistency in outcome reporting is not restricted to gastric cancer surgery and has been extensively demonstrated in other cancer disciplines such as oesophageal, colorectal and prostate cancer[58–60]. It is also mirrored in many other clinical specialties including women's health[61], otolaryngology[62] and rheumatology[63].

1.9.2 Standardising Outcome Measurement

One solution to this problem is the standardisation of outcome measurement through the development of 'core outcome sets' (COS). A COS is an agreed minimum set of outcomes that should be measured and reported in all trials for a specific condition. It is a recommendation of **'what'** should be measured and reported[64]. Accompanying the domains in the COS should be an appropriate method to quantify the outcome (the 'measurement instrument') - **'how'** - in addition to a recommendation for the timing of its use - **'when'**. Standardizing 'what', 'how' and 'when' outcomes should be measured in research would significantly improve overall trial design and enable more reliable synthesis of evidence, in order to produce robust recommendations for optimal clinical practice.

1.9.3 Lessons from Other Disciplines

COS development is a relatively new discipline with an evolving methodology. Nonetheless, there are currently more than 400 completed, ongoing or planned COS studies across a wide spectrum of clinical specialties referenced in the online database developed by COMET

(Core Outcome Measures in Effectiveness Trials) – an international group focused on supporting the development of COS studies[65]. OMERACT (Outcome Measures in Rheumatology Clinical Trials) was an early adopter with multiple COS projects in rheumatology and has informed many aspects of COS development[63]. In particular, it highlighted the invaluable contribution that patients make when prioritizing which outcomes should be measured in trials as patients often prioritize different outcomes compared to clinicians. Consequently, if research is to be relevant to all major stakeholders, patients must be involved in its design.

Several groups, in addition to COMET, currently work to promote the development of COS, including ICHOM (International Consortium for Health Outcomes Measurement – www.ichom.org) and regulatory bodies such as the FDA (USA Food and Drug Administration – www.fda.gov). Collaborative approaches between some of these groups has already begun (The Red Hat group[66]) which will be essential as the field evolves.

CROWN (Core Outcomes in Women's Health) is an international initiative, led by journal editors, to standardise reporting in women's health research[61]. CROWN has highlighted the necessity of setting out a clear implementation strategy for a COS project during its development and prior to finalisation. Without early 'buy-in' and acceptance from researchers, a COS may fall at the first hurdle and have the potential of perpetuating the 'research waste' that it aims to address. CROWN's approach to this is for journal editors to drive forward the process by 'encouraging' researchers submitting publications for peer-review to use an existing COS in their research. Bold approaches such as this one, in addition to significant support from major research funders including the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) will undoubtedly see COS development and uptake become integral to future research.

1.10 Aim & Rationale of Research

The aim of this study was to develop a COS for trials examining therapeutic surgical interventions for gastric cancer. As previously described, surgery is the mainstay of curative treatment for gastric cancer, yet there is significant variation in practice and the optimal approaches are still unknown. Standardising the reporting of outcomes is a major step in addressing the problems inherent within the evidence base which contribute to this situation.

Whilst the COS will primarily seek to influence future surgical intervention trials, there will inevitably be several other areas which will benefit from its development. For example, by understanding the priority that clinicians and patients place on certain outcomes following gastric cancer surgery, there is the opportunity to make well-established national audits (such as the UK's National Oesophago-Gastric Cancer Audit – NOGCA[15]) more relevant to all stakeholders. In addition, understanding priorities from a patient's perspective has the potential to significantly guide and influence the clinician-patient consultation prior to surgery.

This study also sought to make a significant contribution to the methodology used in the development of a COS. As described previously, COS development is a relatively new discipline and whilst there are areas with well-established approaches, naturally there will be scope for improvement - particularly in advancing the methodology associated with international participation of stakeholders.

1.11 References

1. Cancer Research UK. Stomach (gastric) cancer. http://www.cancerresearchuk.org/about-cancer/type/stomach-cancer/. Published May 5, 2016. Accessed May 16, 2016.

2. Boswell JT, Helwig EB. Squamous cell carcinoma and adenoacanthoma of the stomach.A clinicopathologic study. Cancer. 1965;18(2):181-192. doi:10.1002/1097-0142(196502)18:2<181::AID-CNCR2820180209>3.0.CO;2-3

3. Fact Sheets by Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed July 24, 2017.

4. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol. 2006;12(3):354-362. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4066052&tool=pmcentrez&rendertype=abstract. Accessed April 12, 2016.

5. Inoue M, Tsugane S. Epidemiology of gastric cancer in Japan. Postgrad Med J. 2005;81(957):419-424. doi:10.1136/pgmj.2004.029330

6. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015;64(12):1881-1888. doi:10.1136/gutjnl-2014-308915

7. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116(3):544-573. doi:10.1002/cncr.24760

8. Cristescu R, Lee J, Nebozhyn M, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015;21(5):449-456. doi:10.1038/nm.3850

9. Stomach cancer statistics | Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer#heading-Zero. Accessed February 3, 2016.

10. Kamineni A, Williams MA, Schwartz SM, Cook LS, Weiss NS. The incidence of gastric carcinoma in Asian migrants to the United States and their descendants. Cancer Causes Control. 1999;10(1):77-83. http://www.ncbi.nlm.nih.gov/pubmed/10334646. Accessed May 16, 2016.

11. Gigerenzer G, Wegwarth O. Five year survival rates can mislead. BMJ. 2013;346(jan29_2):f548. doi:10.1136/bmj.f548

12. Yeh JM, Hur C, Ward Z, Schrag D, Goldie SJ. Gastric adenocarcinoma screening and prevention in the era of new biomarker and endoscopic technologies: a cost-effectiveness analysis. Gut. 2016;65(4):563-574. doi:10.1136/gutjnl-2014-308588

13. Choi KS, Jun JK, Suh M, et al. Effect of endoscopy screening on stage at gastric cancer diagnosis: results of the National Cancer Screening Programme in Korea. Br J Cancer. 2015;112(3):608-612. doi:10.1038/bjc.2014.608

14. Matsuda T, Saika K. The 5-year relative survival rate of stomach cancer in the USA, Europe and Japan. Jpn J Clin Oncol. 2013;43(11):1157-1158. doi:10.1093/jjco/hyt166

15. Centre H& SCI. National OesophagoGastric Cancer Audit 2015. http://www.hscic.gov.uk/article/1165/searchcatalogue?q=%22National+Oesophago-Gastric+Cancer+Audits%22&sort=Date&size=10&page=1#top. Published 2015. Accessed May 16, 2016.

16. Suspected cancer: recognition and referral | 1-Recommendations-organised-by-site-of-cancer | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#upper-gastrointestinal-tract-cancers. Accessed May 16, 2016.

17. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol. 2010;17(12):3077-3079. doi:10.1245/s10434-010-1362-z

18. Surgeons S of AG and E. Guidelines for Diagnostic Laparoscopy - A SAGES Guideline. http://www.sages.org/publications/guidelines/guidelines-for-diagnostic-laparoscopy/. Accessed May 16, 2016.

19. Cunningham D, Allum WH, Stenning SP, et al. MAGIC Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20. doi:10.1056/NEJMoa055531

20. Bélanger E, Rodríguez C, Groleau D. Shared decision-making in palliative care: A systematic mixed studies review using narrative synthesis. Palliat Med. 2011;25(3):242-261. doi:10.1177/0269216310389348

21. Lee KS, Oh DK, Han MA, et al. Gastric cancer screening in Korea: report on the national cancer screening program in 2008. Cancer Res Treat. 2011;43(2):83-88. doi:10.4143/crt.2011.43.2.83

22. Lee JH, Kim JG, Jung H-K, et al. Clinical practice guidelines for gastric cancer in

Korea: an evidence-based approach. J Gastric Cancer. 2014;14(2):87-104. doi:10.5230/jgc.2014.14.2.87

23. Mocellin S, Pasquali S. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. Cochrane database Syst Rev. 2015;2:CD009944. doi:10.1002/14651858.CD009944.pub2

24. Hopkins S, Yang GY. FDG PET imaging in the staging and management of gastric cancer. J Gastrointest Oncol. 2011;2(1):39-44. doi:10.3978/j.issn.2078-6891.2010.004

25. NCI Dictionary of Cancer Terms - National Cancer Institute. http://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed May 16, 2016.

26. Cancer survival for common cancers | Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/survival/common-cancers-compared#heading-Three. Accessed May 16, 2016.

27. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-1472. doi:10.1136/gut.2010.228254

28. Ohtsu A, Sasako M. Overview of adjuvant therapy for resected gastric cancer: Differences in Japan and the United States. Semin Oncol. 2005;32(6 Suppl 9):1-4. doi:10.1053/j.seminoncol.2005.06.001

29. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113-123. doi:10.1007/s10120-011-0042-4

30. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-730. doi:10.1056/NEJMoa010187

31. Macdonald JS, Benedetti J, Smalley S, et al. Chemoradiation of resected gastric cancer: A 10-year follow-up of the phase III trial INT0116 (SWOG 9008) . 2009;27:4515. https://urldefense.proofpoint.com/v2/url?u=http-3A__meeting.ascopubs.org_cgi_content_abstract_27_15S_4515&d=BQIGaQ&c=bMxC-A1upgdsx4J2OmDkk2Eep4PyO1BA6pjHrrW-ii0&r=cCBH3peyAhqeqZPMNXa51fxfKkQTPqMwBHOx6ZAMGvE&m=lgOOHAjGwhKEw0Eos87zHJjyRQ6wMLYhZ2M_Qydro8g&s=.

32. Messager M, de Steur WO, van Sandick JW, et al. Variations among 5 European countries for curative treatment of resectable oesophageal and gastric cancer: A survey from the EURECCA Upper GI Group (EUropean REgistration of Cancer CAre). Eur J Surg Oncol. 2016;42(1):116-122. doi:10.1016/j.ejso.2015.09.017

33. Dikken JL, van Sandick JW, Allum WH, et al. Differences in outcomes of oesophageal and gastric cancer surgery across Europe. Br J Surg. 2013;100(1):83-94. doi:10.1002/bjs.8966

34. Barbour AP, Lagergren P, Hughes R, Alderson D, Barham CP, Blazeby JM. Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. Br J Surg. 2008;95(1):80-84. doi:10.1002/bjs.5912

35. Strong VE, ed. Gastric Cancer. Cham: Springer International Publishing; 2015. doi:10.1007/978-3-319-15826-6

36. Roth A, Kolaric K, Zupanc D, Oresic V, Ebling Z. High doses of 5-fluorouracil and epirubicin with or without cisplatin in advanced gastric cancer: a randomized study. Tumori. 1999;85(4):234-238. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=10587023.

37. Theodor Billroth. Wikipedia. https://en.wikipedia.org/wiki/Theodor_Billroth. Accessed May 19, 2016.

38. Grantcharov TP, Rosenberg J. Vertical compared with transverse incisions in abdominal surgery. Eur J Surg. 2001;167(4):260-267. doi:10.1080/110241501300091408

39. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc. 1994;4(2):146-148. http://www.ncbi.nlm.nih.gov/pubmed/8180768. Accessed April 13, 2016.

40. Kitano S, Shiraishi N, Uyama I, Sugihara K, Tanigawa N. A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. Ann Surg. 2007;245(1):68-72. doi:10.1097/01.sla.0000225364.03133.f8

41. Wang W, Zhang X, Shen C, Zhi X, Wang B, Xu Z. Laparoscopic versus open total gastrectomy for gastric cancer: an updated meta-analysis. PLoS One. 2014;9(2):e88753. doi:10.1371/journal.pone.0088753

42. Kim MG, Kwon SJ. Comparison of the outcomes for laparoscopic gastrectomy

performed by the same surgeon between a low-volume hospital and a high-volume center. Surg Endosc. 2014;28(5):1563-1570. doi:10.1007/s00464-013-3352-2

43. Sahu D, Mathew MJ, Reddy PK. 3D Laparoscopy - Help or Hype; Initial Experience of A Tertiary Health Centre. J Clin Diagn Res. 2014;8(7):NC01-3. doi:10.7860/JCDR/2014/8234.4543

44. Noshiro H, Ikeda O, Urata M. Robotically-enhanced surgical anatomy enables surgeons to perform distal gastrectomy for gastric cancer using electric cautery devices alone. Surg Endosc Other Interv Tech. 2014;28(4):1180-1187. doi:10.1007/s00464-013-3304-x

45. Marano A, Hyung WJ. Robotic gastrectomy: the current state of the art. J Gastric Cancer. 2012;12(2):63-72. doi:10.5230/jgc.2012.12.2.63

46. Lee SS, Chung HY, Kwon OK, Yu W. Long-term Quality of Life After Distal Subtotal and Total Gastrectomy: Symptom- and Behavior-oriented Consequences. Ann Surg. 2016;263(4):738-744. doi:10.1097/SLA.0000000000001481

47. An JY, Youn HG, Choi MG, Noh JH, Sohn TS, Kim S. The difficult choice between total and proximal gastrectomy in proximal early gastric cancer. Am J Surg. 2008;196(4):587-591. doi:10.1016/j.amjsurg.2007.09.040

48. Kang KJ, Kim K-M, Min B-H, Lee JH, Kim JJ. Endoscopic submucosal dissection of early gastric cancer. Gut Liver. 2011;5(4):418-426. doi:10.5009/gnl.2011.5.4.418

49. *Japanese Research Society for Gastric Cancer: Japanese Classification of Gastric* Garcinoma. Kanehara &. Tokyo: Kanehara &Co, Ltd; 1995.

50. Roukos DH, Kappas AM. Perspectives in the treatment of gastric cancer. Nat Clin Pract Oncol. 2005;2(2):98-107. doi:10.1038/ncponc0099

51. Mocellin S, McCulloch P, Kazi H, Gama-Rodrigues JJ, Yuan Y, Nitti D. Extent of lymph node dissection for adenocarcinoma of the stomach. Cochrane database Syst Rev. 2015;8:CD001964. doi:10.1002/14651858.CD001964.pub4

52. Brar SS, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. A systematic review of spleen and pancreas preservation in extended lymphadenectomy for gastric cancer. Gastric Cancer. 2012;15 Suppl 1:S89-99. doi:10.1007/s10120-011-0087-4

53. Shen W-S, Xi H-Q, Wei B, Chen L. Effect of gastrectomy with bursectomy on prognosis of gastric cancer: a meta-analysis. World J Gastroenterol. 2014;20(40):14986-14991. doi:10.3748/wjg.v20.i40.14986

54. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet (London, England). 2009;374(9683):86-89. doi:10.1016/S0140-6736(09)60329-9

55. BMJ Blogs: The BMJ » Blog Archive » Paul Glasziou and Iain Chalmers: Is 85% of health research really “wasted”? http://blogs.bmj.com/bmj/2016/01/14/paul-glasziou-and-iain-chalmers-is-85-of-health-research-really-wasted/. Accessed May 19, 2016.

56. Gurusamy Kurinchi S. Laparoscopic versus open gastrectomy for gastric cancer. Cochrane Database Syst Rev. 2014;9(2):e88753. doi:10.1002/14651858.CD011389

57. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. J Health Serv Res Policy. 2012;17(1):1-2. doi:10.1258/jhsrp.2011.011131

58. Blencowe NS, Strong S, McNair AGK, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg. 2012;255(4):658-666. doi:10.1097/SLA.0b013e3182480a6a

59. Whistance RN, Forsythe RO, McNair AGK, et al. A systematic review of outcome reporting in colorectal cancer surgery. Colorectal Dis. 2013;15(10):e548-60. doi:10.1111/codi.12378

60. Efficace F, Feuerstein M, Fayers P, et al. Patient-reported outcomes in randomised controlled trials of prostate cancer: methodological quality and impact on clinical decision making. Eur Urol. 2014;66(3):416-427. doi:10.1016/j.eururo.2013.10.017

61. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women’s health. BJOG. 2014;121(10):1181-1182. doi:10.1111/1471-0528.12929

62. Harman NL, Bruce IA, Callery P, et al. MOMENT--Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials. 2013;14:70. doi:10.1186/1745-6215-14-70

63. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials. 2007;8(1):38. doi:10.1186/1745-6215-8-38

64. Glossary: Core Outcome Set (COS). http://www.comet-initiative.org/glossary/cos/. Accessed July 24, 2017.

65. Database Search - Core Outcome Measures in Effectiveness Trials Initiative

(COMET). http://www.comet-initiative.org/studies/search. Accessed May 19, 2016.

66. Gargon E, Rhonda Facile, Robby Nieuwlaat J, Schmitt, Holger Schunemann, Lee Simon, Allison Tong, Jonathan Craig, Caroline Terwee, Peter Tugwell, Sean Tunis PW. The Red Hat Group: an initiative to promote broader uptake of core outcome sets through the healthcare research ecosystem. https://www.comet-initiative.org/UploadedDocuments/06fb6f06-6ce1-42e5-98c2-92fb3b9afb33-RHG EQUATOR_REWARD 2020.pdf. Accessed December 21, 2020.

2 Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study)

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2.1 Abstract

Background

Gastric cancer is one of the leading causes of cancer-related deaths worldwide. Whilst surgery is the mainstay of curative treatment, it is associated with significant risks. Surgical strategies for gastric cancer should be based on evidence from systematic reviews of well-designed randomised controlled trials. However, inconsistencies in the reporting of outcomes from these trials makes evidence synthesis unreliable.

We present a protocol for an international consensus study to develop a standardised set of outcomes and measurement tools – a 'core outcome set' (COS) – to be used by all future trials examining therapeutic surgical interventions for gastric cancer.

Methods

The first of three stages in the study will identify a 'long-list' of potentially important outcomes to be prioritised. These will be extracted from a systematic review of relevant literature and patient interviews. Stage 2 will comprise an eDelphi survey which will consider the views of patients, nurse specialists and surgeons to prioritise the most important outcomes. A meeting of stakeholder representatives will ratify the COS. Stage three will focus on identifying appropriate instruments to measure the prioritised outcomes, by means of quality assessment of available measurement instruments and stakeholder consultation.

Discussion

This study aims to standardise the reporting of outcomes in future trials examining therapeutic surgical interventions for gastric cancer. It is anticipated that standardisation of outcome reporting in these surgical effectiveness trials will enhance the evidence base for clinical practice. Highlighting outcomes of greatest importance to patients will ensure that their perspectives are central to research in this field.

2.2 Introduction

2.2.1 Background

Gastric cancer is one of the leading causes of cancer-related deaths worldwide[1] and despite developments in multi-modal treatment approaches, overall survival rates have not improved significantly over the last 4 decades[2]. Surgery to remove part or all the stomach continues to be the main stay of treatment that offers a potential cure, however this is associated with significant risks of short and long-term complications[3,4]. Variations in surgical approaches aim to minimise these risks without compromising the oncological resection of the tumour. These variations can be broadly categorised into those related to accessing the stomach (e.g. open, laparoscopic or robotic surgery) and those related to the extent of surgery (e.g. partial or total of gastrectomy, level of lymphadenectomy and splenectomy).

In principle, assessing the optimal surgical strategies for gastric cancer should involve analyses of well-designed and conducted randomised controlled trials (RCTs) with systematic reviews and meta-analyses of data. However, trials are often methodologically heterogenous, report and measure their outcomes differently and preclude comprehensive evidence synthesis. Consequently, strong recommendations for clinical practice can seldom be made[5,6]. In instances where trials may report the same outcomes, the definitions of these outcomes are often inconsistent, and it is not known to what degree these outcomes may be relevant to key stakeholders such as patients.

In preparing this protocol, a rapid review of RCTs (published between January 2014 and January 2016) examining therapeutic surgical interventions for gastric cancer was undertaken using a structured search strategy applied to MEDLINE and EMBASE via Ovid. In the six trials identified, a total of 102 outcomes were reported, only fifteen per cent of which were defined. No single outcome was reported by every trial and only one trial described patient-reported outcomes. No trial measured quality of life after surgery.

Many groups have now demonstrated similar, widespread inconsistencies in outcome reporting[7–10]. Consequently, there has been a drive, with the support of initiatives such as COMET (Core Outcomes Measurement in Effectiveness Trials – www.comet-initiative.org) and the Medical Research Council's Hubs for Trials Methodology Research, to standardise the reporting of outcomes as an important step in improving trial design and reducing research waste.

2.2.2 Aims & Objectives

One solution to this problem is through the development of a 'core outcome set' (COS). A COS is defined as an agreed minimum set of outcomes that should be measured and reported in all trials in a specific condition[11]. The aim of the GASTROS study (**GA**stric cancer **S**urgery **T**rials **R**eported **O**utcomes **S**tandardisation) is to develop a COS to be used

by all trials examining therapeutic surgical interventions for gastric cancer, which reflects the interests of both patients and healthcare professionals.

The specific objectives include:

1) To determine the degree of variation in the reporting of outcomes in the literature.
2) To identify a list of potentially important outcomes from published trials and trial protocols.
3) To identify a list of potentially important outcomes reported by patients in semi-structured interviews who have been treated for gastric cancer (to augment the list generated in 2).
4) To reach consensus regarding the most important outcomes from the perspective of patients and healthcare professionals into a core outcome set.
5) To identify appropriate outcome measurement instruments to be used in the reporting of the COS and at what time points the outcomes should be measured.

2.3 Methods

This study will draw its methodological principles from recommendations developed by initiatives such as COMET and COSMIN (**CO**nsensus-based **S**tandards for the selection of health **M**easurement **IN**struments) and modified where necessary and appropriate[12–17]. The COMET initiative has been instrumental in propagating the agenda for change in relation to outcomes reporting internationally and have amassed a wealth of knowledge and experience during the last 6 years. Whilst the field of COS is still relatively new, COMET is supporting the development of multiple COS demonstrated by over 400 completed, ongoing or planned studies across a wide spectrum of clinical specialties referenced in its online database[18]. COSMIN, whose focus lies on developing rigorous methods of outcome measurement instrument selection, is working closely with COMET and collaboratively they have developed standards for selecting instruments used in the reporting of COS[16].

2.3.1 Scope

This COS is primarily aimed at pragmatic trials examining therapeutic surgical interventions for gastric cancer. The target population is male and female adults. We foresee that the COS will also be beneficial for the design of non-randomised studies and will inform the design of databases and national audits by identifying the priorities of patients and healthcare professionals.

Given that there is now a greater acceptance that the management of gastric cancer is often multi-modal (involving a combination of surgical excision and chemotherapy or chemo-radiotherapy)[19], it may be argued that a COS would be more relevant if it were to encompass all therapeutic interventions and not just surgical ones. A structured search of the World Health Organisation's International Clinical Trials Registry Portal (http://apps.who.int/trialsearch/, last accessed 3rd of August 2016) and ClinicalTrials.Gov (https://clinicaltrials.gov/, last accessed 3rd August 2016) has identified 26 ongoing surgical gastric cancer trials planning to recruit over eleven thousand patients. The rate at which these surgical trials are being set-up does not show signs of slowing. As such, a surgically focused COS is highly relevant given the research activity within this field. Furthermore, there are a significant proportion of patients that do not require multimodal therapy due to early stage disease or on the account that they are unfit for additional therapies. In addition, given the large variation in surgical practice that already exists, and the range of therapeutic surgical interventions which have been and are being investigated, we believe a surgically orientated COS is both desirable and necessary. Nonetheless, our group recognises that future work is required to develop a COS which will be relevant to non-surgical interventions and this is within our planned programme of work in conjunction with endoscopic and medical and clinical oncology groups.

2.3.2 Definitions

The development of COS by different groups has highlighted some of the issues which arise with the inconsistent use of nomenclature and definitions in a new and developing research field. There are no widely-agreed definitions for several commonly used terms in COS, however, the COMET initiative recommends that studies clearly define their own terms. Our definitions are summarized in table 1.

Table 2.1 Definition of terms used in the GASTROS study.

Core Outcome Set (COS)	An agreed minimum set of outcomes that should be measured and reported in all trials in a specific condition[11].
Outcome	A unique endpoint which attempts to describe health-related changes that occur secondary to a therapeutic intervention e.g. hospital acquired pneumonia.
Outcome Domain	A collection of 'outcomes' which share common features e.g. the outcome domain 'respiratory complications' would include outcomes such as 'pleural effusion', 'hospital-acquired pneumonia' and 'atelectasis'.
Outcome Measurement Instrument (OMI)	A method or tool used to measure an 'outcome' or an 'outcome domain'.
Outcome Measurement Instrument Set	A collection of OMIs which are used to measure outcome domains in a COS.

2.3.3 Stakeholder Involvement

An important aspect of the GASTROS study design is ensuring that key stakeholder opinion is represented at every stage of COS development. Our primary stakeholder groups include patients (with 'lived experience' of the condition and its management), surgeons (those directly delivering and developing the clinical interventions) and clinical nurse specialists (as they have an important dual role as healthcare professionals and patient advocates). In addition to their participation highlighted below (see 'study design'), representatives from each group have been recruited to our Study Advisory Group to support the general delivery of the study against its stated objectives and ensure that the viewpoints of all stakeholders are considered throughout the process.

Most surgical gastric cancer trials are undertaken in the Far East where the incidence and prevalence is highest[1]. It is therefore essential that aspects of the COS development take this international perspective into account. As such, representatives from all stakeholder groups will be invited to participate in the eDelphi survey. They will be drawn from a broad network of national and international patient groups, charities, professional associations and institutions. This is further elaborated upon below (see 'Dissemination and Implementation Strategy').

2.3.4 Study Design

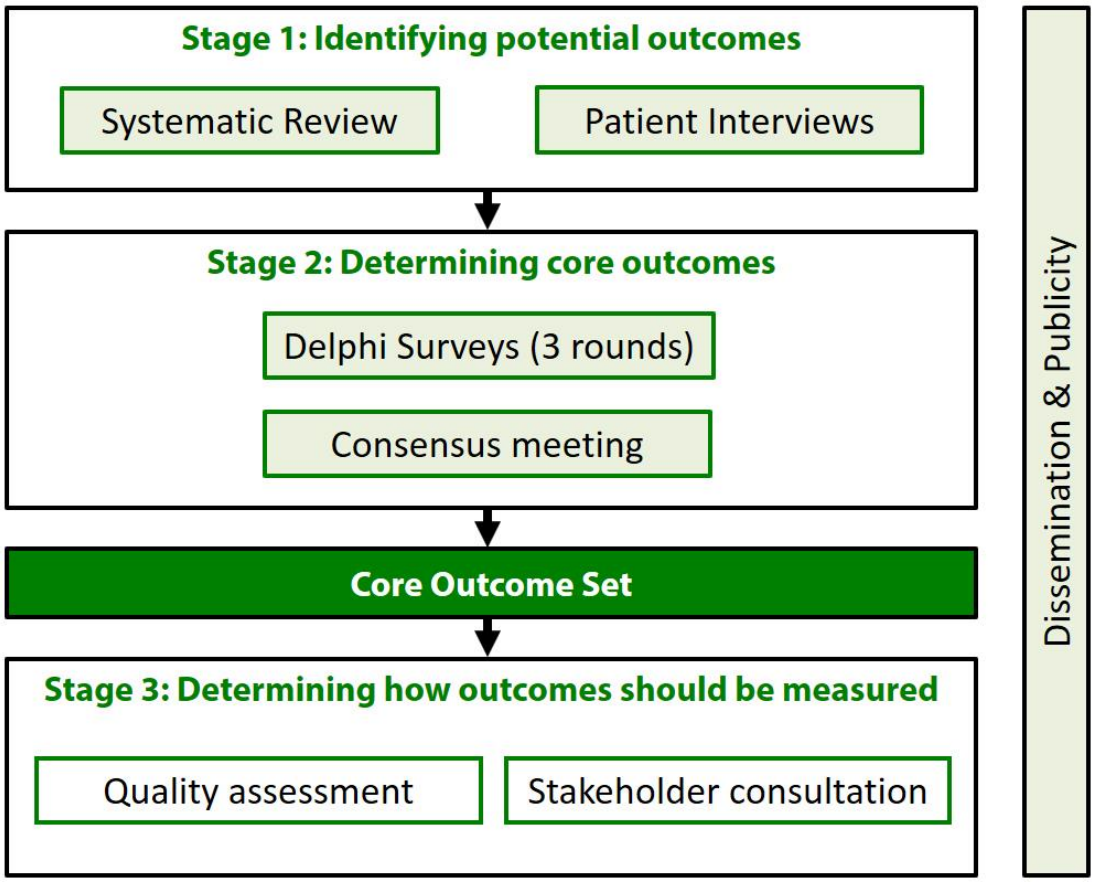
The GASTROS Study will be divided into three distinct stages, summarized in figure 1:

Stage 1. Generation of 'long-list' of outcomes,

Stage 2. Prioritization of outcomes and finalization of COS,

Stage 3. Identification of Outcome Measurement Instruments.

Figure 2-1 GASTROS study overview.



2.3.4.1 Stage 1. Generation of 'long-list' of outcomes

A long-list of potentially important outcomes will be identified by means of a systematic literature search and semi-structured patient interviews. This will be followed by a consultation exercise to finalize a list of outcomes to be prioritized by stakeholder in stage 2 of the study.

2.3.4.1.1 Systematic Literature Search

A systematic review of randomized control trials (RCTs) and protocols of RCTs examining therapeutic surgical interventions for gastric cancer will be undertaken. Systematic reviews of RCTs will be interrogated to identify publications not previously identified. We will limit our analysis to RCTs as the primary purpose of the GASTROS study is to influence future RCTs.

Abstracts will be screened by two researchers and relevant publications identified. All reported outcomes will be extracted verbatim in addition to definitions and outcome measurement instruments used. Validated Patient Reported Outcome Measurements (PROMs) such as those used to report 'quality of life' will be critically reviewed to identify further outcomes to be added to the 'long-list'[20]. Whilst overall quality of life may be deemed an outcome that should be prioritized and included in a COS, there may be components related to eating and drinking, for example, that may be deemed important outcomes within their own right.

2.3.4.1.2 Patient Interviews

Previous reports have highlighted that patients often have differing priorities and perspectives relating to outcomes measured in trials[21–24]. To ensure that the views of patients are adequately considered, a series of semi-structured qualitative interviews, with patients who have previously undergone surgery, will be undertaken. All interviews will be audio recorded, transcribed and interrogated for themes which may supplement the outcomes already gathered from the systematic literature review. There is no 'sample size' calculation for qualitative research. The total number of participants should be guided by the concept of 'saturation', whereby further interviews do not result in the identification of new outcomes, and can range from between 5 and 50 participants[25,26]. Based on the authors' experience in qualitative research methods in COS development, we expect that between 15 and 30 patients will need to be interviewed before 'saturation' is reached.

To ensure a broad range of views are expressed during the interviews, we aim to purposefully sample patients based on several characteristics. These include age, sex and time since surgery, type of surgical approach (open or minimally invasive) and whether patients have undergone other peri-operative therapies (chemotherapy or chemo-radiotherapy).

2.3.4.2 Stage 2: Prioritisation of Outcomes to finalise a COS

2.3.4.2.1 Overview

Delphi surveys have been used in many COS projects to reach consensus on the most important outcomes to include[14,27,28]. One of the main benefits of this approach is that the views of all participants are equally heard. This may not be the case in a face-to-face forum where the views of one individual or group of participants may be more vociferous. There is no fixed methodological approach to undertake a Delphi survey. Some groups have retained

all potential outcome domains in each round and used the participant responses to inform a final consensus meeting[27,29], whilst others have only retained outcome domains deemed important in each round[28]. We intend to use a hybrid approach over three rounds described in greater detail below. Following the Delphi survey, a meeting of key stakeholder representatives will take place to ratify the prioritised outcomes into a core outcome set.

2.3.4.2.2 Organising the outcome list in preparation for stage 2

Once potentially important outcomes have been identified from the systematic review and patient interviews, a final long-list of items will be compiled for the Delphi survey. We plan to recruit at least 100 participants and so to minimise non-response and attrition between survey rounds, the initial number of items submitted to the Delphi survey will need to be carefully managed. Previous COS developers have aimed for less than 100 initial items for participants to prioritise[28]. To achieve this, individual outcomes will be organised into 'outcome domains' (table 1) whilst ensuring that domains do not become too broad. For example, the outcomes 'hospital-acquired pneumonia', 'pleural effusion' and 'atelectasis' grouped together under the outcome domain 'respiratory complications' may be appropriate, whereas grouping the same outcomes under the domain 'complications' may be too non-specific. The process of compiling and finalising the outcome domains will be undertaken during a meeting of key stakeholder representatives to ensure transparency. This meeting will involve open discussion of each outcome domain, including information relating to how the outcome domain was formulated, to ensure that it is not too broad or specific. An outcome domain will be admitted into the long-list for the subsequent eDelphi survey once agreement by majority regarding its appropriateness has been reached by all stakeholder representatives.

Each item entered into the survey will be described in lay terms with an additional scientific description. For example, an 'anastomotic leak' may be described as 'a leak from the join between the stomach and the bowel'. All item descriptions will be reviewed by the study group and patient representatives. Items will be presented to participants as collections with similar characteristics (e.g. outcomes related to 'adverse events' or 'technical aspects of surgery').

2.3.4.2.3 Participants & Sample size

Representatives from our three primary stakeholder groups – patients, clinical nurse specialists and surgeons – will be invited to participate in the Delphi survey. Whilst there is no accepted or required 'sample size' requirement for a Delphi survey[30], we aim to recruit at least 100 participants in total. The views of each stakeholder group will be considered separately which will enable intra and inter-stakeholder group variability to be explored. As explained previously, gastric cancer is a worldwide disease, and as such, participants will be sought internationally through a network of patient groups, organisations, professional associations and cancer institutes. The Delphi survey will be internet-based; however, we

will give participants the opportunity to complete hard copies of the surveys so as not to exclude those with limited internet access or knowledge of the internet.

2.3.4.2.4 Delphi Survey

2.3.4.2.4.1 Round 1

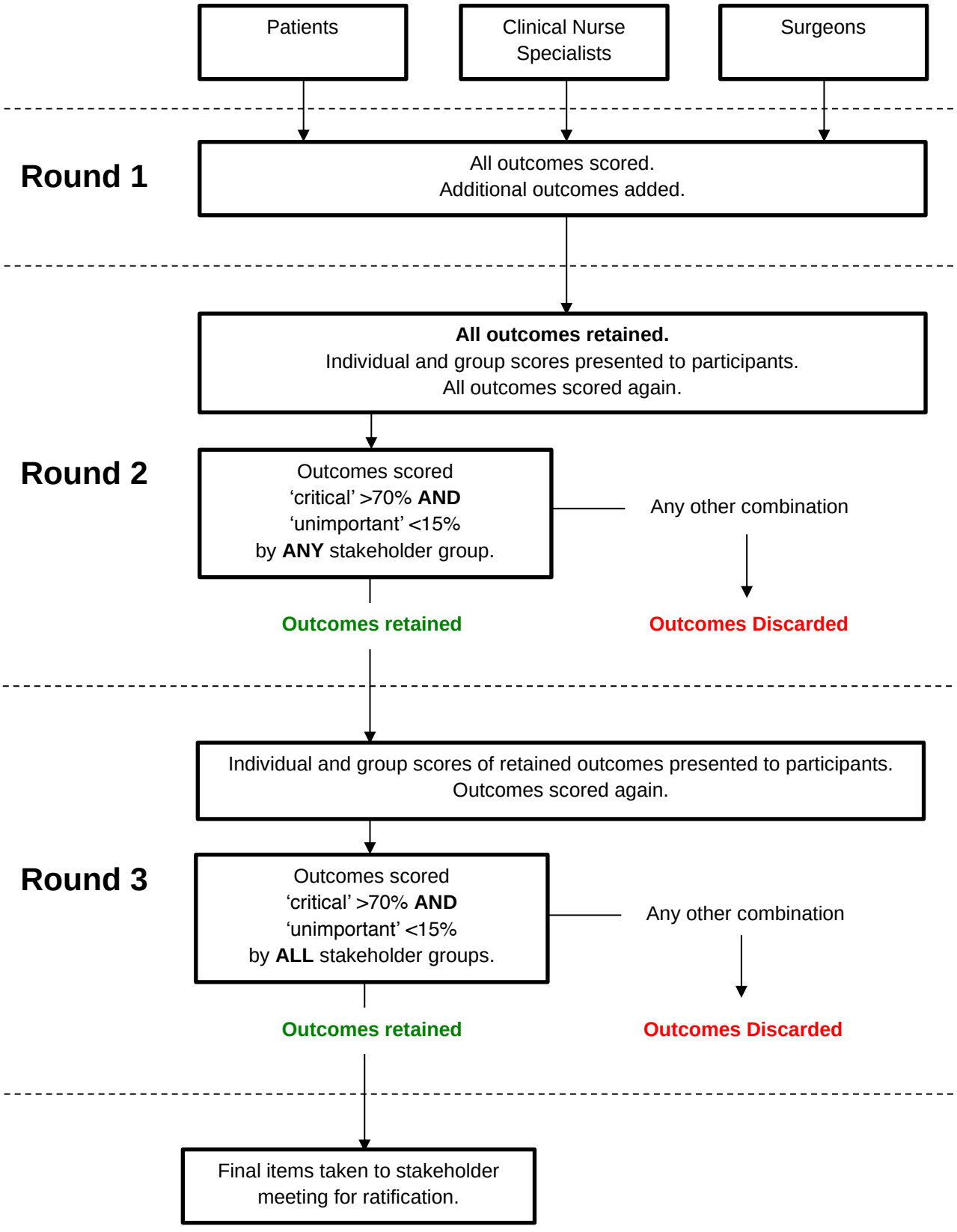
A summary of the entire eDelphi survey process is illustrated in figure 2. Participants will be asked to score each outcome domain on a 9 point scale proposed by the GRADE group [http://www.gradeworkinggroup.org], in which 1 to 3 signifies an outcome of 'limited importance', 4 to 6 'important but not critical', and 7 to 9 'critical'. Round 1 will also provide participants with the opportunity to add further outcomes which they think may be important. Any suggested outcomes deemed to represent a new outcome domain by the study group (following discussion and a majority decision) will be added to the list for consideration in round two. In addition, prior to commencing round 1, participants will be asked to enter demographic information about themselves including country of residence and language spoken. Surgeons will also be asked about the volume of gastrectomies performed. This will enable us to explore the impact of language, cultural variation and surgical experience in relation to the Delphi survey responses.

2.3.4.2.4.2 Round 2

All items in addition to further new outcome domains identified by participants in round 1 will be carried forward for consideration in round 2. Descriptive statistics will be used to summarise the scores from round 1 and presented to participants. Participants will see the results of their individual score for each outcome in addition to the median score of each stakeholder group. The rationale for showing participants the scores from other groups is that it may improve consensus between the stakeholder groups[15]. In addition, by carrying all items forward from round 1, it may be possible to identify changes in scoring patterns as a result of viewing other scores. Participants will be asked to score all items once again using the 9-point scale.

Outcome domains which are scored 'critical' by greater than 70 per cent of participants from **ANY** stakeholder group, **AND** 'unimportant' by less than 15 per cent of the group, will be carried forward for further consideration in round 3. The rationale for this threshold is that for an outcome domain to be included in the COS, it requires agreement by the majority regarding the critical importance of the outcome, with only a small minority considering it to have little importance. By carrying forward outcomes relevant to at least one stakeholder group, participants will be given another opportunity to reflect on the importance of the outcome domain in the final round. As the scope of this study is to identify the MOST important outcomes, all other outcomes will be discarded.

Figure 2-2 Summary of Delphi Survey Process



2.3.4.2.4.3 Round 3

All retained outcomes will be summarised and participants will view both their individual scores and those of the other groups before being asked to score items a final time using the 9-point scale. Outcome domains which are scored as 'critical' by greater than 70 per cent **AND** 'unimportant' by less than 15 per cent of participants from **ALL THREE GROUPS** will be retained for inclusion in the COS.

2.3.4.2.4.4 Missing Responses

If a participant does not complete a subsequent round of the Delphi survey, their scores from previous rounds will be counted as valid and retained in the study. Similarly, if a participant fails to score a specific item during a survey round, the answers to other items will be held as valid and retained. The rate of missing responses will be reported with the results of the Delphi survey.

2.3.4.2.4.5 Stakeholder Meeting

Following the Delphi survey, a meeting of stakeholder representatives will take place to review the results and recommend the outcome domains as a COS.

2.3.4.3 Stage 3: Identification of Outcome Measurement Tools

The final stage of the study will be based on guidance set out by COMET and COSMIN in the selection of appropriate measurement instruments for the outcome domains included in the COS[16]. Our strategy is summarised in figure 3 and involves 4 stages:

1) Conceptual considerations
2) Finding existing outcome measurement instruments (OMIs)
3) Quality assessment of OMIs
4) Recommendations on the selection of outcome measurement instruments for a COS and at what time points they should be used.

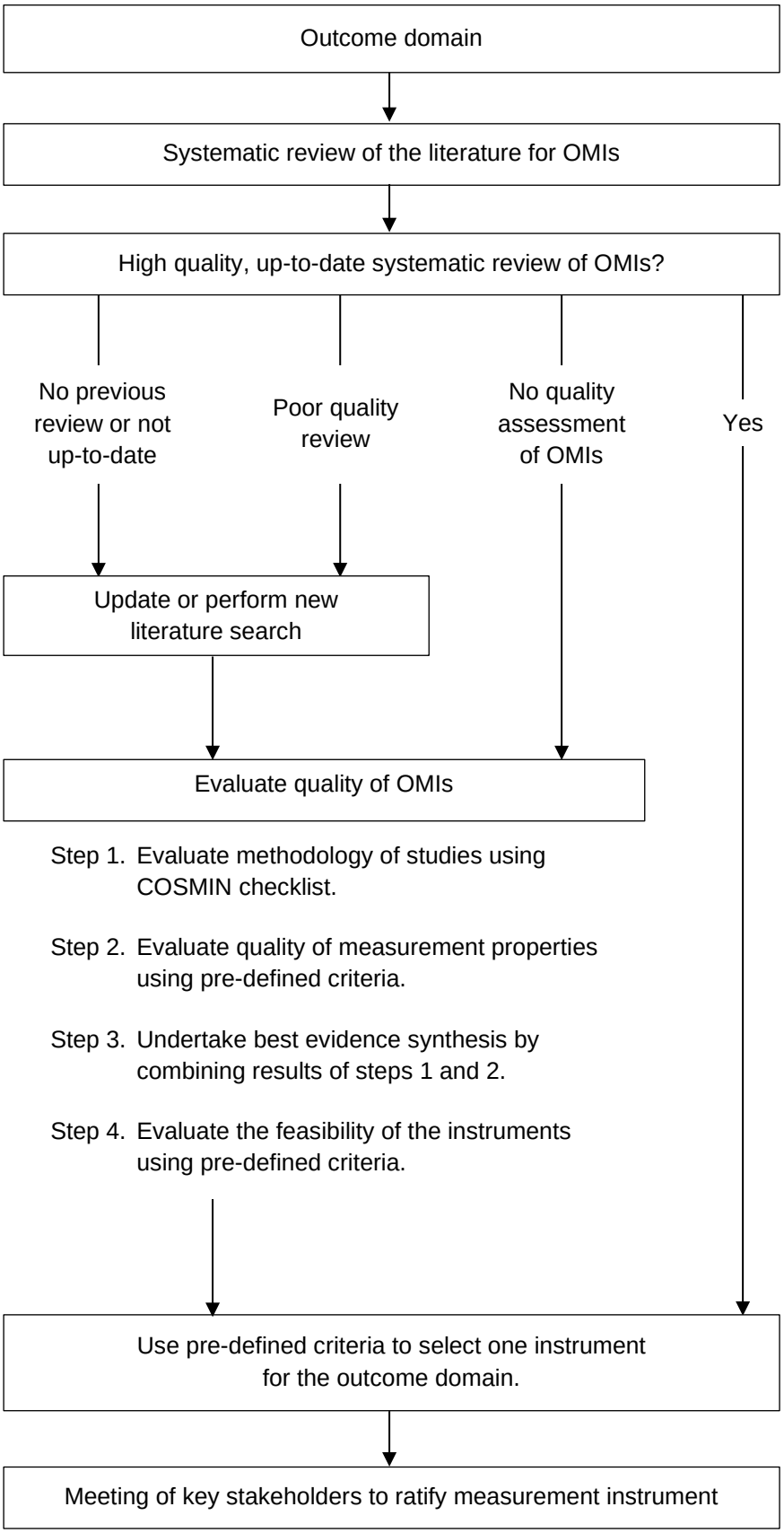
2.3.4.4 Conceptual considerations

The first step involves identifying the scope of outcomes to be measured. These will be identified in stage 2 of the study. The scope of the COS has been described earlier in this protocol.

2.3.4.5 Finding existing outcome measurement instruments (OMIs)

Existing OMIs will be identified through several approaches. A structured search of MEDLINE and EMBASE via Ovid will identify systematic reviews of OMIs for the outcome domain concerned. If the systematic reviews are of high quality and have undertaken a quality assessment of the OMIs, then one OMI will be selected and presented to a group of key stakeholder representatives at the end of the process.

Figure 2-3 Process of identifying OMIs for outcome domains in the COS.



If there are no systematic reviews or they are of poor quality, then a new or updated literature search will be performed. We will search MEDLINE and EMBASE via Ovid to identify studies of OMIs. We will also interrogate reference lists and examine trials and protocols identified in stage 1 of the GASTROS study to identify further OMIs. Studies describing these OMIs will be quality assessed as described below. OMIs identified through up-to-date systematic reviews where quality assessments were not undertaken will also be assessed by the pre-defined standards below.

2.3.4.6 Quality assessment of OMIs

Each OMI related-study identified will undergo an evaluation of its methodological quality using the COSMIN checklist[31]. In addition, an evaluation of the measurement properties of the OMI will be undertaken against several pre-defined criteria[16] including 'content validity' and 'internal structure'. Content validity is defined as 'the degree to which the content of a measurement instrument is an adequate reflection of the outcome to be measured'. 'Internal structure' is comprised of two aspects – 'internal consistency' (the degree of interrelatedness among the items within the OMI) and 'structural validity' (the degree to which the scores of a measurement instrument are an adequate reflection of the dimensionality of the outcome to be measured). If either 'content validity' or 'internal structure' are considered poor or unknown, then the OMI will not be assessed further. The results of this quality assessment will be combined in a 'best evidence synthesis' exercise against criteria defined by the COMET-COSMIN guidance. It is also essential that OMIs are assessed in terms of their feasibility of use. The COMET-COSMIN guidance provides 17 different factors against which feasibility can be assessed. These include 'patient comprehensibility', 'interpretability', 'ease of administration' and 'completion time'.

2.3.4.7 Generic recommendations on the selection of outcome measurement instruments for a COS

An OMI will be recommended if it meets the following criteria:

1) There is 'high quality' evidence of 'good' content validity and 'good' internal structure **AND**
2) The OMI is feasible to use.

'High quality evidence' is defined as consistent findings in multiple studies of at least 'good' quality OR in one study of 'excellent' quality AND a total sample size of 100 patients or more (see the COSMIN checklist[31] for clarification of the terms 'good' and 'excellent' quality).

It is possible that more than one OMI can be recommended for an outcome domain. Conversely it is possible that no OMIs are recommended. This scenario may form the basis of future work to develop an OMI for that domain.

2.3.4.8 Key Stakeholder Meeting

Following quality assessment for OMIs for each outcome domain included in the COS, we will invite representatives from each key stakeholder group to review the evidence from this stage of study and ratify the recommended OMIs as an outcome measurement instrument set. The primary function of the stakeholder meeting is to ensure transparency of the process, raise further questions and seek further clarifications (if any). The evidence considered will also inform recommendations made through the stakeholder meeting regarding when these OMIs should be used to measure the core outcomes.

2.3.5 Implementation Strategy

A COS must be implemented widely within its clinical field to have its intended benefit. Whilst grant awarding bodies and international research groups are increasingly promoting the use of COS, researchers must be willing to incorporate them in trial designs. Our approach to maximise the use of our COS is one of inclusion of key stakeholders in designing and delivering our study and wide dissemination of our findings at every stage. Given that most surgical gastric cancer trials are being undertaken in the Far East, this inevitably means involvement of international stakeholders. We are working with several groups in South Korea, Japan and China in addition to European and North and South American teams to ensure that this aspect of our study is facilitated. It is not yet fully understood how language or cultural differences may affect the results of consensus processes such as the one we propose. Our study will provide the opportunity to explore this question further.

Some of the steps that we have considered as part of our dissemination and implementation strategy include:

1) Registration of our study with COMET database (http://www.comet-initiative.org/studies/details/764?result=true),
2) Development of our study website (www.GASTROSstudy.org) where key stakeholders and interested parties can find regular updates and register for participation,
3) Development of our social media identity e.g. twitter (@GASTROSstudy),
4) Widespread dissemination of our work at every stage of the study through:
    a. National and international scientific meetings
    b. Journal publications
    c. Patient events
    d. Regular updates to our network of international patient groups and charities, professional associations and cancer centres.

Engagement with, and ‘ownership’ of, the COS by professional bodies will also be an important way to facilitate the necessary regular review of the COS. Such reviews are needed to ensure that individual outcomes remain relevant and to add new outcomes as

appropriate. No recommendation exists regarding the time interval between reviews, but we anticipate the need for review within 3-5 years.

2.4 Discussion

There is no COS for trials examining surgical interventions for gastric cancer. Through the GASTROS study, we aim to standardise the definition, collection and measurement of core outcomes which can be used to compare future trials in this field. This will:

1. improve the reliability of evidence synthesis on which robust clinical guidelines can be based,
2. improve shared decision-making and the pre-operative consent process as outcomes from surgical interventions which are relevant to both clinicians and patients become more apparent,
3. better equip healthcare providers how best to prioritise funding for interventions that reflect the needs and priorities of patients.

The COS will also inform non-RCT trial design and additionally provide a minimum set of outcomes relevant to key stakeholders, which can be collected by healthcare providers and organisations designing national audits and prospective databases.

The GASTROS study will also provide a platform for future work which includes the development of PROMs where they are deficient and the further development of a COS which is relevant to multi-modal therapies. Once core outcomes are identified, work can also commence on developing a minimum dataset of factors which can influence these outcomes so that risk-adjustment of outcomes and ultimately the external validity of trials can improve.

2.5 References

1. Fact Sheets by Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed February 3, 2016.

2. Cancer survival for common cancers | Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/survival/common-cancers-compared#heading-Three. Accessed May 16, 2016.

3. Centre H& SCI. National OesophagoGastric Cancer Audit 2015. http://www.hscic.gov.uk/article/1165/searchcatalogue?q=%22National+Oesophago-Gastric+Cancer+Audits%22&sort=Date&size=10&page=1#top. Published 2015. Accessed May 16, 2016.

4. Messager M, de Steur WO, van Sandick JW, et al. Variations among 5 European countries for curative treatment of resectable oesophageal and gastric cancer: A survey from the EURECCA Upper GI Group (EUropean REgistration of Cancer CAre). Eur J Surg Oncol. 2016;42(1):116-122. doi:10.1016/j.ejso.2015.09.017.

5. Gurusamy Kurinchi S. Laparoscopic versus open gastrectomy for gastric cancer. Cochrane Database Syst Rev. 2014;9(2):e88753. doi:10.1002/14651858.CD011389.

6. Mocellin S, McCulloch P, Kazi H, Gama-Rodrigues JJ, Yuan Y, Nitti D. Extent of lymph node dissection for adenocarcinoma of the stomach. Cochrane database Syst Rev. 2015;8:CD001964. doi:10.1002/14651858.CD001964.pub4.

7. Blencowe NS, Strong S, McNair AGK, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg. 2012;255(4):658-666. doi:10.1097/SLA.0b013e3182480a6a.

8. Currie A, Brigic A, Blencowe NS, et al. Systematic review of surgical innovation reporting in laparoendoscopic colonic polyp resection. Br J Surg. 2015;102(2):e108-e116. doi:10.1002/bjs.9675.

9. Whistance RN, Forsythe RO, McNair AGK, et al. A systematic review of outcome reporting in colorectal cancer surgery. Colorectal Dis. 2013;15(10):e548-60. doi:10.1111/codi.12378.

10. Hopkins JC, Howes N, Chalmers K, et al. Outcome reporting in bariatric surgery: an in-depth analysis to inform the development of a core outcome set, the BARIACT Study. Obes Rev. 2015;16(1):88-106. doi:10.1111/obr.12240.

11. Glossary: Core Outcome Set (COS). http://www.comet-initiative.org/glossary/cos/. Accessed May 19, 2016.

12. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(1):132. doi:10.1186/1745-6215-13-132.

13. Keeley T, Williamson P, Callery P, et al. The use of qualitative methods to inform Delphi surveys in core outcome set development. Trials. 2016;17(1):230. doi:10.1186/s13063-016-1356-7.

14. Sinha IP, Smyth RL, Williamson PR, et al. 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(1):e1000393. doi:10.1371/journal.pmed.1000393.

15. Brookes ST, Macefield RC, Williamson PR, 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(1):409. doi:10.1186/s13063-016-1479-x.

16. Prinsen CAC, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a “Core Outcome Set” – a practical guideline. Trials. 2016;17(1):449. doi:10.1186/s13063-016-1555-2.

17. Kirkham JJ, Gorst S, Altman DG, et al. COS-STAR: a reporting guideline for studies developing core outcome sets (protocol). Trials. 2015;16(1):373. doi:10.1186/s13063-015-0913-9.

18. Database Search - Core Outcome Measures in Effectiveness Trials Initiative (COMET). http://www.comet-initiative.org/studies/search. Accessed May 19, 2016.

19. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-1472. doi:10.1136/gut.2010.228254.

20. Macefield RC, Jacobs M, Korfage IJ, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). Trials. 2014;15(1):49. doi:10.1186/1745-6215-15-49.

21. Crowe S, Fenton M, Hall M, et al. Patients’, clinicians’ and the research communities’ priorities for treatment research: there is an important mismatch. Res Involv Engagem. 2015;1(1):2. doi:10.1186/s40900-015-0003-x.

22. Tallon D, Chard J, Dieppe P, et al. Relation between agendas of the research community and the research consumer. Lancet (London, England). 2000;355(9220):2037-2040. doi:10.1016/S0140-6736(00)02351-5.

23. Rosenheck R, Stroup S, Keefe RSE, et al. Measuring outcome priorities and preferences in people with schizophrenia. Br J Psychiatry. 2005;187(6).

24. Urquhart-Secord R, Craig JC, Hemmelgarn B, et al. Patient and Caregiver Priorities for Outcomes in Hemodialysis: An International Nominal Group Technique Study. Am J Kidney Dis. 2016;68(3):444-454. doi:10.1053/j.ajkd.2016.02.037.

25. Mason M. Sample Size and Saturation in PhD Studies Using Qualitative Interviews. Forum Qual Sozialforsch / Forum Qual Soc Res. 2010;11(3).

26. Baker SE, Edwards R. How many qualitative interviews is enough? Expert voices and early career reflections on sampling and cases in qualitative research.

27. Harman NL, Bruce IA, Callery P, et al. MOMENT--Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials. 2013;14:70. doi:10.1186/1745-6215-14-70.

28. McNair AGK, Whistance RN, Forsythe RO, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLOS Med. 2016;13(8):e1002071. doi:10.1371/journal.pmed.1002071.

29. MacLennan S, Bekema HJ, Williamson PR, et al. A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey. Trials. 2015;16:76. doi:10.1186/s13063-015-0598-0.

30. Powell C. The Delphi technique: myths and realities. J Adv Nurs. 2003;41(4):376-382. doi:10.1046/j.1365-2648.2003.02537.x.

31. Terwee CB, Mokkink LB, Knol DL, Ostelo RWJG, Bouter LM, De Vet HCW. Rating the methodological quality in systematic reviews of studies on measurement properties: A scoring system for the COSMIN checklist. Qual Life Res. 2012;21(4):651-657. doi:10.1007/s11136-011-9960-1.

3 Reporting of Outcomes in Gastric Cancer Surgery Trials: A Systematic Review

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3.1 Abstract

Background

The development of clinical guidelines for the surgical management of gastric cancer should be based on robust evidence from well-designed trials. Being able to reliably compare and combine the outcomes of these trials is a key factor in this process.

Objectives

To examine variation in outcome reporting by surgical trials for gastric cancer; to identify outcomes for prioritisation in an international consensus study to develop a core outcome set in this field.

Data Sources

Systematic literature searches (Evidence Based Medicine, MEDLINE, EMBASE, CINAHL, ClinicalTrials.gov and WHO ICTRP) and a review of study protocols of randomized controlled trials, published between 1996 and 2016.

Intervention

Therapeutic surgical interventions for gastric cancer. Outcomes were listed verbatim, categorized into groups (outcome themes) and examined for definitions and measurement instruments

Results

Of 1919 abstracts screened, 32 trials (9,073 participants) were identified. A total of 749 outcomes were reported of which 96 (13 per cent) were accompanied by an attempted definition. No single outcome was reported by all trials. ‘Adverse events’ was the most frequently reported ‘outcome theme’ in which 240 unique terms were described. 12 trials (38%) classified complications according to severity, with 5 (16%) using a formal classification system (Clavien-Dindo or Accordion scale). Of 27 trials which described ‘short-term’ mortality, 15 (47%) used one of 5 different definitions. Six out of the 32 trials (19%) described ‘patient-reported outcomes’.

Conclusion

Reporting of outcomes in gastric cancer surgery trials is inconsistent. A consensus approach to develop a minimum set of well-defined, standardized outcomes to be used by all future trials examining therapeutic surgical interventions for gastric cancer is needed. This should consider the views of all key stakeholders, including patients.

3.2 Introduction

3.2.1 Background

Gastric cancer remains a leading cause of cancer-related death globally[1]. Long-term survival remains poor and has not improved significantly over the last four decades[2]. Whilst there has been a shift to multi-modal therapy over the last decade, surgery remains the primary method of curative treatment. Many developments in surgical techniques aim to improve long-term survival, whilst minimizing post-operative complications. Understanding which of these approaches are optimal for patients should be based on robust evidence from well-designed trials. This process involves the synthesis of evidence in the form of systematic reviews which can only be reliably undertaken if trials report the same outcomes and measure them in the same manner.

This review forms part of the first stage of a three-stage study, which intends to examine and address problems with inconsistent outcome reporting in gastric cancer surgery trials (GASTROS – **GA**stric Cancer **S**urgery **TR**ials **R**eported **O**utcome **S**tandardisation). The study aims to develop a 'core outcome set' (COS) – a minimum group of standardized and well-defined outcomes, relevant to key stakeholders and measured by all trials[3] – to harmonise the reporting of outcomes in randomized control trials within this field. Our previously published study protocol contains an overview of all three stages[4].

Within our study protocol, we described the results from a 'rapid review' of gastric cancer surgery trials during a 24-month period which demonstrated significant variations in outcome reporting. We hypothesised that these variations were likely to represent a more widespread problem within this field. Inconsistencies in outcome reporting are prevalent within the medical literature and contribute significantly to 'research waste'[5]. Several reviews have demonstrated that trials within the same field often report different outcomes, define them poorly and use various outcome measurement instruments[6–9]. This results in data which cannot be reliably compared or combined leading to further confusion within the evidence base. As such, initiatives such as COMET (Core Outcome Measures in Effectiveness Trials) were formed to promote the development of COS to address these issues[3].

With respect to surgical trials for gastric cancer, a) no rigorous examination of outcome reporting has been previously undertaken and b) there is no COS for use in this field.

3.2.2 Aims & Objectives

This review aims to demonstrate whether further work to develop a COS to be used in surgical trials for gastric cancer is required. Specifically, the objectives are:

- to examine the degree of variation in the reporting of outcomes described by gastric cancer surgery trials.

- to generate a ‘long-list’ of potentially important outcomes which will be prioritized during a Delphi survey in stage two of the study.

3.3 Methods

3.3.1 Definitions

The GASTROS study, and more specifically this review, focuses on outcome reporting in ‘therapeutic surgical trials’. A ‘surgical trial’ has been previously defined as one of the following[10]:

- Type 1 - A trial of medical interventions in surgical patients
- Type 2 - A trial which compares a surgical intervention to another surgical intervention
- Type 3 - A trial which compares a surgical intervention to a non-surgical intervention

The GASTROS study focuses on ‘type 2’ trials due to the significant research activity within this field (a detailed justification can be found in our study protocol)[4]. In the context of gastric cancer, a ‘therapeutic surgical intervention’ is defined as a potentially curative procedure which aims to excise the gastric neoplasm resulting in partial or total organ loss.

3.3.2 Search strategy

A summary of the review’s inclusion and exclusion criteria is summarised in table 1, with details of our search strategy presented below. An example search algorithm for the Medline via OVID database is presented in appendix 1.

3.3.2.1 Timeline

Trials were searched from 1996 when the first CONSORT statement for the reporting of RCTs was published up to and including March 2016. The COS aims to influence trial design regardless of the country of origin of participating centres and patients. Many of the surgical interventions (e.g. D2 lymphadenectomy) which have recently been examined in the West have long been established practice in the Far East and Asia. Searching trials over a 20-year period allows a comprehensive understanding of which outcomes have been measured for similar trials regardless of the trial location.

Table 3.1 Inclusion and exclusion criteria for this review.

	Included	Excluded
Types of Studies	• Type 2* surgical randomized controlled trials (RCTs) and protocols of surgical RCTs (all trial phases). • Systematic reviews of type 2 surgical RCTs. • English Language studies.	• Type 1 or type 3* surgical RCTs and systematic reviews of type 1 or type 3 RCTs. • Non-randomized studies. • Non-English language studies.
Population	• Patients aged 18 years and over.	• Patients below the age of 18.
Interventions	• Partial or total gastrectomy. • Surgery with curative intent.	• Esophagectomy for gastro-esophageal junctional tumors. • Surgery with non-curative intent (i.e. in stage 4 cancer with prior expectation of an R1 or R2 resection) for the relief of symptoms such as gastric outlet obstruction or bleeding. • Endoscopic interventions.
Conditions	• Invasive cancer of the stomach and gastro-oesophageal junction.	• Dysplasia or non-invasive gastric neoplasms. • Sarcoma (including gastrointestinal stromal tumours). • Gastric lymphoma.

*Type 1 - a trial of medical interventions in surgical patients, type 2 - a trial which compares a surgical intervention to another surgical intervention, type 3 - a trial which compares a surgical intervention to a non-surgical intervention[10].

3.3.2.2 Identifying studies

Detailed search strategies were developed for each of the following electronic databases examined:

- Evidence Based Medicine Reviews via OVID
    - Cochrane Database of Systematic Reviews 2005 to March 30, 2016,
    - ACP Journal Club 1991 to March 2016,
    - Database of Abstracts of Reviews of Effects 1st Quarter 2016
    - Cochrane Central Register of Controlled Trials February 2016
    - Health Technology Assessment 1st Quarter 2016
    - NHS Economic Evaluation Database 1st Quarter 2016
- MEDLINE via OVID (January 1st 1996 to March 30, 2016)
- EMBASE via OVID (January 1st 1996 to March 30, 2016);
- CINAHL via EBSCO (January 1st 1996 to March 30, 2016).

In order to identify surgical interventions and outcome measures being used in current studies, we searched the following databases for protocols of ongoing trials, including completed trials not yet published:

- The US National Institutes of Health Trials Register (http://clinicaltrials.gov);
- The WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/default.aspx).

Non-English language studies were excluded from this review due to resource limitations. Trials published only as conference abstracts were excluded as they are often limited by 'word count' and hence the abstract would not represent a comprehensive list of outcomes measured in the respective study.

3.3.3 Assessment of eligibility

For quality assurance, two review authors (BA and AMG) independently screened the titles and abstracts retrieved from the electronic searches. This assessment was undertaken in groups of ten abstracts in reverse chronological order. Once there was complete agreement with two consecutive groups of ten abstracts, the remaining abstracts were split, and each reviewer screened independently. Full text copies of all study publications that appeared to meet the inclusion criteria were obtained. Full text copies were also obtained where there was insufficient information in the title or abstract to make a clear judgement. Systematic reviews of RCTs were also retrieved to find studies which had previously not been identified.

BA and AMG independently assessed the full text copies for eligibility. This assessment was undertaken in groups of ten publications in reverse chronological order. Once there was

complete agreement with two consecutive groups of ten abstracts, the remaining publications were split, and each reviewer extracted data independently. Any disagreements were resolved through discussion. There were no unresolved disagreements that required referral to the GASTROS study management team for a final decision.

3.3.4 Data Extraction

BA and AMG independently reviewed all eligible publications and extracted data (described below) into a Microsoft Excel (Version 2013, Microsoft, Washington, DC, USA) spreadsheet.

3.3.5 Publication versus Study

It is not uncommon that investigators publish results at different stages of their trial and with each publication present a new set of outcomes. The GASTROS study team decided to amalgamate the outcomes published in all publications associated with a single trial to more fairly reflect outcomes being reported by research groups.

3.3.6 Trial Characteristics

The following data were recorded for each trial:

1. Author details
2. Title of publication
3. Journal
4. Year of publication
5. Number of participating centres
6. Country of 1st Author
7. Countries of participating centres
8. Total number of patients recruited to the study
9. Length of follow up
10. Interventions being investigated

3.3.7 Outcomes

We defined an outcome as ‘a unique endpoint which attempts to describe health-related changes that occur secondary to a therapeutic intervention’[4]. The following data were recorded for each outcome:

1. Outcome measured (and whether stated as primary or secondary outcome). Where a primary outcome was not explicitly stated, the outcome on which the sample size calculation was based was taken as the primary outcome.

2. Whether the outcome was defined or not. Outcomes were considered defined if text of their meaning or a citation was provided.
3. The definition of the outcome.
4. The method of outcome measurement (indicators and/or tools used, if relevant).
5. Time points and time-period at or during which the outcome was measured (for example quality of life at 3-months post-surgery).

3.3.8 Merging Outcomes & Grouping Under 'Themes'

Outcomes were extracted verbatim from publications and minimal merging of terms was undertaken. Outcomes were merged to accommodate for variant spellings of the same words. For example, 'anastomotic leak', 'anastomotic leakage' and 'anastomotic leak**s**' were merged into 'anastomotic leak'. The verbatim texts and merged terms were verified and authorized respectively by the study management group.

From the experience of other groups undertaking reviews of outcome reporting, the resulting lists of outcomes are generally extremely long and unwieldy[6]. Consequently, developing a method to organize these outcomes has been necessary. The subject of taxonomy in outcome reporting, including hierarchical structure and which terms/definitions to use, is an emerging area of great significance. We set out our definitions a priori, which can be found in our study protocol[11]. Many COS developers have organized their outcomes into broad categories with common 'themes'. Our study is one of only a handful addressing outcome reporting in surgical trials related to the gastro-intestinal (GI) tract. At the time of data analysis, we opted to group outcomes under 'themes' (detailed in table 3) similar to those described by other surgical COS[6–8,12]. Doing so enables COS researchers to more readily understand trends in outcome reporting within the field of GI surgery. Whilst the themes used in our review enable the reader to understand the types of outcomes being reported, this system has not been developed through wider consensus and has not been subject to a validation process.

At the time of writing, a broader taxonomy for outcome classification had been proposed[13]. This system aims to address some of the ambiguity associated with outcome classification on a wider-scale and organizes outcomes under 38 'outcomes domains' which sit under 5 'outcomes areas' ('mortality/survival', 'physiological/clinical', 'life impact', 'resource use' and 'adverse events'). Whilst the authors have demonstrated that this system is comprehensive and applicable to trials irrespective of the field being studied, they have called for further validation of their work.

3.3.9 Patient & Public Involvement

A Study Advisory Group (SAG) forms part of the management structure of the wider GASTROS study[4], of which this review forms part of the first stage. The SAG is made up of key stakeholder representatives including patients, oncology nurses and surgeons. The group provides advice on the methodology of the study, general delivery of the study against its stated objectives, and ensures that the viewpoints of all stakeholder groups are considered. The results of this systematic review were presented to a SAG meeting; the ensuing discussion influenced certain aspects of the results section within this paper such as the emphasis on patient-reported outcomes.

3.4 Results

3.4.1 Summary

A total of 1,919 abstracts were screened which resulted in the identification of 48 publications from 32 trials (having recruited a total of 9073 patients) eligible for inclusion in the review (figure 1). A further 875 protocols were screened which identified 24 active or unpublished trials aiming to recruit 10,761 patients. A summary of all trials included in the analysis is described in table 2. During the data extraction process, no disagreements requiring discussion in the study management group arose between the two independent reviewers. A total of 749 (392 unique terms) outcomes were reported of which 13% (96 out of 749) were accompanied by an attempted definition. Thirty-eight percent of trials (12 out of 32) described a primary outcome or provided a sample size calculation. No single outcome was reported in every trial.

3.4.2 Analysis of Outcomes According to Themes

Outcomes were organised into eight ‘outcome themes’, illustrated in figure 2 and described in table 3. A comprehensive list of reported outcomes is presented in appendix 2. Below, we present a summary of some of the most commonly reported short and long-term outcome themes.

Figure 3-1 Study selection and inclusion.

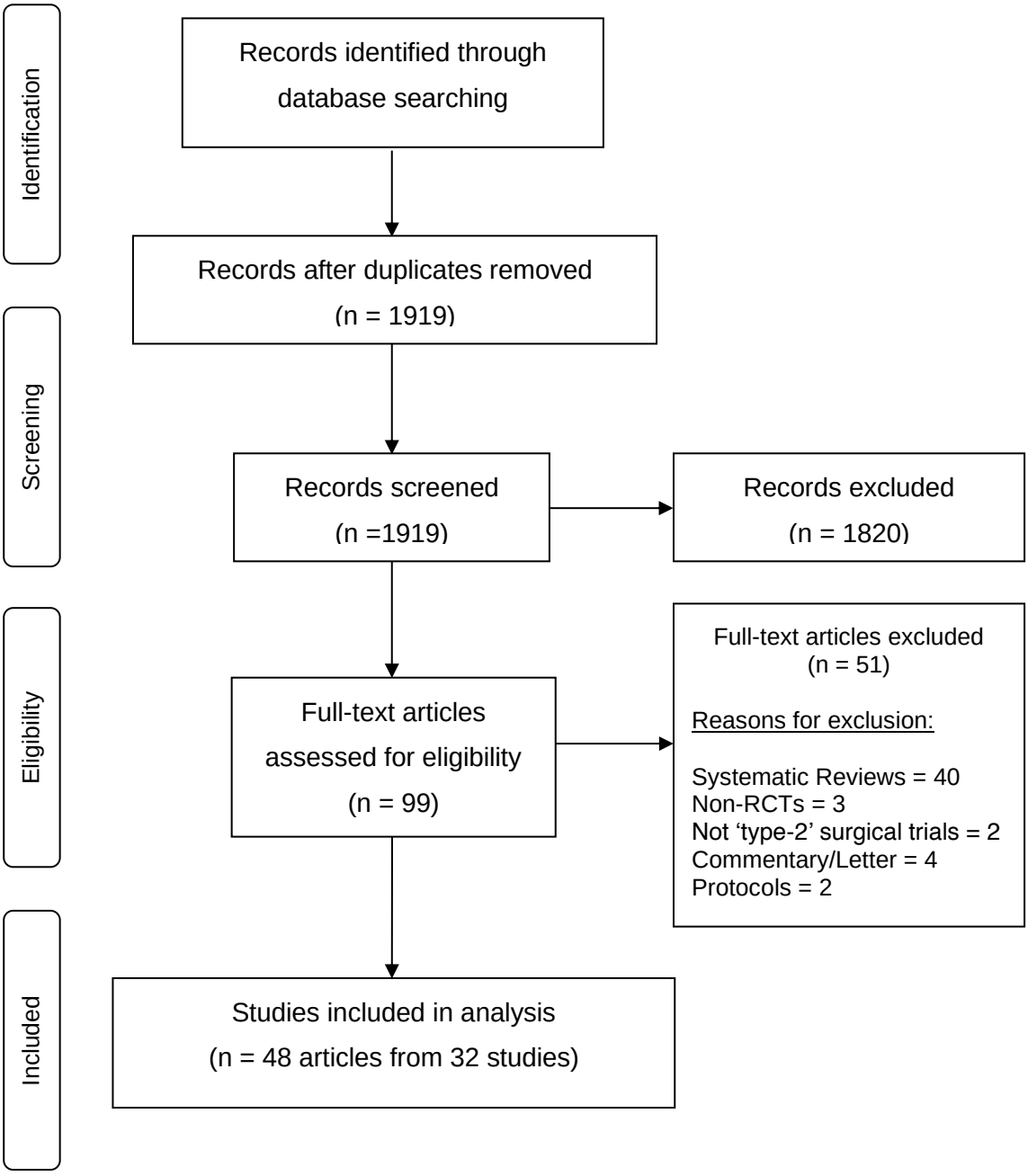


Table 3.2 Published gastric cancer surgery trials included in the study analysis.

Trial Reference(s)	Trial Number	Author	Year of 1st Publication	Participating Countries	Number of Recruiting Sites	Patients Recruited	Interventions
[38–41]	1	Hartgrink et al, Bonenkamp et al., Sasako et al., Songun et al.	1995	Netherlands	80	1078	• D1 lymphadenectomy • D2 lymphadenectomy
[42,43]	2	Cuschieri et al.	1996	UK	32 surgeons*	737	• D1 lymphadenectomy • D2 lymphadenectomy
[44,45]	3	Marubini et al. Bozzetti et al.	1999	Italy	31	615	• D2 subtotal gastrectomy • D2 total gastrectomy
[46]	4	Maeta et al	1999	Japan	1	70	• D3 total gastrectomy • D4 total gastrectomy
[47]	5	Furukawa et al.	2000	Japan	1	110	• Total gastrectomy and distal pancreatectomy • Pancreas preserving total gastrectomy

[48]	6	Csendes et al.	2002	Chile	1	187	• D2 total gastrectomy with splenectomy • Spleen preserving D2 total gastrectomy
[49]	7	Kitano et al.	2002	Japan	1	28	• Laparoscopic assisted distal gastrectomy • Open distal gastrectomy
[50]	8	Fujii et al	2003	Japan	1	20	• Laparoscopic assisted distal gastrectomy • Open distal gastrectomy
[51–53]	9	Degiuili et al	2004	Italy	5	267	• D1 lymphadenectomy • D2 lymphadenectomy
[54–57]	10	Sano et al., Sasako et al., Kodera et al, Tsujinaka et al.	2004	Japan	24	523	• D2 lymphadenectomy • D2 lymphadenectomy & para-aortic node dissection
[58]	11	Shibata et al	2004	Japan	9	81	• Pylorus-preserving gastrectomy • Distal gastrectomy
[59]	12	Inaba et el.	2004	Japan	1	410	• Midline laparotomy • Transverse laparotomy
[60]	13	Lee et al.	2005	South Korea	1	47	• Laparoscopic assisted D2 distal gastrectomy

							• Open D2 distal gastrectomy
[61]	14	Hayashi et al	2005	Japan	1	28	• Laparoscopic assisted distal gastrectomy with extra-perigastric node dissection. • Open distal gastrectomy with extra-perigastric node dissection.
[62]	15	Huscher et al	2005	Italy	1	59	• Laparoscopic sub-total gastrectomy • Open sub-total gastrectomy
[63–66]	16	Wu et al.	2006	Taiwan	1	221	• D1 lymphadenectomy • D3 lymphadenectomy
[67,68]	17	Sasako et al. Kurokawa et al.	2006	Japan	27	167	• Left Thoracoabdominal approach • Abdominal trans-hiatal approach
[69]	18	Yu et al	2006	South Korea	1	207	• Total gastrectomy with splenectomy • Spleen preserving total gastrectomy
[70]	19	Kulig et al.	2007	Poland	6	275	• D2 lymphadenectomy • D2 lymphadenectomy & para-aortic node dissection
[71,72]	20	Kim et al.	2008	South Korea	1	164	• Laparoscopic assisted distal gastrectomy

							• Open distal gastrectomy
[73]	21	Yonemura et al.	2008	Japan, Taiwan, South Korea	10	269	• D2 lymphadenectomy • D4 lymphadenectomy
[74,75]	22	Kim et al.	2010	South Korea	13	1416	• Laparoscopic assisted D2 distal gastrectomy • Open distal D2 gastrectomy
[76]	23	Imamura et al	2011	Japan	11	210	• D2 gastrectomy and bursectomy • D2 gastrectomy without bursectomy
[77]	24	Cai et al.	2012	China	1	123	• Laparoscopic assisted distal gastrectomy • Open distal gastrectomy
[78]	25	Chen Hu et al.	2012	China	1	88	• Laparoscopic gastrectomy • Open gastrectomy • Standard post-operative protocol • Fast-track post-operative protocol
[79]	26	Takiguchi	2013	Japan	1	40	• Laparoscopic assisted distal gastrectomy • Open distal gastrectomy
[80]	27	Lee et al.	2013	South Korea	1	204	• D2 distal gastrectomy • D2 total gastrectomy

[81]	28	Sakuramoto et al	2013	Japan	1	64	• Laparoscopic assisted distal gastrectomy • Open distal gastrectomy
[82]	29	Aoyama et al	2014	Japan	1	26	• Laparoscopic assisted distal gastrectomy • Open distal gastrectomy
[83]	30	Hirao et al.	2015	Japan	11	210	• D2 gastrectomy with bursectomy • D2 gastrectomy without bursectomy
[84]	31	Galizia et al	2015	Italy	1	73	• D1'+' total gastrectomy • D2 total gastrectomy
[85]	32	Hu et al.	2016	China	14	1056	• Laparoscopic assisted D2 distal gastrectomy • Open D2 distal gastrectomy

*Number of sites not specified.

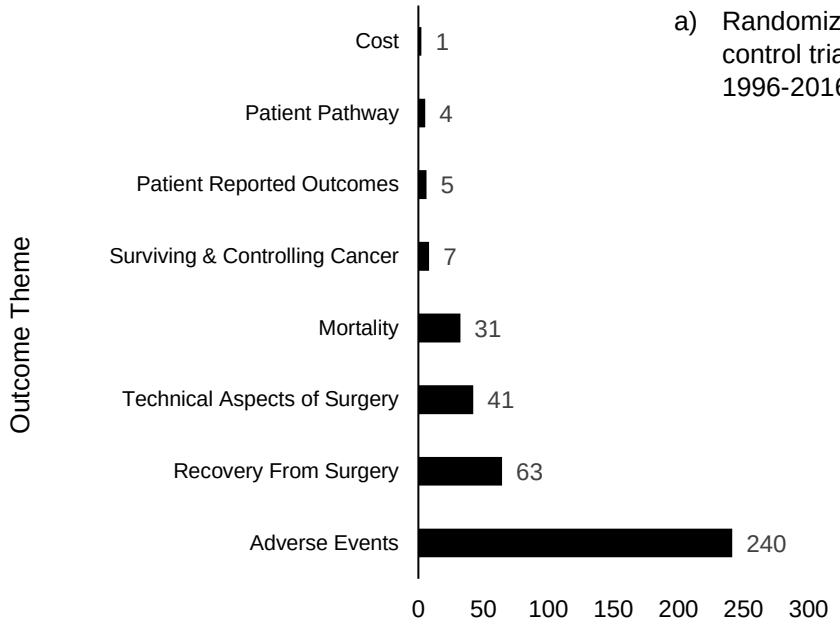
Table 3.3 Number of times at least one outcome from respective theme was reported in published trials and unpublished or actively recruiting trial protocols.

Outcome Theme	Theme Definition	Published Trials (n=32) (%)	Unpublished or Actively Recruiting Trial Protocols (n=23**) (%)
Cost	Relating to delivery of surgery as part of clinical care within a healthcare system.	1 (3)	5 (23)
Patient Pathway	Outcomes related to the flow of patients through the healthcare system (e.g. hospital stay, readmission).	20 (63)	4 (17)
Patient-Reported Outcomes	Outcomes taken from the patient perspective.*	6 (19)	13 (57)
Surviving & Controlling Cancer	Measures of disease recurrence or disease progression.	15 (47)	17 (74)
Mortality	Outcomes related to short and long-term survival/death rates and cause of death.	27 (84)	19 (83)
	Short-term mortality/peri-operative death.	27 (84)	10 (43)
	Long-term survival.	13 (41)	19 (44)

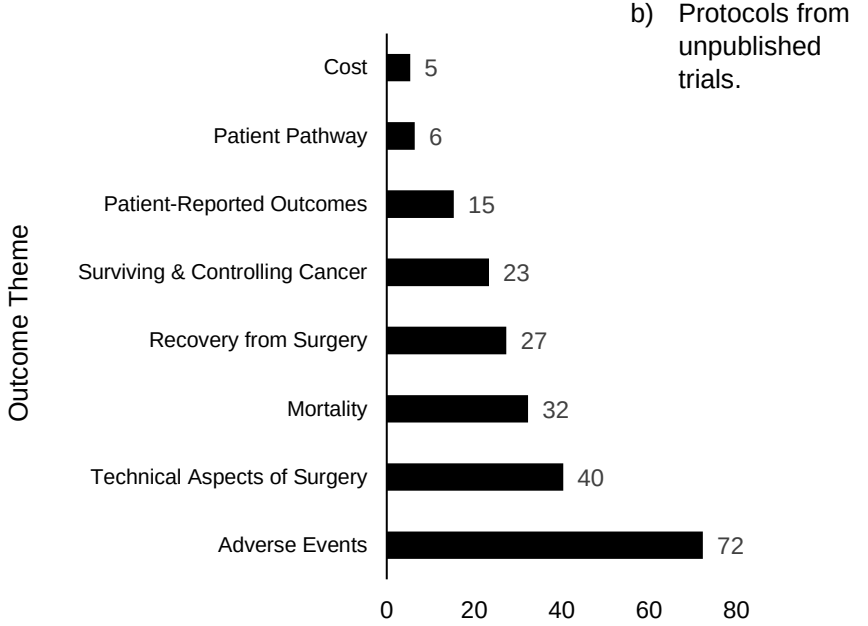
Outcome Theme	**Theme Definition**	**Published Trials (n=32) (%)**	**Unpublished or Actively Recruiting Trial Protocols (n=23**) (%)**
Technical Aspects of Surgery	Outcomes recorded directly in the operating theatre (e.g. operation time, blood loss).	31 (97)	13 (57)
Recovery from Surgery	Report of patient condition following surgery and the ability to return to preoperative or premorbid state.	16 (50)	9 (39)
Adverse Events	Forms of short- and long-term postoperative complications following surgery.	31 (97)	18 (78)

* Certain patient-reported outcomes may fall under other 'themes', e.g. 'post-operative pain' may relate to 'recovery from surgery'. ** One trial protocol contained no information about planned outcomes to report, therefore 23 out of total 24 trials were included in this table.

Figure 3-2 Outcome themes reported in a) gastric cancer surgery trials and b) in future trials based on study protocols.



Number of times an outcome from respective theme was reported.



Number of times an outcome from respective theme identified from protocols.

3.4.2.1 Mortality

Death after surgery was generally described as ‘short-term’ and ‘long-term’ survival. Long-term survival was used as a primary outcome measure in 41% of trials (13 out of 32). The terms used to describe long-term mortality and the time-points at which they were measured was inconsistent (table 4). ‘Short-term’ mortality was reported by 84% of trials (27 out of 32) of which fifteen provided one of the following definitions (frequency each definition was used is presented in brackets):

1. ‘Death within **30-days** of surgery’ (3/15)
2. ‘Death of **any cause** within **30 days**, or death within the **same hospitalization**’ **(9/15)**
3. **‘In-hospital** deaths and ‘deaths’ **within 1 month’ (1/15)**
4. ‘Death within **30 days** of the operation or during **any hospital stay**’ **(1/15)**
5. **‘Any death** that occurred during the **hospital stay (1/15)**

3.4.2.2 Adverse Events

Adverse events were the commonest outcome theme to be reported and made up half of the ten most reported outcomes (table 5). ‘Anastomotic leak’ was the commonest adverse event to be reported and was described using 5 different definitions (frequency each definition was used is presented in brackets):

- ‘Clinical and radiological diagnosis’ (2).
- ‘Confirmed by gastrointestinal x-ray imaging, endoscopy, or angiography’ (1).
- ‘Dehiscence confirmed by radiographic examination using contrast medium’ (1).
- ‘Type I anastomotic leakage: a small, localized leakage at the esophago-jejunal anastomosis, without pleural or abdominal spillage, demonstrated by radiologic studies with barium’ (1).
- ‘Type II anastomotic leakage: an important dehiscence of the esophago-jejunal anastomosis, with pleural or abdominal dissemination, appearance of intestinal content through the drains, a positive methylene blue test (appearance of orally ingested methylene blue through the drains), and clear demonstration of this leakage by radiologic contrast studies’ (1).

Adverse events were categorized by 12 out of 32 trials using terms including ‘major’, ‘minor’, ‘short-term’ and ‘long-term’. Five trials used a formal classification system (Clavien-Dindo Classification or Accordion Severity Grading).

Table 3.4 Reporting of 'long-term mortality' in gastric cancer surgery trials.

Term used	Number of trials reporting outcome	Follow-up period used	Frequency defined	Definitions provided
'Overall Survival' including 'death from all causes'	19	Not described 3 years 5 years 6 years 7 years 10 years	7	• Date of randomisation until the day of death or the day of last follow-up (censored). • Date of surgery to the date of death from any cause, censoring the follow-up time at the most recent date for living patients. • Date of randomization to the date of death. • Date of randomization to the date of death from any cause. • OS included operative deaths. • OS excluded post-operative deaths.
'Survival' including 'survival period'	13	Not described 5 years 11 years	4	• Survival excluding operative mortality • Survival 5 years after curative surgery

Term used	Number of trials reporting outcome	Follow-up period used	Frequency defined	Definitions provided
'Disease-specific survival' including 'gastric cancer related deaths'	4	Not described 5 years	1	• Proportion of patients who had not died from gastric cancer.
Disease-free survival*	1	Not described	1	• Time from randomization to recurrence or death due to any cause.
Recurrence-free survival*	2	Not described	2	• Time from randomization to either the first recurrence or death from any cause. • Time from randomization to the first documentation of cancer recurrence or death from any cause.

*Although these terms do not relate to mortality, they have been included in this table as the definitions provided by papers describe death as an end-point.

Table 3.5 The ten most frequently reported outcomes.

Outcome	Theme	Number of trials reporting outcome	Trials reporting the outcome*
Number of lymph nodes dissected/resected/retrieved	Technical aspects of surgery	22	2, 3, 5, 7, 9, 10, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 29, 31, 32
Operative time	Technical aspects of surgery	18	4, 5, 7, 8, 10, 11, 13, 14, 15, 16, 20, 22, 23, 24, 25, 26, 27, 30
Anastomotic leak	Adverse events	17	1, 2, 4, 6, 10, 14, 16, 17, 19, 22, 23, 24, 25, 27, 28, 31, 32
Pancreatic fistula	Adverse events	15	1, 2, 4, 5, 10, 16, 17, 19, 22, 23, 26, 27, 28, 29, 32
Duration of hospital stay	Patient pathway	12	1, 2, 5, 6, 7, 9, 13, 15, 20, 23, 26, 28
Duration of post-operative hospital stay	Recovery from surgery	11	2, 7, 9, 11, 14, 16, 19, 24, 25, 27, 32
Pneumonia	Adverse events	11	7, 10, 11, 12, 17, 23, 27, 28, 29, 31, 32
‘5-year’ survival	Mortality	11	1, 2, 6, 9, 10, 16, 17, 18, 19, 22, 26
Wound infection	Adverse events	10	2, 6, 12, 15, 16, 18, 19, 22, 24, 28
Abdominal abscess	Adverse events	10	5, 9, 10, 16, 17, 19, 23, 26, 28, 29

*See table 1 for trial numbers and associated publications.

3.4.2.3 Patient Reported Outcomes

Patient-Reported Outcomes (PROs) were reported in 19% of trials (6 out of 32) and included measures of quality of life (QoL) (n=3) and 'pain' (n=3). QoL was measured using validated tools for gastric cancer in two trials (EORTC QLQ-C30 with QLQ-STO22, and Spitzer QoL Index) and a non-validated tool in one trial. Pain was measured using 3 different visual-analogue scales.

3.4.2.4 Multi-Centre Trials

Forty per cent (13 out of 32) of studies were multi-centre trials (table 2). Ninety-two percent (12 out of 13) of trials stated a primary outcome measure (5-year overall survival, 5-year survival, all-cause mortality and 3-year disease free survival). Sixteen percent (63 out of 393) of all outcomes reported in these trials were accompanied by an attempted definition. PRO's were reported in 23% of trials (3 out of 13) with 8% (1 out of 13) of studies reporting 'quality of life' as an outcome.

3.4.3 Findings from Study Protocols

Most of the 24 ongoing or unpublished trials[14–37] are recruiting in China (n=13), with twenty examining 'extent of lymphadenectomy' or minimally invasive approaches to surgery. A total of 220 uniquely termed outcomes are planned to be reported, thirty-five of which (16%) have an accompanying definition in the respective protocol. The commonest term used to report 'long-term survival' is 'overall survival' (OS) which will be measured by sixteen trials. Seven of these trials plan to measure OS after 5-years of follow-up, three at 3-years of follow-up, and six did not identify time points at which OS would be measured. At the time of our search, one trial protocol contained no information about which outcomes are to be measured.

QoL is due to be measured by ten trials (42 per cent) with five trials proposing to use one or a combination of four different measurement instruments (EORTC QLQ-C30 with QLQ-STO22, SF-36, GIQLI and Euro-Quality of Life-5D). Seven protocols described the timing of the quality of life measurements as follows:

- 'Preoperative, postoperative **3 weeks** and postoperative **12 months'.**
- 'In **pre-therapy <7 days**, **pre-operative <7 days**, and post-operative at **12 months** after surgery'.
- **'90th postoperative day'.**
- **'Regularly** for three years after surgery'.
- **'Preoperatively**, **five days postoperatively**, **three** months, **six** months and **one year** postoperatively'.
- **'Baseline**, **1 week**, **1** month, **6**-month, **1 year**, **3 years'.**
- **'6 weeks**, **12**, **24**, **36**, **48** and **50 months** after surgery'.

3.5 Discussion

This review is the first to examine the subject of outcome reporting in this field and demonstrates significant inconsistencies in the outcomes measured in trials examining therapeutic surgical interventions for gastric cancer. Not only is there disagreement about 'what' outcomes should be measured, but also 'when' and 'how' they should be measured. Consequently, undertaking meta-analyses and systematic reviews of these interventions becomes problematic and impacts negatively on the ability of researchers and clinicians to formulate robust clinical guidelines for the radical treatment of gastric cancer.

This problem is not confined to previously reported trials. Our analysis of outcome reporting in multi-centre studies and review of active trial protocols has demonstrated similar issues and further highlights the potential 'research waste' within this field. Glasziou and Chambers' estimate that 85 per cent of all biomedical research is 'wasted', and that a significant proportion of this can be attributed to problems choosing and reporting relevant outcomes in trials[5]. Thus, if we combine the number of patients who have participated in gastric cancer surgery trials over the last two decades with those that actively recruiting trials wish to attract, a total of twenty thousand patients may have participated in trials which, from a methodological perspective, could have had a far greater benefit and impact. Not only does this represent an inefficient use of time and scarce financial resource, but it may also have a longer-lasting negative impact on future trial participation by patients. Similar issues related to outcome reporting have been identified by several other groups supporting the theory that this is a widespread problem[6–8,12].

Furthermore, if the methodology of a particular trial is not sufficiently robust or the outcomes reported are not relevant to key stakeholders, the natural course will be for other researchers to examine the same interventions again, using a different approach. If these subsequent trials do not address the underlying methodological issues, they only contribute to a perpetual cycle which serves to weaken the evidence base. This is reflected within the field of gastric cancer surgery where thirteen trials have examined minimally invasive gastrectomy and a further 13 are actively recruiting to trials examining the same intervention.

Reported outcomes should be relevant to key stakeholders including patients. Given the sheer volume of complications that are reported by gastric surgical trials, one may expect to find the impact on QoL is routinely reported. Indeed, QoL has been demonstrated as an important outcome to measure in other gastrointestinal cancer fields[86]. This has certainly not been the case with gastric cancer surgery trials over the last two decades and whilst there seems to be a greater acceptance by trials currently in recruitment that QoL is important to measure (although this group still represents less than half of ongoing trials), there remains great variation in relation to 'how' and 'when' it is measured.

To address these inconsistencies, we believe that a 'core outcome set' (COS) is required for gastric cancer surgery studies. Developing a minimum reporting standard will contribute to maximising the benefits from randomized control trials which are expensive, labour intensive and logistically challenging to set up. A COS does not aim to restrict the outcomes that are reported, but merely to ensure that the most critical outcomes (as decided by key stakeholders) are clearly defined and measured uniformly.

The challenges associated with inconsistent outcome reporting in trials is certainly not confined to the field of gastric cancer. The COMET (Core Outcome Measurement in Effectiveness Trials) initiative database (http://www.comet-initiative.org/studies/search) contains details of over 400 completed, active or planned COS projects from across many different specialities[87]. Whilst experience within this relatively new research field has grown considerably over the last decade, there is still much work to be done to further develop the various methodological approaches which can be applied. The GASTROS study aims to add to this in several ways including examining the role of 'internationalising' COS development by undertaking a multi-language Delphi survey as part of a consensus-seeking process.

3.5.1 Strengths and Limitations

In addition to being the first systematic review to examine this subject, this study is based on a reproducible and transparent methodology which has been subjected to critical appraisal from a study management team and peer-review process; a protocol of the GASTROS study which aims to develop this COS has been published previously[4]. Nonetheless, there are limitations. Including non-English and non-randomized studies in our search strategy may have identified other different outcomes reported in this field. However, when finalising our inclusion criteria for this review, the two primary objectives of this review were considered - namely a) to describe the current landscape of outcome reporting in gastric cancer surgery RCTs and b) to take forward a 'long-list' of outcomes to be prioritised (by means of a Delphi survey) to form the basis of a COS for RCTs. Whilst we accept that such a COS would have benefits to non-RCTs and national audits, our primary focus was to improve the quality of RCTs and hence excluding other study types. In addition, there will be an opportunity during the Delphi survey (stage 2 of the GASTROS study) for participants to add further outcomes (not already identified from this review) which key stakeholders deem important to be considered for prioritisation. A further limitation to this review was that it was not prospectively registered on a public database. However, as we describe above, the GASTROS study, including its scope and systematic review plan, has been peer-reviewed and published previously[4].

In summary, the reporting of outcomes in gastric cancer surgery trials is inconsistent and there is large variation with respect to definitions, measurement tools and timing of measurement. This means that data cannot be synthesized efficiently. We believe that a

COS to define a minimum set of standards to implement across all gastric surgical trial is warranted.

3.6 References

1. Fact Sheets by Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed July 24, 2017.

2. Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971–2011: a population-based study. Lancet. 2015;385(9974):1206-1218. doi:10.1016/S0140-6736(14)61396-9.

3. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(S3):280. doi:10.1186/s13063-017-1978-4.

4. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study). Trials. 2017;18(1):370. doi:10.1186/s13063-017-2100-7.

5. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet (London, England). 2009;374(9683):86-89. doi:10.1016/S0140-6736(09)60329-9.

6. Hopkins JC, Howes N, Chalmers K, et al. Outcome reporting in bariatric surgery: an in-depth analysis to inform the development of a core outcome set, the BARIACT Study. Obes Rev. 2015;16(1):88-106. doi:10.1111/obr.12240.

7. Blencowe NS, Strong S, McNair AGK, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg. 2012;255(4):658-666. doi:10.1097/SLA.0b013e3182480a6a.

8. Whistance RN, Forsythe RO, McNair AGK, et al. A systematic review of outcome reporting in colorectal cancer surgery. Colorectal Dis. 2013;15(10):e548-60. doi:10.1111/codi.12378.

9. Duffy JMN, Hirsch M, Gale C, et al. A systematic review of primary outcomes and outcome measure reporting in randomized trials evaluating treatments for pre-eclampsia. Int J Gynecol Obstet. 2017;139(3):262-267. doi:10.1002/ijgo.12298.

10. McCulloch P. Randomised trials in surgery: problems and possible solutions. BMJ. 2002;324(7351):1448-1451. doi:10.1136/bmj.324.7351.1448.

11. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the

reporting of outcomes in gastric cancer surgery trials: Protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study). Trials. 2017;18(1). doi:10.1186/s13063-017-2100-7.

12. Currie A, Brigic A, Blencowe NS, et al. Systematic review of surgical innovation reporting in laparoendoscopic colonic polyp resection. Br J Surg. 2015;102(2):e108-e116. doi:10.1002/bjs.9675.

13. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84-92. doi:10.1016/j.jclinepi.2017.12.020.

14. Hasegawa S, Yamamoto Y, Taguri M, et al. A Randomized Phase II Trial of Omentum-preserving Gastrectomy for Advanced Gastric Cancer. doi:10.1093/jjco/hys208.

15. Nakamura K, Katai H, Mizusawa J, et al. A Phase III Study of Laparoscopy-assisted Versus Open Distal Gastrectomy with Nodal Dissection for Clinical Stage IA/IB Gastric Cancer (JCOG0912). Jpn J Clin Oncol. 2013;43(3):324-327. doi:10.1093/jjco/hys220.

16. Yoshikawa T, Fukunaga T, Taguri M, et al. Laparoscopic or Open Distal Gastrectomy After Neoadjuvant Chemotherapy for Operable Gastric Cancer, a Randomized Phase II Trial (LANDSCOPE Trial). Jpn J Clin Oncol. 2012;42(7):654-657. doi:10.1093/jjco/hys057.

17. Effect of Laparoscopy-Assisted Distal Gastrectomy for Locally Advanced Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02464215. Accessed July 25, 2017.

18. The Long-term Effect of D4 Lymphadenectomy for Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02423278. Accessed July 25, 2017.

19. A Comparison of Laparoscopic With Open Distal Gastrectomy in Advanced Gastric Cancer After Neoadjuvant Chemotherapy - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02404753. Accessed July 25, 2017.

20. Randomized Controlled Trials Comparing Clinical Outcomes of 3D Versus 2D Laparoscopic Surgery for Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02327481. Accessed July 25, 2017.

21. Prospective Study on Modified Delta-shaped Gastroduodenostomy in Totally

Laparoscopic Surgery for Distal Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02289183. Accessed July 25, 2017.

22. Haverkamp L, Brenkman HJF, Seesing MFJ, et al. Laparoscopic versus open gastrectomy for gastric cancer, a multicenter prospectively randomized controlled trial (LOGICA-trial). BMC Cancer. 2015;15:556. doi:10.1186/s12885-015-1551-z.

23. Laparoscopy-assisted and Open Distal Gastrectomy for Gastric Cancer in the Elderly Patients. https://clinicaltrials.gov/ct2/show/NCT02246153.

24. A Clinical Trial of D1+ Versus D2 Distal Gastrectomy for Stage IB & II Advanced Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02144727. Accessed July 25, 2017.

25. Straatman J, van der Wielen N, Cuesta MA, et al. Surgical techniques, open versus minimally invasive gastrectomy after chemotherapy (STOMACH trial): study protocol for a randomized controlled trial. Trials. 2015;16(1):123. doi:10.1186/s13063-015-0638-9.

26. D2 and D2+ Radical Surgery for the Treatment of Advanced Distal Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01836991. Accessed July 25, 2017.

27. Park JY, Kim Y-W, Ryu KW, et al. Assessment of laparoscopic stomach preserving surgery with sentinel basin dissection versus standard gastrectomy with lymphadenectomy in early gastric cancer–A multicenter randomized phase III clinical trial (SENORITA trial) protocol. BMC Cancer. 2016;16(1):340. doi:10.1186/s12885-016-2336-8.

28. Laparoscopy-assisted Total Gastrectomy for Clinical Stage I Gastric Cancer (KLASS-03). https://clinicaltrials.gov/ct2/show/study/NCT01584336. Accessed July 25, 2017.

29. Efficacy of Laparoscopic Subtotal Gastrectomy With D2 Lymph Node Dissection for Locally Advanced Gastric Cancer (KLASS-02-RCT). https://clinicaltrials.gov/ct2/show/NCT01456598.

30. GCSSG-SPNX: Trial to Evaluate Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma: JCOG0110 - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT00112099. Accessed July 25, 2017.

31. Randomized Controlled Trial to Evaluate Laparoscopic versus Open Surgery for Advanced Gastric Cancer (JLSSG0901: Adv.GC-LAP/OPEN, PII/III). http://apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000003420. Accessed

July 25, 2017.

32. Comparsion of D2 verus D3 surgical procedure outcome in locally advanced gastric cancer patients following perioperative chemotherapy. http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=6992&EncHid=&userName=CTRI/2013/08/003882. Accessed July 25, 2017.

33. Prospective clinical trial on the long-term outcome and survival of vagus (coeliac branch)-preserving gastrectomy for cT1-3 gastric cancer. http://www.chictr.org.cn/showprojen.aspx?proj=4360. Accessed July 25, 2017.

34. Prospective clinical trial on the long-term outcome and survival of pylorus-preserving gastrectomy for early gastric cancer. http://www.chictr.org.cn/showprojen.aspx?proj=4361. Accessed July 25, 2017.

35. Prospective and open multicenter randomize control study for enlarged lymphadenectomy of gastric cancer. http://www.chictr.org.cn/showprojen.aspx?proj=7870. Accessed July 25, 2017.

36. Open vs minimal invasive surgery for gastric submucosal tumor: a randomized trial on efficacy and safety. http://www.chictr.org.cn/showprojen.aspx?proj=4811. Accessed July 25, 2017.

37. A Multicenter Clinical Trial on Laparoscopic Gastric Cancer Surgery Compared With Open Surgery - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02302794. Accessed July 25, 2017.

38. Hartgrink HH. Extended Lymph Node Dissection for Gastric Cancer: Who May Benefit? Final Results of the Randomized Dutch Gastric Cancer Group Trial. J Clin Oncol. 2004;22(11):2069-2077. doi:10.1200/JCO.2004.08.026.

39. Bonenkamp JJ, Songun I, Welvaart K, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet. 1995;345(8952):745-748. doi:10.1016/S0140-6736(95)90637-1.

40. Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. Br J Surg. 1997;84(11):1567-1571.

41. Songun I, Putter H, Kranenbarg EM-K, Sasako M, van de Velde CJH. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11(5):439-449. doi:10.1016/S1470-2045(10)70070-X.

42. Cuschieri a, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections

for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer. 1999;79(9-10):1522-1530. doi:10.1016/S0959-8049(01)80998-9.

43. Cuschieri a, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet. 1996;347:995-999. doi:10.1016/S0959-8049(01)80998-9.

44. Marubini E, Bozzetti F, Miceli R, Bonfanti G, Gennari L. Lymphadenectomy in gastric cancer: prognostic role and therapeutic implications. Eur J Surg Oncol. 2002;28(4):406-412. doi:Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't.

45. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann Surg. 1999;230(2):170-178. doi:10.1097/00000658-199908000-00006.

46. Maeta M, Yamashiro H, Saito H, et al. A prospective pilot study of extended (D3) and superextended para-aortic lymphadenectomy (D4) in patients with T3 or T4 gastric cancer managed by total gastrectomy. Surgery. 1999;125(3):325-331. doi:10.1016/S0039-6060(99)70244-8.

47. Furukawa H, Hiratsuka M, Ishikawa O, et al. Total gastrectomy with dissection of lymph nodes along the splenic artery: a pancreas-preserving method. Ann Surg Oncol. 2000;7(9):669-673.

48. Csendes A, Burdiles P, Rojas J, Braghetto I, Diaz JC, Maluenda F. A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. Surgery. 2002;131(4):401-407. doi:10.1067/msy.2002.121891.

49. Kitano S, Shiraishi N, Fujii K, Yasuda K, Inomata M, Adachi Y. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. Surgery. 2002;131(1 Suppl):0-11. doi:a120115 [pii].

50. Fujii K, Sonoda K, Izumi K, Shiraishi N, Adachi Y, Kitano S. T lymphocyte subsets and Th1/Th2 balance after laparoscopy-assisted distal gastrectomy. Surg Endosc Other Interv Tech. 2003;17(9):1440-1444. doi:10.1007/s00464-002-9149-3.

51. Degiuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2

gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol. 2004;30(3):303-308. doi:10.1016/j.ejso.2003.11.020.

52. Degiuli M, Sasako M, Ponti a. Morbidity and mortality in the italian gastric cancer study group randomized clinical trial of D1 versus D2 resection for gastric cancer. Br J Surg. 2010;97(5):643-649. doi:10.1002/bjs.6936.

53. Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg. 2014;101(2):23-31. doi:10.1002/bjs.9345.

54. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008;359(5):453-462. doi:10.1056/NEJMoa0707035.

55. Takeshi Sano. Gastric Cancer Surgery : Morbidity and Mortality Results From a Prospective Randomized Controlled Trial Comparing D2 and Extended Para-Aortic Lymphadenectomy — Japan Clinical Oncology Group Study 9501. J Clin Oncol. 2004;22(14):2767-2773. doi:10.1200/JCO.2004.10.184.

56. Kodera Y, Sasako M, Yamamoto S, Sano T, Nashimoto a, Kurita a. Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer. Br J Surg. 2005;92(9):1103-1109. doi:10.1002/bjs.4979.

57. Tsujinaka T, Sasako M, Yamamoto S, et al. Influence of overweight on surgical complications for gastric cancer: results from a randomized control trial comparing D2 and extended para-aortic D3 lymphadenectomy (JCOG9501). Ann Surg Oncol. 2007;14(2):355-361. doi:10.1245/s10434-006-9209-3.

58. Shibata C, Shiiba K, Funayama Y, et al. Outcomes after Pylorus-preserving Gastrectomy for Early Gastric Cancer: A Prospective Multicenter Trial. World J Surg. 2004;28(9):857-861. doi:10.1007/s00268-004-7369-5.

59. Inaba T, Okinaga K, Fukushima R, et al. Prospective randomized study of two laparotomy incisions for gastrectomy: Midline incision versus transverse incision. Gastric Cancer. 2004;7(3):167-171. doi:10.1007/s10120-004-0291-6.

60. Lee JH, Han HS. A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. Surg Endosc. 2005;19(2):168-173. doi:10.1007/s00464-004-8808-y.

61. Hayashi H, Ochiai T, Shimada H, Gunji Y. Prospective randomized study of open versus laparoscopy-assisted distal gastrectomy with extraperigastric lymph node dissection for early gastric cancer. Surg Endosc. 2005;19(9):1172-1176. doi:10.1007/s00464-004-8207-4.

62. Huscher CGSS, Mingoli A, Sgarzini G, et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. Ann Surg. 2005;241(2):232-237. doi:10.1097/01.sla.0000151892.35922.f2.

63. Wu C-W, Hsiung C a, Lo S-S, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol. 2006;7(4):309-315. doi:10.1016/S1470-2045(06)70623-4.

64. Wu C-W, Chiou J-M, Ko F-S, et al. Quality of life after curative gastrectomy for gastric cancer in a randomised controlled trial. Br J Cancer. 2008;98(1):54-59. doi:10.1038/sj.bjc.6604097.

65. Wu CW, Hsiung C a., Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. Br J Surg. 2004;91(3):283-287. doi:10.1002/bjs.4433.

66. Wu C-W, Chang I-S, Lo S, et al. Complications following D3 gastrectomy: post hoc analysis of a randomized trial. World J Surg. 2006;30(1):12-16. doi:10.1007/s00268-005-7951-5.

67. Sasako M, Sano T, Yamamoto S, et al. Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol. 2006;7(8):644-651. doi:10.1016/S1470-2045(06)70766-5.

68. Kurokawa Y, Sasako M, Sano T, et al. Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg. 2015;102(4):341-348. doi:10.1002/bjs.9764.

69. Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. Br J Surg. 2006;93(5):559-563. doi:10.1002/bjs.5353.

70. Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A. Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. Am J Surg. 2007;193(1):10-15. doi:10.1016/j.amjsurg.2006.04.018.

71. Kim YW, Baik YH, Yun YH, et al. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg. 2008;248(5):721-727. doi:10.1097/SLA.0b013e318185e62e\r00000658-200811000-00006 [pii].

72. Kim YW, Yoon HM, Yun YH, et al. Long-term outcomes of laparoscopy-assisted distal gastrectomy for early gastric cancer: Result of a randomized controlled trial (COACT 0301). Surg Endosc Other Interv Tech. 2013;27(11):4267-4276. doi:10.1007/s00464-013-3037-x.

73. Yonemura Y, Wu CC, Fukushima N, et al. Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. Int J Clin Oncol. 2008;13(2):132-137. doi:10.1007/s10147-007-0727-1.

74. Kim W, Kim H-H, Han S-U, et al. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer. Ann Surg. 2015;XX(X):1. doi:10.1097/SLA.0000000000001346.

75. Kim H-H, Hyung WJ, Cho GS, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report--a phase III multicenter, prospective, randomized Trial (KLASS Trial). Ann Surg. 2010;251(3):417-420. doi:10.1097/SLA.0b013e3181cc8f6b.

76. Imamura H, Kurokawa Y, Kawada J, et al. Influence of bursectomy on operative morbidity and mortality after radical gastrectomy for gastric cancer: Results of a randomized controlled trial. World J Surg. 2011;35(3):625-630. doi:10.1007/s00268-010-0914-5.

77. Cai J, Wei D, Gao CF, Zhang CS, Zhang H, Zhao T. A prospective randomized study comparing open versus laparoscopy-assisted D2 radical gastrectomy in advanced gastric cancer. Dig Surg. 2012;28(5-6):331-337. doi:10.1159/000330782.

78. Chen Hu J, Xin Jiang L, Cai L, et al. Preliminary experience of fast-track surgery combined with laparoscopy-assisted radical distal gastrectomy for gastric cancer. J Gastrointest Surg. 2012;16(10):1830-1839. doi:10.1007/s11605-012-1969-4.

79. Takiguchi S, Fujiwara Y, Yamasaki M. Laparoscopy-Assisted Distal Gastrectomy Versus Open Distal. World J Surg. 2013;37(10):2379-2386. doi:10.1007/s00268-013-2121-7.

80. Lee J-H, Son S-Y, Lee CM, Ahn SH, Park DJ, Kim H-H. Morbidity and mortality after laparoscopic gastrectomy for advanced gastric cancer: Results of a phase II clinical trial. Surg Endosc Other Interv Tech. 2013;27(8):2877-2885. doi:10.1007/s00464-

013-2848-0.

81. Sakuramoto S, Yamashita K, Kikuchi S, et al. Laparoscopy versus open distal gastrectomy by expert surgeons for early gastric cancer in Japanese patients: short-term clinical outcomes of a randomized clinical trial. Surg Endosc. 2013;27(5):1695-1705. doi:10.1007/s00464-012-2658-9.

82. Aoyama T, Yoshikawa T, Hayashi T, et al. Randomized comparison of surgical stress and the nutritional status between laparoscopy-assisted and open distal gastrectomy for gastric cancer. Ann Surg Oncol. 2014;21(6):1983-1990. doi:10.1245/s10434-014-3509-9.

83. Hirao M, Kurokawa Y, Fujita J, et al. Long-term outcomes after prophylactic bursectomy in patients with resectable gastric cancer: Final analysis of a multicenter randomized controlled trial. Surgery. 2015;157(6):1099-1105. doi:10.1016/j.surg.2014.12.024.

84. Galizia G, Lieto E, De Vita F, et al. Modified versus standard D2 lymphadenectomy in total gastrectomy for nonjunctional gastric carcinoma with lymph node metastasis. Surg (United States). 2015;157(2):285-296. doi:10.1016/j.surg.2014.09.012.

85. Hu Y, Huang C, Sun Y, et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. J Clin Oncol. 2016. doi:10.1200/JCO.2015.63.7215.

86. Avery KNL, Chalmers KA, Brookes ST, et al. Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. Ann Surg. March 2017:1. doi:10.1097/SLA.0000000000002204.

87. Database Search - Core Outcome Measures in Effectiveness Trials Initiative (COMET). http://www.comet-initiative.org/studies/search. Accessed May 19, 2016.

3.7 Appendices

3.7.1 Appendix 1. Search Algorithm

Database: Ovid MEDLINE (R)
Search Strategy:
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1 (Gastr$ or stomach$ or oesophagogastric junction or esophagogastric junction).mp. (645201)
2 exp Stomach/ (112711)
3 adenocarcinoma/ or neoplasms/ (457904)
4 1 or 2 (648680)
5 3 and 4 (37749)
6 exp Stomach Neoplasms/ (81208)
7 5 or 6 (100682)
8 chemoradiotherapy/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or antineoplastic combined chemotherapy protocols/ or induction chemotherapy/ (140865)
9 (antineoplast$ or antitumor$ or anti-tumor$ or anti-neoplast$ or chemotherp$).mp. (454727)
10 exp Gastrectomy/ or endoscopy, gastrointestinal/ or duodenoscopy/ or esophagoscopy/ or gastroscopy/ (69973)
11 (gastrectom$ or duodenoscop$ or esophagoscop$ or oesophagoscop$ or gastroscop$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (66259)
12 radiotherapy/ or brachytherapy/ or radioimmunotherapy/ or radiotherapy, adjuvant/ (74386)
13 (radiotherap$ or chemoradiotherap$ or chemo-radiotherap$ or "radiation therap$" or bracytherap$ or irradiat$).mp. (366760)
14 8 or 9 or 10 or 12 or 13 (854226)
15 7 and 14 (32194)
16 randomi?ed controlled trial.pt. (416592)
17 controlled clinical trial.pt. (92207)
18 randomized.ab. (308489)
19 randomly.ab. (218498)
20 exp animals/ not humans.sh. (4150916)
21 16 or 17 or 18 or 19 (743790)
22 21 not 20 (673762)
23 15 and 22 (2255)
24 limit 23 to yr="1996 -Current" (1806)

25 (Gastr$ or stomach$ or oesophagogastric junction or esophagogastric junction).mp. (645201)
26 exp Stomach/ (112711)
27 adenocarcinoma/ or neoplasms/ (457904)
28 25 or 26 (648680)
29 27 and 28 (37749)
30 exp Stomach Neoplasms/ (81208)
31 29 or 30 (100682)
32 chemoradiotherapy/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or antineoplastic combined chemotherapy protocols/ or induction chemotherapy/ (140865)
33 (antineoplast$ or antitumor$ or anti-tumor$ or anti-neoplast$ or chemotherp$).mp. (454727)
34 exp Gastrectomy/ or endoscopy, gastrointestinal/ or duodenoscopy/ or esophagoscopy/ or gastroscopy/ (69973)
35 (gastrectom$ or duodenoscop$ or esophagoscop$ or oesophagoscop$ or gastroscop$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (66259)
36 radiotherapy/ or brachytherapy/ or radioimmunotherapy/ or radiotherapy, adjuvant/ (74386)
37 (radiotherap$ or chemoradiotherap$ or chemo-radiotherap$ or "radiation therap$" or bracytherap$ or irradiat$).mp. (366760)
38 32 or 33 or 34 or 36 or 37 (854226)
39 31 and 38 (32194)
40 randomi?ed controlled trial.pt. (416592)
41 controlled clinical trial.pt. (92207)
42 randomized.ab. (308489)
43 randomly.ab. (218498)
44 exp animals/ not humans.sh. (4150916)
45 40 or 41 or 42 or 43 (743790)
46 45 not 44 (673762)
47 39 and 46 (2255)
48 limit 47 to yr="1996 -Current" (1806)

3.7.2 Appendix 2. Outcomes reported in 48 publications from 32 gastric cancer surgery trials.

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Abdominal abscess	10
Adverse Events	Abdominal distention	1
Adverse Events	Abdominal drainage	1
Adverse Events	Abdominal liquid accumulation	1
Adverse Events	Abscess intra-abdominal	7
Adverse Events	Abscess subphrenic	1
Adverse Events	Acute enteritis	1
Adverse Events	Acute urinary retention	1
Adverse Events	Adverse drug reaction	1
Adverse Events	Afferent loop syndrome	2
Adverse Events	Allogenic blood transfusion	1
Adverse Events	Amylase level in drainage fluid	1
Adverse Events	Anastomosis failure	1
Adverse Events	Anastomosis stricture	2
Adverse Events	Anastomotic bleeding	1
Adverse Events	Anastomotic dehiscence	2
Adverse Events	Anastomotic leak	17
Adverse Events	Anastomotic leakage from GJ	1
Adverse Events	Anastomotic leakage from OJ	1
Adverse Events	Anastomotic leakage type 1	1
Adverse Events	Anastomotic leakage type 2	1
Adverse Events	Anastomotic stenosis	5
Adverse Events	Any complication	2
Adverse Events	ARDS	1
Adverse Events	Arteriosclerosis obliterans of the leg	1
Adverse Events	Ascites	2
Adverse Events	Atelectasis	2
Adverse Events	Atelectasis or pleural effusion	1
Adverse Events	Atrial fibrillation	1
Adverse Events	Bleeding	4
Adverse Events	Bleeding abdominal	1
Adverse Events	Bleeding from anastomosis	1
Adverse Events	Blood transfusion	2
Adverse Events	Blood transfusion volume	2
Adverse Events	Body temperature exceeding 37 ° C (days)	2

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Bowel obstruction	1
Adverse Events	Bowel obstruction/ileus	1
Adverse Events	Bronchopneumonia	1
Adverse Events	Bronchoscopic toilet	1
Adverse Events	Cardiac complications	6
Adverse Events	Cardiac failure	1
Adverse Events	Cardiocirculatory	1
Adverse Events	Cardiopulmonary disease	1
Adverse Events	Catheter-induced sepsis	1
Adverse Events	Cerebrovascular	1
Adverse Events	Cholecystitis	3
Adverse Events	Cholecystitis acute	1
Adverse Events	Cholecystitis requiring percutaneous drainage	1
Adverse Events	Chyle leakage	2
Adverse Events	Chylous drainage	1
Adverse Events	Chylous lymphorrhea	1
Adverse Events	Colonic perforation	1
Adverse Events	Complications	3
Adverse Events	Complications after discharge	1
Adverse Events	Complications number of	1
Adverse Events	Deep vein thrombosis	3
Adverse Events	Delayed gastric emptying	2
Adverse Events	Delayed gastric emptying without obstruction	1
Adverse Events	Diarrhoea	1
Adverse Events	Drug-induced hepatitis	1
Adverse Events	Dumping syndrome	1
Adverse Events	Duodenal leak	1
Adverse Events	Duodenal stump leak	3
Adverse Events	Early dumping syndrome	1
Adverse Events	Early surgical complications	1
Adverse Events	Empyema thoracis	1
Adverse Events	Endocrine complications	1
Adverse Events	Endocrine events	1
Adverse Events	Enterocutaneous fistula	3
Adverse Events	Esophagus and remnant stomach infarction	1
Adverse Events	Fever	1
Adverse Events	Fluid collection	1
Adverse Events	Fluid collection/abscesses	1

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Gastric atonia	1
Adverse Events	Gastric remnant necrosis	1
Adverse Events	Gastrointestinal bleeding	1
Adverse Events	Gastrointestinal complications	1
Adverse Events	Gastrointestinal injury	1
Adverse Events	Gastroparesis	3
Adverse Events	Haemorrhage	2
Adverse Events	Hb	2
Adverse Events	Hepatic complications	2
Adverse Events	Hepatic failure	1
Adverse Events	Herpes zoster	1
Adverse Events	Hiccups	1
Adverse Events	Hospital morbidity	1
Adverse Events	Hypercapnia	1
Adverse Events	Iatrogenic spleen injury	1
Adverse Events	Idiopathic small bowel perforation	1
Adverse Events	Ileus mechanical	1
Adverse Events	Ileus	2
Adverse Events	Ileus adhesive	2
Adverse Events	Ileus paralytic	1
Adverse Events	Ileus prolonged	1
Adverse Events	Incision fat liquefaction	1
Adverse Events	Incision infection	1
Adverse Events	Infection	1
Adverse Events	Intestinal fistula	2
Adverse Events	Intestinal ischaemia	1
Adverse Events	Intestinal obstruction	3
Adverse Events	Intra-abdominal bleeding	3
Adverse Events	Intra-abdominal collections	1
Adverse Events	Intra-abdominal complications	1
Adverse Events	Intra-abdominal infection	1
Adverse Events	Intraluminal bleeding	3
Adverse Events	Intraoperative blood transfusion	2
Adverse Events	Intraoperative complications	3
Adverse Events	intraoperative major bleeding	1
Adverse Events	Intraperitoneal haemorrhage	1
Adverse Events	Late surgical complications	1
Adverse Events	Leakage	1

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Liver dysfunction	1
Adverse Events	Local complications	1
Adverse Events	Long-term complications	1
Adverse Events	Lung Infection	1
Adverse Events	Lymphatic leakage	1
Adverse Events	Lymphorrhoea	1
Adverse Events	Major abdominal infections	1
Adverse Events	Major cardiorespiratory incidents	1
Adverse Events	Major complications	2
Adverse Events	Major post-operative complication	1
Adverse Events	Major surgical complications	1
Adverse Events	Malabsorption	1
Adverse Events	Mediastinitis	1
Adverse Events	Medical complications	1
Adverse Events	Metabolic complications	1
Adverse Events	Minor complications	1
Adverse Events	Minor discharge of pancreatic juice	1
Adverse Events	Minor leakage	1
Adverse Events	Minor patchy pulmonary collapse	1
Adverse Events	Minor pulmonary atelectasis	2
Adverse Events	Morbidity	8
Adverse Events	Morbidity rate	1
Adverse Events	Multiple organ failure	1
Adverse Events	Myocardial infarction	1
Adverse Events	Nausea	1
Adverse Events	Need for blood transfusion	1
Adverse Events	Non-surgical Complications	6
Adverse Events	Number of patients with complications	1
Adverse Events	Operative complications	1
Adverse Events	Operative morbidity	3
Adverse Events	Other complications	7
Adverse Events	Overall complications	2
Adverse Events	Overall Post-operative complications	1
Adverse Events	Pancreas-related complications	1
Adverse Events	Pancreatic fistula	15
Adverse Events	Pancreatic injury	2
Adverse Events	Pancreatic leak	4
Adverse Events	Pancreatitis	1

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Pancreatitis acute	3
Adverse Events	Pancreatitis edematous	1
Adverse Events	Pancreatitis severe	1
Adverse Events	Pancreatitis traumatic	1
Adverse Events	Peri-operative complications	1
Adverse Events	Peritoneal haemorrhage	1
Adverse Events	Pleural	1
Adverse Events	Pleural effusion	5
Adverse Events	Pleural fluid	1
Adverse Events	Pneumonia	11
Adverse Events	Post-operative bleeding	1
Adverse Events	Post-operative complications	5
Adverse Events	Post-operative drain discharge	1
Adverse Events	Post-operative glucose tolerance	1
Adverse Events	Post-operative hemorrhage	2
Adverse Events	Post-operative major complications	1
Adverse Events	Post-operative minor complication	1
Adverse Events	Post-operative morbidity	1
Adverse Events	Post-operative psychosis	1
Adverse Events	Post-operative respiratory care	1
Adverse Events	Post-operative respiratory function	1
Adverse Events	Post-operative surgical parameters	1
Adverse Events	Post-operative symptoms	1
Adverse Events	Presence of gallstones	1
Adverse Events	Procedure-related morbidity and mortality	1
Adverse Events	Prolonged diarrhea	1
Adverse Events	Prolonged retention of intra-abdominal fluid	1
Adverse Events	Pulmonary	4
Adverse Events	Pulmonary complications	4
Adverse Events	Pulmonary edema	1
Adverse Events	Pulmonary embolism	2
Adverse Events	Pulmonary infection	1
Adverse Events	Pyothorax	1
Adverse Events	Rate of reinsertion of NG tube	1
Adverse Events	Recurrent laryngeal nerve palsy	1
Adverse Events	Reflux oesophagitis	2
Adverse Events	Re-laparotomy	2
Adverse Events	Renal complications	2

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Renal failure	2
Adverse Events	Re-operation	8
Adverse Events	Re-operation details	1
Adverse Events	Respirator use after surgery	1
Adverse Events	Respiratory complications	1
Adverse Events	Respiratory failure	1
Adverse Events	Return to theatre	1
Adverse Events	Septic complications	1
Adverse Events	Serious and potentially fatal complications	1
Adverse Events	Severe diarrhoea	1
Adverse Events	Severe feeding problem requiring prolonged hyperalimentation	1
Adverse Events	Severity of complications	2
Adverse Events	Severity of post-operative complications	1
Adverse Events	Short-term complications	1
Adverse Events	Small-bowel obstruction	1
Adverse Events	Splenic artery pseudoaneurysm	1
Adverse Events	Splenic injury	1
Adverse Events	Stasis	1
Adverse Events	Stenosis	1
Adverse Events	Surgical complications	8
Adverse Events	Surgical risk	1
Adverse Events	Systemic complications	1
Adverse Events	Systemic infections	1
Adverse Events	Thermal injury	1
Adverse Events	Thoracic effusion requiring thoracic drainage	1
Adverse Events	Thromboembolic complications	1
Adverse Events	Total complications	1
Adverse Events	Total major complications	1
Adverse Events	Total morbidity	4
Adverse Events	Tracheotomy	1
Adverse Events	Transfusion	3
Adverse Events	Transfusions received	1
Adverse Events	Transient ischemic attack	1
Adverse Events	Transient LFT abnormality	1
Adverse Events	Trocar related injury	1
Adverse Events	Tube tracheotomy	1
Adverse Events	Uncomplicated calf vein thrombosis	1

Theme	**Original Outcome**	**Frequency Reported**
Adverse Events	Upper gastro-intestinal haemorrhage	1
Adverse Events	Urinary complications	2
Adverse Events	Urinary retention	1
Adverse Events	Urinary tract complications	1
Adverse Events	Urinary tract infection	3
Adverse Events	Viral infection	1
Adverse Events	Vomiting	1
Adverse Events	Wound abscess	1
Adverse Events	Wound complications	2
Adverse Events	Wound dehiscence	2
Adverse Events	Wound evisceration	1
Adverse Events	Wound haematoma	1
Adverse Events	Wound infection	10
Adverse Events	Wound infection/dehiscence	1
Adverse Events	Wound problem	1
Adverse Events	Wound seroma	2
Cost	Medical cost	1
Mortality	Death	8
Mortality	Death from a post-operative complication	1
Mortality	Death from all causes	1
Mortality	Death from gastric cancer as a cause	1
Mortality	Disease free survival	4
Mortality	Disease free survival 4-year	2
Mortality	Disease free survival 5-year	3
Mortality	Disease specific survival	1
Mortality	Disease specific survival 5-year	1
Mortality	Gastric cancer related deaths	1
Mortality	Hospital death	3
Mortality	Hospital mortality	7
Mortality	In-hospital mortality	2
Mortality	Mortality not related to surgery	1
Mortality	Operative death	1
Mortality	Operative mortality	3
Mortality	Overall survival	8
Mortality	Overall survival 10-year	1
Mortality	Overall survival 3-year	2
Mortality	Overall survival 5-year	6
Mortality	Overall survival 6-year	1

Theme	**Original Outcome**	**Frequency Reported**
Mortality	Overall survival 7-year	1
Mortality	Post-operative death	4
Mortality	Post-operative mortality	3
Mortality	Post-operative survival	1
Mortality	Recurrence-free survival	5
Mortality	Relapse-free survival	1
Mortality	Survival 11-year	1
Mortality	Survival 5-year	11
Mortality	Survival Period	1
Mortality	Treatment related deaths	1
Patient Pathway	Days of hospitalization	1
Patient Pathway	Duration of hospital stay	12
Patient Pathway	Duration of post-operative hospital stay	11
Patient Pathway	Readmission	1
Patient Reported Outcomes	Degree of pain	1
Patient Reported Outcomes	Overall satisfaction	1
Patient Reported Outcomes	Pain	1
Patient Reported Outcomes	Post-operative Pain	1
Patient Reported Outcomes	QoL	3
Recovery from Surgery	4-day post-operative use of analgesics	1
Recovery from Surgery	Blood urea nitrogen	1
Recovery from Surgery	Body weight	1
Recovery from Surgery	CK	1
Recovery from Surgery	CRP	4
Recovery from Surgery	CRP 3 days after surgery	1
Recovery from Surgery	Days of fever	1
Recovery from Surgery	Days to sips of water	1
Recovery from Surgery	Decrease in body weight	1
Recovery from Surgery	Decrease of body weight 1 month after the operation	1
Recovery from Surgery	Dose of analgesic (mg)	1
Recovery from Surgery	Duration of pain control	1
Recovery from Surgery	Eating	1

Theme	**Original Outcome**	**Frequency Reported**
Recovery from Surgery	FEV1(L)	1
Recovery from Surgery	FEVC(L)	1
Recovery from Surgery	Fever	1
Recovery from Surgery	First eating (post-operative day)	1
Recovery from Surgery	First walking (post-operative day)	1
Recovery from Surgery	Food intake	1
Recovery from Surgery	Frequency of analgesics injection	1
Recovery from Surgery	Frequency of injection given according to analgesic requests	1
Recovery from Surgery	IL-6	1
Recovery from Surgery	Immediate postoperative inflammatory and immune responses	1
Recovery from Surgery	Immunological response to surgery	2
Recovery from Surgery	Lean body mass	1
Recovery from Surgery	LFT	1
Recovery from Surgery	Number of days to get out of bed	1
Recovery from Surgery	Nutritional Status	1
Recovery from Surgery	Pain control	2
Recovery from Surgery	Post-operative analgesia	1
Recovery from Surgery	Post-operative course	1
Recovery from Surgery	Post-operative pain	1
Recovery from Surgery	Post-operative recovery	1
Recovery from Surgery	Prealbumin	1
Recovery from Surgery	Progression of oral intake	1
Recovery from Surgery	Pulmonary function	1
Recovery from Surgery	Recovery of Physical Activity	1
Recovery from Surgery	Residual pain at day 7	1
Recovery from Surgery	SaO2	1
Recovery from Surgery	Serum Albumin	1
Recovery from Surgery	Surgical stress response	1
Recovery from Surgery	The early recovery course	1
Recovery from Surgery	Time of first flatus/index of peristalsis recovery	1
Recovery from Surgery	Time to ambulation	1
Recovery from Surgery	Time to first flatus	4
Recovery from Surgery	Time to first flatus (days)	5
Recovery from Surgery	Time to first liquid intake	1
Recovery from Surgery	Time to first soft diet uptake	1
Recovery from Surgery	Time to food intake	1

Theme	**Original Outcome**	**Frequency Reported**
Recovery from Surgery	Time to liquid diet	1
Recovery from Surgery	Time to removal of epidural anesthesia (days)	1
Recovery from Surgery	Time to sips of water	2
Recovery from Surgery	Time to start oral intake (days)	1
Recovery from Surgery	Time until removal of the naso-gastric tube	1
Recovery from Surgery	Time until start of meals	1
Recovery from Surgery	Times analgesic given	1
Recovery from Surgery	Times of pain rescue	1
Recovery from Surgery	Total amount of analgesics infused	1
Recovery from Surgery	Total body weight	1
Recovery from Surgery	Total protein	1
Recovery from Surgery	Walking	1
Recovery from Surgery	WBC	1
Recovery from Surgery	WCC	3
Surviving & Controlling Cancer	Cumulative risk of recurrence	2
Surviving & Controlling Cancer	Disease recurrence rate	1
Surviving & Controlling Cancer	Port site metastasis	2
Surviving & Controlling Cancer	Recurrence	4
Surviving & Controlling Cancer	Recurrence patterns	1
Surviving & Controlling Cancer	Recurrent disease	1
Surviving & Controlling Cancer	Tumor recurrence	1
Technical Aspects of Surgery	Amount of bleeding	1
Technical Aspects of Surgery	Blood loss	7
Technical Aspects of Surgery	Clear margin distance	1
Technical Aspects of Surgery	Conversion to open surgery	3
Technical Aspects of Surgery	Dissected Lymph nodes - mediastinal	1

Theme	**Original Outcome**	**Frequency Reported**
Technical Aspects of Surgery	Dissected Lymph nodes - para-aortic	1
Technical Aspects of Surgery	Distal resection margin	2
Technical Aspects of Surgery	Duration of surgery	3
Technical Aspects of Surgery	Estimated blood loss	5
Technical Aspects of Surgery	Intraoperative blood loss	7
Technical Aspects of Surgery	Length of laparotomy incision	1
Technical Aspects of Surgery	Length of lesser curvature of resected stomach	1
Technical Aspects of Surgery	Length of lesser curvature of resected stomach	1
Technical Aspects of Surgery	Length of longest wound	1
Technical Aspects of Surgery	Length of resection on greater curve	1
Technical Aspects of Surgery	Length of resection on lesser curve	1
Technical Aspects of Surgery	Main wound size	1
Technical Aspects of Surgery	Mean blood loss	2
Technical Aspects of Surgery	Mean operating time	1
Technical Aspects of Surgery	Number of lymph nodes dissected or resected or retrieved	22
Technical Aspects of Surgery	Number of lymph nodes removed N1 group	1
Technical Aspects of Surgery	Number of lymph nodes removed N2 group	1
Technical Aspects of Surgery	Number of lymph nodes removed N3 group	1
Technical Aspects of Surgery	Number of lymph nodes removed N4 group	1

Theme	**Original Outcome**	**Frequency Reported**
Technical Aspects of Surgery	Operative blood loss	2
Technical Aspects of Surgery	Operative time	18
Technical Aspects of Surgery	Pathological outcomes	1
Technical Aspects of Surgery	Proximal margin positive/negative	1
Technical Aspects of Surgery	Proximal resection margin	2
Technical Aspects of Surgery	R0 resection	2
Technical Aspects of Surgery	Radicality R0	1
Technical Aspects of Surgery	Radicality R1	1
Technical Aspects of Surgery	Resection line involvement - distal	1
Technical Aspects of Surgery	Resection line involvement - proximal	1
Technical Aspects of Surgery	Residual Tumour	1
Technical Aspects of Surgery	Residual tumour R0	2
Technical Aspects of Surgery	Residual tumour R1/2	1
Technical Aspects of Surgery	Residual tumour R1/2	1
Technical Aspects of Surgery	Surgical time	2
Technical Aspects of Surgery	Time for operation	1
Technical Aspects of Surgery	Wound size	5

4 Patient Priorities in Relation to Surgery for Gastric Cancer: Qualitative Interviews with Gastric Cancer Surgery Patients to Inform the Development of a Core Outcome Set

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4.1 Abstract

Objective

The reporting of outcomes in surgical trials for gastric cancer is inconsistent. The GASTROS study (**GA**stric Cancer **S**urgery **TR**ials **R**eported **O**utcome **S**tandardisation) aims to address this by developing a core outcome set (COS) for use in all future trials within this field. A COS should reflect the views of all stakeholders, including patients. We undertook a series of interviews to identify outcomes important to patients which would be considered for inclusion in a COS.

Setting

All interviews took place within the United Kingdom. Interviews were carried out face-to-face at hospitals and cancer support centres or via the telephone.

Participants

Twenty participants at varying stages of recovery following surgery for gastric cancer with curative intent.

Design

Qualitative design using semi-structured interviews, supported by an interview guide which was iteratively modified; thematic analysis was used to explore patient priorities.

Results

Six themes enveloping 38 outcomes were identified: surviving and controlling cancer, technical aspects of surgery, adverse events from surgery, recovering from surgery, long-term problems following surgery and long-term life impact of surgery. The 'most important' patient priority was to be 'cured of cancer'.

Conclusion

Surgical trials for gastric cancer should consider broader priorities of patients when choosing which outcomes to report. This study highlighted the importance of longer-term outcomes such as cancer survival. Outcomes identified in this study will be used to inform an international Delphi survey to develop a COS in this field.

4.2 Introduction

4.2.1 Background

Gastric cancer is a leading cause of cancer-related death world-wide[1,2]. Whilst surgery remains the only treatment which can offer a potential cure from this disease, it is associated with significant rates of morbidity in both the short and long-term[3,4]. Ideally, the optimal surgical approach would minimise the risk of short and long-term complications without jeopardising the oncological resection.

Identifying the optimal surgical approach for gastric cancer should be based on comparing and combining robust clinical evidence from well-designed randomised control trials. One of the present challenges to achieving this is the inconsistency in the reporting of outcomes in this field[5]. This limits evidence synthesis and contributes to 'research waste'. The GASTROS study (GASTROS – **GA**stric Cancer **S**urgery **TR**ials **R**eported **O**utcome **S**tandardisation - www.gastrosstudy.org)[6] aims to address this issue by developing a 'core outcome set' (COS) – a minimum group of standardized and well-defined outcomes, measured by all future gastric cancer surgery trials[7].

A guiding principle in the development of COS is that outcomes reflect the views and priorities of key stakeholders, including patients, to maximise the relevance and impact of future research. Previous studies have demonstrated variations in the views and priorities of clinicians and patients[8–10], which can result in trials reporting outcomes which bear little relevance to patients. A systematic review of outcome reporting in surgical trials for gastric cancer has demonstrated that outcomes which may be important to gastric cancer patients, such as 'quality of life' after surgery are poorly represented within this field[5]. It is therefore important to understand which outcomes are important for patients undergoing gastric cancer surgery.

4.2.2 Objective

This research forms part of the GASTROS study, for which the protocol has been previously described[6]. The first stage in the study involves identifying a 'long-list' of potentially important outcomes which will be prioritised in stage two by participants undertaking a Delphi survey. It is not known to what degree outcomes reported in previously published trials represent the priorities of patients undergoing gastric cancer surgery, and as such, solely relying on these as a source to populate the 'long-list' may overlook potentially important outcomes. By exploring the experiences, perceptions and priorities of patients who have undergone surgery for gastric cancer, this study aimed to identify outcomes which may not have been previously reported in the literature.

4.3 Methods

4.3.1 Study Design

The role of qualitative research methods in the development of COS has been previously explored[11] and has been advocated by groups such as the COMET initiative[7] as one of several approaches to ensure that outcome lists being considered for prioritisation are exhaustive. This qualitative study used a semi-structured interview approach to achieve the primary objective of identifying outcomes of importance to patients. A series of open questions were used to facilitate a patient-led discussion, guided by additional prompts from a pre-prepared interview schedule (table 1) to ensure key areas were covered.

Additional focused questioning around the use of outcomes in research was also included. In the context of clinical research, terms such as 'outcomes' may not be well understood by patients[11] and so a mixture of open and closed questioning was important. Participant interviews were undertaken in series of three following which transcript analysis (see below) was undertaken and the interview schedule was modified iteratively. This ensured that areas raised by earlier participants, but not included in the original schedule, were covered in subsequent discussions.

4.3.2 Sampling

The eligibility criteria for this study are summarized in table 2. A purposive sampling strategy was adopted across the following characteristics:

- Age (above and below 70 years).
- Gender (men and women)
- Time since surgery (less than a year, one to three years and more than three years)

Interviews were undertaken until 'data-saturation' was achieved. Data saturation was determined when there was no new data emerging that had interpretive value. The aim was to achieve data saturation across the overall cohort and not in each sub-group.

Participants were recruited from across the United Kingdom from three sources:

1. A regional specialist gastric cancer centre: patients were approached in the outpatient clinic by their direct care team.
2. Patient organisations: patient groups were asked to contact their membership through e-mail and social media.
3. Snowball sampling: patients who had been recruited or contacted to participate were asked to identify other patients who would be interested in the study.

Table 4.1 Interview schedule.

1.	I understand you have (had) gastric cancer. Can you tell me about that?
2.	Could you tell me about how you first found out you had gastric cancer? Prompts: • What questions did you most want to ask, when you were told that you had gastric cancer?
3	Were there were any areas you wanted more information about but were unable to find? Prompts: • Were you given any leaflets at the time of diagnosis? Did you find these useful?
4	What treatment was offered and how did you decide about undergoing treatment? Prompts: • What information did you want about the treatment you would be receiving? • What factors did you consider when deciding on the treatment?
5	What effects did the treatment have on you after surgery? Prompts: • Did the treatment affect your physical or mental well-being? • Did the treatment have an effect on relationships with those around you? • Did you have to make any changes to your behaviour as a result of treatment?
6	What long-term effects did the treatment have on you? Prompts: • Did the treatment affect your physical or mental well-being? • Did the treatment have an effect on relationships with those around you? • Did you have to make any changes to your behaviour as a result of treatment?
7	What was the worst side effect of treatment?
8	What are your concerns for the future, especially those relating to their diagnosis/history of gastric cancer?

9	Did the explanation of what you should expect from surgery match your real experience?
10	In the context of research studies, can you explain what an outcome is in your own words? The interviewer will then provide a definition of the term ‘outcome’ in the context of clinical research.
11	What, in your opinion, is the most important outcome to measure in gastric cancer surgery trials?
12	Are there any other outcomes which may be important to measure?
13	Has your perspective on what is important changed over time?
14	Is there anything else that you feel is important to talk about that we have not discussed?

Table 4.2 Eligibility criteria for study participants.

	Potential Participants Approached	**Potential Participants Not Approached**
Participant	• Male and females aged 18 years and older. • Individuals able to participate in an interview in the English language.	• Patients unable to give informed consent • Patients too unwell to comfortably participate in an interview lasting approximately 30-60 minutes.
Pathology	• Adenocarcinoma and squamous cell carcinoma of the stomach, (which makes up 95 per cent of all stomach tumours).	• Gastrointestinal Stromal Tumours • Neuro-endocrine tumours • Lymphoma • Benign disease
Intervention	• Total and partial gastrectomy • Open and laparoscopic approaches	• Surgery with palliative intent • Endoscopic therapies such as EMR (endoscopic mucosal resection) and ESD (endoscopic Submucosal dissection)

4.3.3 Data Collection

Interviews were undertaken between February and May 2017 and were conducted by BA, a consultant surgeon and researcher with approximately ten years' experience of managing and communicating with gastric cancer patients. Participants were invited to choose between a University Teaching Hospital, two purpose-built patient cancer centres, or their home for the location of the meeting. Participants were also offered the opportunity to have their interviews over the telephone. Participants were offered travel expenses to minimise any financial burden on taking part in the study. In addition to the purposive sampling strategy, the following demographic data was collected:

- Gender (male/female)
- Social circumstances (e.g. lives alone/with partner/lives with dependents)
- Age
- Time since surgery (in months)
- The type of gastrectomy (total or partial gastrectomy)
- The approach to their surgery (open or laparoscopic)
- Whether they had undergone additional treatment (e.g. chemotherapy)
- Whether they had suffered a post-operative complication
- Ethnicity
- Previous trial enrolment
- Participant post-code (to identify location and social deprivation score)

Full written consent was taken immediately prior to the interview and the participant was reminded that they were able to stop at any point or withdraw from the study without needing to give a reason.

4.3.4 Data Analysis

All interviews were digitally recorded and professionally transcribed (intelligent verbatim transcription). A thematic analysis was used to identify emerging themes and was guided by a general inductive approach[12,13]. This was used to create the framework applied to subsequent interviews. Themes were developed using a three-step approach of open coding, axial coding and selective coding[14] of the transcripts. Given the objective of this study was to identify themes and outcomes not previously reported in trials, it was important not to base data analysis and outcome identification on a framework built on previously published literature. BA and RM (a researcher with significant experience in qualitative research methods) independently analysed the first two transcripts and through discussion identified themes and adjustments to the interview schedule. There were no disagreements about coding, but had there been, these would have been discussed with the study management team. The final themes were agreed by all authors through discussion. Data analysis was supported using NVivo 11

(http://www.qsrinternational.com/products_nvivo.aspx, QSR International, Burlington, MA, USA).

4.3.5 Approvals and Portfolio Adoption

The study was given ethical approval by the National Research Ethics Service North West—Cheshire (11/NW/0739) and governance approvals by Central Manchester University Hospital NHS Foundation Trust. The study was adopted by the National Institute for Health Research (NIHR) Clinical Research Network Portfolio (ID 33312).

4.3.6 Reporting

This paper uses the SRQR checklist to structure the report of the study findings[15].

4.3.7 Patient and Public involvement

A Study Advisory Group (SAG) forms part of the management structure of the wider GASTROS study[6], of which this qualitative study forms part of the first stage. The SAG is made up of key stakeholder representatives including patients, oncology nurses and surgeons. The group provides advice on the methodology of the study, general delivery of the study against its stated objectives and ensures that the viewpoints of all stakeholder groups are considered. The results of this study were presented to a SAG meeting; the ensuing discussion influenced the design of the next stage of the study in preparation for an international Delphi Survey.

Best practice guidelines for patient and public engagement were followed as set out by INVOLVE (part of and funded by the United Kingdom's National Institute for Health Research)[16].

4.4 Results

4.4.1 Overview

In total, 20 patients were interviewed. Table 3 summarises demographic data and treatment-related characteristics of participants. Interviews lasted a median of 50.5 minutes (29-75 minutes). No patients withdrew from the study. Data saturation was deemed to have been reached by 20 interviews; one new outcome was identified in interview number 18 (related to sexual activity), however, no further outcomes were identified from the following two transcripts.

Table 4.3 Patient characteristics and demographic data.

Patient	Sex	Age	Ethnicity*	Social deprivation quintile**	Home circumstances	Months since surgery	Type of surgery	Approach to surgery	Post-operative complications	Peri-operative treatment
1	F	74	A	3rd	Lives alone	15	Partial Gastrectomy	Laparoscopic	Yes	Nil
2	M	59	B	3rd	Lives alone	27	Total Gastrectomy	Open surgery	Yes	Chemotherapy
3	M	71	A	1st	Lives alone	16	Partial Gastrectomy	Open surgery	Yes	Nil
4	M	43	A	2nd	Lives with parents	15	Total Gastrectomy	Open surgery	Yes	Chemotherapy
5	M	80	A	3rd	Lives alone	23	Partial Gastrectomy	Laparoscopic	Yes	Nil
6	F	52	A	2nd	Lives with children	32	Total Gastrectomy	Open surgery	No	Chemotherapy
7	M	79	A	1st	Lives with spouse	58	Total Gastrectomy	Laparoscopic	Yes	Chemotherapy
8	F	63	A	1st	Lives alone	5	Total Gastrectomy	Open surgery	No	Nil
9	M	61	A	3rd	Lives with spouse	170	Total Gastrectomy	Open surgery	No	Nil
10	M	61	C	1st	Lives alone	79	Total Gastrectomy	Open surgery	No	Chemotherapy
11	M	76	A	4th	Lives with spouse	110	Total Gastrectomy	Laparoscopic	Yes	Chemotherapy
12	F	82	A	4th	Lives alone	62	Partial Gastrectomy	Open surgery	No	Nil

Patient	Sex	Age	Ethnicity*	Social deprivation quintile**	Home circumstances	Months since surgery	Type of surgery	Approach to surgery	Post-operative complications	Peri-operative treatment
13	F	59	A	2nd	Lives with spouse	19	Partial Gastrectomy	Open surgery	No	Chemotherapy
14	M	70	B	1st	Lives alone	11	Partial Gastrectomy	Open surgery	No	Nil
15	F	56	M	5th	Lives with parent	33	Total Gastrectomy	Open surgery	Yes	Chemotherapy
16	F	84	A	1st	Lives alone	17	Partial Gastrectomy	Laparoscopic	Yes	Nil
17	M	48	A	4th	Lives with parent	9	Total Gastrectomy	Laparoscopic	Yes	Chemotherapy
18	M	77	A	4th	Lives with spouse	78	Total Gastrectomy	Open surgery	Yes	Nil
19	Fe	58	A	3rd	Lives with spouse	11	Partial Gastrectomy	Laparoscopic	No	Nil
20	M	54	A	1st	Lives with spouse	48	Partial Gastrectomy	Open surgery	No	Chemotherapy

*A= British, Mixed British, B= Irish, C= Any other White background , M=Caribbean. **Social deprivation quintile: 1st quintile being the least deprived, 5th quintile being the most deprived.

4.4.2 Outcome Themes

Six broad themes enveloping 38 outcomes were identified.

1. Surviving and controlling cancer,
2. Technical aspects of surgery,
3. Adverse events from surgery,
4. Recovering from surgery,
5. Long-term problems following surgery and
6. Long-term life impact of surgery.

Appendix 1 provides a breakdown of how all themes were developed from outcomes identified during the interviews. Themes were well represented in each interview; each theme was discussed by at least 18 of 20 participants. Appendix 2 demonstrated the outcomes identified during the interviews and how often they were referenced.

4.4.2.1 Theme 1: Surviving and controlling cancer

For most, details of their initial consultation were sketchy; participants often described being given lots of information about their diagnosis, much of which was not absorbed. However, patients clearly remember their reaction to being told their cancer diagnosis; for most, the response was the same:

> "When you hear the word, cancer, you think that's it. I'm going to die." (participant 6)

There was a range of personal experience with cancer within our patient group. Some had direct family members who had undergone chemotherapy and had an intimate knowledge of its effects.

> "it was my worst nightmare come true because I lost my dad to cancer and I always had it in the back of my mind, well if one person in the family could get cancer from somewhere then we could as well." (participant 19)

Some patients had a vague knowledge of friends or work colleagues who had undergone treatments for cancer and others had no prior experience of cancer at all. Despite these differences, the initial responses to their diagnosis were similar.

All participants in our study had undergone radical surgery with curative intent. At the time of interview, no participants had confirmed evidence of disease recurrence although one was being investigated for potential recurrence. Once the discussion with their surgeon moved away from the diagnosis and onto potentially curative treatments, participants often focused their questions on 'survival':

> "I wanted to know what the chances were of me having this removed and not, well, basically not dying from it." (participant 4)

Despite radical surgery (and peri-operative chemotherapy in half of our participants), for many of the participants the fear of recurrence remained a permanent anxiety. Many participants seemed to understand that due to the aggressive nature of gastric cancer, recurrence is a possibility for many:

> "…you're always worried that it's going to come back..." (participant 7)

The study cohort included participants who had undergone surgery between 5 months and 14 years prior to the interviews. There did not seem to be a relationship between the length of time out of surgery and concerns about cancer recurrence.

4.4.2.2 Theme 2: Technical aspects of surgery

Several outcomes related to this theme were discussed by participants. Most importantly, participants focused on whether the surgical team was able to excise the 'cancer' in its entirety. This priority was often referenced in relation to the 'success' of surgery and its contribution to 'curing' participants of cancer:

> "…thinking to yourself that, you know, everything has been done to the best of the hospital's ability, and, you know, they've taken absolutely everything out." (participant 4)

Whilst participants mostly referred to the cancer as a single 'entity', there were a small number who demonstrated some knowledge of the importance of different aspects of surgery such as lymph node excision:

> "And yeah, I remember the news about the pathology on the bits they'd taken away, and the lymph node system and what not, came a week or two before I was due to go back on the chemo." (participant 20)

Six participants underwent a minimally invasive surgery with the remainder undergoing open surgery. The size of the wounds or type of surgical approach was referred to by only a minority of our participants. In the main, these were made in passing as little importance was placed on the surgical approach:

> Interviewer: "Okay, and what...what did that mean for you to have keyhole surgery?"
> Respondent: "It didn't mean anything really, you know, I had...I'd heard about keyhole and people who'd had it." (participant 5)

4.4.2.3 Theme 3: Adverse events following surgery

Eleven participants suffered a complication following surgery; however, this theme was important to all interviewees. Peri-operative death was the most frequently discussed surgical complication:

> "…the fear of dying on the operating table is really real." (participant 2)

During their surgical consultation, participants retained some understanding of the risk of peri-operative death and many were able to quote figures about how likely this complication was. Other complications were highlighted when recounting a personal experience. While all complications occurred in the post-operative period, there were several different causes attributed to these events (e.g. direct surgical, anaesthesia-related and medication-related). The severity and consequences of the complications also varied significantly; some were self-limiting and resulted in a minor extension of the length of hospital stay:

> "But I was out of it for three days, I was just hallucinating, and God knows what, probably because of the morphine." (participant 7)

And those which were life-threatening and required significant clinical intervention:

> "It was a twisted bowel. Yeah, I was told it was a twisted bowel. Because I always remember that when they brought me back from obviously having a look and everything, I always remember [they] said…we're going to have to take you back to surgery." (participant 15)

The severity of the complications suffered did not seem to shape the key priorities in relation to participants' 'worst side effect' of surgery or 'most important outcome'; these almost entirely related to 'long-term impacts of surgery' and 'cure' respectively (see below) regardless of how long ago their operation was and which surgical approach (laparoscopic or open surgery) was employed.

Whilst participants recounted that some of the more serious complications (e.g. death, anastomotic leak and cardio-pulmonary complications) were described by surgeons during the consent process, some were exposed to other sources of information in the pre-operative stage. Participants were regularly provided with written information about their cancer and its management, however the quality and content of this varied depending on the location of their hospital. The response to this format was varied:

> "I'm going to be honest with you, I didn't actually read them… because I didn't want things going in my head that I couldn't take in." (participant 17)

Participants that read the written information often found them difficult to digest for several reasons including the volume of information and fear of the gravity of the diagnosis or prognosis:

> "Well some of it were just waste of time, but others, you know, if you've got a book about that thick and you read through it and half of it applies to you, and the others just sort...doesn't apply, you know." (participant 5)

> "As much as it's alright handing leaflets out, I can…I am a bit of a reader so I will read stuff, but when you think you've got a death sentence you think, what's the point in reading that?" (participant 13)

Several hospitals had patient-support groups which provide a 'buddy' system for those awaiting surgery. These support groups became an important part of the recovery process and continue to be relevant many years after surgery. Patients found these more useful as they had the opportunity to speak to those with lived experience of the diagnosis and treatment. Whilst this served as an important source of information to tackle the longer-term impacts of surgery (below), these groups also provided comfort to patients:

> "I think the support group and speaking to people that have been through it, because it can demystify it quite a lot." (participant 2)

Peer support also provided additional sources of information to participants in the pre-operative period with respect to some of the complications that could arise:

> "And I know one guy, where the oesophagus junction was, he'd had that leaking, and he couldn't eat more than, like, grains of rice and things; so that would be pretty horrendous." (participant 4)

As a result of verbal and written information from healthcare professionals and additional peer support, participants were able to describe key adverse events without necessarily having experienced them first-hand.

4.4.2.4 Theme 4: Recovery from surgery

Experiences during the immediate post-operative recovery period were referenced by 18 study participants. Whilst some participants' experience of recovery from surgery was directly linked to complications, there were aspects of recovery such as post-operative pain, mobility and the recommencement of oral intake that were common amongst all those who spoke this theme.

Most participants did not mention post-operative pain as an important focus. Those that did, expected to suffer a degree of pain, however experiences of its severity varied widely. Pain levels amongst interviewees who had undergone similar operations through laparotomy incisions were not uniform. One participant who had open surgery described:

> "I do remember waking up and really being in a hell of a lot of pain and being really out of it." (participant 6)

Whilst another who had undergone their surgery using the same approach recounted:

> “I didn't really have much pain.” (participant 14)

Discussions around post-operative pain were not confined to discomfort from the surgical incisions, but also related to post-operative complications:

> “I was back in writhing in agony with a serious infection in the wound.” (participant 9)

Participants recounted the limitations in their mobility during the post-operative period. There were many factors contributing to this, including physical weakness, not receiving appropriate encouragement to mobilise, and being restricted by surgical drains:

> “…really difficult to be mobile I suppose, and move around, yourself, ‘cause obviously you’ve got quite a lot of tubes and different things coming out. I felt very, very swollen.” (participant 6)

4.4.2.5 Theme 5: Long-term problems following surgery

All participants described significant long-term symptoms related to surgery. For the most, this represented the ‘worst side effect’ in relation to their treatment and outcomes from this theme were referenced more than any other theme further emphasising its importance. All participants described experience with struggling to eat and drink following surgery and the majority (16/20) talked extensively about the impact of fatigue on their daily lives. Problems with maintaining weight, issues with ongoing gastro-intestinal symptoms and chronic pain were discussed by most participants.

Fatigue was described in many ways; ‘exhaustion’, ‘feeling tired all the time’, ‘feeling so weak’ and ‘having no energy’. For the main, fatigue was a symptom which persisted for months after surgery and could impact on a participant’s ability to undertake day-to-day activities or to socialise:

> “Well, I'm so weak, I used to go out, you know, and do fishing and do things with my lads. I'm just getting that little bit better now after eight months, but I'm so weak and tired.” (participant 18)

Adapting to fatigue was and for many continued to be a difficult challenge, however many participants understood that this was a recognised and acceptable symptom to them given the magnitude of the surgery:

> “I've come out with…more…appreciation for looking after myself and my...And if I'm tired, I stop.” (participant 15)

There were several causes for the challenges participants associated with eating and drinking. Participants often described having to eat and drink smaller volumes more frequently and some were unable to tolerate certain food types or consistencies. This had a direct effect on the pleasure associated with eating and an impact on where participants could eat:

> "Well I don't eat what I would like to…But I know that for the rest of my life, I won't be able to go out for big meals, to big venues and eat like I used to eat before, you know." (participant 5)

Most participants recounted being told prior to their surgery that their diet would be different and that they would have to 'learn how to eat again'. Despite this, some participants felt that not enough information was given to highlight the true impact of this long-term issue and methods to address it:

> "I think it's a lot worse than what they tell you. Because like some days, I'll eat a certain thing which I've ate before, and you just can't breathe properly, it's choking you." (participant 18)

A broad range of gastro-intestinal symptoms were reported by participants. The time frame relating to how long these persisted was similarly broad (sometimes months and years) and did not seem to follow a pattern. Nausea, vomiting, diarrhoea, reflux and belching were the commonest problems described. Many of these symptoms resulted in significant impacts on quality of life (see theme 6 below):

> "…I still get the bile reflux and I get this constant pain in the oesophagus which affects my sleeping as well." (participant 7)

> "The dumping syndrome was mentioned. Never understood it until it happened. You know, how my body reacted to certain foods that I'd normally eat that it doesn't like anymore." (participant 15)

4.4.2.6 Theme 6: Long-term life impact of surgery

The long-term effects on 'normality', quality of life, and psychological impact of surgery were discussed extensively by all patients. A strong desire to return to a form of 'normality' was regularly expressed. Whilst the reference point for 'normality' differed amongst patients, common characteristics existed; namely a desire to do what they used to do such as working, exercising, socialising with friends and family and being able to travel:

> "it's about living as I did before, and forgetting what had happened, and I do that quite often." (participant 6)

The experience of returning to normality varied amongst those interviewed. Many participants were largely able to return to their 'normal' activities albeit with some modifications:

> "Yes. I want to go on holidays again. I love cruises and I want…but until my eating's improved, I wouldn't do that." (participant 1)

> "Now that it's 18 months on, I am back to having what would be a normal life again, now, albeit with smaller portions of meals and things" (participant 4)

Some participants however have not been able to return to activities that provided them with significant enjoyment:

> "I've never actually got back to my normal activity. I've never played golf since that day and I used to love golf." (participant 4)

In general, participants understood that life after gastrectomy would be different:

> "I'm still alive, and then I need to get back to normal. It takes a while for you to realise your new normality is not like your old normality." (participant 2)

Whilst much of the discussion relating to 'normality' centred around specific tasks which participants valued or missed, the impact of gastrectomy on a participant's overall general quality of life was important to many. Many understood that quality of life needed to be redefined in comparison to life before surgery, but nonetheless there was a minimum level that would need to be achieved:

> "if I have some sort of quality of life, where I can get up and wash myself and do, that is something that I'd live for. But I couldn't be sat there and nursed 24/7" (participant 17)

The psychological burden on participants following gastrectomy is a significant one. Each of the previously discussed themes could impact on a participant's mental state and whilst certain phases of the treatment pathway were time-limited, the psychological effects could persist for much longer;

> "You don't just suffer from physical; you suffer from mental. And I think the mental is a lot more powerful that the physical, because you can shut pain off by taking medication, but it's very hard to shut problems off mentally." (participant 18)

> "You know, 'cause psychologically you think you've still got this poison in your body, as much as I've got rid of, you know, my monster." (participant 13)

Some of the psychological impacts were associated with participants having to adapt to a new normality in relation to what they were able to do, what they were able to eat, how they looked physically or how they felt around others:

> "Well, it was a problem because like I say, I've always been a proud chap and proud of my body because I kept myself fit and everything. When I looked in the mirror, quite distressing. That was it, yeah. It makes you feel inferior." (participant 18)

> "I feel a freak, I feel when I go into a big room with people that everybody has got a stomach and I haven't got one, it's not that I want them to know, but I just don't feel the same anymore…" (participant 8)

4.4.3 Definition of 'outcome' by patients

All participants were asked what their understanding of the term 'outcome' was in the context of clinical research. Two participants were able to provide a broad-ranging definition which encompassed some of the benefits and adverse effects of treatment:

> "my perception of what would be meant by that phrase would…at a variety of levels; it could be does the patient live or die? Does the patient recover to an acceptable state for an extended period of time, and my understanding of what that might be, would be a, sort of, five-year period…?" (participant 20)

One person stated that they did not know how to define the term, whilst the remainder defined 'outcome' by recounting a single outcome, which was most important to them:

> "Okay, my understanding is that at the…the outcome would be that the cancer would be possibly all gone." (participant 19)

Participants were asked to provide a single outcome that was 'most important to them'. Fifteen participants identified that the most important outcome was that they were 'cured of cancer' with the remaining five describing outcomes related to 'returning to normal' and being able to enjoy a 'good quality of life'. These priorities did not alter with respect to how long-ago surgery was performed, which approach was undertaken or how old the patient was.

4.5 Discussion

To our knowledge, this is the first in-depth qualitative study exploring the priorities of patients following potentially curative surgery for gastric cancer. The study focussed on this cohort as one of the main aims was to identify outcomes which would be considered for inclusion in a COS for potentially curative surgical trials in gastric cancer. This present study will be used to help generate a list of outcomes that will be presented for prioritisation to healthcare professionals and patients in an international, multi-language online Delphi survey. The results of the Delphi survey will inform a consensus meeting to finalise the COS. Whilst other COS studies in the field of cancer[17–19] may have identified similar important outcomes such as survival, it was important to consider our participants separately given the unique problems which arise with gastrectomy. These include distinctive short and long-term problems related to surgery such as anastomotic leak and reactive hypoglycaemia (Dumping Syndrome[20]) which would not be relevant in other COS.

The themes identified highlight the profound and wide-ranging physical, social and psychological impacts that gastrectomy has on patients which can persist for months and years. We have previously described the reporting of outcomes in surgical trials for gastric cancer over a twenty-year period[5]. Most surgical trials in this field have focused on reporting short-term post-operative outcomes. Whilst these are important to patients, they are not representative of the whole picture. This work highlights how patient priorities for outcomes may differ from the traditional surgical focus. More work is now needed to develop the COS which incorporates views of all key stakeholders including patients.

More than half of the 'top-ten' most frequently discussed outcomes in our study related to longer-term issues such as problems with eating, returning to 'normality', fatigue, weight loss, gastro-intestinal symptoms and psychological impacts. These types of outcomes, which could be measured as Patient-Reported Outcomes (PROs), are infrequently reported in surgical trials and demonstrate that researchers within this field have not reflected the priorities of patients. This challenge needs to be addressed using an approach which is inclusive of patients and their views.

The GASTROS study aims to develop a COS; critically important outcomes which should be reported - as a minimum - by future surgical trials for gastric cancer[6]. By standardising the reporting of such outcomes, it aims to improve the ability to synthesise evidence, reduce research waste and ultimately aid researchers in answering important questions related to gastrectomy. The first stage in developing the COS consists of identifying a 'long-list' of outcomes which will then be prioritised by key stakeholders during an international online Delphi survey. The process of developing the long-list should be comprehensive and involve both healthcare professionals and patients in order to minimise the risk of omitting potentially important outcomes. Our study reaffirms the importance of a mixed-methods approach to

identifying potentially important outcomes. As others COS developers have found, building a long-list based solely on outcomes reported in previous trials or as developed by clinicians often neglects the views of key stakeholders[8–10]. This ultimately runs the risk of producing a COS which does not reflect the priorities of patients which does little to address the current challenges with outcome reporting.

Understanding patient priorities following gastrectomy is invaluable for other reasons. Patients with gastric cancer want detailed information about their condition and treatment[21]. With the knowledge that long-term impacts of surgery are important, healthcare professionals can tailor the consent process prior to surgery to ensure that the patient has a better understanding of these and is making an informed decision. Considering patient priorities may also have implications for the future development of national and international audits[3,4]. For several pragmatic reasons, most comprehensive gastric cancer surgery audits focus on short-term outcomes. Identifying methods to report longer-term quality outcome measures may make such audits more relevant to patients. Studies assessing patients' views in similar disease areas had similar findings; that long term outcomes (survival and long term quality of life) were important[22].

4.5.1 Strengths and weaknesses

The study was able to gain an in-depth understanding of patient priorities based on the experience of participants with a broad range of characteristics representative of those undergoing surgery for gastric cancer in the UK[4]. Furthermore, our purposive sampling approach was established a priori in a study protocol which had undergone a robust peer-review process.

This study was also able to highlight and address significant challenges associated with the comprehension of medical language by patients; particularly terms central to the development of a COS. Patients largely did not understand the use of the term 'outcome' within the context of medical research. Once it was defined as an 'impact or effect of a treatment which may be beneficial or harmful', participants were more easily able to describe their key priorities in outcome reporting for future trials. This has several implications for the GASTROS study as well as other COS projects moving forward. It highlights the importance of ensuring that the premise of the study is clear and understood by all participants, especially patients. Outcomes included in the Delphi survey must be presented and explained in a manner which is accessible to all. Finally, the term 'outcome' must be clear when adapting it to other regions where there may be no direct translation for the term.

The interviews were conducted by an expert in the field of gastric cancer surgery which may have resulted in a degree of observer bias. To mitigate this potential limitation, the study management team (which was made up primarily of members unfamiliar with gastric cancer surgery) was involved in ongoing discussions during data collection and analysis. It is also

possible that patients modified their responses because of awareness of the background of the interviewer. Every effort was made to follow the semi-structured interview schedule, to put the patients at ease and take time to let them talk. The average length of the interviews (greater than 45 mins) reflects the time patients were given to express their views.

A further potential limitation of this present interview study is a lack of international patient participation. Consequently, there may be outcomes which are relevant to non-UK patients that have not been identified. Gastric cancer is an international disease and cultural and regional influences may alter expectations and priorities of patients. Whilst we have not identified evidence from COS developers in other fields that confirms these variations, it remains a possibility. Our reasons for limiting the interviews to UK-only patients were primarily down to pragmatism and finite resources. To mitigate this, the Delphi survey will be available in several languages and during the first round, all participants will be able to submit additional outcomes that they believe were omitted. These will be considered by the study team and presented for prioritisation by participants in round two of the Delphi survey, if appropriate. Adopting this approach also enables the exploration of regional variations in outcome priorities which may form the basis of a future international qualitative study.

This study focusses primarily on the impact of gastrectomy from the perspective of patients. However, we acknowledge that major complex surgery such as gastrectomy inevitably results in both direct and indirect effects on family members and caregivers. Whilst these wider impacts warrant further examination, we limited participation in this present study to patients, as the scope of the COS aims to consider the perspective and priorities of patients, surgeons and oncology nurses. Part of our planned future work is to review the COS to ensure that it remains up-to-date and relevant. At this point, it will be possible to widen participation beyond these three groups to include caregivers and other allied healthcare professionals.

Recruitment to the study stopped when no new data with interpretative value was identified[23]. However, ‘data saturation’ is a topic which deserves further discussion as there is no way of knowing for certain that no new outcomes would have been identified had further interviews been undertaken. Some argue that the term ‘data saturation’ is often mis-used and misunderstood and should be operationalised in a way consistent with the scope of the study being undertaken[24]. As described above, the ability of patients and healthcare participants to suggest further outcomes in round one of the Delphi survey aims to mitigate against this potential limitation.

Most participants had undergone their surgery at least 12 months prior to this study. As such, it should be acknowledged that there may have been a greater exploration of and emphasis on shorter-term outcomes had we recruited more participants from a shorter post-operative time-period. Again, to address this potential limitation, we plan to recruit

participants for the Delphi survey from all post-operative periods and will have the opportunity to examine whether ‘time from surgery’ affects patient priorities.

In summary, this study identified 38 unique outcomes which are important to patients following surgery for gastric cancer. Many of these outcomes are poorly represented by trials within this research field. These outcomes will be added to other potentially important outcomes to be considered for prioritisation by key stakeholders to develop a COS for surgical trials in gastric cancer.

4.6 References

1. Fact Sheets by Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed July 24, 2017.

2. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015;64(12):1881-1888. doi:10.1136/gutjnl-2014-308915

3. Messager M, de Steur WO, van Sandick JW, et al. Variations among 5 European countries for curative treatment of resectable oesophageal and gastric cancer: A survey from the EURECCA Upper GI Group (EUropean REgistration of Cancer CAre). Eur J Surg Oncol. 2016;42(1):116-122. doi:10.1016/j.ejso.2015.09.017

4. Michalowski J, Salvador A, Napper R. Commissioned by Healthcare Quality Improvement Partnership National Oesophago-Gastric Cancer Audit 2018 An Audit of the Care Received by People with Oesophago-Gastric Cancer in England and Wales 2018 Annual Report.; 2018.

5. Alkhaffaf B, Blazeby JM, Williamson PR, Bruce IA, Glenny A-M. Reporting of outcomes in gastric cancer surgery trials: a systematic review. BMJ Open. 2018;8(10):e021796. doi:10.1136/BMJOPEN-2018-021796

6. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study). Trials. 2017;18(1):370. doi:10.1186/s13063-017-2100-7

7. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(S3):280. doi:10.1186/s13063-017-1978-4

8. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. Arthritis Care Res (Hoboken). 2010;62(5):640-646. doi:10.1002/acr.20034

9. Allard A, Fellowes A, Shilling V, Janssens A, Beresford B, Morris C. Key health outcomes for children and young people with neurodisability: qualitative research with young people and parents. BMJ Open. 2014;4(4):e004611. doi:10.1136/bmjopen-2013-004611

10. Arnold LM, Crofford LJ, Mease PJ, et al. Patient perspectives on the impact of

fibromyalgia. Patient Educ Couns. 2008;73(1):114-120. doi:10.1016/j.pec.2008.06.005

11. Keeley T, Williamson P, Callery P, et al. The use of qualitative methods to inform Delphi surveys in core outcome set development. Trials. 2016;17(1):230. doi:10.1186/s13063-016-1356-7

12. Thomas DR. A General Inductive Approach for Analyzing Qualitative Evaluation Data. Am J Eval. 2006;27(2):237-246. doi:10.1177/1098214005283748

13. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77-101. doi:10.1191/1478088706qp063oa

14. Corbin J, Strauss A. Grounded Theory Research: Procedures, Canons, and Evaluative Criteria. Vol 13.; 1990.

15. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for Reporting Qualitative Research. Acad Med. 2014;89(9):1245-1251. doi:10.1097/ACM.0000000000000388

16. Standards | INVOLVE. https://www.invo.org.uk/current-work/standards/. Accessed December 7, 2019.

17. McNair AGK, Whistance RN, Forsythe RO, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLOS Med. 2016;13(8):e1002071. doi:10.1371/journal.pmed.1002071

18. Fish R, Sanders C, Adams R, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. lancet Gastroenterol Hepatol. 2018;3(12):865-873. doi:10.1016/S2468-1253(18)30264-4

19. MacLennan S, Bekema HJ, Williamson PR, et al. A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey. Trials. 2015;16:76. doi:10.1186/s13063-015-0598-0

20. van Beek AP, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. Obes Rev. 2017;18(1):68-85. doi:10.1111/obr.12467

21. McNair AGK, Brookes ST, Kinnersley P, Blazeby JM. What surgeons should tell patients with oesophago-gastric cancer: A cross sectional study of information needs. Eur J Surg Oncol. 2013;39(11):1278-1286. doi:10.1016/J.EJSO.2013.08.005

22. Avery KNL, Chalmers KA, Brookes ST, et al. Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. Ann Surg. March 2017:1. doi:10.1097/SLA.0000000000002204

23. Onwuegbuzie AJ, Dickinson WB, Leech NL, Zoran AG. A Qualitative Framework for Collecting and Analyzing Data in Focus Group Research.; 2009.

24. Saunders B, Sim J, Kingstone T, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Qual Quant. 2018;52(4):1893-1907. doi:10.1007/s11135-017-0574-8

4.7 Appendices

4.7.1 Appendix 1. Development of themes

Theme: Surviving and Controlling Cancer

Issues identified on initial coding	Outcome	Outcome theme
Being cured of cancer Cancer returning to other parts of the body Cancer returning in the abdomen Possibility of cancer returning	Recurrence of Cancer	Surviving and Controlling Cancer
Being able to live (a little/a lot) longer Being alive/surviving for a 'long time' Chances of (not) dying from cancer Chances of survival	Survival	

Theme: Adverse events following surgery

Issues identified on initial coding	Outcome	Outcome theme
Complications related to anaesthesia	Anaesthetic complications	Adverse events following of Surgery
Anastomotic leak Anastomotic stricture	Anastomotic complications	
Internal bleeding requiring further intervention	Bleeding	
Concern about cardiac complications in context of previous myocardial infarction Racing heartbeat	Cardiac complications	
Stroke following surgery	Cerebro-vascular complications	
Bowel perforation Gastro-intestinal symptoms e.g. constipation Obstruction of bowel	Intestinal complications	
Epidural related complications Hallucinations Overdose of medications such as morphine Side effects of sedatives	Medication related complications	
Drains and tubes to manage complications Endoscopic treatment of anastomotic	Need for re-intervention	

stricture Requiring further surgery to manage complications Surgery for incisional hernia		
'Surviving' surgery Dying from a complication of surgery Dying on the operating table	Peri-operative death	
Hospital acquired pneumonia Pleural effusion Pneumothorax	Respiratory complications	
Re-admission due to complications such as infections Re-admission due to pain	Re-admission to hospital	
Wound dehiscence Wound infection Wound leak Wound numbness	Wound complications	
Catheter-related problems	Urinary complications	

Theme: Long-term impact of surgery

Issues identified on initial coding	**Outcome**	**Outcome theme**
Being able to enjoy a good quality of life Uncertainty as to what life will be like following surgery	Overall 'quality of life'	Long-term impact of surgery
Changes in mood Clinical depression Feeling 'abnormal' and 'different' to others Feelings of insecurity Feelings of isolation Issues related to body image Low mood	Psychological impact	
Being able to enjoy eating again Being able to exercise again Being able to interact and socialise with others Being able to live 'as they did before' Being able to rely on oneself to undertake tasks Being able to undertake household	Returning to 'normality'	

activities such as shopping and gardening Returning to employment		

Theme: Technical aspects of surgery

Issues identified on initial coding	**Outcome**	**Outcome theme**
'Cutting' the cancer out Ensuring no cancer is left behind Getting 'rid' of the cancer Inability to resect cancer at surgery Removing all lymph nodes Removing spleen if necessary	Complete resection of cancer	Technical aspects of surgery
Ability to perform laparoscopic 'keyhole' surgery Large scars	Size of incisions	
Duration of surgery	Duration of surgery	

Theme: Long-term problems following surgery

Issues identified on initial coding	**Outcome**	**Outcome theme**
Amounts able to eat and drink Being able to eat 'properly' Being able to eat at home Change in diet and types of food patient can consume Difficulties swallowing	Eating and Drinking	Long-term problems following surgery
Requirement for ongoing nutritional support Vitamin B12 deficiency	Nutritional problems	
Feeling persistently tired Feeling extremely weak/lethargic/tired Having no energy or stamina Loss of energy following simple tasks	Fatigue	
Abdominal bloating Belching Diarrhoea Dumping syndrome Excessive flatus Nausea Reflux symptoms (acid or bile) Vomiting	Gastro-intestinal symptoms	
Abdominal pain or cramps Headaches and migraines	Chronic Pain	

Long-term wound related pain Muscle cramps Pain on swallowing Painful abdominal distension or bloating		
Inability to regain weight to desired level Readjusting to new weight Speed of weight loss Weight loss in general	Weight problems	

Theme: Recovery Following surgery

Issues identified on initial coding	**Outcome**	**Outcome theme**
Post-operative plan for physiotherapy Restricted mobility due to drains and tubes attached Time to be able to undertake tasks such as standing up, walking, or bathing	Ambulation	Recovery following surgery
Time before being allowed to eat and drink Time before bowel function returned	Return of gastrointestinal function	
Concern about being too unwell for further chemotherapy	Ability to have more chemotherapy	
Length of time in hospital Length of time in intensive care	Duration of hospital stay	
Length of time in pain Patterns of pain Requirement for analgesia Severity of pain	Post-operative pain	

4.7.2 Appendix 2. Summary of outcomes and outcome themes identified from interviews.

Outcome Theme	**Outcome**	**How many interviews outcome was referenced in**	**Total number of references in all interviews**
Surviving and controlling cancer Referenced in 20 interviews Referenced 90 times in all interviews.	Curing Cancer	4	6
	Recurrence of Cancer	18	28
	Survival	20	56
Technical aspects of surgery Referenced in 18 interviews Referenced 52 times in all interviews.	Complete Excision of Cancer	18	52
	Excision of Lymph Nodes	5	5
	Need for splenectomy	1	1
	Operative time	1	2
	Wound Size	7	11
Adverse events Referenced in 20 interviews Referenced 97 times in all interviews.	Ability to have adjuvant chemotherapy	1	1
	Anaesthetic Complications	1	1
	Anastomotic Leak	6	9
	Anastomotic Stricture	1	1
	B12 Deficiency	5	5

Outcome Theme	Outcome	How many interviews outcome was referenced in	Total number of references in all interviews
	Bleeding	1	2
	Cardiac Complications	2	2
	Catheter related complications	1	1
	Cerebro-vascular complications	1	1
	Gastrointestinal problems	1	1
	Hernia	1	1
	Intestinal complications	4	10
	Medication-related complications	10	12
	Need for reintervention	8	13
	Peri-operative death	12	20
	Re-Admission to Hospital	3	4
	Respiratory complications	3	3
	Wound Complications	8	10
Recovery from surgery	In Hospital Recovery	11	23

Outcome Theme	Outcome	How many interviews outcome was referenced in	Total number of references in all interviews
Referenced in 18 interviews Referenced 57 times in all interviews.	Length of Stay Following Surgery	11	18
	Peripheral Oedema	1	1
Long-terms problems following surgery Referenced in 20 interviews Referenced 175 times in all interviews.	Eating & Drinking	20	75
	Fatigue	16	38
	Gastrointestinal symptoms	11	27
	Pain	10	14
	Weight Loss	12	21
Long-term impacts of surgery Referenced in 20 interviews Referenced 133 times in all interviews.	Necessity of long-term feeding	1	1
	Overall QoL	8	10
	Psychological impact	11	40
	Returning to normality	20	82

5 Methods for conducting international Delphi surveys to optimise global participation in Core Outcome Set development: a case study in gastric cancer informed by a comprehensive literature review

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5.1 Abstract

Background

Core outcome sets (COS) should be relevant to key stakeholders, and widely applicable and usable. Ideally, they are developed for international use to allow optimal data synthesis from trials. Electronic Delphi surveys are commonly used to facilitate global participation; however, this has limitations. It is common for these surveys to be conducted in a single language potentially excluding important opinion. The aim of this study is to summarise current approaches for optimising international participation in Delphi studies and make recommendations for future practice.

Methods

A comprehensive literature review of current approaches to translating Delphi surveys for COS development was undertaken. The COMET database was used to identify relevant COS up until March 2019. Two independent reviewers screened the results. A standardised methodology adapted from international guidance derived from 12 major sets of translation guidelines in the field of outcomes reporting was developed. As a case study this was applied to a COS project for surgical trials in gastric cancer to translate a Delphi survey into 7 target languages from regions active in gastric cancer research.

Results

332 abstracts were screened and four studies addressing COS development in rheumatoid and osteo-arthritis, vascular malformations and polypharmacy were eligible for inclusion. There was wide variation in methodological approaches to translation, including the number of forward translations, the inclusion of back translation, the employment of cognitive debriefing and how discrepancies and disagreements were handled. Important considerations were identified during the development of the gastric cancer survey including establishing translation groups, timelines, understanding financial implications, strategies to maximise recruitment and regulatory approvals. The methodological approach to translating the Delphi surveys were easily reproducible by local collaborators and resulted in an additional 637 participants to the 315 recruited to complete the source language survey. 99% of patients and 97% of healthcare professionals from non-English speaking regions used translated surveys.

Conclusion

Consideration of the issues described will improve planning by other COS developers and can be used to widen international participation from both patients and healthcare professionals.

5.2 Introduction

A core outcome set (COS) is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or healthcare[1]. COS should be relevant to key stakeholders and widely applicable such that researchers are encouraged and willing to incorporate them in trials. Approaches to improve the relevance of COS can take many forms, including involving stakeholders with lived experience of the condition or intervention in question. Many COS developers (up to 85%) are using Delphi surveys during stages to prioritise potentially important outcomes[2,3]. A Delphi survey is a method of seeking consensus and asks participants to score items in terms of importance, usually using a Likert-type scale, across multiple survey rounds. In subsequent rounds, participants can reflect on their score and the ratings of others before being given the opportunity to change their scores if they wish. Using an online platform to undertake a Delphi survey enables overseas stakeholders to participate more readily in this process. Such broad participation can give COS greater validity across different geographical regions and consequently make them more likely to be used in future trials regardless of the location where trials are undertaken. Unless COS are widely used in trials within the same research field, the challenge of inconsistent outcome reporting will persist[4].

Most research groups developing 'international' Delphi surveys have restricted themselves to their native language (usually, but not exclusively, English). This approach is less resource intensive than translating the survey into multiple languages and overcomes issues with ambiguity or changes in meaning - a recognized challenge with translation[5]. However, these methodological challenges are not insurmountable, and some COS developers are translating Delphi surveys to minimise the risk of excluding important opinion from those not fluent in the study's primary language.

The GASTROS study (**GA**stric **C**ancer **S**urgery **TR**ials **R**eported **O**utcome **S**tandardisation) aims to develop an international COS for surgical trials in gastric cancer[6]. The scope and design of the GASTROS study has been previously detailed[6]. In summary, following a systematic review of randomized control trials[4] and a series of in-depth patient interviews[7], a long-list of potentially important outcomes was rationalized into a list of 56 outcomes. Following a consultative exercise with key stakeholders, these 56 outcomes were presented to patients and healthcare professionals in a two-round, multi-language Delphi survey. Currently, there is no standardized method of translating Delphi surveys for use in the development of international COS. This paper aimed to address this need by using GASTROS as a case study to implement a methodological approach to translation developed from international consensus guidelines in the field of outcomes reporting[5].

5.2.1 Objectives

The objectives of this paper include:

1. To describe the current methodological approaches used by COS developers in the translation of Delphi surveys,
2. To outline a pragmatic, robust and replicable approach to translating Delphi surveys for use in COS development, and
3. To outline important logistical considerations in preparation for an international Delphi survey.

5.3 Methods

5.3.1 Assessing current approaches to translating Delphi Surveys (Methodology)

To gain an understanding of current translation approaches for multi-language Delphi-surveys, a comprehensive literature review of the COMET database was undertaken[8]. The COMET database is a comprehensive registry which (as of 03/09/2019) contained 337 published and 280 ongoing COS respectively dating back from 1981. The database is kept up-to-date through annual systematic reviews of scientific databases (using MEDLINE via OVID and SCOPUS), automated alerts from MEDLINE via OVID, SCOPUS and Google Scholar and direct submissions from COS developers[9].

5.3.2 Search Strategy and Inclusion Criteria

The COMET database enables users to search for terms within the 'title', 'abstract' or 'author names' categories. Searches can be restricted according to health area, target population, methods, stakeholder involvement, study type and publication year. A broad search for the terms 'international', 'language' or 'translat$' in the title and abstract was undertaken with no other restrictions.

Studies included in our review were those that used a multi-language Delphi survey in the development of their respective COS. Only publications from completed studies were included - COS methodology is a relatively new research field and so planned approaches may not accurately reflect the final methodology used. The COMET database may contain several different references to COS development for the same project. Any related publications were consolidated and handled as a single COS study.

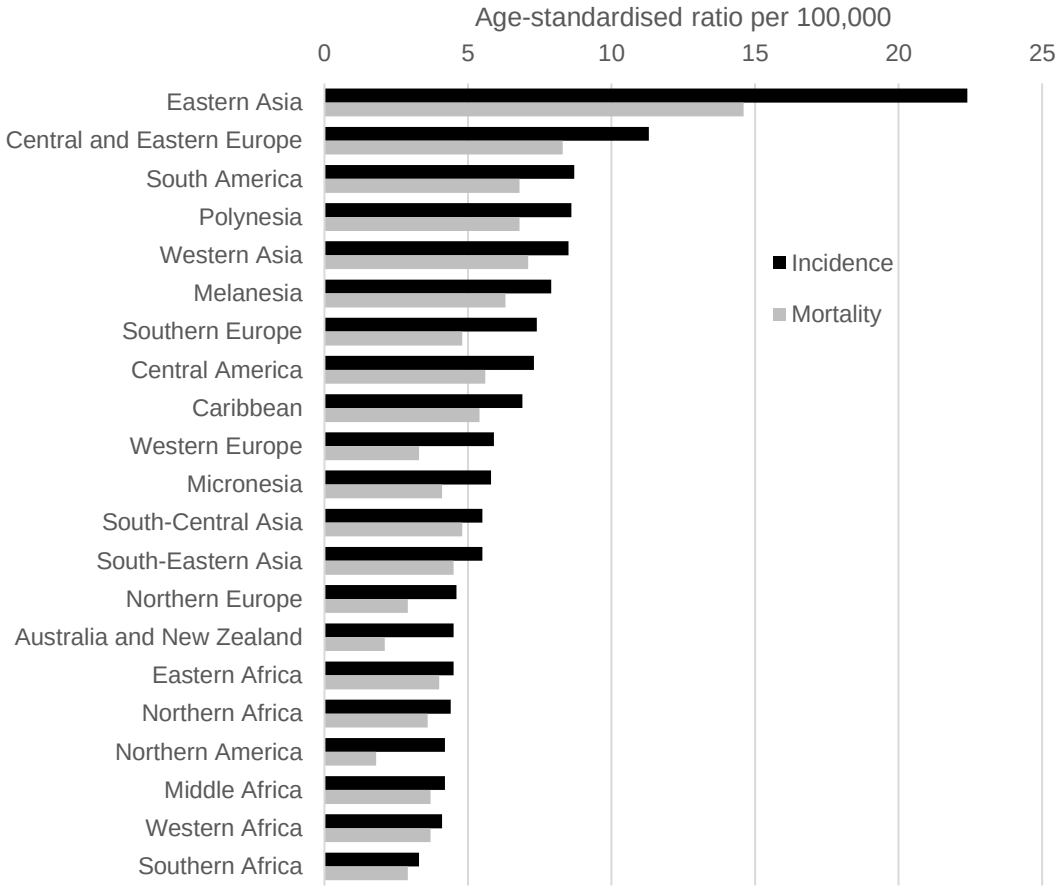
Corresponding authors were contacted and asked to participate in a questionnaire examining various aspects of their respective methodological approaches (supplementary appendix 1). The questionnaire focused on how items presented in the Delphi surveys were translated and how discrepancies and conflict was resolved. For example, authors were asked about how they undertook forward and backward translations. The terms 'forward' and 'backward' refer to the direction of translation between the source and target languages, with

forward referring to a translation from the source language and backward referring to a translation from the target language back to the source language Responses were received from the corresponding authors of all studies identified and combined with data from the respective publications.

5.3.3 Approach to translating the GASTROS Delphi survey

One of the principal aims of translating the Delphi survey in the development of COS is to include the opinions of stakeholders who are not fluent in the source language. With respect to the GASTROS study, this was especially important given that the highest incidence of gastric cancer exists outside of English-speaking countries, in the Far East, Central and South America and Southern Europe (figure 1).

Figure 5-1 Estimated age-standardised world-wide incidence rates of stomach cancer (all ages, both sexes). Reproduced from GLOBOCAN 2020. All rights reserved.



The results from the literature review of current approaches to translation (see below) highlighted the need for further research in this area. In developing our approach to translate the survey, the study management group was keen to ensure that it was both methodologically sound yet pragmatic, such that it could be easily reproduced by multiple international collaborators within a relatively short period of time.

In 1999, the ISPOR-TCA group (The Professional Society for Health Economics and Outcomes Research – Translation and Cultural Adaptation group) was formed to discuss and develop guidelines for translating patient-reported outcome measures. The group highlighted inconsistencies with previous methodologies and nomenclature in this field and sought to address these by developing guidance setting out 'principles of good practice'[5]. These principles were derived from 12 major sets of translation guidelines from the following groups:

- American Association of Orthopaedic Surgeons (AAOS)
- Association of Test Publishers
- EORTC group
- Euro QoL group
- Evidence: Clinical and Pharmaceutical Research
- FACIT group
- Health Outcomes group (HOG)
- Health Utilities Inc. (HUInc)
- International Quality of Life Assessment (IQOLA) group
- Kidney Disease Quality of Life (KDQOL)
- Medical Outcomes Trust (MOT)
- World Health Organization

Other consensus guidelines have been developed for translating surveys. The Survey Research Centre (SRC) guidelines provide broader consideration of the translation process and describe practical support from expert contributors' experience of different survey types[10]. There is much cross-over between the two guidelines. Given the focus of our work was primarily outcome related translation, the principles as set out by the ISPOR-TCA group formed the basis of our methodology, with references made to the SRC guidance and some pragmatic amendments which are explained in further detail below.

5.3.4 Eligibility criteria for target languages

The target languages were chosen to enable increased recruitment from regions with a significant incidence of gastric cancer and experience of research activity within this field. The source survey was developed in English and translated into seven target languages (Simplified Chinese, Dutch, German, Italian, European Portuguese, European Spanish and Turkish). By facilitating participation from these regions, we aimed to improve the validity of our COS such that it would be more likely to be used by researchers in future trials.

5.4 Results

5.4.1 Comprehensive literature review of previous translation approaches

346 records were identified from the COMET database from which four studies (summarized in table 1) were deemed eligible for inclusion in the comprehensive literature review. The process through which these were identified are summarised in figure 1.

5.4.1.1 General Approaches to Translation currently in use

All 4 COS groups summarized their approach to translating surveys with one providing a reference to their methodology and another referring to methodology described by the OMERACT group at a COS development meeting [10,11]. In addition to forward translations, three groups undertook a backward translation of the survey from the target to source language. The number of forward and backward translations differed in each study. Two studies undertook a single forward translation whilst the others undertook two and three. One group used no backward translations, one study undertook a single backward translation whilst the other two undertook two backward translations. The characteristics of those involved in the translation processes also differed amongst the groups (figure 2); no paid translation services were employed, and all translations were undertaken by healthcare professionals or lay translators.

Table 5.1 Studies using multi-language Delphi surveys in the development of international COS.

Condition/Group	Original Language	Target Language(s)	Total Participants in Surveys	Total Participants Using Translated Survey(s) (%)
Hip and Knee Osteoarthritis OMERACT-OARSI[12]	English	Italian & Spanish	426	2 (0.5%)
Medication review in multi-morbid older patients with polypharmacy OPERAM[13]	French	Dutch, German, English	150	118 (79%)
Idiopathic inflammatory myopathy OMERACT[14]	English	Swedish, Dutch & Korean	500	120 (24%)
Vascular Malformations OVAMA Group[15]	English	Dutch	301	72 (24%)
Gastric cancer GASTROS Study	English	Chinese, Dutch, German, Italian, Portuguese, Spanish, Turkish,	952	637 (66%)

Figure 5-2 Flow diagram demonstrating which studies were included in the systematic review.

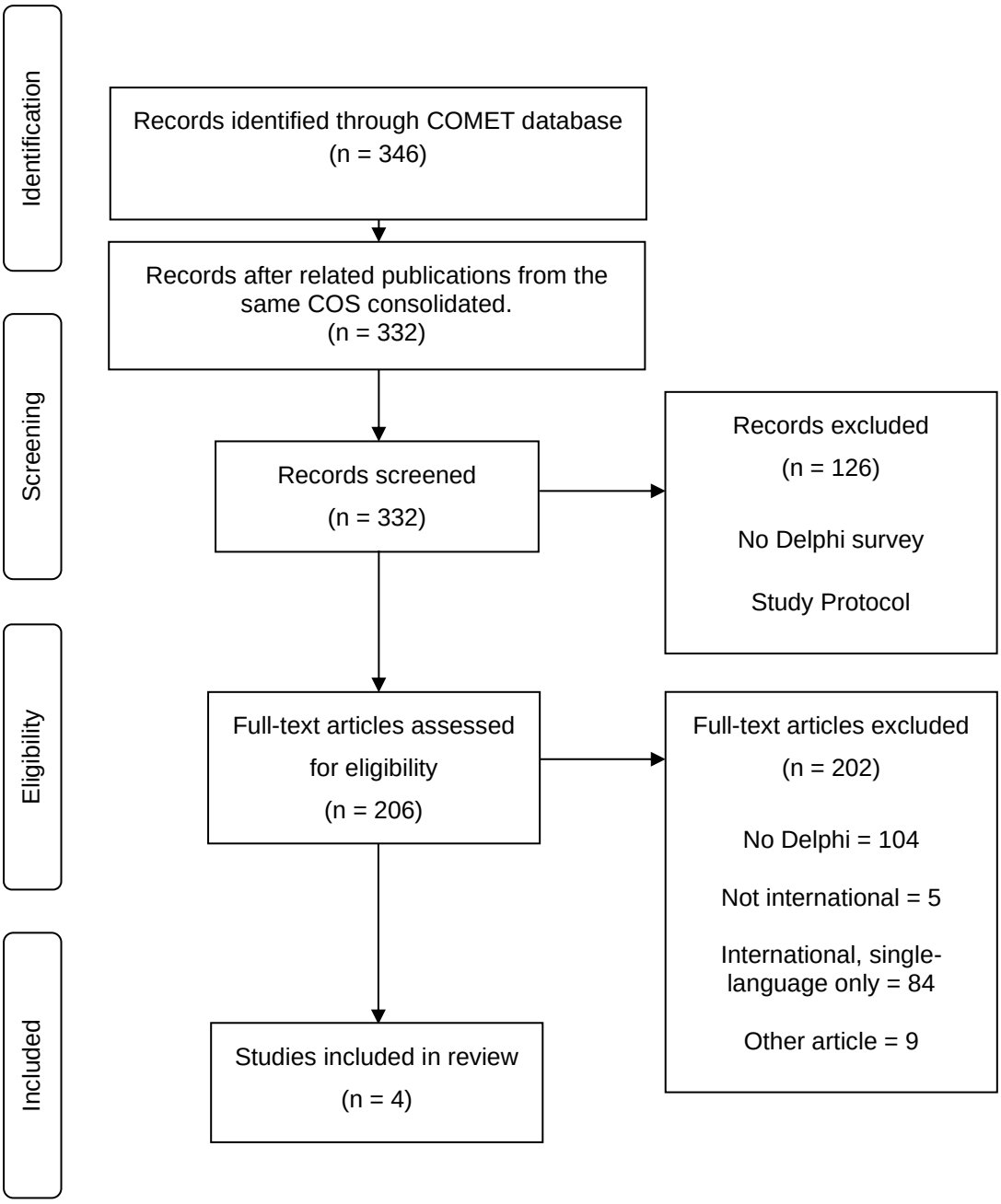
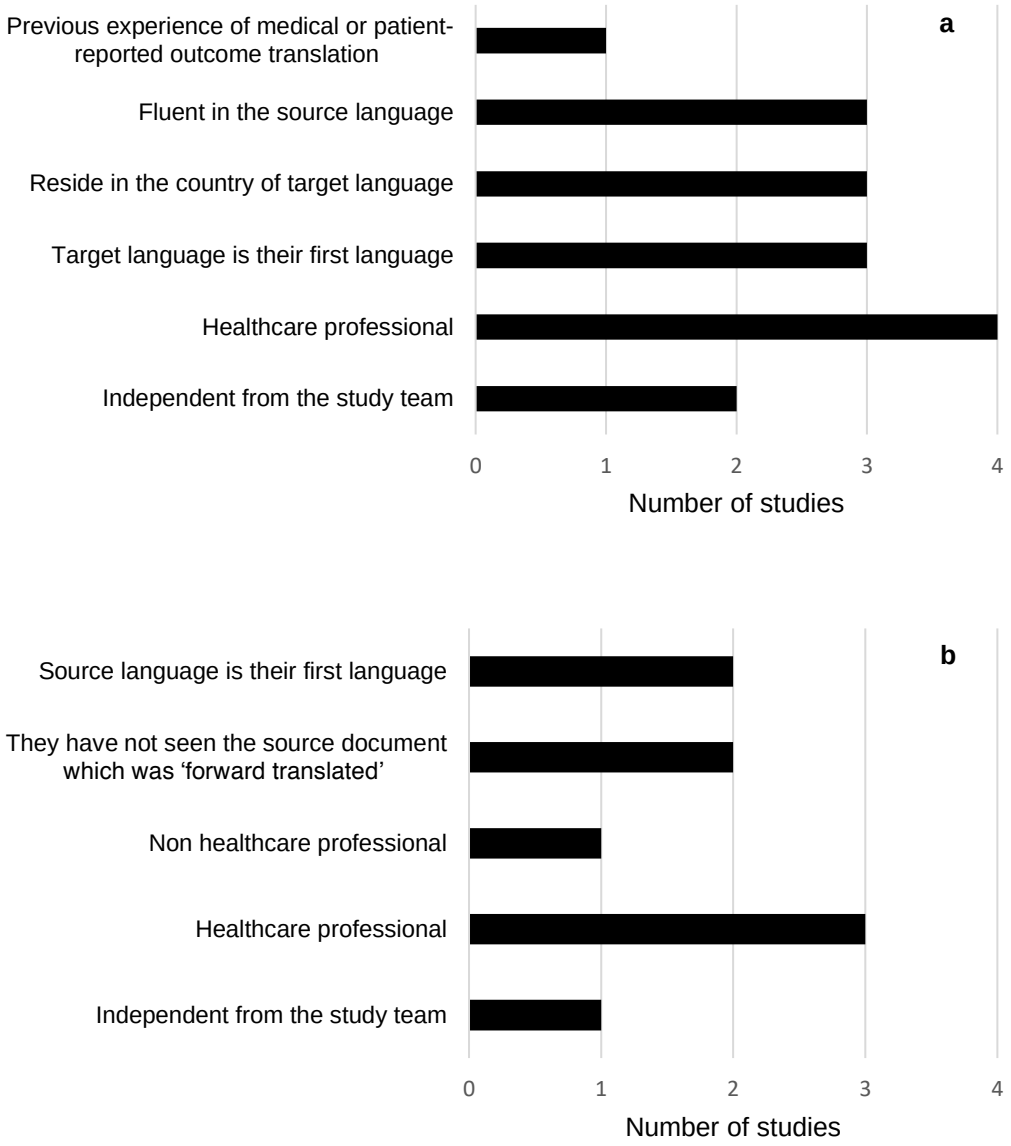


Figure 5-3 a) Characteristics of translators undertaking forward translation(s) b) Characteristics of translators undertaking backward translation(s).



5.4.1.2 Discrepancies and Harmonization

All four groups described an approach to managing discrepancies in translations. Two groups reported that discrepancies were discussed within the 'research group' until consensus was reached, whilst the remaining two referred to individuals outside of the 'research group' who were fluent in the target language to resolve any language issues.

5.4.1.3 Cognitive Debriefing

Three groups described undertaking an exercise to test alternative wording and check understandability, interpretation, and cultural relevance of the proposed Delphi survey in the target language. Using interviews, they studied patients/relatives and health professionals' interpretation of the translations to examine face validity (the degree to which the survey

appears effective in terms of its stated aims). Two of these involved patients and/or their relatives whilst the third was based on the opinion of healthcare professionals alone.

5.4.2 Results from GASTROS Study

The GASTROS study was able to recruit 952 eligible participants (445 surgeons, 268 patients, 239 nurses) in the first round of the Delphi survey, with 315 participants using the English language version and 637 using one of the seven other language versions (table 2). 62% (166/268) of patients used translated surveys compared to 69% (471/684) of healthcare professionals (62% of surgeons and 82% of nurses).

5.4.2.1 Development of translation approach

Below, we describe ten steps involved in translating the Delphi survey used in the development of a COS for surgical trials in gastric cancer. The full rationale for each step, and the risks of omitting them, is described in detail in the ISPOR-TCA guidance; we have stated the rationale for the steps below (particularly in relation to pragmatic deviations) where we believed it was necessary to do so.

Supplementary appendix 2 details the instructions which were provided to each international collaborator responsible for leading the translation process in their respective country. These outlined which files required translation, how the translation should be undertaken, and by whom.

5.4.2.1.1 Step 1: Preparation

a. Cognitive Debriefing:
    i. Cognitive debriefing describes a process which aims to identify issues with comprehensibility of key concepts and understanding amongst potential participants. As previously stated, we presented survey participants with 56 outcomes which had been rationalized following a process that had identified a long-list of potentially important outcomes from a systematic review and in-depth patient interviews. The rationalization process from the long-list to the 56 survey items involved key-stakeholders (members of the GASTROS study group, surgeons, oncology nurses and patients) who also ensured that the outcomes were accompanied with plain English-language explanations that could be understood by all participants including patients. A further consultative exercise with an English-speaking patient-group was held to ensure that the meaning of each outcome, in addition to other survey-related files were clearly understood. Undertaking this work prior to translation was essential as it minimized the possibility of ambiguous meanings which could result in a mistranslation.

Table 5.2 Uptake of translated Delphi surveys in non-English speaking regions.

Regional Language	**Patients (n=268)**		**Surgeons (n=445)**		**Nurses (n=239)**	
	Translated Version	English Version (%)	Translated Version (%)	English Version (%)	Translated Version (%)	English Version (%)
Chinese	60 (97%)	2 (3%)	109 (97%)	3 (3%)	109 (100%)	0 (0%)
Dutch	5 (100%)	0 (0%)	22 (100%)	0 (0%)	10 (100%)	0 (0%)
German	4 (100%)	0 (0%)	10 (100%)	0 (0%)	-	-
Italian	57 (100%)	0 (0%)	57 (95%)	3 (5%)	12 (100%)	0 (0%)
Portuguese	1 (100%)	0 (0%)	28 (88%)	4 (12%)	8 (100%)	0 (0%)
Spanish	-	-	33 (94%)	2 (6%)	0 (100%)	0 (0%)
Turkish	39 (100%)	0 (0%)	17 (94%)	1 (6%)	56 (100%)	0 (0%)
Other language*	No translation undertaken.	0	No translation undertaken.	97	No translation undertaken.	13
TOTAL	166 (99%)	2 (1%)	276 (96%)	13 (4%)	195 (100%)	0 (0%)

Percentages reported refer to the proportion of participants from the respective region within each stakeholder group. *'Other language' refers to regions where English was not the first language, but where the survey was not translated.

b. Preparing documents for translation

   i. Four documents were needed to run the Delphi survey; a participant information sheet and three further files which were required to set up the web-based survey. We used DelphiManager 3.0 platform, developed and maintained by the COMET Initiative (http://www.comet-initiative.org/), to undertake the Delphi survey (see 'important considerations'). The three files included:

      1. File 1 (appendix 3): An excel file containing details of each outcome, accompanying meaning and the 'outcome area' under which the outcome was categorised[16].
      2. File 2: User-defined text: A file containing text specific to our surveys (in this case the GASTROS Delphi survey).
      3. File 3: Static text: A file containing text common to all Delphi surveys which was used in the setting up process by the DelphiManager team.

   ii. Preparation for Round 2 of the Delphi survey: Additional translations were required to support the second round of the survey. These included:

      1. Outcomes identified by participants in round 1 as being important to consider that were not identified from the systematic review or patient interviews.
      2. Legends and terms required to produce charts which were presented to survey participants in round 2.
      3. Comments and feedback from study participants.

   iii. Following Round 2 of the survey:

      1. Participants who changed their scores between rounds were given the opportunity to provide their reasons for doing so.
      2. Participants were also given the opportunity to provide further comments after completing the survey.

c. Understanding which methodological approaches to employ

   Due to the resources required for different methodologies, we opted for two approaches to translation. Our rationale for applying each approach is described below:

   1. "Two forward, one back translation"; This approach was the most comprehensive and labour intensive as it required a further nine steps (below) before a final file version was agreed. Following discussion amongst the study management team, it was deemed content which could alter the meaning of the outcomes being presented and ultimately influence how the

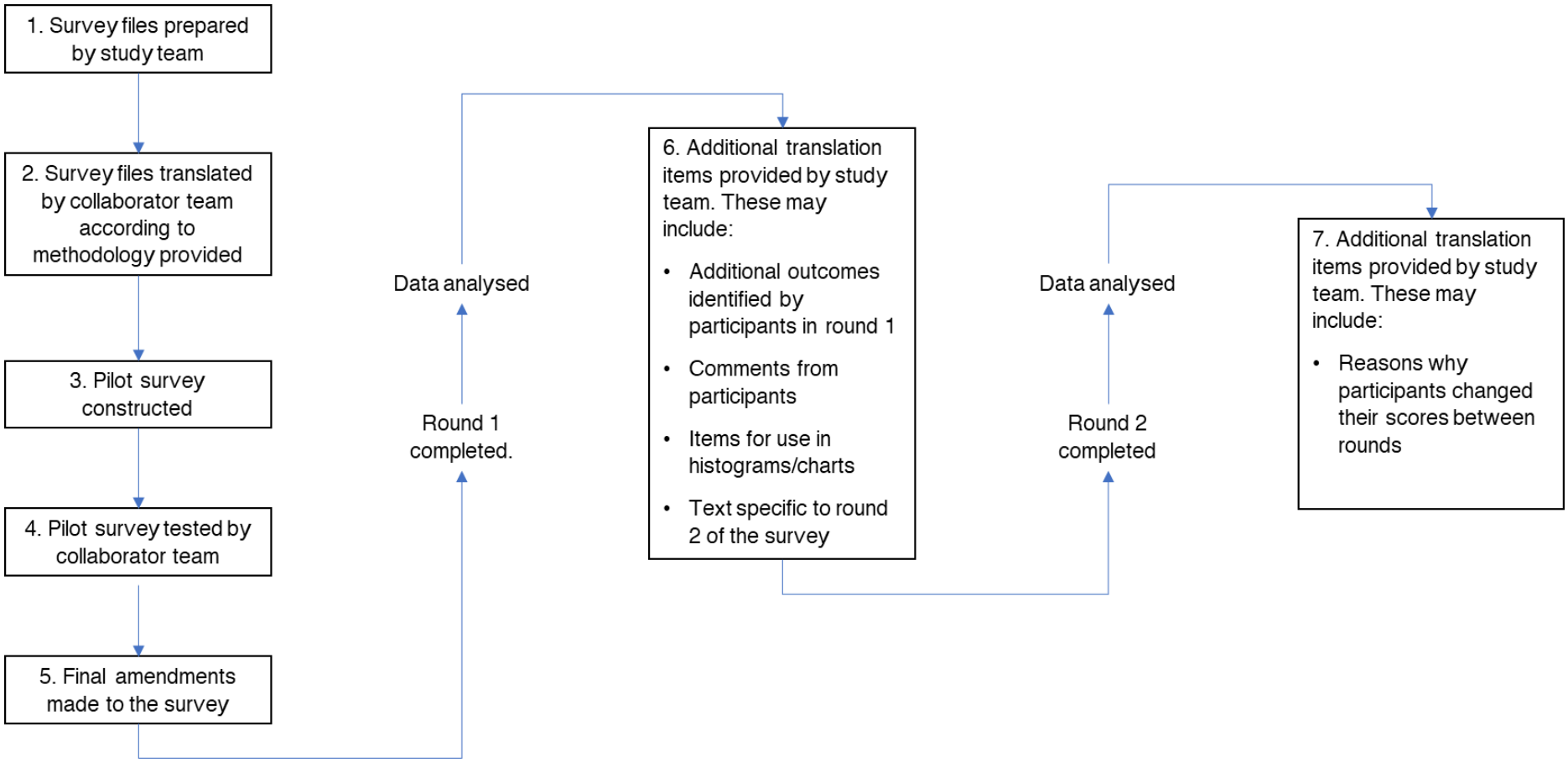
overall aims of the survey was received and understood by participants (file 1, file 2, and additional outcomes identified by participants in round 1) underwent this approach. The steps involved in this process are described in greater detail in points 2 to 10.

2. “One forward, dual independent proofreading”; File 3 consisted primarily of short instructional phrases (e.g. ‘click here’, ‘register’, and ‘next page’) which were necessary for the functionality of the survey. As these terms would not materially influence the comprehension of the survey’s purpose or outcomes presented within it, a simplified, less resource intensive approach was adopted. This file underwent a single forward translation followed by two independent proof-readings by translators who compared the translated and source files for accuracy and quality. Any corrections or amendments were undertaken through discussion between the translator and proof-readers. This approach was also adopted for the translation of participant comments, feedback and reasons for changing scores between round 1 and round 2.

d. Setting up translation teams

To support the translation work, an international working group (IWG) was established (see ‘important considerations’). Each collaborator within the IWG was responsible for overseeing a team which would undertake the translation and ensuring that the key concepts of the study were appropriately communicated. The translation process was supported by the GASTROS study Chief Investigator (BA) if any clarifications were required. The characteristics of individuals involved in this process are described in greater detail in supplementary appendix 2. In summary, each team was made up of an IWG lead, two forward translators and a single backward translator.

Figure 5-4 Step by step translation process for multi-language Delphi surveys.



e. Developing instructions for translations

Setting out the methodology a priori in a clear and structured document ensured that collaborators and their teams understood what would be required of them at each stage of the translation. These instructions included ongoing responsibilities prior to and following future rounds of the Delphi survey. This was essential given that one of our primary aims was to ensure that our approach was easily replicable. Figure 3 is a flow diagram which details these stages and the order in which they were to be undertaken. Feedback from the IWG was positive in response to these instructions with collaborators reporting that the document enabled them to undertake the translation process efficiently.

f. Quality assurance

IWG collaborators were asked to provide documented evidence for each step of the translation process. These could then be reviewed by the study management team as required.

5.4.2.1.2 Step 2: Forward Translation

Two independent forward translations by individuals who were native speakers of the target language were undertaken. Culture is a primary determinant of language and therefore native speakers have advantages with language abilities compared to second-language speakers. Having two independent forward translations enables detection of errors and divergent interpretations that could otherwise lead to bias.

5.4.2.1.3 Step 3: Reconciliation

There are several approaches which can be used to reconcile the forward translations. We opted to use the 'in-country' IWG collaborator who was also involved in cognitive debriefing and piloting of the survey as this was pragmatic and would not require the identification of further individuals to undertake this step. No issues arose from the reconciliation process, however, had further clarifications been required, they would have been directed to the Chief Investigator (CI).

5.4.2.1.4 Step 4: Back Translation

The issue of whether 'back translation' is required is one on which there is disagreement; the ISPOR-TCA guidance states that 'back translation' is necessary, whilst the Survey Research Centre guidance suggests that it is not. COS developers may therefore be justified in omitting steps 4 and 5 of our approach. This should however be done after careful consideration as the importance of back translation may depend on the type of outcomes that are being translated. It is possible that certain outcomes are conceptually alien between cultures or geographical regions and undergoing an added step to reduce the risk of mistranslation is warranted. In the field of patient-reported outcome measurement (PROM), it

is common for questionnaires to undergo translations (for use in international trials). The methods required for PROM translation is rigorous and includes back translation[17]. Whilst it may be argued that less rigorous methods could be used in Delphi surveys for COS, to ensure optimal face validity of items the same standards are recommended.

We opted to undertake a single back translation to provide quality-control of the forward translations. Whilst the ISPOR-TCA guidance suggests that this should be undertaken by individuals who are native speakers of the source language (i.e. English), we found it challenging to identify seven native English-speakers who were also fluent in the required target languages and had an understanding of outcome reporting without referring to a professional service (paid professionals with expertise in translation). We opted to ensure that back-translators were fluent in English and independent from the forward translators.

5.4.2.1.5 Step 5: Back Translation Review

This step is important as it ensures that the cross-cultural adaptation needs of the translation is met. Cross-cultural adaptation ensures that the imprinted knowledge, attitudes, values, perceptions and behaviours of different regions are accounted for in the understanding of the terms being translated. Without it, there is a risk of that a mistranslation or omission would remain in the translation. This was undertaken by the CI in combination with the IWG collaborator by comparing the back translation to the source document. No significant discrepancies between the source and back-translated files were identified across any of the translations.

5.4.2.1.6 Step 6: Harmonization Across Different Languages

There is no agreed method to how harmonization across different translations should be enforced; many approaches omit this step. However, our group opted to ensure harmonization between each language at each step of the process. This was undertaken by the CI. We did not encounter significant differences between translations. An example of a minor change that was made across surveys was the term ‘last round scores’ which in the context of the survey meant ‘previous round scores’. Some teams translated this as ‘the final round scores’ which had to be altered to ensure all versions contained the same meaning.

5.4.2.1.7 Step 7: Cognitive Debriefing of the Translation

Following harmonization across translations, all survey versions were built using the DelphiManager platform (see ‘important considerations’). A further cognitive debriefing exercise was undertaken by asking IWG collaborators and their translation teams to complete a pilot version of the survey to identify grammatical or stylistic errors and check understandability, interpretation and cultural relevance of instructions and outcomes within the survey.

5.4.2.1.8 Step 8: Review of Cognitive Debriefing Results and Finalization

There were no issues highlighted with comprehensibility or understanding. Spelling mistakes and minor grammatical errors (e.g. pronouns ‘you’ formal and informal) were altered.

5.4.2.1.9 Step 9: Proofreading

IWG collaborators were once again asked to examine the survey and ensure that any issues highlighted in the previous steps had been addressed. No further changes were identified in any of the language versions by this stage.

5.4.2.1.10 Step 10: Final Report and ‘Start of Survey’

The ISPOR-TCA group guidance recommends that a report should be produced detailing the methodological approach for translation and rationale for each step. The final report for translations undertaken for the GASTROS study is represented by this paper.

5.4.3 Important Considerations

Whilst applying the described approach to translating the GASTROS Delphi survey, several key issues were identified that are summarised in table 3 and described in greater detail below. These should be considered alongside the translation work to maximise recruitment. We describe the rationale for each consideration and the potential risks of not applying these steps (where applicable).

5.4.3.1 International Working Group

The GASTROS study is a collaborative international initiative which sought to attract global representation within the study group. Motivated, research-active collaborators from countries with a significant incidence of gastric cancer were approached to form an IWG. Individuals signed a ‘terms of reference’ document which outlined the benefits of their involvement in addition to the following responsibilities:

- To form a local team and oversee the translation of the Delphi survey (where applicable)
- To drive recruitment locally, regionally, nationally, and internationally through organisations and personal networks
- To garner and develop links specifically with patient groups who would be able to participate in advertising the Delphi survey
- To identify the need and apply for relevant local ethical and regulatory approvals

Table 5.3 Nine key considerations for COS developers undertaking multi-language Delphi surveys.

1	**International working group**	To ensure that study and its aims are promoted in regions from where the study team wish to target recruitment.
2	**Patient and public involvement**	To ensure that the patient perspective is represented.
3	**Who should undertake the translation work?**	Deciding whether to employ professionally paid services or identify clinically trained individuals to undertake the translations.
4	**Milestones and timelines planning**	Providing a pre-agreed timetable for translation work and checks ahead of recruitment to the Delphi survey.
5	**Recruitment and retention targets**	Planning how long to keep Delphi survey rounds open to ensure an appropriate number of participants have been recruited.
6	**Paper and internet-based survey versions**	Giving stakeholders without easy access to the internet an opportunity to participate in the study.
7	**Measures to maximise recruitment**	Dissemination strategy Local recruitment Support from stakeholder group and research networks Collaborations Personalised emails Social media and multimedia
8	**Ethical approval**	Identifying what type of approvals are required as these vary between regions.
9	**Financial planning**	Ensuring that a robust plan for resource allocation is made in advance.

The IWG was made up of collaborators from the following countries:

- Brazil
- Mainland China and Hong Kong
- Germany
- Ireland
- Italy
- Japan
- The Netherlands
- Nigeria
- Portugal
- South Korea
- Spain
- Turkey
- United Kingdom

Ensuring the IWG was set up early maximized our ability to develop translations in a timely manner and recruit evenly across all stakeholder groups from a broad range of countries.

5.4.3.2 Patient and Public involvement

A Study Advisory Group (SAG) separate to the IWG formed part of the management structure of the wider GASTROS study. The SAG was made up of key stakeholder representatives including patients (three surgeons, three nurses and three patients). The group provided advice on the methodology of the study, general delivery of the study against its stated objectives and ensured that the viewpoints of all stakeholder groups were considered. In addition, patient groups (see acknowledgements) were vitally important in reviewing and piloting the translated surveys prior to recruitment to the Delphi. These groups were also instrumental in recruiting patients (see below).

5.4.3.3 Who should undertake the translation work?

The GASTROS study management group opted to set up local translation teams made up of healthcare professionals who met the rigorous criteria as set out by the ISPOR-TCA group. An alternative approach would have been to employ a professional translation service to undertake this work. One of the benefits of professional services is the ability to complete the translations in a relatively short period of time, in addition to developing an unlimited number of translations which may have resulted in wider participation in the Delphi survey. The main disadvantage to this approach is cost. Quotes from three different professional translation services (all familiar with the ISPOR-TCA guidance) were requested to support rounds 1 and 2 of the survey. In April 2018, the estimated costs were in the region of 3200GBP-4000GBP per language. All translations for rounds 1 and 2 of the survey would be finalized within 5

and 2 weeks respectively. Due to the financial limitations of undertaking the survey in 7 languages, we did not pursue this option.

5.4.3.4 Milestone & timeline planning

A summary of the resulting timelines involved in producing all versions of the survey using our approach to translation is provided in table 4. Setting aside enough time for the translation process is of paramount importance, particularly if COS developers are seeking to translate their surveys into more than one language. Some of the translation steps required all language versions to have reached the same stage prior to moving onto the next stage. For example, all initial translations had to have been completed before harmonization across surveys could be achieved. Without this, we were unable to ask collaborators and their teams to pilot their respective surveys. Furthermore, we chose to open recruitment to all language versions simultaneously and so all translations needed to have been fully completed before participants could complete their surveys. This was also the case for the second survey round. The impact of ethical approval applications on timelines is discussed below in greater detail. The time to return the initial translation documents and obtain ethical approvals resulted in the greatest variations with respect to the overall timelines. We found that setting regular milestones and realistic timelines helped achieve the required translation objectives. Regular communication between the CI and collaborators underpinned this process.

Our aspiration was to translate the Delphi survey into Japanese and Korean to enable wider patient participation from these countries. Due to challenges in identifying collaborators at an early stage, assembling a translation team and meeting timelines, this could not be pursued. However, potential participants were invited to complete the English language version of the survey.

5.4.3.5 Recruitment and retention targets

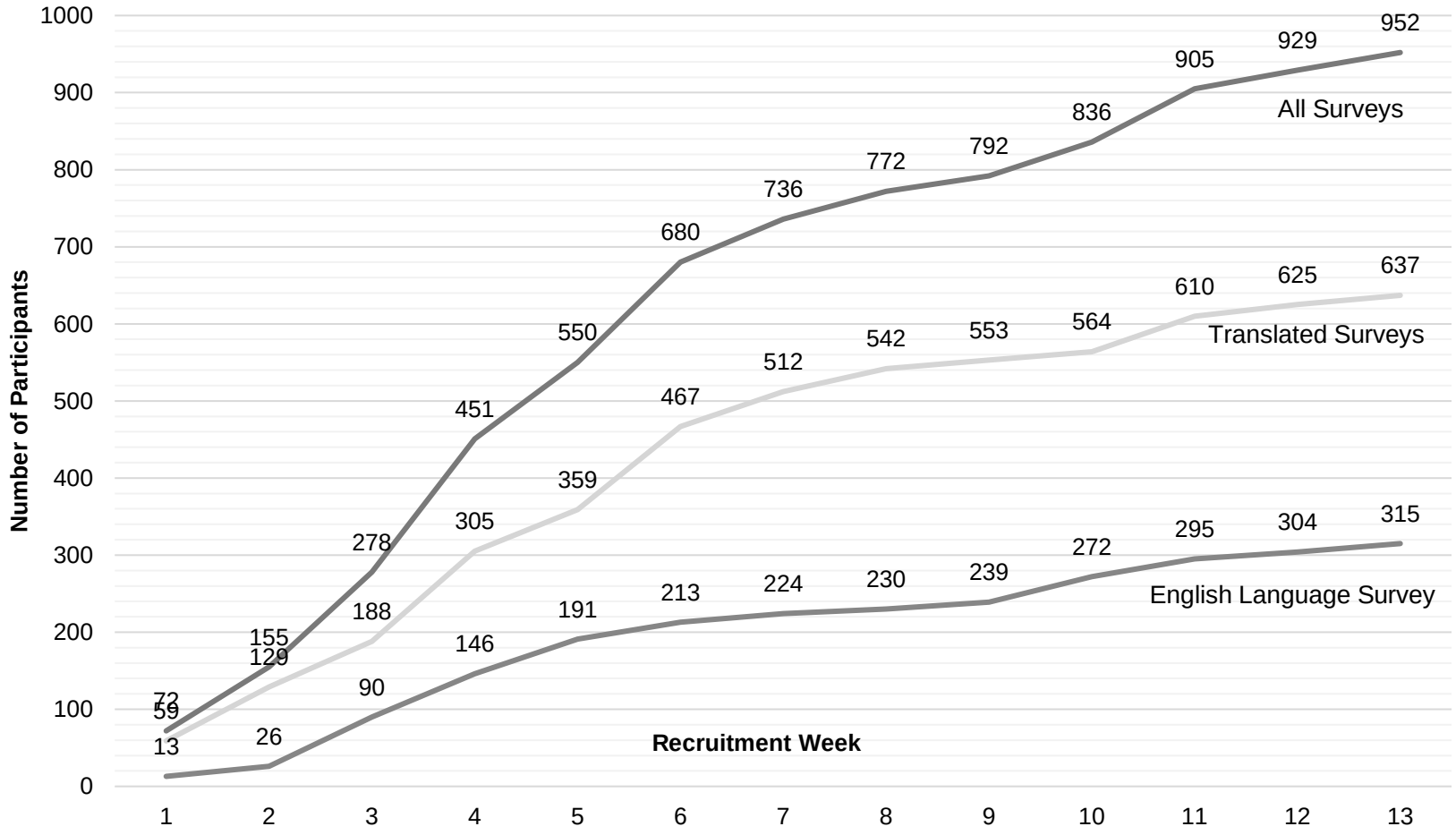
COS developers should consider minimum recruitment targets. Whilst there is no sample size requirement for Delphi surveys, the GASTROS protocol initially set a conservative target of 100 participants in total to be recruited over a period of 6 to 8 weeks in round 1. However, as interest in the study and international collaboration grew, it was clear to see that this target would easily be surpassed. As described below, once the survey opened and momentum began to gather, we witnessed a ‘snowballing’ effect amongst all three stakeholder groups. We therefore extended recruitment to 13 weeks by which time new participation had plateaued (figure 4).

Table 5.4 Timeline related considerations in undertaking multi-language Delphi survey in the GASTROS study.

Language Version*	Document Preparation	Time to return completed translations for r1	Harmonization across language versions	Time to set up online surveys	Time to pilot survey and complete amendments	Time to obtain ethical approval**	Time r1 Open	Time to analyse results from r1 and produce additional translation files	Time to return translation documents for r2	Time r2 Open
Translation 1	2 weeks	6 weeks	2 weeks	1 week	1 week	25 weeks	13 weeks	3 weeks	2 weeks	12 weeks
Translation 2		10 weeks			1 week	29 weeks		3 weeks	1 week	
Translation 3		3 weeks			1 week	Not required		3 weeks	1 week	
Translation 4		10 weeks			1 week	Not required		3 weeks	1 week	
Translation		18 weeks			1 week	***Not received		3 weeks	1 week	
Translation 6		12 weeks			3 weeks	40 Weeks		3 weeks	1 week	
Translation 7		2 weeks			1 week	2 weeks		3 weeks	1 week	

* The language versions are anonymized. **This represented the time the study management group requested collaborators to begin ethical approval applications until IRB approval was received and not necessarily the time between actual submission of the application and receiving approvals. ***Ethical approval was not received before the end of round 1 of the Delphi survey. No patients were recruited from this team's country.

Figure 5-5 Cumulative weekly recruitment figures for round 1 of GASTROS Delphi survey.



For round 2, an initial retention target of 80% was set following discussions with members of our study management group who have extensive knowledge and experience of COS development. Automated reminder emails were sent out on a weekly basis to participants and support from professional bodies (in countries where round 2 responses were slow) was sought to encourage completion of the survey. Personalised e-mails from the CI to professionals were also sent. Using this strategy, we were able to retain 70% of participants from round 1 by week 13, by which time no further responses were being received.

5.4.3.6 Paper and Internet-based Delphi survey versions

The GASTROS study used both internet-based and paper versions of the Delphi survey. The internet-based versions enabled us to reach participants in nearly 60 countries, the vast majority of which did not have formal IWG collaborators. The paper-versions (printed versions of the internet-based survey which were uploaded electronically by local collaboration teams) also enabled us to recruit participants (particularly patients) who either did not readily have access to the internet or were not 'electronically-literate'. We did not collect data about the proportion of surveys which were completed using paper versions.

Several platforms exist to enable COS developers to run Delphi-surveys. These include platforms specifically designed for Delphi surveys and other generic survey platforms which researchers can use. When considering multi-language surveys, it is essential to ensure that the servers on which the surveys are hosted meet the necessary data protection regulations and are accessible particularly from countries where restrictions to certain domains exist. Furthermore, COS developers must ensure that the platforms used are able to run surveys using different language scripts and writing systems.

Our group used DelphiManager as it fulfils the required data protection criteria (as set out by our United Kingdom ethical approval) and can work with all language systems including English, Chinese, Japanese and Korean. Furthermore, the online survey domains are accessible from countries which commonly restrict access to other foreign domains. DelphiManager has additional features which simplified recruitment and completion of the surveys such as being able to send automated reminders to individuals who had yet to complete all their answers.

5.4.3.7 Measures to maximize survey recruitment

One of the strengths of our Delphi survey was that it was able to recruit approximately 1000 eligible patients and healthcare professionals from nearly 60 countries in round one. From the study's inception, the study team recognised the importance of developing a clear networking and dissemination strategy[6]. We hypothesised that this was necessary to achieve broad stakeholder participation both nationally and internationally. Several strategies were employed to maximise recruitment:

5.4.3.7.1 Dissemination of results from previous study stages

The study protocol and findings from previous study stages[4,6,7] were presented at targeted national and international meetings which were well-attended by potential healthcare worker participants. This was integral to generating interest and support for our study and ensured that participants understood the premise for GASTROS long before the Delphi survey opened for recruitment. All presentations contained directions to the study website and social media accounts (see below).

5.4.3.7.2 Local recruitment of patients through outpatient clinics

Ethical approval enabled the study team to recruit patients directly from outpatient clinics. Our experience from the United Kingdom is that many patients regularly attend patient support groups and are in contact with other eligible patients. As a result, a snowballing effect resulted in patients being recruited by patients already within the study.

5.4.3.7.3 Support from stakeholder groups/associations and national research networks

Support from national and international professional associations and organisations was sought in the early stages of the study. Study group members presented the study objectives at closed executive level meetings to gain support and adoption from influential bodies including professional associations, patient groups and charities. Many of these organisations have large memberships (and corresponding electronic mailing lists) through which the study was advertised. Most of the groups through whom we sent out invitations followed up an initial e-mail with a further reminder approximately 4 weeks later resulting in further recruitment spikes. Furthermore, the GASTROS study was adopted onto the National Institute for Health Research (NIHR) Portfolio (CPMS study ID 38318). This enabled us to advertise the study to healthcare professionals and patient support groups within the United Kingdom through the national Clinical Research Networks. Our experience suggests that recognition by respected associations and groups results in a ‘snow-balling’ effect with subsequent support from others becoming easier to harness.

5.4.3.7.4 Collaborations

Standardising the reporting of outcomes can be achieved through several approaches. The GASTROS study aims to identify important outcomes across the entire spectrum of outcome types. Others have concentrated on the reporting of outcomes within a defined area. For example, the Gastrectomy Complications Consensus Group (GCCG - www.gastrodata.org) have sought to standardise the reporting of all major post-gastrectomy complications[18]. Whilst the goals of both studies are different, both teams have been able to work closely to minimise duplication of work. In addition, the GCCG was able to promote recruitment to the GASTROS Delphi survey through its membership and respective networks. Such

collaborations will also be vital for the future development of outcomes research within the field of gastric cancer surgery.

5.4.3.7.5 Personalized emails

a. Most of the study management group, study advisory group and international working group members have extensive research experience within the field of gastric cancer surgery. Each member was asked to promote the study through their personal research and clinical networks. Bulk e-mails through professional bodies may be ignored by potential participants or diverted into 'spam' e-mail folders, hence why this approach was employed.
b. Corresponding email addresses for authors from previous trials and protocols included in our systematic review[4] were identified and personal invitations sent. This captured research-active healthcare professionals from non-English speaking regions where no formal national gastric cancer associations exist (e.g. Eastern Europe).

5.4.3.7.6 Study website, social media and multimedia

a. The study website (http://www.gastrosstudy.org) provides detailed information about the GASTROS study aims as well as all its outputs. Prior to the commencement of the Delphi survey, potential participants who had heard about the study were able to register their interest to participate in the Delphi survey. In the preceding 18 months before the survey opened, 150 healthcare professionals and patients had registered.
b. In addition to the study's twitter account (https://twitter.com/GASTROSStudy), members of the research team posted updates on their personal Twitter and LinkedIn accounts. Regular study updates provided potential participants with an opportunity to better understand the study aims and keep up to date with its progress. Examination of analytics revealed that Twitter and LinkedIn posts in the run-up to and during round 1 of the survey regularly received over 4000 and 3000 views, respectively.
c. A series of short videos were produced for the study. These provided potential participants with an alternative way to engage with the study. At the time of writing, these videos had been viewed over 600 times. In addition to an introductory video on the study, a detailed step-by-step guide to completing the online Delphi survey was developed. This created additional content for social media platforms and the GASTROS website which in turn enabled the study to maintain a regular online presence. COS developers may wish to produce different language

versions or translate video captions relatively easily to expand their reach. Additional COS-related material is already available from the COMET initiative YouTube site[19] with versions available in Dutch, Portuguese and Chinese. Work is underway to develop other language versions as well.

Whilst advertising the study through these avenues increased the number of recruits, care must also be taken that potential participants are not 'bombarded' with requests to participate in the survey. A small number of healthcare professionals highlighted that this was an issue. This coupled with the well-recognised challenges of 'survey-fatigue', may in fact be counter-productive and result in apathy amongst potential participants.

5.4.3.8 Ethical Approval

The requirement for regulatory or ethical approval varied across different regions. In the United Kingdom, the approach to ethical approval has not been consistent; our group was asked to submit a full application for ethical approval committee consideration, whilst other groups have been able to gain approval through proportionate review[20]. Particular attention was required to accurately document data protection approaches given new European laws with respect to GDPR (General Data Protection Regulation). Whilst the UK ethical approval application referred to international recruitment, each IWG collaborator was responsible for understanding local requirements and applying for approvals if they were required locally. They were asked to enquire about these at the start of their agreement to participate in the study and applications were made in parallel to the translation work. Two of our international collaborating centres did not require ethical approval as local collaborators did not recruit patients directly from their clinical practice but instead advertised the study through local patient groups and recruited healthcare professionals by advertising through national Societies and networks. The time taken to complete this process varied significantly (table 4) and was largely dependent on the frequency of and access to ethics committee meetings, requirements to amend submitted materials and delays in final decisions reaching the collaborators. COS developers should investigate the need for ethical approval as early as possible to avoid unnecessary delays.

5.4.3.9 Financial Planning

Several aspects of undertaking multi-language Delphi surveys may incur significant costs depending on which approaches are adopted. COS developers should take these into account when planning their studies. These include:

1. Cost of professional translations; this represents the largest financial burden and has been discussed above.
2. Ethical and regulatory approvals; some of our non-UK ethical approval applications required payments of up to 250 EUR.

3. Use of electronic mailing lists; some stakeholder groups may charge administration fees to send out invitations to their membership.
4. Cost of Delphi survey platform; whilst open-access platforms exist, our group opted to pay to use a dedicated Delphi survey platform designed for the development of COS. As an indicator, the total cost of the initial set-up and additional language surveys was 2280 GBP.
5. Statistical and qualitative methods support may be required when analysing scores in rounds one and two, depending on the nature of feedback to be given. We opted to undertake this within the study management team.

5.5 Discussion

This study is the first to address the topic of translation and cross-cultural adaptation in the context of developing Delphi surveys for COS. We have presented a detailed and easily reproducible approach adapted from international consensus guidelines which was illustrated within the context of developing of a COS for gastric cancer surgery. The approach was accurately replicated by seven different translation teams within an acceptable timeframe.

Undertaking 'international' Delphi surveys has become easier as web-based platforms enable wider participation across different geographical regions. Whether or not this is warranted depends on the scope and target audience of the COS in question. As very few pathologies and interventions are limited to one geographical region, most clinical trials are undertaken globally. For these trials to include outcomes relevant to all stakeholders, trialists need to be confident that the COS relevant to their fields are robust. In our example, stakeholders from Asia, South America and Europe were essential to the development of the COS as gastric cancer is most prevalent in these countries and most trials are undertaken in these regions. The resulting number of participants from non-English speaking nations was significantly higher than those recruited from English-speaking countries. It was therefore important that processes used for ensuring accurate translations were valid and transparently reported.

Whilst translation of our Delphi survey aimed to widen participation and broaden the views taken into consideration, the value of doing so is one which warrants further discussion. English is the most commonly spoken language across the world[21] and is used by most scientific and healthcare publications. It is therefore unsurprising that most 'international' COS projects employing Delphi surveys identified from the COMET database used an English-only version. The English version of our Delphi survey was offered to all participants, however most preferred to complete the Delphi in their native language. This was the case for both patients and healthcare professionals. Patients were primarily recruited from regions

in which surveys were translated to the local language. Whilst for many the choice of using a non-English survey version would have been because they did not speak English, a significant proportion of bi-lingual healthcare professionals known to the study team preferred to use a non-English version. One may argue that this enabled participants to engage more confidently in the process, that their understanding of what was being asked of them was clearer and the quality of their responses may consequently have been better.

Such a high uptake in non-English surveys was not experienced by three of the four groups who completed our questionnaire on methodology. This was also reflected in certain subsets of stakeholder groups which had access to translated surveys in the GASTROS study. For example, despite translations being available, no Spanish patients were recruited to the study. This likely represented the logistical challenges related to recruitment in non-English speaking regions which we have addressed above.

Undoubtedly, achieving high quality and accurate translations is resource intensive. The process can take time if undertaken by healthcare professionals or pose significant financial costs if study groups employ professional services. However, restricting a consensus-seeking process in the development of an international COS to a single language exposes studies to the risk of excluding important opinion. It may therefore be argued that for a COS to be truly regarded as 'international', the consensus-seeking process should be undertaken in the native language of the participant. Whilst we have demonstrated that non-English Delphi surveys coupled with local study promotion can increase the number of total participants, it is not known whether these additional participants bring a different perspective that has not already been captured through the English-language version. It is likely that there are many additional factors which may contribute to the validity of Delphi survey results (e.g. cultural and geographical differences of participants) and COS developers should consider these carefully during the planning phase. These, along with other factors will be the focus of a future analysis by our study group.

5.5.1 Strengths, limitations, and implications for methodological practice

We have demonstrated that there is no standardised approach to translation in this field. Each of the four COS groups reviewed in this paper used different methods to forward translate and utilised translation teams with different member characteristics. A strength of our approach is that it is based on international consensus guidelines and was easily reproduced in several culturally diverse regions. We also provided detailed justifications for each step we adopted and the pragmatic adaptations which will help other COS developers, particularly those who may be limited with respect to financial resources. Our recommendation is therefore that COS developers should consider adopting this approach alongside other important considerations to broaden recruitment to their Delphi surveys.

Limitations of our study include that it focussed on examining current translation methodology used in Delphi surveys for COS. It is possible that a broader review of survey translations could have yielded a greater understanding of current approaches to translations and methodological aspects that have not been accounted for. Furthermore, it can be argued that the process by which the ISPOR-TCA consensus guidelines were adapted to meet our needs was not undertaken using a formalised approach[22]. We opted to use an informal approach to guideline adaptation due to the limited resources available to us. Furthermore, whilst we have translated our survey into 7 target languages, this may not have been a sufficient number needed for a COS. However, it may be argued that the need for such broad participation of stakeholders in a Delphi survey is not necessary and that more targeted recruitment of individuals is sufficient, negating the requirement for the approaches discussed. This is an area which will be examined as part of our future work.

5.5.2 Conclusion

We present a method of translating Delphi surveys for use in the development of COS adapted from international consensus guidelines in the field of outcome reporting. Consideration of the issues described will improve planning by other COS developers and can be used to widen international participation from both patients and healthcare professionals. Ultimately, internationally developed COS will improve the relevance of the core set to large scale clinical trials and therefore improve health care decision-making.

5.6 References

1. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(S3):280. doi:10.1186/s13063-017-1978-4

2. Gargon E, Gorst SL, Harman NL, Smith V, Matvienko-Sikar K, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 4th annual update to a systematic review of core outcome sets for research. Gillies K, ed. PLoS One. 2018;13(12):e0209869. doi:10.1371/journal.pone.0209869

3. Biggane AM, Brading L, Ravaud P, Young B, Williamson PR. Survey indicated that core outcome set development is increasingly including patients, being conducted internationally and using Delphi surveys. Trials. 2018;19(1):113. doi:10.1186/s13063-018-2493-y

4. Alkhaffaf B, Blazeby JM, Williamson PR, Bruce IA, Glenny A-M. Reporting of outcomes in gastric cancer surgery trials: a systematic review. BMJ Open. 2018;8(10):e021796. doi:10.1136/BMJOPEN-2018-021796

5. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation Background and Rationale.

6. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study). Trials. 2017;18(1):370. doi:10.1186/s13063-017-2100-7

7. Alkhaffaf B, Blazeby JM, Bruce IA, Morris RL. Patient priorities in relation to surgery for gastric cancer: qualitative interviews with gastric cancer surgery patients to inform the development of a core outcome set. BMJ Open. 2020;10(2):e034782. doi:10.1136/bmjopen-2019-034782

8. Core Outcome Measures in Effectiveness Trials Initiative (COMET). COMET Database. http://cometinitiative.org/studies/search. Accessed January 8, 2019.

9. Gargon E, Gorst SL, Harman NL, Smith V, Matvienko-Sikar K, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 4th annual update to a systematic review of core outcome sets for research. Gillies K, ed. PLoS One. 2018;13(12):e0209869. doi:10.1371/journal.pone.0209869

10. Ann Arbor, MI: Survey Research Center, Institute for Social Research U of M. Guidelines for Best Practice in Cross-Cultural Surveys.

11. OMERACT: Outcome Measures in Rheumatology. Handbook | OMERACT Handbook. https://omeracthandbook.org/handbook. Accessed October 5, 2019.

12. Smith TO, Hawker GA, Hunter DJ, et al. The OMERACT-OARSI Core Domain Set for Measurement in Clinical Trials of Hip and/or Knee Osteoarthritis. J Rheumatol. 2019;46(8):981-989. doi:10.3899/JRHEUM.181194

13. Beuscart J-B, Knol W, Cullinan S, et al. International core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy. BMC Med. 2018;16(1):21. doi:10.1186/s12916-018-1007-9

14. Park JK, Mecoli CA, Alexanderson H, et al. Advancing the Development of Patient-reported Outcomes for Adult Myositis at OMERACT 2016: An International Delphi Study. J Rheumatol. 2017;44(11):1683-1687. doi:10.3899/jrheum.161252

15. Horbach SER, van der Horst CMAM, Blei F, et al. Development of an international core outcome set for peripheral vascular malformations: the OVAMA project. Br J Dermatol. 2018;178(2):473-481. doi:10.1111/bjd.16029

16. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84-92. doi:10.1016/j.jclinepi.2017.12.020

17. Kuliś D, Whittaker C, Greimel E, Bottomley A, Koller M. Reviewing back translation reports of questionnaires: the EORTC conceptual framework and experience. Expert Rev Pharmacoeconomics Outcomes Res. 2017;17(6):523-530. doi:10.1080/14737167.2017.1384316

18. Baiocchi GL, Giacopuzzi S, Marrelli D, et al. International consensus on a complications list after gastrectomy for cancer. Gastric Cancer. 2019;22(1):172-189. doi:10.1007/s10120-018-0839-5

19. COMET Initiative - YouTube. https://www.youtube.com/channel/UCxkjZ-gL12_QXAzn8cO2nsg?&ab_channel=COMETInitiative. Accessed September 7, 2019.

20. Fish R, Sanders C, Adams R, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. lancet Gastroenterol Hepatol. 2018;3(12):865-873. doi:10.1016/S2468-1253(18)30264-4

21. What are the top 200 most spoken languages? | Ethnologue. https://www.ethnologue.com/guides/ethnologue200. Accessed October 12, 2019.

22. Wang Z, Norris SL, Bero L. The advantages and limitations of guideline adaptation frameworks. Implement Sci. 2018;13(1):72. doi:10.1186/s13012-018-0763-4

5.7 Appendices

5.7.1 Appendix 1. Translation Methodology Questionnaire

Translations in Delphi Surveys for Core Outcome Set Development

Thank you for answering this short survey on using translations in Delphi surveys for core outcome set development. We are developing a core outcome set for surgical trials in gastric cancer and would like to learn from your experience.

1. Name

_____

2. Name/topic of your core outcome set study

_____

3. What was the primary language of your Delphi survey?

_____

4. Which languages did you translate your Delphi survey into?

_____

5. How many participants completed all versions of the survey?

_____

6. How many participants completed the translated version of the Delphi survey?

_____

Translation Methodology

7. What methodological approach did you base your translations on? Please provide any references as appropriate.

_____

8. Did you use a professional translation service?

- ☐ Yes
- ☐ No

9. How many 'forward' translations of the 'outcomes' presented in the Delphi survey were undertaken?

- ☐ 1
- ☐ 2
- ☐ More than 2

10. Which of the following best describes the 'forward' translator(s) used for your survey? Please tick all relevant options.

- ☐ Professional translator
- ☐ Independent from the study team
- ☐ Healthcare professional
- ☐ Non healthcare professional
- ☐ Target language is their first language
- ☐ Previous experience of medical or patient-reported outcome translation
- ☐ Reside in the country of target language
- ☐ Fluent in the source language
- ☐ Not sure

11. How many 'backward' translations of the 'outcomes' presented in the Delphi survey were undertaken?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ More than 2

Backward Translation

12. Which of the following best describes the 'backward' translators used for your survey? Please tick all relevant options.

- ☐ Independent from the study team
- ☐ Professional translator
- ☐ Healthcare professional
- ☐ Non healthcare professional
- ☐ Source language is their first language
- ☐ They have not seen the source document which was 'forward translated'
- ☐ Not sure

Discrepancies & Harmonization

13. Please summarize how was a final version of the translation agreed?

_____

14. Please summarize what plans were in place to deal with discrepancies or disputes with translations?

_____

Cognitive Debriefing

15. 'Cognitive debriefing' involves piloting the survey on a small group of stakeholders to test alternative wording and to check understandability, interpretation, and cultural relevance of the translation. Was this undertaken?

- ☐ Yes
- ☐ No

16. Who did the cognitive debriefing exercise involve? Please tick all relevant options.

- ☐ Healthcare professional(s)
- ☐ Patient(s)
- ☐ Member(s) of the study team
- ☐ Other…

5.7.2 Appendix 2. Instructions for translating files related to the GASTROS Delphi Survey

Introduction

Thank you for agreeing to manage the translation of the GASTROS Delphi survey into your local language. The aim is to develop a translation which is clear and understandable to patients, oncology specialist nurses and surgeons.

The survey has two rounds. Following rounds 1 and 2, additional translations will be required and are detailed in section 6 of this document.

There are two types of documents which will require translation; one group requiring only one forward translation ('1FT' - from English to the target language) and another group requiring two independent forward translations and an additional backward translation ('2F1BT' - from the target back to English). This document outlines the methodology to be used for each type of translation.

All material during each step of the translation process should be kept and submitted to the chief investigator (CI), Dr Bilal Alkhaffaf, at the end of the process.

All materials related to this study are confidential and may not be shared under any circumstances without written consent from the CI.

Time-frame for translations

The time to complete all tasks associated with this translation work is 1 month from the time you receive the source documents.

Team members required for the translation

Three types of members will be needed for the translation process, each with specific characteristics which are required to comply with methodological guidelines for translations in this field[1].

1.1 GASTROS International working group collaborator

The collaborator is responsible for overseeing the translation of the Delphi survey and associated supporting documents with support from the CI. The collaborator is a

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

research-active surgeon who manages gastric cancer and adheres to the 'terms of reference' document (agreed to prior to their involvement in the GASTROS study). The collaborator should have the following additional characteristics:

- Native speaker of the target language
- Fluent in the English language
- Resides in the target country

1.2 Forward translator(s)

We would advise that there is one lead forward translator. The collaborator may take on this role if they deem it appropriate. Forward translators should have the following characteristics:

- Native speaker of the target language
- Fluent in the English language
- Reside in the target country
- Familiar with medical terms used to describe outcomes, preferably with previous experience in translating outcomes (although this is not mandatory).

1.3 Backward translator

The backward translator should have the following characteristics:

- Fluent in the English-language.
- Fluent in the target language

Translation of documents only requiring one forward translation (1FT)

The following files require 1FT:

- GASTROS Delphi survey – PIS Version 2 290518
- GASTROS Delphi survey – static text Version 2 220918

There are two steps to this process:

Forward Translation

What is involved?

The source text is translated into the target language using the same layout and formatting where appropriate.

Who performs this step?

A single forward translator as described in section 3.2.

Dual proofreading & final verification

What is involved?

The translation is proofread for accuracy and quality. The proof-readers do not perform the original translation of the source file(s). Any corrections or amendments in the translation is undertaken through discussion between the translator and proof-readers.

Any content found to be missing from the existing translation undergoes standard translation and separate proofreading steps.

Who performs this step?

Two separate persons fluent in English and native in the target language. This may be the international collaborator and a second forward translator as set out in sections 3.1 and 3.2.

Translation of documents requiring two forward and one backward translation (2F1BT)

The following files require 2F1BT:

GASTROS Delphi survey – user-defined text

GASTROS Delphi survey – outcomes

The methodology used for this translation is based on consensus guidelines as set out by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[1].

Dual Forward Translation

What is involved?

The source text is translated into the target language using the templates provided.

Who performs this step?

Two independent forward translators as set out in section 3.2.

Forward Translation Reconciliation

What is involved?

The two forward translations are reconciled into a third consensus ("best of both") translation by the lead forward translator. Any issues that arise from this stage are discussed with the international collaborator and CI (as appropriate) and the reconciliation refined if necessary.

Single Back Translation

What is involved?

The forward translation is back translated into English.

Who performs this step?

A single back translator as set out in section 3.3.

Back Translation Review

What is involved?

The back translation is reviewed against the original source document.

Who performs this step?

The international collaborator: any issues arising from this review are passed to the lead forward translator for comment. Where appropriate, the lead translator provides alternative wordings (along with their own back translation) to get closer to achieving conceptual equivalence with the original English. Where necessary, support and advice from the study CI should be sought.

Piloting and review of the online survey

What is involved?

The translated texts are provided to the CI, who will organise for a pilot Delphi survey to be compiled.

Who performs this step?

The pilot survey is undertaken by the international collaborator. Any issues with wording, comprehension and formatting are highlighted and further discussion and refinement is made by the international collaborator in conjunction with the translation team and CI.

Additional translations

The translation work described above will enable participants to complete round 1 of the survey. Further translations will be required during the following stages of the study:

After completion of round 1 of the survey

Additional Outcomes

During round 1 of the survey, participants will be given the opportunity to add outcomes that they believe should be considered by participants in round 2. Any additional outcomes will require dual translation (target language to English) and proof-reading using the methodology as set out in section 4 of this document.

Should the GASTROS research team believe that a new outcome has been identified by a participant, this additional outcome will require a 2F1BT translation as outlined above.

Chart Legends

All survey responses will be analysed following round 1. These responses will be presented to participants in round 2 where they will have the opportunity to re-score all the outcomes again (plus any additional outcomes). The responses from round 1 will be presented using histogram charts which will require translation.

After completion of round 2

Participants will be given the opportunity to provide a reason why they changed their score from round 1 (if applicable). Responses will require dual translation (target language to English) and proof-reading using the methodology as set out in section 4 of this document.

Further information

If you require any further clarification or information, please do not hesitate to contact…

5.7.3 Appendix 3. Outcomes for translation.

Outcome	Plain Language Description	Domain
Disease-free survival	How long someone is alive without cancer returning.	Outcomes Related to Death
Dying from stomach cancer	Dying from stomach cancer. This does not include dying from treatment for stomach cancer.	Outcomes Related to Death
Dying from any cause	Dying from any cause. This includes dying from treatment for stomach cancer.	Outcomes Related to Death
Surgery-related death	Dying as a direct consequence of surgery	Outcomes Related to Death
Cardiac complications	Complications related to the heart, such as a heart attack or abnormal heart rhythms.	Physiological & Clinical Outcomes
Endocrine complications	Complications related to the body's hormones, such as developing diabetes.	Physiological & Clinical Outcomes
Anastomotic complications	Complications related to surgical joins made as a result of removing stomach cancer.	Physiological & Clinical Outcomes
Gastro-intestinal functional problems	Symptoms related to how the digestive system works, including those which may become problematic months after discharge from hospital.	Physiological & Clinical Outcomes

Outcome	Plain Language Description	Domain
Bowel Complications	Problems with the bowel, such as those which occur while still in hospital (not including anastomotic complications).	Physiological & Clinical Outcomes
Time to recommencing oral intake	The time taken for a patient's bowel function to return after surgery, such that they can start eating and drinking again.	Physiological & Clinical Outcomes
Fatigue	Feeling of tiredness.	Physiological & Clinical Outcomes
Multiple organ failure	A severe complication which leads to several organs (such as the heart or lungs) not functioning properly.	Physiological & Clinical Outcomes
Pain		Physiological & Clinical Outcomes
Surgical Stress Response	The body's response to the stress of surgery.	Physiological & Clinical Outcomes
Gallbladder complications	Complications related to the gallbladder.	Physiological & Clinical Outcomes
Hepatic Complications	Complications related to the liver.	Physiological & Clinical Outcomes

Outcome	Plain Language Description	Domain
Pancreatic Complications	Complications related to the pancreas.	Physiological & Clinical Outcomes
Abdominal Collection	Fluid or infections in the abdomen.	Physiological & Clinical Outcomes
Other infections	General infections which are not related to the abdomen, lungs or wounds.	Physiological & Clinical Outcomes
Nutritional Effects	The extent to which the body can consume and use the nutrients needed to function properly.	Physiological & Clinical Outcomes
Recurrence of Cancer	The chances of the cancer coming back.	Physiological & Clinical Outcomes
Renal complications	Complications related to the kidneys, such as kidney failure.	Physiological & Clinical Outcomes
Urinary complications	Complications related to the bladder and urinary tract, such as a urinary infection.	Physiological & Clinical Outcomes
Post-operative psychosis	A temporary altered mental state after surgery which includes not being able to tell what is or isn't real.	Physiological & Clinical Outcomes

Outcome	Plain Language Description	Domain
Respiratory complications	Complications such as a chest infection, a collapsed lung or fluid on the lungs.	Physiological & Clinical Outcomes
Wound complications	Problems with the surgical incisions, including infection and problems with healing.	Physiological & Clinical Outcomes
Cerebro-vascular complications	Complications such as strokes and mini-strokes.	Physiological & Clinical Outcomes
Thrombo-embolic complications	Complications such as blood-clots in the legs and lungs.	Physiological & Clinical Outcomes
Bleeding	Blood loss as a result of surgery	Physiological & Clinical Outcomes
Ability to undertake physical activities	Ability to undertake day-to-day activities including exercise	Life Impact
Insomnia	Problems with sleeping.	Life Impact
Impact on sexual function	The effect of surgery on a patient's sexual activity.	Life Impact
Ability to eat socially	Ability to eat with friends and family.	Life Impact

Outcome	Plain Language Description	Domain
Ability to interact socially	The ability to have relationships with family and friends.	Life Impact
Impact of surgery on social and work roles	The effect of surgery on being able to work and caring for others.	Life Impact
Impact on mental health	The effect of surgery on a patient's psychological well-being.	Life Impact
Impact on Physical Appearance	The effect of surgery on a patient's physical appearance	Life Impact
Impact on cognitive functioning	The effect of surgery on concentration and memory.	Life Impact
Impact on spirituality or faith	The effect of surgery on a patient's spirituality or faith.	Life Impact
Overall quality of life	An overall measure of how a person's general wellbeing has been affected by surgery.	Life Impact
Impact on perception of physical health	How healthy a patient believes they are following surgery.	Life Impact
Ability to complete treatment pathway.	Being well enough to complete all aspects of treatment, such as chemotherapy and/or radiotherapy following surgery.	Life Impact
Completeness of tumour removal	Ensuring that the tumour has been surgically removed.	Life Impact
Conversion to open surgery	The surgical team having to unexpectedly change the approach from a	Life Impact

Outcome	Plain Language Description	Domain
	minimally invasive (laparoscopic or key-hole) operation to a traditional open approach, usually involving a larger incision.	
Duration of surgery	The length of time taken to perform the surgery.	Life Impact
Wound size	The size of the wound or wounds needed to perform the surgery.	Life Impact
Cost	The overall cost of surgery.	Resource Use
Duration of hospital stay	How long a patient stays in hospital.	Resource Use
Readmission to hospital	Whether a patient needs to return to hospital after being discharged following surgery.	Resource Use
Destination on Discharge	The location where a patient is discharged to from hospital.	Resource Use
Need for an additional intervention.	Unexpected additional procedures or surgeries which may be required.	Resource Use
Need for pain relief	The need for a patient to take or be given pain relief after surgery.	Resource Use
Adverse drug reaction	Complications related to medications.	Adverse Events
All-cause complications	Any complication which may arise after surgery.	Adverse Events

Outcome	Plain Language Description	Domain
Intra-operative complications	Complications which occur during surgery such as accidental injury to an organ.	Adverse Events
Anaesthetic complications	Complications specifically related to anaesthesia.	Adverse Events

6 Exploring the impact of regional variation on outcome prioritisation in core outcome set development: a case study in the field of gastric cancer surgery

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6.1 Abstract

Background

International stakeholder participation is important in the development of core outcome sets (COS). Stakeholders, however, may value health outcomes differently when regional differences are considered. Here, we explore how region, health income and participant characteristics influence prioritisation of outcomes during development of a COS for gastric cancer surgery trials (the GASTROS study).

Methods

952 participants from 55 countries participating in a Delphi survey during COS development were eligible for inclusion. Recruits were grouped according to region (East or West), country income classification (high and low-to-middle income) and other characteristics (e.g. patients; age, sex, time since surgery, mode of treatment, surgical approach and healthcare professionals; clinical experience). Groups were compared with respect to how they categorised outcomes ('consensus in', 'consensus out', 'no consensus'). Outcomes categorised as 'consensus in' or 'consensus out' by all 3 stakeholder groups would be automatically included in or excluded from the COS respectively.

Results

In total, 13 outcomes were categorised 'consensus in', 13 'consensus out' and 31 'no consensus'. There was little variation in prioritisation of outcomes by stakeholders from Eastern or Western countries and high or low-to-middle income countries. There was little variation in outcome prioritisation within either health professional or patient groups.

Conclusion

Our study suggests that there is little variation in opinion within stakeholder groups when participant region and other characteristics are considered. This finding may help COS developers when designing their Delphi surveys and recruitment strategies. Further work across other clinical fields is needed before broad recommendations can be made.

6.2 Introduction

A core outcome set (COS) is an agreed minimum group of critically important outcomes which should be reported by all trials within a research field[1]. The GASTROS study (www.gastrosstudy.org) aims to develop a COS in the field of gastric cancer surgery to promote uniform reporting of important outcomes and facilitate evidence synthesis[2]. This is necessary as there is significant variation and heterogeneity in this field with respect to reporting and measurement of outcomes[3]. Furthermore, the outcomes chosen by researchers to report in surgical trials for gastric cancer often do not reflect the priorities held by patients[4]. For this reason, the GASTROS study has sought consensus between patients and healthcare professionals with respect to outcome selection.

Delphi surveys and consensus meetings are commonly used methodologies in the development of COS[1,5]. Delphi surveys ask participants deemed by the study group to hold an important perspective (key stakeholders) to prioritise outcomes and achieve consensus. The completed Delphi survey often informs and influences discussions during a subsequent consensus meeting, with the aim of resolving uncertainties regarding prioritisation and ratifying the final composition of the COS. Clear recruitment strategies for Delphi surveys are an important consideration. If recruitment does not result in representative stakeholder groups, there is a risk that the results of the Delphi may not be valid[6]. This is particularly important in international COS where significant regional and cultural differences may influence the results ahead of a consensus meeting and, ultimately, the final COS.

Ensuring stakeholder groups are representative can be a challenging task. There is a need to consider many factors including the incidence of the disease, treatment protocols, international variation in healthcare systems and values and socio-economic issues. In the case of curative surgery for gastric cancer it is known that practice varies worldwide (e.g. how surgery is carried out and the extent of resection) and typically surgeons value different outcomes to patients[4]. There is therefore a need to explore these issues to understand how key stakeholders are selected for survey participation. In the GASTROS study 952 participants were recruited to a Delphi survey (268 were patients, 445 surgeons and 239 nurses) from 55 countries. It was therefore possible to explore how stakeholder charachteristics influenced outcome prioritisation.

This study had two main objectives:

1. To describe the characteristics of Delphi participants and explore their possible influence on the prioritisation of outcomes within stakeholder groups.
2. To explore whether there were regional differences across all stakeholder groups with respect to the categorisation of outcomes.

6.3 Methods

This was an analysis of registration data supplied by Delphi survey participants as part of the GASTROS study. Details of the scope, objectives and methodology of the study have been previously described[2–4]. In summary, participants were asked to score outcomes in terms of importance. The results of the Delphi survey informed discussions in a consensus meeting where final recommendations were made regarding which outcomes to include in the COS.

6.3.1 Stakeholder selection and baseline information

The GASTROS study sought to involve key stakeholders – patients, surgeons, and oncology nurses - to identify a COS for surgical trials in gastric cancer. Our guiding principle has been to promote the 'patient voice' as they are the beneficiaries of trials in this field and have all-important 'lived experience'. The patient voice has previously been shown to be under-represented in COS development[7]. Surgeons provide a clinical perspective and the experience of treating large volumes of patients. Oncology nurses were invited to participate given their central roles as care-givers, patient advocates and core members of the clinical team.

Participation in the Delphi survey was open to all interested stakeholders who fulfilled the following criteria:

- Surgeons who had completed their training and routinely treat gastric cancer.
- Oncology nurses with a recognised proportion of their role involved in the care and follow-up of gastric cancer patients.
- Patients who have undergone surgical resection for gastric cancer with the intention of cure.

There is no sample size requirement for Delphi surveys. To be able to demonstrate the enrolment of a broad and representative range of stakeholders, participants were asked to provide the information listed below:

Patients:

- Age
- Sex
- Surgical approach (laparoscopic or open)
- Type of gastrectomy (total or partial)
- Modality of treatment (surgery alone or a combination of surgery and chemotherapy or radiotherapy)
- Time since surgery

Surgeons:

- Experience (number of gastrectomies undertaken)

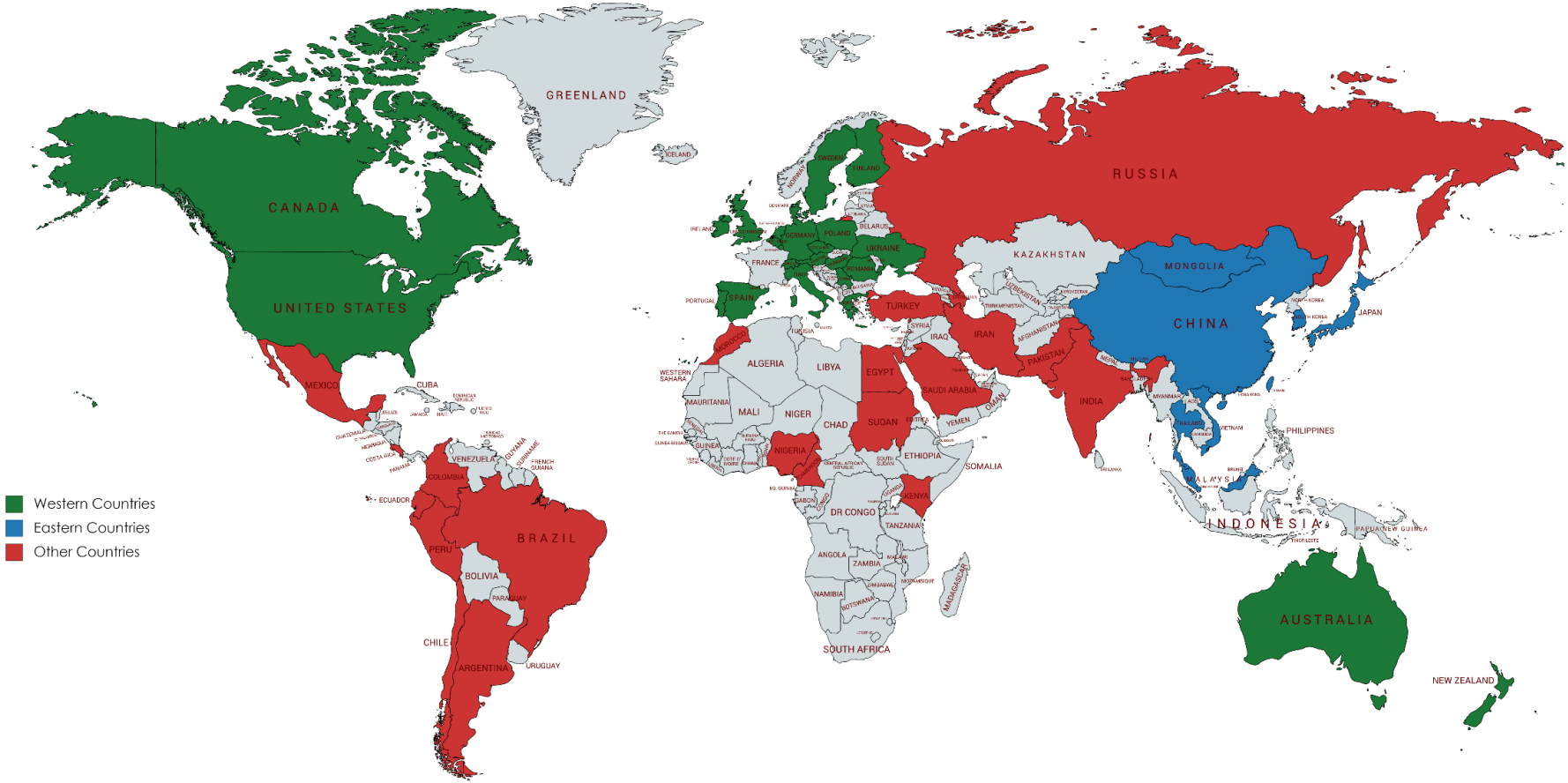
Nurses:

- Experience (years of service)

These datapoints were developed based on information that was likely to be readily known to participants and the expert opinion of the GASTROS study management group (SMG) with respect to important factors that may influence outcomes or perspectives. In the context of patients, different health outcomes, such as complications and survival, may impact their lived experience and ultimately how outcomes are prioritised. Similarly, as clinical experience changes with time, there may be a greater exposure to and therefore appreciation of the impact or importance of longer-term consequences of surgery.

Additionally, all participants were asked to provide their country of residence so that regional differences could be considered. Participants were categorised into 'Eastern' or 'Western' countries (figure 1) and 'high-income' or 'low- to medium-income countries' as defined by the Organisation for Economic Co-operation and Development's Development Assistance Committee[8]. Eastern countries were defined as those within East Asia, South East Asia, and Eastern Russia, and included China, Japan, South Korea, Thailand, Vietnam, Malaysia, and Singapore[9]. Western countries were defined as those from Western Europe, North America, Australia, and New Zealand[10]. Contrasting between the 'East' and 'West' is of particular importance to gastric cancer given the differences in incidence, pathology, treatment and outcome. It was hypothesised that these differences in approach and survival may influence how stakeholders in these regions prioritise different health outcomes which could be examined further in this study[11,12]. Similarly, health priorities may be influenced by resource availability as categorised by country income.

Figure 6-1 Countries from which participants were recruited. Eastern countries were defined as those within East Asia, South East Asia, and Eastern Russia, and included China, Japan, South Korea, Thailand, Vietnam, Malaysia, and Singapore[9]. Western countries were defined as those from Western Europe, North America, Australia, and New Zealand[10]



6.3.2 Scoring of outcomes in the Delphi survey and categorisation of outcomes

A list of 56 outcomes identified from previous trials and patient interviews[3,4] were presented to survey participants who were asked to rate each outcome on a scale of importance (1-3: not important, 4-6: important, 7-9: critically important). Patients, surgeons, and nurses group ratings were considered separately to ensure that each group had an equal voice. Participants had the opportunity to suggest further outcomes that they believed had not been presented in round 1. One additional new outcome suggested by participants in round 1 was identified and after consideration by the SMG was presented to participants for scoring in round 2. Therefore, a total of 57 outcomes were presented in round 2 where, for each outcome, participants were shown the scores from each stakeholder group, and given the opportunity to change their rating if they wished.

After two rounds of rating, outcomes were categorised as follows:

- To be included in the COS ('consensus in')
- To be excluded from the COS ('consensus out')
- 'No consensus' reached i.e. no decision reached as to whether the outcome should be included in of excluded from the COS.

Criteria for categorising outcomes was set a priori by the SMG and based on established COS methodology[1]. If an outcome was rated 7-9 (critically important) by 70% or more of a stakeholder group and 1-3 (not important) by no more than 15% of the group, then the consensus amongst that group was that the outcome should be included in the COS. If an outcome was rated 7-9 (critically important) by less than 50% of the group, the consensus amongst that group was for the outcome to be excluded from the COS. Unanimous agreement amongst all three stakeholder groups was required for inclusion in, or exclusion from, the COS. Any other combination resulted in the outcome being placed in the 'no consensus' category and was discussed at a pre-planned consensus meeting to finalise the COS.

6.3.3 Data analysis and interpretation

In round 1, participants completing 50% or more of the Delphi survey were included in the round 1 analysis and invited to participate in round 2. Likewise, participants completing 50% or more of the survey in round 2 were included in the round 2 analysis. For the purpose of this present analysis, participants were placed into 'sub-groups' according to the registration data they submitted (e.g. patient treatment type, surgeon experience etc) to examine the differences in outcome scoring. The following analyses were performed after 2 rounds of ratings:

1. The proportion of participants scoring each outcome as ‘critically important’ (score 7-9). This analysis approach was chosen as these figures were presented in the consensus meeting discussing results from the Delphi survey.
2. The consensus opinion of each sub-group with respect to whether the outcome should be ‘included’ in the COS, ‘excluded’ from the COS or whether ‘no consensus’ could be reached. These categorisations were compared against the overall ‘in’, ‘out’ and ‘no consensus’ categorisations by each stakeholder group (patients, surgeons and nurses) which was presented to the consensus meeting participants.

Participants not providing demographic data during registration were excluded from the sub-group analyses. When exploring differences in prioritisation, particular focus was placed on outcomes that were categorised as ‘consensus in’ by one sub-group and ‘consensus out’ by another.

To examine the possible influence of attrition bias between rounds, the characteristics of stakeholders participating in both rounds were compared to those who only completed round 1. A descriptive analysis was undertaken, and the Chi squared test applied to examine for statistically significant differences at the 0.05 level.

6.3.4 Ethical Approval

The study was given ethical approval by the North West - Greater Manchester East Research Ethics Committee (18/NW/0347) and governance approvals by Manchester University Hospitals NHS Foundation Trust.

6.4 Results

6.4.1 Overview

The characteristics of participants included in the analysis and attrition rates are summarised in table 1. After 2 rounds of voting, agreement was reached amongst all three stakeholder groups to include 13 outcomes and exclude 13 outcomes from the COS, leaving 31 no consensus outcomes for discussion at the consensus meeting.

Table 6.1 Demographic characteristics of participants included in analysis of round 1 and 2 scores.

Stakeholder Group	Variable	Sub-Group	Total	Completed round 1 only (%)*	Completed both rounds (%)*	p value
Patients	All	-	268	84	184	
	Age	<60		38 (45)	77 (42)	0.69
		>=60		46 (55)	107 (58)	
	Sex	Male		52 (62)	101 (55)	0.345
		Female		32 (38)	83 (45)	
	Region	West		53 (62)	113 (74)	0.461
		East		23 (38)	39 (26)	
	Country income	HIC		53 (63)	113 (61)	0.792
		LMIC		31 (37)	71 (39)	
	Years since surgery	<1 year		15 (19)	30 (17)	0.656
		1 to 3 years		34 (44)	68 (39)	
		>3 years		29 (37)	75 (43)	
	Surgical approach	Open		70 (83)	145 (78)	0.850
		MIS		14 (17)	31 (22)	
	Type of surgery	Total		40 (49)	78 (44)	0.503
		Partial		42 (51)	98 (56)	
	Treatment Modality	Surgery alone		28 (34)	69 (39)	0.495
		Multimodal therapy		54 (66)	110 (61)	
Surgeons	All	-	445	102	343	
	Region	West		33 (38)	174 (61)	0.000
		East		53 (62)	109 (39)	
	Country income	HIC		45 (44)	201 (59)	0.010
		LMIC		57 (56)	142 (41)	
	Surgeon experience	<50		21 (29)	70 (23)	0.45
		50-199		20 (27)	103 (34)	
		>200		32 (44)	127 (43)	
Nurses	All	-	239	104	135	
	Region	West		22 (35)	40 (40)	0.100
		East		57 (65)	61 (60)	
	Country income	HIC		24 (23)	46 (34)	0.064
		LMIC		80 (77)	89 (66)	
	Nurse experience	0-5 years		59 (57)	59 (45)	0.056
		>5 years		44 (43)	73 (55)	

Table legend: HIC =high income country, LMIC = low- to middle-income country; MIS = minimally invasive surgery. *All percentages refer to the proportion of participants from each sub-group completing either round 1 or both rounds.

6.4.2 Patients

A summary of outcomes categorised for ‘inclusion’ by at least one patient sub-group after 2 rounds of voting is presented in table 2. Thirty outcomes were categorised for inclusion in the COS by at least one subgroup. Four outcomes were simultaneously categorised both for ‘inclusion’ and ‘exclusion’ by different subgroups. None of the outcomes categorised for automatic inclusion by all stakeholder groups were voted ‘consensus out’ by any patient sub-group. Seven outcomes were categorised for inclusion in the COS by all patient subgroups.

6.4.3 Surgeons

Table 3 summarises and compares outcomes categorised for inclusion by at least one surgeon sub-group after 2 rounds of voting. Twenty-one outcomes were categorised for inclusion by at least one subgroup. No outcomes were simultaneously categorised both for ‘inclusion’ and ‘exclusion’ by different subgroups. Twelve outcomes were categorised by all surgeon subgroups for inclusion.

6.4.4 Nurses

Table 4 summarises and compares the outcomes categorised for inclusion by at least one nurse sub-group after 2 rounds of voting. Twenty-two outcomes were categorised for inclusion by at least one subgroup. Five outcomes were simultaneously categorised both for ‘inclusion’ and ‘exclusion’ by different subgroups. None of the outcomes categorised for automatic inclusion by all stakeholder groups were voted ‘consensus out’ by any nurse sub-group. Ten outcomes were categorised by all nurses’ subgroups for inclusion.

6.4.5 Regional variations

Table 5 details the final categorisation list of outcomes which was presented to participants at the consensus meeting. This is compared to alternative outcome categorisation lists based on the region and country income differences described above. Consensus agreement to include 8 and exclude 7 outcomes was reached across all regional sub-groups. No outcomes were simultaneously categorised as ‘consensus in’ and ‘consensus out’ across different regional sub-groups.

Table 6.2 Outcomes categorised for inclusion in the COS by at least one subgroup of patients.

	Overall	Region**		Country Income		Age in years		Sex		Years since surgery			Surgical approach		Type of gastrectomy		Treatment Modality	
	All patients	West	East	HIC	LMIC	<60	>=60	M	F	< 1	1- 3	>3	Open	MIS	Total	Partial	Surgery	Multi-modal
Outcome	n = 184	n=113	n=39	n=113	n=71	n=77	n=107	n=101	n=83	n=30	n=68	n=75	n=145	n=31	n=78	n=98	n=69	n=110
1. Disease-free survival*	85.4	87.0	76.3	87.0	82.9	86.7	84.5	83.0	88.5	86.2	89.4	86.1	85.9	85.7	84.9	85.6	80.3	87.9
2. Dying from stomach cancer*	86.4	88.7	74.4	88.7	82.9	85.5	87.0	88.8	83.3	86.2	89.2	85.9	88.4	80.0	85.3	87.1	81.8	88.6
3. Dying from any cause	66.7	65.0	77.8	65.0	69.1	72.6	62.2	59.6	75.3	77.8	63.6	66.2	67.2	63.0	65.3	66.3	71.4	62.1
4. Surgery-related death*	84.0	86.9	72.2	86.9	79.4	76.7	89.2	80.2	88.6	81.5	85.1	88.7	86.2	73.3	82.7	84.9	79.7	86.8
7. Anastomotic complications*	76.7	80.0	74.4	80.0	71.8	74.3	78.4	75.0	78.8	82.8	77.6	74.3	76.1	74.2	69.3	80.9	74.6	76.9
8. Gastro-intestinal functional problems	72.8	85.3	71.8	85.3	53.5	69.7	75.0	66.0	81.3	75.9	63.2	80.6	70.2	77.4	70.1	72.6	67.7	74.5
9. Bowel Complications	71.8	80.0	76.9	80.0	59.2	65.8	76.2	66.0	79.0	75.9	64.7	76.7	69.7	74.2	67.5	72.9	68.2	72.7
12. Multiple organ failure*	86.4	87.9	86.5	87.9	84.1	87.8	85.3	86.7	85.9	86.2	86.4	85.7	87.8	79.3	83.8	87.2	80.3	89.5
16. Hepatic Complications	62.4	65.0	73.7	65.0	57.1	71.6	54.5	52.1	73.4	78.6	52.3	60.9	61.0	62.1	60.8	59.3	67.2	56.4
17. Pancreatic Complications	70.3	75.5	73.7	75.5	61.4	74.0	66.7	63.8	76.9	82.1	57.8	72.5	68.9	69.0	67.1	69.2	68.7	69.0
18. Abdominal Collection	71.5	72.3	82.1	72.3	70.4	71.6	71.4	65.3	79.2	75.9	70.8	67.2	69.2	77.4	63.9	75.0	73.1	69.0

	Overall	Region**		Country Income		Age in years		Sex		Years since surgery			Surgical approach		Type of gastrectomy		Treatment Modality	
	All patients	West	East	HIC	LMIC	<60	>=60	M	F	< 1	1- 3	>3	Open	MIS	Total	Partial	Surgery	Multi-modal
20. Nutritional Effects*	73.8	77.7	69.2	77.7	66.2	75.3	71.7	69.0	78.3	73.3	72.1	75.7	72.9	71.0	75.6	70.1	69.1	74.5
21. Recurrence of Cancer*	92.2	95.4	84.6	95.4	85.9	88.0	94.3	92.0	91.3	93.1	88.1	95.9	91.5	90.3	88.0	93.8	88.1	93.5
22. Renal complications	70.0	80.0	65.8	80.0	54.3	66.2	71.7	67.0	72.4	82.1	53.8	80.3	69.2	65.5	64.8	71.4	67.2	71.4
23. Urinary complications	58.1	65.7	57.9	65.7	45.7	54.2	60.0	54.2	61.8	64.3	40.0	70.6	57.8	51.7	50.0	60.9	56.1	59.4
25. Respiratory complications	69.5	67.0	66.7	67.0	73.2	70.3	68.9	70.7	67.9	75.0	73.1	63.4	71.2	56.7	60.8	73.7	68.2	68.9
27. Cerebro-vascular complications	77.6	81.0	68.4	81.0	72.9	68.6	84.0	80.9	73.7	75.0	72.3	84.8	78.0	73.3	69.0	82.4	71.2	82.8
28. Thrombo-embolic complications	76.7	80.4	63.2	80.4	71.4	73.2	79.2	78.9	74.0	71.4	73.8	82.4	79.9	60.0	73.6	77.2	66.7	84.2
29. Bleeding*	72.3	67.6	76.9	67.6	78.9	77.5	68.6	67.0	78.9	75.0	72.7	69.1	73.3	66.7	70.0	71.6	72.7	70.6
30. Ability to undertake physical activities	60.4	65.8	56.4	65.8	50.7	56.6	62.3	63.0	56.1	51.7	55.9	64.9	56.6	71.0	50.6	63.9	55.2	61.8
36. Impact on mental health	58.8	61.3	48.7	61.3	56.3	57.9	60.4	61.0	57.3	55.2	58.8	64.9	55.9	71.0	63.6	54.6	52.2	63.6
40. Overall quality of life*	74.0	79.1	56.4	79.1	66.2	72.4	75.2	74.0	74.1	72.4	77.9	74.0	72.5	80.6	77.9	69.8	64.2	81.7
42. Ability to complete treatment pathway.	79.8	83.2	69.2	83.2	74.6	81.1	78.8	81.8	77.2	79.3	83.6	78.9	77.7	83.9	81.3	76.8	71.2	85.0

	Overall	Region**		Country Income		Age in years		Sex		Years since surgery			Surgical approach		Type of gastrectomy		Treatment Modality	
	All patients	West	East	HIC	LMIC	<60	>=60	M	F	< 1	1- 3	>3	Open	MIS	Total	Partial	Surgery	Multi-modal
43. Completeness of tumour removal*	92.8	95.5	87.2	95.5	88.7	90.9	94.2	93.9	91.5	93.3	91.2	97.2	91.5	96.8	92.2	92.7	88.2	95.4
44. Conversion to open surgery	51.2	53.6	81.6	53.6	47.7	52.2	50.5	43.0	60.5	73.3	31.7	58.1	48.0	62.1	48.5	50.6	59.1	42.9
53. Duration of stay in an intensive care ward	64.1	54.4	62.9	54.4	77.6	59.2	66.7	60.6	67.1	57.7	71.2	56.7	65.7	46.4	64.3	59.8	62.5	63.4
54. Adverse drug reaction	67.0	72.2	59.0	72.2	59.2	64.5	68.9	64.3	70.4	51.7	64.7	77.5	66.0	66.7	66.7	64.6	67.6	66.0
55. All-cause complications*	75.8	76.6	71.8	76.6	74.6	76.0	75.7	70.7	82.3	67.9	79.1	77.8	77.0	71.0	77.0	72.9	77.6	73.6
56. Intra-operative complications*	80.6	82.9	79.5	82.9	77.1	76.7	83.3	77.3	84.6	79.3	77.3	84.3	80.9	80.6	76.7	81.9	80.3	79.8
57. Anaesthetic complications*	74.9	78.1	66.7	78.1	70.0	74.0	75.5	71.4	79.2	55.2	75.8	81.4	77.2	61.3	74.0	73.4	73.8	74.3

Values are the percentage of participants voting the outcome as critically important (score 7-9).

Table legend. Green = for inclusion, Yellow = no consensus, Red = for exclusion. HIC =high income country, LMIC = low- to middle-income country; MIS = minimally invasive surgery. *Denotes outcomes are those which were included in the final list of outcomes for automatic inclusion in the COS. **Participants not from either Western or Eastern countries were excluded from this analysis.

Table 6.3 Outcomes categorised for inclusion in the COS by at least one subgroup of surgeons.

	Overall	Region**		Country Income		Cases performed		
	All surgeons	West	East	HIC	LMIC	<50	50-199	>200
Outcome	n = 343	n=174	n=109	n=201	n=142	n=70	n=103	n=127
1. Disease-free survival*	97.7	97.7	98.1	98.0	97.2	95.7	99.0	97.6
2. Dying from stomach cancer*	96.5	97.7	95.4	96.0	97.2	95.7	95.1	96.9
4. Surgery-related death*	96.8	96.6	99.1	97.5	95.8	94.3	96.1	98.4
7. Anastomotic complications*	95.3	95.4	95.4	96.0	95.1	95.7	94.2	96.1
8. Gastro-intestinal functional problems	74.9	75.3	70.6	75.1	76.1	82.9	76.7	67.7
12. Multiple organ failure*	81.3	81.0	78.9	81.1	80.9	75.7	83.5	81.7
18. Abdominal Collection	73.4	75.1	67.0	74.5	73.2	71.4	69.9	78.7
20. Nutritional Effects*	72.8	74.6	66.1	73.5	73.9	77.1	75.7	69.3
21. Recurrence of Cancer*	97.7	99.4	95.4	99.0	96.5	97.1	100.0	97.6
25. Respiratory complications	66.5	70.1	59.6	70.6	62.0	65.7	67.0	70.1
28. Thrombo-embolic complications	64.1	63.2	60.6	63.2	65.5	61.4	59.2	70.9
29. Bleeding*	87.5	84.5	95.4	86.1	90.1	81.4	85.4	92.9
30. Ability to undertake physical activities	66.4	71.8	59.6	69.7	63.4	65.7	70.9	66.9
40. Overall quality of life*	86.5	93.1	75.9	90.0	82.3	91.4	87.4	85.7
42. Ability to complete treatment pathway.	78.6	86.2	61.1	82.6	73.6	87.0	74.8	75.4
43. Completeness of tumour removal*	97.4	98.3	97.2	98.5	95.7	91.4	99.0	99.2
49. Readmission to hospital	78.9	78.7	82.4	78.6	80.9	80.0	81.6	81.0
51. Need for an additional intervention.	75.4	82.8	59.3	81.6	66.7	78.6	78.6	71.4

	Overall	Region**		Country Income		Cases performed		
	All surgeons	West	East	HIC	LMIC	<50	50-199	>200
55. All-cause complications*	81.2	81.5	84.3	83.0	79.4	81.4	76.7	88.1
56. Intra-operative complications*	91.5	88.4	93.5	89.5	93.6	91.4	92.2	92.9
57. Anaesthetic complications*	70.5	70.3	71.0	70.4	70.7	68.6	66.0	75.2

Values are the percentage of participants voting the outcome as critically important (score 7-9).

Table legend. Green = for inclusion, Yellow = no consensus. HIC =high income country, LMIC = low- to middle-income country; *Denotes outcomes are those which were included in the final list of outcomes for automatic inclusion in the COS. **Participants not from either Western or Eastern countries were excluded from this analysis.

Table 6.4 Outcomes categorised for inclusion in the COS by at least one subgroup of nurses.

	Overall	Region**		Country Income		Experience in years	
	All nurses	**West**	**East**	**HIC**	**LMIC**	0-5 years	>5
Outcome	n = 135	n=40	n=61	n=46	n=89	n=59	n=73
1. Disease-free survival*	85.1	92.5	85.2	93.5	80.9	81.4	89.0
2. Dying from stomach cancer*	80.0	90.0	72.1	91.3	74.2	74.6	83.6
3. Dying from any cause	63.4	64.1	70.5	64.4	65.2	58.6	71.2
4. Surgery-related death	77.6	95.0	65.6	93.5	69.3	72.9	81.9
7. Anastomotic complications*	84.4	97.5	82.0	97.8	76.4	79.7	89.0
8. Gastro-intestinal functional problems	69.6	90.0	65.6	89.1	57.3	59.3	75.3
12. Multiple organ failure*	79.9	82.5	78.3	84.8	78.4	83.1	79.2
13. Pain	59.3	85.0	59.0	87.0	44.9	49.2	65.8
18. Abdominal Collection	65.9	65.0	67.2	69.6	61.8	49.2	76.7
19. Other infections	61.2	55.0	70.0	58.7	61.4	54.2	65.3
20. Nutritional Effects*	74.8	87.5	77.0	87.0	66.3	69.5	76.7
21. Recurrence of Cancer*	88.0	97.5	86.9	97.8	82.8	84.5	90.3
26. Wound complications	67.4	62.5	73.8	63.0	67.4	67.8	64.4
29. Bleeding*	80.7	72.5	85.2	76.1	82.0	79.7	80.8
30. Ability to undertake physical activities	56.3	72.5	54.1	73.9	46.1	54.2	56.2
36. Impact on mental health	54.5	70.0	48.3	71.7	44.3	54.2	52.8

	Overall	Region**		Country Income		Experience in years	
	All nurses	**West**	**East**	**HIC**	**LMIC**	0-5 years	>5
40. Overall quality of life*	70.4	90.0	67.2	89.1	59.6	61.0	76.7
42. Ability to complete treatment pathway.	65.9	77.5	60.7	78.3	58.4	54.2	75.3
43. Completeness of tumour removal*	87.3	100.0	86.9	97.8	82.0	83.1	91.8
49. Readmission to hospital	69.9	77.5	68.3	78.3	62.1	60.3	73.6
51. Need for an additional intervention.	56.7	75.0	48.3	76.1	45.5	44.1	63.9
52. Need for pain relief	68.4	72.5	72.9	73.9	63.2	57.6	74.6
55. All-cause complications*	77.9	77.5	77.2	80.4	75.3	70.2	83.1
56. Intra-operative complications*	85.4	90.0	91.1	91.3	83.3	85.7	87.3
57. Anaesthetic complications*	78.0	80.0	77.8	80.4	76.5	70.9	84.1

Values are the percentage of participants voting the outcome as critically important (score 7-9). Table legend. Green = for inclusion, Red = for exclusion, Yellow = no consensus. HIC =high income country, LMIC = low- to middle-income country; *Denotes outcomes are those which were included in the final list of outcomes for automatic inclusion in the COS. **Participants not from either Western or Eastern countries were excluded from this analysis.

Table 6.5 Regional differences in consensus on outcomes voted for inclusion or exclusion from the COS by at least 1 subgroup.

Consensus outcome	Final List	Region**		Country Consensus income	
		West (n=327)	East (n=209)	HIC (n=360)	LMIC (n=302)
1. Disease-free survival*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
2. Dying from stomach cancer*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
4. Surgery-related death	Consensus in	Consensus in	No consensus	Consensus in	No consensus
6. Endocrine complications	Consensus out	Consensus out	No consensus	Consensus out	Consensus out
7. Anastomotic complications*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
8. Gastro-Intestinal functional problems	No consensus	Consensus in	No consensus	Consensus in	No consensus
11. Fatigue	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
12. Multiple organ failure*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
14. Surgical Stress Response	Consensus out	Consensus out	No consensus	Consensus out	No consensus
15. Gallbladder complications	No consensus	No consensus	No consensus	No consensus	Consensus out
20. Nutritional Effects	Consensus in	Consensus in	No consensus	Consensus in	No consensus
21. Recurrence of Cancer*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
23. Urinary complications	No consensus	No consensus	No consensus	No consensus	Consensus out
24. Post-operative psychosis	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
29. Bleeding	Consensus in	No consensus	Consensus in	No consensus	Consensus in
31. Insomnia	Consensus out	Consensus out	No consensus	Consensus out	Consensus out
32. Impact on sexual function	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
33. Ability to eat socially	Consensus out	No consensus	Consensus out	No consensus	Consensus out
34. Ability to Interact socially	Consensus out	No consensus	Consensus out	No consensus	Consensus out
35. Impact of surgery on social and work	No consensus	No consensus	Consensus out	No consensus	Consensus out

Consensus outcome	Final List	Region**		Country Consensus income	
		West (n=327)	East (n=209)	HIC (n=360)	LMIC (n=302)
roles					
36. Impact on mental health	No consensus	No consensus	Consensus out	No consensus	No consensus
37. Impact on Physical Appearance	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
39. Impact on spirituality or faith	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
40. Overall quality of life	Consensus in	Consensus in	No consensus	Consensus in	No consensus
41. Impact on perception of physical health	No consensus	No consensus	No consensus	No consensus	Consensus out
42. Ability to complete treatment pathway.	No consensus	Consensus in	No consensus	Consensus in	No consensus
43. Completeness of tumour removal*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
45. Duration of surgery	No consensus	Consensus out	No consensus	Consensus out	No consensus
46. Wound size	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
47. Cost	Consensus out	Consensus out	No consensus	Consensus out	No consensus
50. Destination on Discharge	Consensus out	Consensus out	Consensus out	Consensus out	Consensus out
55. All-cause complications*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
56. Intra-operative complications*	Consensus in	Consensus in	Consensus in	Consensus in	Consensus in
57. Anaesthetic complications	Consensus in	Consensus in	No consensus	Consensus in	Consensus in

Table legend. Green = for inclusion, Red = for exclusion, Yellow = no consensus. HIC =high income country, LMIC = low- to middle-income country; *Denotes outcome was categorised as for 'inclusion' in COS by all subgroups. **Participants not from either Western or Eastern countries were excluded from this analysis.

6.5 Discussion

The GASTROS study (www.gastrosstudy.org) is the first to bring together healthcare professionals and patients with the purpose of identifying outcomes to include in a COS for surgical trials in gastric cancer. The multi-language survey recruited a broad spectrum of stakeholders with different personal and professional experiences from over 50 countries across 6 continents. We aimed to examine whether certain stakeholder characteristics influenced how outcomes were prioritised and whether there were regional influences also. Our analysis from nearly 1000 survey participants suggested that little variation within the stakeholder groups exists. Similarly, when all stakeholders were categorised according to region or country income, significant differences were not identified. These are important findings which should serve to reassure researchers and patients that the resulting COS has sought and considered international opinion. Furthermore, these findings suggest that priorities within stakeholder groups and across regions are more aligned than may have been previously thought.

6.5.1 Planning recruitment to Delphi surveys

Few studies have previously examined factors which influence how stakeholders prioritise outcomes in the field of COS development. The BRAVO study explored this in the field of breast cancer reconstruction and found that priorities varied within patient and healthcare professional groups[6]. This led them to recommend careful participant selection for Delphi surveys by COS developers. These same differences, however, were not identified in our study. The BRAVO study's healthcare professional stakeholder group was more heterogenous than the groups in this study (breast surgeons, plastic surgeons, nurses and psychologists grouped together) and so these differences may be expected. Furthermore, reconstructive breast surgery is a complex area which covers many different types of procedures. This may also account for the significant variation in outcome prioritisation by patients which was not mirrored in the GASTROS study. Similarly, a COS study in the field of bariatric surgery identified significant variation in outcome prioritisation amongst healthcare professionals[13]. Again, healthcare professionals in this study were heterogenous, which supports our strategy to separate surgeons and nurses into different stakeholder groups.

Achieving the 'correct balance' of representative stakeholders is an important consideration during the design phase. For example, knowledge of the patient demographic and which types of interventions are prevalent within that group, will enable researchers to recruit an appropriate number of stakeholders with those characteristics. With respect to the GASTROS study, the importance of seeking international agreement on core outcomes was identified at the conception stage and subsequently influenced the design of the prioritisation exercise. Our strategy for addressing the significant challenges associated with international

involvement included 1) an international working group with regional collaborators, 2) translating surveys and 3) seeking the support of relevant patient and professional groups (see chapter 5). Transparent reporting of methodological approaches adopted during COS development are of paramount importance. Ultimately, a COS will only achieve its stated goals if researchers use it. And whilst there are likely several factors which influence the uptake of COS, ensuring researchers have the confidence that the COS is relevant to them and has been developed through a methodologically robust process are likely to be important factors which influence uptake and dissemination[14].

There are challenges in deciding how to sample participants for a Delphi study. Epidemiological studies, registries and audits provide descriptive regional or national information[15–17]. However, in the case of gastric cancer, these resources are not always complete or available. Consequently, the study team widened the promotion and enrolment into the Delphi to capture as many patients as possible. In our study, we demonstrated that there was not significant variation in outcome prioritisation within stakeholder sub-groups with respect to the characteristics that we examined. Consequently, whilst over 1000 participants were enrolled, it may not have been necessary to recruit such large numbers. This will likely guide our recruitment strategy during future planned stages of work when reviewing the COS and identifying outcome measurement instruments. Our experience may also help guide other COS developers as they consider the number of participants to recruit to their Delphi surveys. However, given some of our findings differed from those in the field of breast surgery reconstruction and bariatric surgery, more work is needed before broad recommendations can be made.

6.5.2 Variations within stakeholder groups

When regional variations across the three stakeholder groups were compared, the greatest differences in prioritisation were observed amongst nurses. For example, in four outcomes (pain, ability to undertake physical exercise, impact on mental health, need for additional intervention) different subgroups of nurses categorised them as ‘consensus in’ and ‘consensus out’. These outcomes seemed less important in LMIC and HIC settings within the nurse group. Understanding the reason for this is likely to be complex. It may be argued that this is simply because nurses are reflecting the importance that patients from these cultures or regions place on these outcomes as similar trends were seen amongst patients. Limited resource in LMIC settings which may affect follow-up may also play a role in understanding how important longer-term problems are in these regions. Further exploration using qualitative research methods may help understand these differences further.

In examining the differences between patient sub-groups, one would expect to see some differences given the number of characteristics that were examined. Despite this, only two outcomes (urinary complications and conversion to open surgery) were simultaneously categorised as ‘consensus in’ and ‘consensus out’ by different sub-groups. This finding

suggests that despite the many possible influences on patient experience following gastric cancer surgery, there is not a significant variation in how health related outcomes are prioritised in this group. Surgeons had the greatest concordance with respect to outcome prioritisation. Overall, the observed differences in outcome prioritisation were small within each stakeholder group reassuring researchers using the COS that it is based on the views of a representative cohort of patients and healthcare professionals.

6.5.3 Impact of regional variations on outcomes automatically included in COS

The aim of a COS is to identify outcomes which are critically important across all stakeholder groups participating in the process. In the case of the GASTROS study, an outcome would only be automatically included in the COS if patients, surgeons, and nurses each categorise it 'consensus in'. Ultimately, it is not possible to confidently assess how regional differences may have affected the final categorisation of outcomes which informed the consensus meeting. Participants in round 2 were shown the scores of all stakeholder groups from round 1 before being asked to change their score if they wish. To assess regional differences, Western participants, for example, in round 2 would have needed to see only Western stakeholder group scores from round 1. Furthermore, there are a number of other confounding factors which influence why participants change scores between rounds (see below) further making an analysis of regional impacts challenging.

Despite this, some assessments could be made. No outcomes categorised for automatic inclusion by all three stakeholder groups were categorised for automatic exclusion by a regional sub-group. And no outcomes categorised for automatic exclusion from the COS by all three stakeholder groups were categorised for automatic inclusion by a regional sub-group. This suggests that the regional differences in approach to management or patient outcome may not significantly influence how stakeholders prioritise outcomes

There were two outcomes (gastrointestinal functional problems and ability to complete treatment pathway) which were categorised for automatic inclusion by stakeholders from the West and HIC that were not included in the final list presented to the consensus meeting. Furthermore, some outcomes (surgery-related death, nutritional outcomes, bleeding, overall quality of life, anaesthetic complications) did not reach consensus for automatic inclusion by regional sub-groups yet were automatically included when the overall views of stakeholders were considered. This may bring some to the conclusion that different COS should be developed for different regions as some researchers may be collecting outcomes that were not deemed critically important in their region. However, researchers should be cognisant of the fact that their trials are internationally relevant and vitally important to the larger picture where evidence synthesis is concerned. From a different perspective, some researchers may feel aggrieved if outcomes which are critically important in their region are not eventually included in the COS. It is important to emphasise that COS are minimum

reporting guidelines and that researchers are encouraged to report additional outcomes that they believe are important.

6.5.4 Strengths and Limitations

Strengths of this study include that it is novel and that is was able to recruit a large number of participants from many countries. However, there are some limitations which should be acknowledged. This was an analysis which was not powered to make definitive conclusions about relationships between sub-groups and how outcomes were rated. Therefore, the results should be viewed in this context. Furthermore, the sub-groups examined in this paper were chosen by members of the study team based on their extensive experience in the field of gastric cancer and their understanding of factors which may impact on stakeholder experience, perceptions and subsequently how outcomes may be prioritised. It is possible that other unexplored characteristics impact on how stakeholders prioritise outcomes. In addition, this study did not explore how different characteristics interact with one another to impact on outcome prioritisation (e.g. years since surgery and type of gastrectomy). Doing so would create results which would remove the focus from regional differences and would be difficult to interpret. Furthermore, there were significantly fewer patients from Eastern countries enrolled compared to their Western counterparts. This may have influenced how outcomes were categorised ahead of the consensus meeting. However, due to the interplay of other factors described above, reaching a definite conclusion about the degree of this possible limitation is difficult. This is an area that may benefit from further exploration using qualitative research methods.

Delphi surveys are an established method of reaching consensus in the design of COS[1]. They give participants the opportunity to reflect on their ratings from previous rounds before giving a final score. Only after this opportunity should all scores be analysed, and outcomes categorised ahead of the consensus meeting. During the process of rating outcomes in round 2 of the survey, participants are shown the results from each separate stakeholder group in round 1. The topic of why participants change their scores between rounds is an interesting one which has been examined elsewhere[18]. Through our previous analysis we identified that the reasons for changing scores provided by stakeholders were varied, including having the time to reflect on the question being asked, changing their minds on the importance, impact or usefulness of the outcome in question, and changes in personal experience of the outcome. In fact, the influence of other stakeholder ratings as a reason for significantly changing a score in round 2 was cited by only a minority of healthcare professionals and patients.

Another factor which may influence scores between rounds is attrition. Our strategy to keep this as low as possible has been previously discussed (see chapter 5). Whilst overall attrition was 30%, the group this affected the most were nurses with nearly 45% attrition. However, the characteristics of those completing both rounds were not significantly different to those

only completing round 1. Likewise, a statistically significant difference was identified in the characteristics of surgeons completing both rounds who were predominantly Western and from HIC compared to the balance of surgeons completing round 1. It could be argued therefore that retaining a greater number of Eastern and LMIC surgeons may have led to slightly different survey results. However, whilst statistically significant, this difference is unlikely to be clinically significant given that the number of surgeons not participating in round 2 was relatively small.

6.5.5 Conclusion

The GASTROS Delphi survey recruited a broad spectrum of international stakeholders to produce a list of outcomes which should be included or excluded from a COS and others which required further discussion at a consensus meeting. Whilst some regional differences were highlighted, there was little variation within stakeholder groups and between regions with respect to how outcomes were prioritised. This may reassure COS users that the adopted methodology was robust and that the views captured during its development were representative. COS developers should carefully consider the characteristics of Delphi survey participants when planning their recruitment strategy.

6.6 References

1. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(S3):280. doi:10.1186/s13063-017-1978-4

2. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study). Trials. 2017;18(1):370. doi:10.1186/s13063-017-2100-7

3. Alkhaffaf B, Blazeby JM, Williamson PR, Bruce IA, Glenny A-M. Reporting of outcomes in gastric cancer surgery trials: a systematic review. BMJ Open. 2018;8(10):e021796. doi:10.1136/BMJOPEN-2018-021796

4. Alkhaffaf B, Blazeby JM, Bruce IA, Morris RL. Patient priorities in relation to surgery for gastric cancer: qualitative interviews with gastric cancer surgery patients to inform the development of a core outcome set. BMJ Open. 2020;10(2):e034782. doi:10.1136/bmjopen-2019-034782

5. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(1):132. doi:10.1186/1745-6215-13-132

6. Potter S, Brookes ST, Holcombe C, Ward JA, Blazeby JM. Exploring methods the for selection and integration of stakeholder views in the development of core outcome sets: A case study in reconstructive breast surgery. Trials. 2016;17(1):1-11. doi:10.1186/s13063-016-1591-y

7. Gargon E, Gurung B, Medley N, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: A Systematic Review. Scherer RW, ed. PLoS One. 2014;9(6):e99111. doi:10.1371/journal.pone.0099111

8. World Bank Country and Lending Groups – World Bank Data Help Desk. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed May 5, 2020.

9. Far East - Wikipedia. https://en.wikipedia.org/wiki/Far_East. Accessed June 28, 2020.

10. Western world - Wikipedia. https://en.wikipedia.org/wiki/Western_world. Accessed June 28, 2020.

11. Yamamoto M, Rashid OM, Wong J. Surgical management of gastric cancer: The

East vs. West perspective. J Gastrointest Oncol. 2015;6(1):79-88. doi:10.3978/j.issn.2078-6891.2014.097

12. Chan WL, Lam KO, Lee VHF, et al. Gastric Cancer – From Aetiology to Management: Differences Between the East and the West. Clin Oncol. 2019;31(8):570-577. doi:10.1016/j.clon.2019.05.012

13. Coulman KD, Howes N, Hopkins J, et al. A Comparison of Health Professionals' and Patients' Views of the Importance of Outcomes of Bariatric Surgery. Obes Surg. 2016;26(11):2738-2746. doi:10.1007/s11695-016-2186-0

14. Kirkham JJ, Bracken M, Hind L, Pennington K, Clarke M, Williamson PR. Industry funding was associated with increased use of core outcome sets. J Clin Epidemiol. 2019;115:90-97. doi:10.1016/j.jclinepi.2019.07.007

15. Bang Y-J, Yalcin S, Roth A, et al. Registry of gastric cancer treatment evaluation (REGATE): I baseline disease characteristics. Asia Pac J Clin Oncol. 2014;10(1):38-52. doi:10.1111/ajco.12112

16. Messager M, De Steur WO, Van Sandick JW, et al. Variations among 5 European countries for curative treatment of resectable oesophageal and gastric cancer: A survey from the EURECCA Upper GI Group (EUropean REgistration of Cancer CAre). Eur J Surg Oncol. 2016;42(1):116-122. doi:10.1016/j.ejso.2015.09.017

17. Michalowski J, Salvador A, Napper R. Commissioned by Healthcare Quality Improvement Partnership National Oesophago-Gastric Cancer Audit 2018 An Audit of the Care Received by People with Oesophago-Gastric Cancer in England and Wales 2018 Annual Report.; 2018.

18. Fish R, MacLennan S, Alkhaffaf B, Williamson PR. "Vicarious thinking" was a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results. J Clin Epidemiol. 2020;128:118-129. doi:10.1016/j.jclinepi.2020.09.028

7 “Vicarious thinking” is a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results

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7.1 Abstract

Objective

The objectives of this nested study were to 1) assess whether changes in scores between rounds altered the final degree of consensus achieved in three Delphi surveys conducted as part of COS development projects (anal, gastric and prostate cancer), and 2) explore participants' reasons for changing scores between rounds.

Study design and setting

All Delphi surveys were conducted online using DelphiManager software and included healthcare professionals and patient participants. Participants were invited to give a free-text reason when they changed their score across an importance threshold in a 1-9 Likert scale (1-3 not important, 4-5 important, 7-9 critically important). Reasons for score change were coded by four researchers independently using an inductive-iterative approach.

Results

In all three Delphi surveys, the number of outcomes reaching criteria for consensus was greater in round 2 than round 1. Twelve themes and 23 sub-themes emerged from 2298 discrete reasons given for score change. The most common reasons for change were 'time to reflect' (482 responses, 23%) and vicarious thinking (424, 21%), with 68% (291) of vicarious thinking attributed to seeing other participants' scores.

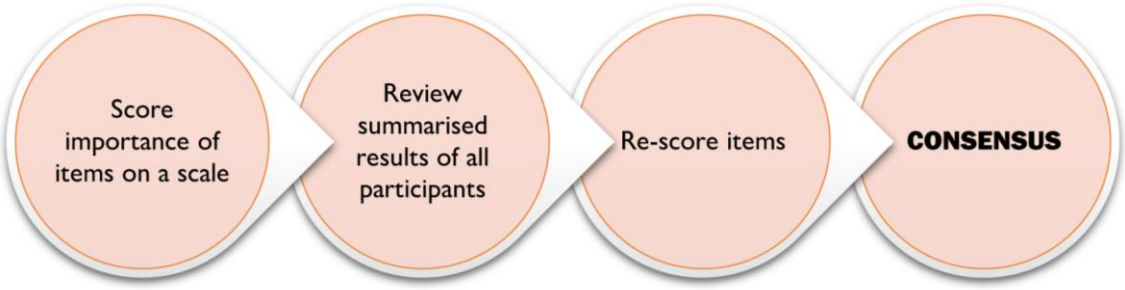
Conclusion

Our findings support conducting a Delphi survey over the use of a single questionnaire where building consensus is the objective. Time to reflect and vicarious thinking, facilitated by seeing other participants scores, were important drivers of score change. How results are presented to participants between rounds and the duration of and time between rounds in a Delphi survey may therefore influence the results and should be clearly reported.

7.2 Background and Aims

Core outcome sets (COS) are increasingly being advocated as a means to ensure relevance of research outcomes to stakeholders, reduce outcome heterogeneity and minimise reporting bias[1-4]. Trial funding bodies, regulatory authorities and guideline development groups, such as the (UK) National Institute for Health Research, the European Medicines Agency and the (UK) National Institute for Health and Care Excellence, now actively endorse the use of COS[5]. The COMET Initiative promotes rigorous consensus methods involving key stakeholders for the development of COS[6] and the consensus derived COS-STAD (core outcome set standards for development) recommendations[7] describe a set of minimum standards for COS development projects. Consensus methodology appropriate to the context is advocated[8] although a 2019 systematic review of COS studies[9] found that 77% of all COS studies published in 2018 included a Delphi survey, increasing from 31% in 2013-2015 and 15% in 1981-2013. A Delphi survey is a method of encouraging consensus, allowing participants to change their responses to a questionnaire after reviewing the anonymised summarised responses of other participants (Figure 1).

Figure 7-1 Schematic representation of how consensus is reached through a Delphi survey.



In a recent questionnaire study[10], Delphi participants reported considering the views of other participants when re-scoring items, indicating that feedback of results in a Delphi can influence scoring in subsequent rounds. However, studies exploring more broadly why Delphi participants choose to change their score between rounds are limited. There also remains uncertainty over whether a Delphi survey with multiple rounds is beneficial to reaching consensus or whether a single round questionnaire could produce the same result.

This nested study aimed to 1) assess whether changes in scores between rounds altered the final degree of consensus achieved and 2) explore participants' reasons for changing scores between rounds in three Delphi surveys conducted as part of COS development projects (anal, gastric and prostate cancer).

7.3 Materials and methods

The scope and methodology of the CORMAC[11], GASTROS[12], and COMPACTERS[13] COS studies are summarised in table 1.

Table 7.1 Scope and methodology of core outcome set projects.

	CORMAC	**GASTROS**	**COMPACTERS**
Health condition	Squamous cell carcinoma of the anus/anal canal	Cancer of the stomach	Localised prostate cancer
Setting	Later phase clinical effectiveness trials that will inform clinical decision making	Later phase clinical effectiveness trials that will inform clinical decision making	Later phase clinical effectiveness trials that will inform clinical decision making
Population	Adults >18 years of age	Adults >18 years of age	Men > 18 years of age
Types of intervention	Primary treatment with radiotherapy with or without concurrent chemotherapy	Surgery – total or partial gastrectomy	All primary treatments including active surveillance, watchful waiting, surgery, radiotherapy, brachytherapy, cryotherapy, high intensity focussed ultrasound, and adjuvant hormonal therapy
Development steps	Systematic review; patient interviews; online e-Delphi; face-to-face consensus meeting	Systematic review; patient interviews; online e-Delphi; face-to-face consensus meeting	Systematic review; patient interviews, online e-Delphi; face-to-face consensus meeting

7.3.1 Format of Delphi Surveys

The Delphi surveys for all three COS development studies are summarised in Table 2. All were run using the online DelphiManager platform[14]. The CORMAC, GASTROS and COMPACTERS Delphi surveys were conducted in 2017, 2019 and 2014-15 respectively. The CORMAC and GASTROS Delphi surveys involved 2 rounds whereas the COMPACTERS Delphi involved 3 rounds. In the interests of comparability therefore, only data from R1 and R2 of the COMPACTERS Delphi has been included. In each Delphi round, participants were asked to rate the importance of including each outcome in the COS on a 1-9 Likert scale described as: not important (1-3); important but not critical (4-6); and critically important (7-9). In the second round, participants were shown a histogram (CORMAC and GASTROS) or a distribution of scoring percentages (COMPACTERS) of the previous round's scores together with their own score for each outcome, before being asked to consider the information presented and score each outcome again (Figure 2).

In the CORMAC and GASTROS Delphi surveys, all stakeholders were shown the scores for each stakeholder group separately. In the COMPACTERS Delphi round two, healthcare professionals (HCP) and patients were randomised to receive round one feedback from peers only, multiple stakeholder groups separately, or multiple stakeholders combined. For comparability therefore, only the group randomised to receive feedback from multiple stakeholder groups separately is included in this study. In the COMPACTERS Delphi, if a participant changed the score for any item from round 1 (R1) to round 2 (R2), a free-text pop up box at the end of the survey asked the participant to describe their reasons for making the change. In the CORMAC and GASTROS Delphi surveys, a free-text pop-up box asked participants to describe the reason for changing their score every time a score was changed over an importance threshold (e.g. 3 to 4, 6 to 7).

Table 7.2 Delphi survey characteristics.

	CORMAC	**GASTROS**	**COMPACTERS**
Languages	English	English, Chinese, Dutch, German, Italian, Portuguese, Spanish, Turkish	English
Participants counties of residence	Australia, Canada, France, Netherlands, New Zealand, Norway, Spain, Sweden, UK & Ireland, USA	Argentina, Australia, Austria, Azerbaijan, Belgium, Brazil, Cameroon, Canada, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, Ecuador, Egypt, Finland, Greece, Hong Kong, Hungary, India, Iran, Ireland, Italy, Japan, Jordan, Kenya, Luxembourg, Malaysia, Mexico, Mongolia, Morocco, Netherlands, New Zealand, Nigeria, Pakistan, Peru, Poland, Portugal, Romania, Russia, Saudi Arabia, Serbia, Singapore, South Korea, Sudan, Sweden, Switzerland, Taiwan, Thailand, Turkey, UK, Ukraine, USA, Vietnam,	France, Germany, Italy, Netherlands, UK, USA
N participants completing R1; R2	Patients: 73; 54 HCP: 109; 93 Total: 182; 147	Patients: 268, 184 HCP: 684, 478 Total: 952, 662	Patients: 118; 109 HCP: 56; 49 Total: 174; 158
Types of HCP completing R1 and R2	Surgeon (coloproctologists) 36 (38%) Oncologist 26 (28%) Infectious diseases clinician 4 (4%) Pathologist 4 (4%)	Surgeons (oesophago-gastric): 343 (71%) Cancer nurse specialists: 135 (29%)	Surgeons (urologist): 33 (68%) Oncologists: 8 (16%) Cancer nurse specialists: 8 (16%)

	Radiographer 6 (6%) Radiologist 5 (5%) Radio-physicist 1 (1%) Specialist nurse 11 (13%) Missing 1 (1%)		
Delphi timeline	April 2017- September 2017 R1 open: 8 weeks Time between rounds: 4 weeks R2 open: 11 weeks	March 2019- October 2019 R1 open: 13 weeks Time between rounds: 8 weeks R2 open: 12 weeks	November 2014 – July 2015 R1 open: 6 weeks Time between rounds: 19 weeks R2 open: 6 weeks
Attrition rate R1-R2	Patients: 26.0% HCP: 14.6% Total: 19.2%	Patients: 31.1% HCP: 30.1% Total: 30.5%	Patients: 7.6% HCP: 12.5% Total: 9.2%
Total number of outcomes scored in R1	73	56	79
Number of outcomes reaching consensus in R1	12	11	9
Number of additional outcomes added to R2	5	1	5
Number of outcomes reaching consensus in R2; of which n additional outcomes	14; 1	13; 0	13; 0
N (%) of people changing score for at least one outcome	Patients: 52 (96.2%) HCP: 90 (96.7%) Total: 142 (96.5%)	Patients: 147 (79.9%) HCP: 410 (85.8%) Total: 557 (84.1%)	Patients: 102 (93.6%) HCP: 44 (89.8%) 146 (92.4%)

N (%) of people crossing a threshold for at least one outcome	Patients: 46 (85.1%) HCP: 86 (92.4%) Total: 132 (89.7%)	Patients: 129 (70.1%) HCP: 365 (76.3%) Total: 494 (74.6%)	Patients: 77 (75.5%) HCP: 18 (40.9%) Total: 95 (60.1%)
N (%) of eligible participants providing at least 1 reason for change	Patients: 28 (61%) HCP: 43 (50%) Total: 71 (53%)	Patients: 74 (40.2%) HCP: 117 (24.5%) Total: 191 (28.9%)	Patients: 77 (75%) HCP: 18 (41%) Total: 95 (65%)
Median and range of number of outcomes with threshold change for those who had at least one such change	Patients: 10.5 [1-16] HCP: 18 [1-25] Total: 19 [1-26]	Patients: 8 [1-33] HCP: 6 [1-40] Total: 8 [1-40]	Patients: 9 [2-49] HCP: 9 [2-29] Overall: 9 [2-49]

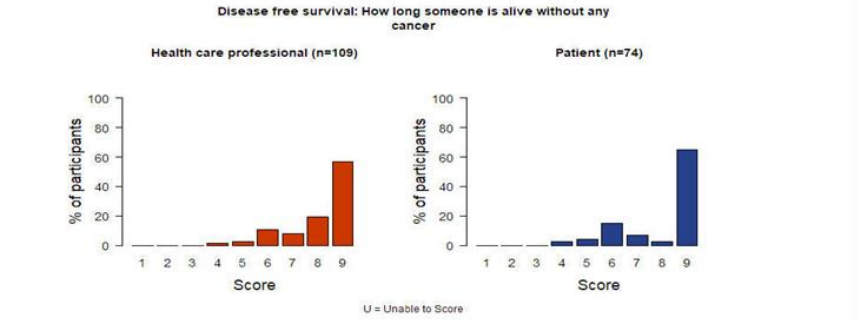
HCP = healthcare professional

Figure 7-2 Screen shots from round 2 of the CORMAC (A), GASTROS (B) and COMPACTERS (C) Delphi surveys showing how participants were shown the summarised results from round 1.

A

Disease free survival: How long someone is alive without any cancer

Your score from Round 1 is highlighted in yellow.

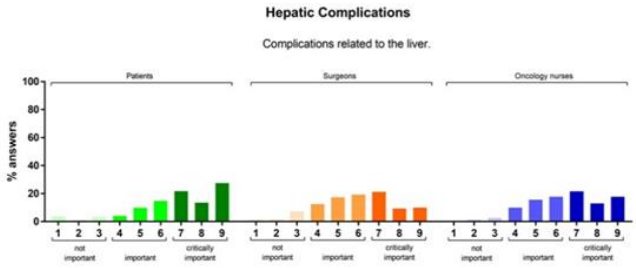


Outcome	Not important			Important but not critical			Critical			
	1	2	3	4	5	6	7	8	9	Unable to score
Disease activity										
Disease free survival: How long someone is alive without any cancer	○	○	○	○	○	○	○	○	○	●

B

Hepatic Complications

Your score from Round 1 is highlighted in yellow.



Outcome	Not Important			Important but not critical			Critical			
	1	2	3	4	5	6	7	8	9	Unable to score
Physiological & Clinical Outcomes										
Hepatic Complications	○	○	○	○	○	○	○	○	○	●

C

A. Cancer-specific outcomes and survival outcomes

Outcome	Total No of People Scoring 1 to 9	Importance									Unable to Score
		Not important			Important but not critical			Critical			
		1	2	3	4	5	6	7	8	9	
Applicable to all treatments											
1. Death from any cause											
This outcome refers to the death of someone from any cause, including prostate cancer.		○	○	○	○	○	○	○	○	●	○
Round 2 results for health professionals	15	0%	0%	0%	0%	0%	0%	7%	33%	60%	
Round 2 results for patients	35	6%	0%	3%	3%	6%	6%	6%	11%	60%	
2. Death from prostate cancer											
This outcomes refers to the death of someone as a result of prostate cancer.		○	○	○	○	○	○	○	○	●	○
Round 2 results for health professionals	15	0%	0%	0%	0%	0%	7%	0%	7%	87%	
Round 2 results for patients	35	6%	0%	0%	0%	6%	6%	3%	9%	71%	
3. Death from causes other than prostate cancer											
This outcome refers to the death of someone from any causes other than prostate cancer.		○	○	○	○	○	○	○	○	●	○
Round 2 results for health professionals	15	0%	0%	0%	0%	0%	7%	33%	40%	20%	
Round 2 results for patients	34	6%	0%	0%	3%	3%	12%	9%	3%	65%	

7.3.2 Analysis of reasons for change

Free-text entries from the CORMAC and COMPACTERS Delphi surveys were coded by two researchers (RF, SM) independently using an inductive-iterative approach largely following the framework method outlined by Ritchie and Spencer[15]. The process was that each researcher independently familiarised themselves with the free text reasons for score changes within their own data sets first. Similar reasons were grouped together and assigned a code. The codes were discussed between researchers and the coding scheme refined, and the main themes identified were assigned to 'parent' codes with sub-themes assigned to 'child' codes under each parent. The researchers then applied the coding framework to each other's data, working back and forth across the data and refining the framework until all responses were coded and both researchers were in agreement. The coding framework was then applied to a sample of the GASTROS data by four researchers (RF, SM, BA, PW) independently followed by discussion and further minor refinement of the code descriptions and framework. The refined framework was then applied to all three data sets by four researchers (RF, SM, BA, PW).

7.4 Results

The characteristics of the three Delphi surveys are summarised in Table 2.

7.4.1 Change in score and consensus

The percentage of participants changing score for at least one outcome between R1 and R2 was 97%, 84%, 92% (anal, gastric, prostate). The percentage of participants changing score across an importance threshold for at least one outcome was 90%, 29% and 60%. The median number of outcomes changed over a threshold per participant ranged from 18 (1-25) in HCPs in the CORMAC Delphi survey to 6 (1-40) in the GASTROS Delphi survey. The changes in score resulted in a greater number of outcomes reaching consensus in R2 than R1 in all three studies.

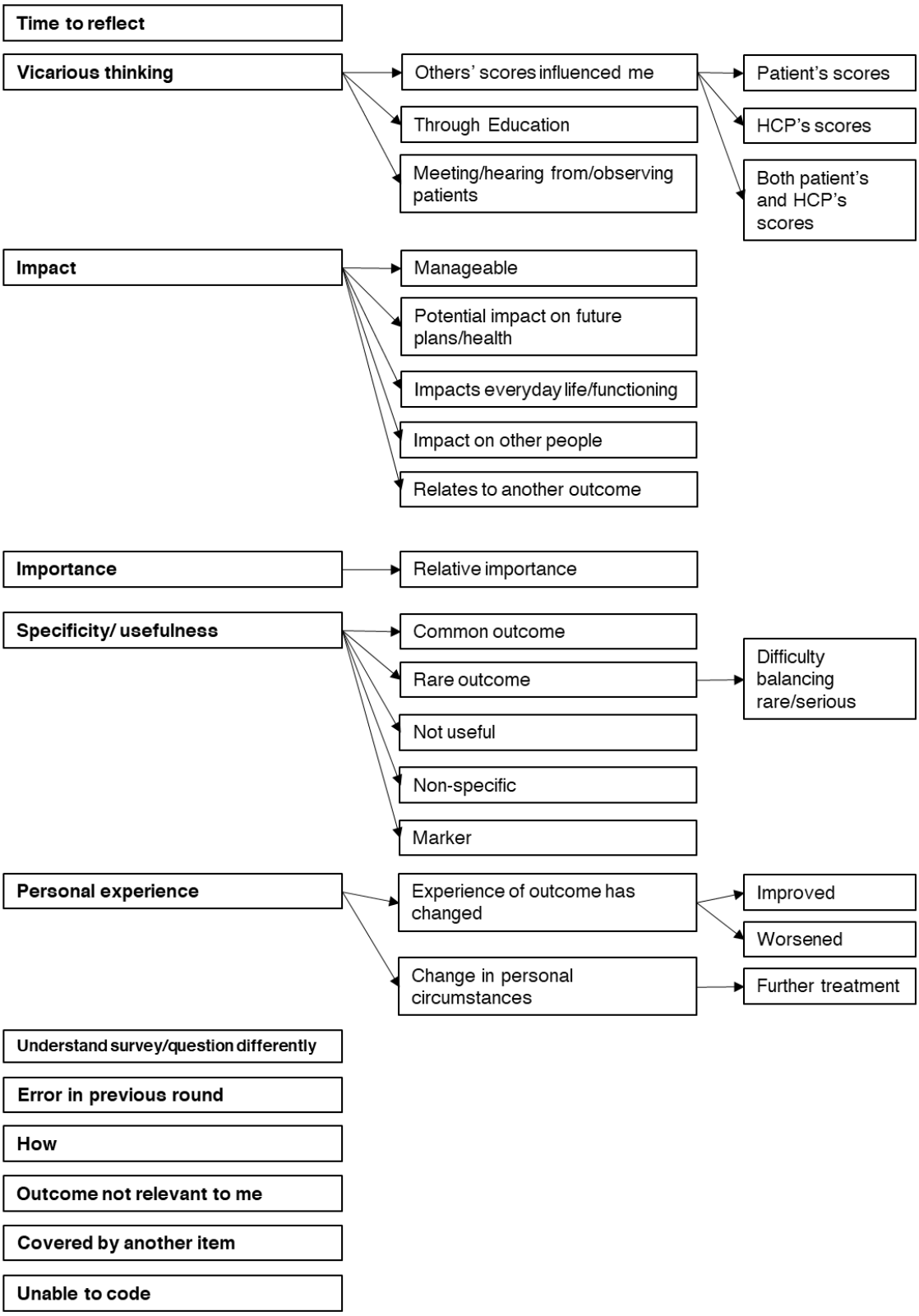
7.4.2 Coding framework

From 967 participants across the three Delphi surveys, 2298 responses were inputted to the free-text box request for a reason for changing score. An overview of the coding framework is shown in Figure 3. Twelve 'parent' codes describe the broad themes identified from the participants' free text reasons for change. Five of the 12 parent codes are further expanded into 'child' codes which describe sub-themes emerging within the parent code. Full descriptions of each code including illustrative quotes from participants responses are available in appendix 1.

The coding framework developed initially from the CORMAC and COMPACTERS data required minimal refinement when applied to the GASTROS data. Modifications included

clarification of the definitions of codes and the addition of new child codes within parent codes, but no new major themes were identified.

Figure 7-3 Coding framework showing the relationship of major themes ("parent codes") and their related sub-themes ("child codes").



7.4.3 Themes

The most frequently applied codes (table 3) overall were ‘time to reflect’ (482 responses, 23%), vicarious thinking (425, 21%); impact (394, 19%) and importance (311, 15%). Although there was some variation in the distribution of codes between the three studies, the three most common reasons for change in the HCP group were common to all Delphi surveys (table 4). Amongst HCP participants, ‘vicarious thinking’ was the most frequently applied code in the CORMAC and COMPACTERS Delphi surveys and was the third most common reason for change in the GASTROS Delphi survey.

There was greater heterogeneity between studies in the patient stakeholder group, with only one reason for change (“personal experience”) being common to the three most frequent codes all three studies. Amongst patient participants, ‘time to reflect’ was the most frequently applied code in the patient groups in the COMPACTERS and GASTROS Delphi surveys. However, in the patient group in the CORMAC Delphi survey, ‘time to reflect’ accounted for only 5% of reasons for change.

7.4.4 Vicarious thinking

In all three studies, ‘vicarious thinking’ was found more commonly in the HCP responses than the patient responses. Within the theme, four sub-themes were identified, detailed in table 5. The most common way participants described ‘vicarious thinking’ was being influenced by the scores of other Delphi participants (‘others’ scores influenced me’), accounting for 68% (291) of the responses coded in this theme. Of these 291, 24% (103) referred to being influenced by patients’ scores, 6% (27) by both patients’ and HCPs’ scores and 4% (14) by HCPs’ scores. HCP participants more frequently referred to patients scores’ than the patient participants did.

Table 7.3 Reasons for change

	CORMAC				GASTROS				COMPACTERS				Total Number of responses	Total % of responses
	HCP		Patient		HCP		Patient		HCP		Patient			
	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses		
Time to reflect	69	21%	9	5%	226	22%	144	31%	4	22%	30	42%	482	23%
Vicarious thinking	160	48%	21	13%	187	18%	30	6%	12	67%	15	21%	424	21%
Impact	40	12%	47	28%	228	23%	76	16%	1	6%	2	3%	394	19%
Importance	29	9%	11	7%	186	18%	85	18%	0	0%	0	0%	311	15%
Specificity/usefulness	26	8%	17	10%	129	13%	37	8%	1	6%	1	1%	211	10%
Personal experience	0	0%	47	28%	0	0%	92	20%	0	0%	16	22%	156	8%
Understand the survey/question differently	0	0%	1	1%	34	3%	1	0%	0	0%	7	10%	43	2%
Error in previous round	3	1%	4	2%	10	1%	1	0%	0	0%	0	0%	18	1%

	CORMAC				GASTROS				COMPACTERS				Total Number of responses	Total % of responses
	HCP		Patient		HCP		Patient		HCP		Patient			
	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses	Number of Responses	% of responses		
How	3	1%	0	0%	10	1%	0	0%	0	0%	0	0%	13	1%
Outcome not relevant to me		0%	6	4%	1	0%	3	1%	0	0%	1	1%	11	1%
Covered by another item	2	1%	3	2%	0	0%	0	0%	0	0%	0	0%	5	0%
Grand Total	**332**	**100%**	**166**	**100%**	**1011**	**100%**	**469**	**100%**	**18**	**100%**	**72**	**100%**	**2068**	**100%**
Unable to code	28	8%	13	8%	72	7%	112	23%	**0**	0%	5	7%	230	11%

Table 7.4 Most frequent reasons given

	CORMAC				GASTROS				COMPACTERS			
	HCP		Patient		HCP		Patient		HCP		Patient	
	Code	% (n) of responses	Code	% (n) of responses	Code	% (n) of responses	Code	% (n) of responses	Code	% (n) of responses	Code	% (n) of responses
1	Vicarious thinking	48 (160)	Personal experience	28 (47)	Impact	23 (228)	Time to reflect	31 (144)	Vicarious thinking	67 (12)	Time to reflect	42 (30)
2	Time to reflect	21 (69)	Impact	28 (47)	Time to reflect	22 (226)	Personal experience	20 (92)	Time to reflect	22 (4)	Personal experience	22 (16)
3	Impact	12 (40)	Vicarious thinking	13 (21)	Vicarious thinking	18 (187)	Importance	18 (85)	Impact; specificity/usefulness	6 (1)	Vicarious thinking	21 (15)

Table 7.5 Vicarious thinking as reason for change in score

	CORMAC				GASTROS				COMPACTERS				Total Number of responses	Total % of responses
	HCP		Patient		HCP		Patient		HCP		Patient			
	Number of responses	% of responses	Number of responses	% of responses	Number of responses	% of responses	Number of responses	% of responses	Number of responses	% of responses	Number of responses	% of responses		
Others' scores influenced me	128	80%	3	14%	109	58%	30	100%	10	83%	11	73%	291	68%
Not further specified	50	31%	3	14%	54	29%	25	83%	7	58%	6	40%	145	34%
Patient's scores	46	29%	0	0%	49	26%	3	10%	2	17%	3	20%	103	24%
Both *patient's and HCP's* scores	26	16%	0	0%	1	1%	0	0%	0	0%	0	0%	27	6%
HCP's scores	6	4%	0	0%	5	3%	2	7%	1	8%	2	13%	16	4%
Meeting/hearing from /observing patients	1	1%	8	38%	69	37%	0	0%	0	0%	1	7%	79	19%

Vicarious thinking- not further specified	31	19%	10	48%	6	3%	0	0%	1	8%	3	20%	51	12%
Through education	0	0%	0	0%	3	2%	0	0%	1	8%	0	0%	4	1%
Grand Total	**160**	**100%**	**21**	**100%**	**187**	**100%**	**30**	**100%**	**12**	**100%**	**15**	**100%**	**425**	**100%**

7.5 Discussion

Most participants in all three Delphi surveys changed score for at least one outcome between rounds and the number of items reaching consensus was subsequently increased. This finding supports conducting a Delphi survey over the use of a single questionnaire for core outcome set projects where building consensus is the objective.

The coding framework derived from two studies showed good applicability across a third, requiring only minimal refinements and no new major themes identified. We encourage other researchers to use and further refine our coding framework as necessary to generate further much needed data in this field.

The reasons participants gave for changing their scores provide useful data for researchers to consider when designing Delphi surveys. It is recognised that the duration of rounds and time between rounds are important factors, with a longer gap allowing for more change in an individual's circumstances, knowledge and situational context[16], however at present there is very little data available on this aspect of Delphi survey design. A 2019 study of the impact of design characteristics on response rates in COS Delphi surveys[17] found that insufficient data were reported on the duration of and time between rounds to allow analysis. Time to reflect on the importance of outcomes between rounds was the most common reason for change in the current study. Furthermore, it was most frequently identified in the COMPACTERS Delphi survey which had a 19-week interval between R1 and R2 compared to the 8-week and 4-week intervals in the GASTROS and COMRAC Delphi survey respectively. This finding is not sufficient to draw any conclusions about a direct correlation between the time between rounds and the degree of consensus. However, it does raise a question of whether the timing between rounds in a Delphi survey might influence participants thinking and their responses, and potentially impact the results. We recommend that the duration of and time between rounds in Delphi surveys is reported to facilitate further work to explore the potential impact of this characteristic on participation and consensus.

Vicarious thinking (trying to understand importance of an outcome from the perspective of another participant) emerged as a major theme and was the second most common reason for change overall. Vicarious thinking appears to be facilitated by seeing other participants' scores, with nearly 70% of participants in the vicarious thinking group making direct reference to the scores of other participants as a reason for their change in score. This finding is consistent with the findings of Turnbull et al[10], who reported that that 83% of respondents to a post-Delphi survey questionnaire reported considering the scores of other participants when scoring in subsequent rounds. Furthermore, we found that of participants being influenced by others' scores, just over 40% cited being influenced by one particular stakeholder group, consistent with the differential weighting to scores from different stakeholder groups reported by Turnbull. This is also consistent with the findings from a

nested randomised study by Brookes et al.[18] who reported that compared to those randomised to receive pooled feedback from all participants, there was a small increase in the number of outcomes reaching consensus in the group randomised to receive separate feedback from each stakeholder group. These findings suggest that the approach to presenting responses to participants between rounds is a key factor in Delphi design that could influence the result. This is an important area for future methodological research.

Vicarious thinking and being influenced by the scores of others was more common in the HCP group than the patient group across all three Delphi surveys. This corroborates the post-Delphi survey findings of Turnbull et al who also found patients considered the results from other stakeholder groups less frequently than all other stakeholder groups. Where other scores were considered however, they found that HCPs prioritised the results from both patients and other HCPs in contrast to our results which show HCPs more commonly referenced being influenced by patients' scores than by the scores from other HCPs. The difference in vicarious thinking that we observed between patient and HCP participants may help to explain the findings of Maclennan et al. in the nested randomised study of feedback composition on consensus. They observed no evidence of difference between groups receiving peer-only, multiple-separate or combined feedback. This may be explained by a high level of agreement in the first round of the Delphi, however it may also be explained if the majority of patients (accounting for two-thirds of the participants in that study) do not use the results of others in their decision making.

We have identified only one other study examining the comments submitted by participants in a Delphi survey for COS development. Sautenet et al[19] identified five broad themes from a thematic analysis of free-text comments submitted by participants in a renal transplant COS. The themes they describe align conceptually with the themes identified in this study. For example their theme "Understanding and awareness of risks" describes patients and caregivers increasing their scores in response to comments from health professionals as well as health professionals gaining increased respect for the impact of outcomes on patients, which maps to our theme of vicarious thinking. Their description of "personal relevance" maps to our theme of "personal experience"; "capacity to control" and "debilitating repercussion" to "Impact" and "importance". The three Delphi surveys included in our study were for cancer COS, so it is encouraging to see broadly similar themes in a non-cancer study. However, it is important to acknowledge that different disease contexts may generate diverse and unique reasons for score change.

This study has some limitations. To allow comparison, a significant proportion of data from the COMPACTERS study had to be excluded; the randomisation to various forms of feedback in that study meant that the sample of participants included in this analysis should, however, be representative of those in the wider study. In addition, participants in the COMPACTERS Delphi survey were given a single opportunity to provide reasons for change

at the end of the survey whereas in the CORMAC and GASTROS Delphi surveys, participants were asked to give a reason each time a score threshold was crossed. These differences resulted in there being only a low number of responses from the COMPACTERS Delphi survey so caution must be employed when drawing any conclusions from comparison of results across the three studies.

Qualitative analysis of free text is inherently subjective and there is likely to be an element of inter-rater and intra-rater variability. We attempted to minimise variability through coding by multiple researchers and frequent coding discussion meetings. It is also important to acknowledge that human decision-making behaviour is complex, and participants written responses to a single direct question about their reasons for changing score can provide only a one-dimensional view of what is a multi-dimensional process. The responses can only reflect why the participant believes they changed their score when it is likely that unconscious factors also play a role. Responses also only represent what participants deem as acceptable or can be influenced by what they believe researchers want to hear.

Vicarious thinking was identified relatively infrequently in the GASTROS Delphi survey in both patients (6%) and HCPs (18%) compared to the CORMAC and COMPACTERS studies. The reasons for this difference are not clear. It is notable that the GASTROS Delphi survey was translated into multiple languages with reverse translation of participants' reasons for change back into English. It is possible that nuances of language or cultural differences were not appreciated during coding which may have affected the results. We did not find any relationship between the types of HCP participating in the Delphi surveys and the frequency of vicarious thinking. Further the responses from specific types of HCP also varied widely between the Delphi surveys; for example, 64% of responses from surgeons in the CORMAC study cited vicarious thinking compared to 15% of responses from surgeons in the GASTROS study. It is interesting to note that the magnitude of the difference between patients and HCPs citing vicarious thinking is similar in all 3 studies (about three times greater from HCPs than patients). This suggests that there may be more in common between different stakeholder groups in the same study population than between the same stakeholder groups in different populations. The degree to which cultural factors might influence attitudes towards consensus methods and health outcomes is an area that should be explored in future work.

The validity and generalisability of the coding framework derived through this study should be further assessed and refined in a broader context including a variety of health conditions and populations. The framework could also be tested for content validity by Delphi participants through the creation of a questionnaire where respondents are invited to select the codes from the framework that best describe their reasons for changing score along with an option to provide a different option of their reason was not represented.

7.5.1 Conclusion

Our findings suggest that within a Delphi, showing participants summarised results and completing a second round are directly beneficial to reaching consensus. Time to reflect on the importance of outcomes between rounds and the opportunity to try to understand the experience of an outcome from the perspective of another are helpful to this process.

7.6 References

1. Williamson P. Core outcome sets will improve the quality of obstetrics research. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121(10):1196-1196.

2. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the Quality and Relevance of Research Through the Use of Agreed Core Outcomes. Journal of Health Services Research & Policy. 2012;17(1):1-2.

3. Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: its role in improving Cochrane Reviews[editorial]. Cochrane Database of Systematic Reviews. 2012;4.

4. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017;18:122.

5. COMET. COS Uptake and Endorsement. 2020; http://www.comet-initiative.org/COSEndorsement, 2020.

6. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(3):280.

7. Kirkham JJ, Davis K, Altman DG, et al. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLOS Medicine. 2017;14(11):e1002447.

8. Williamson PR, Blazeby JM, Brookes ST, Clarke M, Terwee CB, Young B. Comments on Chevance et al; 'Improving the generalizability and credibility of core outcome sets (COS) by a large and international participation of diverse stakeholders' 2019. Journal of Clinical Epidemiology.

9. Gargon E, Gorst SL, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 5th annual update to a systematic review of core outcome sets for research. PLOS ONE. 2019;14(12):e0225980.

10. Turnbull AE, Dinglas VD, Friedman LA, et al. A survey of Delphi panelists after core outcome set development revealed positive feedback and methods to facilitate panel member participation. J Clin Epidemiol. 2018;102:99-106.

11. Fish R, Sanders C, Adams R, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. The Lancet Gastroenterology & Hepatology. 2018;3(12):865-873.

12. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the reporting of outcomes in gastric cancer surgery trials: protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study). Trials. 2017;18(1):370.

13. MacLennan S, Williamson PR, Bekema H, et al. A core outcome set for localised prostate cancer effectiveness trials. BJU Int. 2017;120(5b):E64-e79.

14. COMET DelphiManager. 2018; http://www.comet-initiative.org/delphimanager/index.html, 2018.

15. Ritchie J, Lewis J. Qualitative research practice: a guide for social science students and researchers. London ; Thousand Oaks, Calif: Sage Publications; 2003.

16. Day J, Bobeva M. A generic toolkit for the successful management of delphi studies. Electronic Journal of Business Research Methods. 2005;3(2):103-116.

17. Gargon E, Crew R, Burnside G, Williamson PR. Higher number of items associated with significantly lower response rates in COS Delphi surveys. Journal of Clinical Epidemiology. 2019;108:110-120.

18. Brookes ST, Macefield RC, Williamson PR, 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(1):409.

19. Sautenet B, Tong A, Manera KE, et al. Developing Consensus-Based Priority Outcome Domains for Trials in Kidney Transplantation: A Multinational Delphi Survey With Patients, Caregivers, and Health Professionals. Transplantation. 2017;101(8):1875-1886.

7.7 Appendices

7.7.1 Appendix 1: Codes and descriptions for reasons for change of score

Code	Description	Illustrative quote
Time to reflect	Concept of changing mind/on reflection/thinking through etc with no other qualification. If further explanation is given categorise as per that explanation	“Felt that this was important but not critical having reflected on my previous score” [HCP CORMAC] “Surprised I rated low; I'd think we would want to know this.” [patient, CORMAC] “In retrospect seems more serious” [patient, GASTROS] “At this time; I think that it is less important.” [HCP, GASTROS] "Time. As time since discovery and treatment has passed, I feel better positioned to look back and decide that what I thought was important and what became important were in fact different." [patient, COMPACTERS] “Change of opinion with passage of time.” [patient, COMPACTERS] “reflection on previous answers” [HCP, COMPACTERS]
Vicarious thinking	Specifically referring to considering what other people would consider important (but not referring to scores from previous round)	“importance to patient.” [HCP, CORAMC “I'm not sure why I changed this. Some days I'd want to know; others I

Code	Description	Illustrative quote
		wouldn't. I'd think healthcare professionals would want to know effectiveness of treatment." [patient, CORMAC] "This is a very important issue in elderly patients" [HCP, GASTROS] "Further reflection and evaluation of how the potential outcomes may have been different. And the effect it may have had on my life. Also being more aware of how post op others have been affected both physically and mentally." [patient, COMPACTERS] "The duration of stay is important to the patient and their family but not critical." [HCP, GASTROS] "Further reflection and evaluation of how the potential outcomes may have been different. And the effect it may have had on my life. Also being more aware of how post op others have been affected both physically and mentally." [patient, COMPACTERS] "Thought about the importance to a group of elderly patients and their quality of life" [HCP, COMPACTERS]
Others' scores influenced me	Specifically referring to scores of other participants from the previous round (but not providing detail on which group e.g. HCP or patients).	"my responses did not seem consistent with consensus" [HCP, CORMAC] "Influenced by others but I could have left this as a 6" [patient, CORMAC] The impact of attitude changes and other previous evaluation results" [HCP, GASTROS]

Code	Description	Illustrative quote
		felt less important now after viewing others' scoring [patient, GASTROS] “Influence of others in survey that encouraged me to re-evaluate my previous response in light of time elapsed”. [patient, COMPACTERS] “Reappraising answers based on percentage of other participants scoring each question.” [HCP, COMPACTERS]
Patient’s scores	Specifically referring to scores of patients from the previous round.	“Patient scoring suggests that this is a bigger problem of the patient than I had experienced.” [HCP, CORMAC] “patients ranked this higher” [HCP, GASTROS] “Seen as critical by patient group” [patient, GASTROS] “Somewhat influenced by other patients and experience since last survey.” [patient, COMPACTERS] “Looking at the difference between mine and patient scores. Also, there was a few that I had as important that I would normally have as critical (like anastomotic leak), I must have been going too quickly at round 1!" [HCP, COMPACTERS]
HCP’s scores	Specifically referring to scores of HCP’s from the previous round.	“reflected on importance compared to peers” [HCP, CORMAC] “based on other surgeons' opinion” [HCP, GASTROS] “Health professional scores made me think hard about my scores but generally in the critical areas I feel my score should remain more or less the

Code	Description	Illustrative quote
		same as the first round. Surprisingly I felt that scores of patients had no discernible influence on my scores". [patient, COMPACTERS] "Seeing what my colleagues thought - usually upscaled the score" [HCP, COMPACTERS]
Both patient's and HCP's scores	Specifically referring to scores of patient's and HCP's from the previous round.	"re-considered in view of scores of peers and patients" [HCP, CORMAC] "influenced by patients & peers" [HCP, GASTROS]
Through education	Specifically referring to new knowledge gained through to educational events	"based on RCT (LOGICA study)" [HCP, GASTROS] "Bizarrely I am sat at a sexual medicine conference and as I fill this out and found myself scoring sexual function domains less strongly. Perhaps, I appreciate that there is more we can do to counsel these patients after treatment that can improve HRQoL" [HCP, COMPACTERS]
Meeting/hearing from /observing patients	Specifically referring to meetings or conversations with patients	"Influenced by recent patient who is very troubled by this" [HCP, CORMAC] "Recent complaints from some patients" [HCP, GASTROS]
Impact	Referring to the impact of the outcome	"Should be well aware of its danger" [HCP, GASTROS] "this needs clarity and has profound effects" [Patient, GASTROS]
Manageable	Reference to the manageability of the outcome - usually that although important, the outcome is manageable	"Can be managed" [HCP, CORMAC] "It can be dealt with by appropriate diet and physical activity" [Patient,

Code	Description	Illustrative quote
		GASTROS]
Impacts everyday life/functioning	Referring to the effect an outcome has on the patient's life	"This is critical for patient to live a comfortable life and improve performance" [HCP, GASTROS] "Makes leaving the house difficult" [Patient, CORMAC]
Potential impact on future plans/health	Referring to the impact of the outcome on health in future	"Awareness but will impact future health" [HCP, CORMAC] "On reflection I think that it is important to measure these outcomes more vigorously due to impact on future health" [Patient, CORMAC]
Impact on other people	Referring to the impact of the outcome on people other than the patient	"Impact on relatives; duration of hospitalization and therefore cost" [HCP, GASTROS] "Indicator for impact on (intimacy of) relationship(s)" [Patient, GASTROS]
Relates to another outcome	Referring to the outcome having an impact on another outcome	"conversion hasn't got a crucial effect; however, can result in more complication and reduced QoL" [HCP, GASTROS] "physical activity helps the recovery and improves mental health" [Patient, GASTROS]
Importance	Comment on the importance of the outcome as a justification for score change but not specifically mentioning in relation to other outcomes	"I can't see how this is an important or critical item" [Patient, GASTROS] "Important for evaluating treatment" [HCP, CORMAC] "Sounds important" [Patient, CORMAC]

Code	Description	Illustrative quote
Relative importance	Comment comparing the importance of the outcome against another outcome as a basis for changing score	"Not very relevant. Wound infection rates are more relevant". [Patient, GASTROS] "Not the most important parameter to report" [HCP, GASTROS] "Not as critical as some others" [HCP, CORMAC] "I think this depends on the age of the man; life is more important" [Patient, CORMAC]
Marker	Referring to the outcome being useful because it is a marker or indicator of something else	"Marker of major surgical problem" [HCP, GASTROS] "May indicate an infection" [Patient, CORMAC]
Specificity/usefulness	Comment on how useful/relevant/specific the outcome is in the context of the disease in question	"Not very relevant for these patients" [HCP, CORMAC] "Not directly related to surgery or gastric cancer" [HCP, GASTROS]
Common outcome	Referring to the outcome as common	"A common problem with many other health issues" [HCP, CORMAC] "This is to be expected to some extent" [Patient, GASTROS]
Rare outcome	Referring to the outcome as rare	"Rare complication which I think should not be a focus for research" [HCP, GASTROS] "This seems a relatively rare event; not necessarily directly related to the surgery" [Patient, GASTROS]

Code	Description	Illustrative quote
Difficulty balancing rare/serious	Describing the outcome in question as rare and serious as a reason for the change in score	“critical but rare event” [HCP, CORMAC] “For example, the question, ""How important is rectal pain?"", I know that this is an uncommon outcome and therefore may not be very important. But for those patients in whom it does develop, it is very important!” [Patient, COMPACTERS]
Non-specific	Describing the outcome as not specific enough to be useful	“Need to report for information but depends on reporting reason” [HCP, CORMAC]
Not useful	Describing the outcome as common and therefore not useful	“A common problem with many other health issues” [HCP, CORMAC] “I don't think is relevant at all because accidents would skew the numbers” [Patient, CORMAC]
Personal experience	Referring to personal experience of the outcome in question, but not enough detail given to code further in relation whether experience of the outcome has changed for the better or worse etc.	“Reconsideration of my own circumstances, rather than taking account of other survey results” [Patient, COMPACTERS] “Looking back realise how hard everything was as I live alone” [Patient GASTROS]
Experience of the outcome has changed	Referring to personal experience of the outcome in question with explicit reference to a change but no indication of whether it is better or worse	“You become aware its importance only after a while” [Patient, GASTROS] “Personal experience” [Patient, CORMAC] “As time goes by this is becoming more critical” [Patient, GASTROS]
Experience of outcome	Referring to personal experience of the outcome in question with explicit	“Increased loneliness lately” [Patient, GASTROS]

Code	Description	Illustrative quote
worsened	reference to their experience of the outcome becoming worse	“Personally, having more issues with this recently” [Patient, CORMAC]
Experience of outcome improved	Referring to personal experience of the outcome in question with explicit reference to their experience of the outcome becoming better	“These are now only a memory” [Patient, GASTROS] “My recovery has improved” [Patient, CORMAC]
Change in personal circumstances	Referring to a change in circumstances, but not described specifically referring to further	“Now that my condition has been determined as terminal; I have reconsidered this question” [Patient, GASTROS]
Further treatment	Referring to a change in experiences related to a having had further medical treatment	“I could not comment on Radio Therapy and on Hormone Treatments. I (subsequently) was given 20 courses of Radio Therapy [Patient, COMPACTERS]
Understand the survey/question differently	Describing a change in the understanding of the Delphi survey/question/COS development process since the previous round	“I comprehended the question differently at this time” [patient, CORMAC] “misunderstanding question previously” [HCP, GASTROS] “Misunderstanding on reading original question. Reassessment on reading again.” [patient, COMPACTERS]
Error in previous round	Comment describing an error on the part of the participant in completing the survey/previous round	“My answer in Delphi 1 was probably an error” [HCP, CORMAC] “My error in last round” [patient, CORMAC] “Scored wrongly previous time” [HCP, GASTROS] “Mistake - wanted to score "un-important" - this indicator is too subjective to

Code	Description	Illustrative quote
		mean anything" [Patient, GASTROS]
How	Comment on ease/practicality/reliability of measuring the outcome	"variable and bias depending on how measured" [HCP, CORMAC] "This is very subjective." [HCP, GASTROS]
Outcome not relevant to me	Describing not having personal experience of the outcome in question as a reason for the change in score	"Some questions are very vague, and perhaps only relevant from a professional point of view, but felt I should answer, therefore some answers have changed. " [patient, COMPACTERS] "I'm not a woman" [patient, CORMAC] "I never experienced this." [patient, CORMAC]
Covered by another item	Describing the outcome as being covered by another outcome	"Covered by other areas" [HCP, CORMAC] "quality of life issue" [patient, CORMAC]
Unable to code	The text does not make sense as a reason for score change, does not describe a reason for change or provides insufficient information to apply a code	"Change of thinking" [HCP, GASTROS] "I think my responses are very similar" [Patient, COMPACTERS]

8 A Core Outcome Set for Surgical Trials in Gastric Cancer (GASTROS): International patient and healthcare professional consensus

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Authors

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8.1 Abstract

Background

Surgery is the primary treatment which can offer potential cure for gastric cancer but is associated with significant risks. Identifying optimal surgical approaches should be based on comparing outcomes from well-designed trials. Currently, trials report different outcomes making evidence synthesis difficult. To address this, we aimed to develop a core outcome set (COS) – a standardised group of outcomes important to key international stakeholders – that should be reported by future trials in this field.

Methods

The COS was developed over two stages. Stage 1 involved identifying potentially important outcomes from previous trials through a systematic review of the literature and a series of patient interviews. Stage 2 involved prioritising outcomes using a multi-language international Delphi survey which informed an international consensus meeting at which the COS was finalised.

Results

498 outcomes were identified from previously reported trials and patient interviews and rationalised into 56 items presented in the Delphi survey. 952 patients, surgeons and nurses enrolled into round 1 of the survey and 662 (70%) completed round 2. An additional outcome was identified from participants in round 1 which was presented to for scoring in round 2 (a total of 57 outcomes). Consensus was reached in the Delphi survey to include 13 outcomes in the COS, exclude 13 and discuss a further 31 where no consensus was reached. Following the consensus meeting, 8 outcomes were included in the COS - disease-free survival, disease-specific survival, surgery-related death, recurrence, completeness of tumour removal, overall quality of life, nutritional effects, and complications.

Conclusions

A COS for surgical trials in gastric cancer has been developed with international patients and healthcare professionals. We recommend that this be used be used in all future trials within this field to improve trial design and evidence synthesis.

8.2 Introduction

Gastric cancer is a significant global health burden which is associated with poor survival[1]. Whilst the adoption of multi-modal therapy for the minority of patients who present with early stage disease has improved prognosis, surgery remains the only modality offering a potential cure[2]. Identifying the optimum surgical approach involves balancing the benefits of a radical oncologic resection against the risk and impact of associated complications and physiological consequences. The ability to compare outcomes from surgical trials in a clinically meaningful manner is crucial to this process.

Homogeneity in the selection and reporting of key outcomes between studies is necessary if useful evidence synthesis is to be achieved. However, outcome reporting in surgical trials for gastric cancer is heterogenous and not based on methodologically robust standards[3]. Even when similar outcomes are reported, different definitions, measurement instruments and timepoints are used. Likewise, patient priorities and perspectives tend to be overlooked when outcomes are selected by researchers. This potentially limits the subsequent relevance of aspects of the research effort to the most important stakeholder group[4]. For example, 'quality of life', an area identified as vitally important to patients, is reported in less than 10% of trials[3].

To address this challenge, the GASTROS study (**GA**stric cancer **S**urgery **T**rials **R**eported **O**utcomes **S**tandardisation) was undertaken to develop a core outcome set (COS) for surgical trials in gastric cancer[5]. A COS is 'an agreed, standardised collection of outcomes which should be measured and reported, as a minimum, in all trials for a specific clinical area'[6]. Outcomes should be relevant to key stakeholders who should contribute to the stages of COS development.

These challenges in outcome reporting are not limited to the field of gastric cancer and affect virtually all clinical areas. COMET (Core Outcome Measures in Effectiveness Trials - www.comet-initiative.org) is an initiative which aims to promote the development of COS[7]. Their registry database and up-to-date systematic reviews have comprehensively mapped COS projects across all disciplines[8–12]. Whilst groups have developed COS for different gastrointestinal cancers[13–15], there has yet to be one developed for gastric cancer. The global incidence of gastric cancer and differences in patient characteristics, management and outcomes, necessitated an international approach to this COS[16,17]. An international working group (IWG) of collaborators was set-up to support this project, aided by a comprehensive network of patient organisations, charities, and professional bodies across 6 continents.

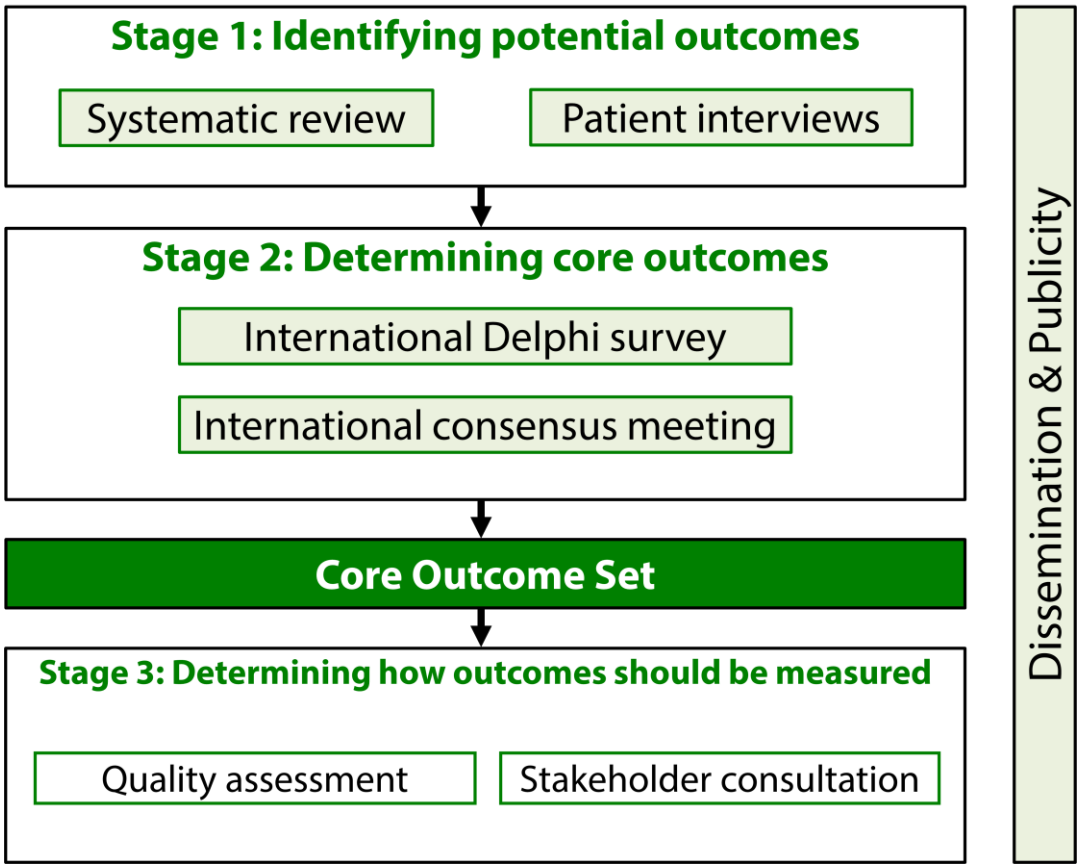
8.3 Methods

The GASTRO study conforms to standards established for the development of COS as outlined by COS-STAD (Core Outcome Set-STAndards for Development)[18]. This report uses the COS-STAR (Core Outcome Set-STAndards for Reporting) standards to describe the development of a COS for surgical trials in gastric cancer[19]. The checklist is provided in appendix 1.

8.3.1 Scope

The scope, objectives and methodological approaches of this study have been previously described in detail[5]. In summary, the COS developed in this study was aimed at all clinical effectiveness trials examining therapeutic surgical trials for patients with early stage (i.e. potentially curable) gastric cancer. The GASTROS study utilised existing best-practice approaches as developed by the COMET Initiative, whilst adapting the methodological principles to the challenges of an international consensus exercise. An overview of the study stages is illustrated in Figure 1. This publication describes stages one and two.

Figure 8-1. Stages of the GASTROS study.



8.3.2 Stakeholder participants and eligibility

The GASTROS study aimed to consider the views of key stakeholders during the process, namely patients, surgeons, and oncology nurses. Our guiding principle has been to promote the 'patient voice' as they are the beneficiaries of trials in this field and have all-important 'lived experience'. Surgeons provide a clinical perspective and the experience of treating large volumes of patients. Oncology nurses were invited to participate given their central roles as caregivers, patient advocates, and core members of the clinical team. Participation in the study was open to all interested stakeholders who fulfilled the following criteria:

- Surgeons who had completed their training and routinely treat gastric cancer.
- Oncology nurses with a recognised proportion of their role involved in the care and follow-up of gastric cancer patients.
- Patients who have undergone surgical resection for gastric cancer with the intention of cure.

Patients and healthcare professionals were identified through local, regional and national clinical and research networks. Support from patient groups, charities and professional societies was also key.

8.3.3 Stages of GASTROS Study

Stage 1 (figure 1) identified outcomes which may be important to stakeholders and stage 2 subsequently prioritised outcomes for inclusion in the final COS ('what to measure'). In addition, the GASTROS study aimed to collate the corresponding outcome measurement instruments (OMI) utilised in surgical trials and determine the variability in measurement timepoints, for use in future outcomes research (to determine 'how' and 'when to measure') in gastric cancer.

8.3.3.1 Stage 1 – Identifying outcomes

A systematic review of surgical trials for gastric cancer over two decades was undertaken from which all reported outcomes were extracted verbatim[3]. Patient-reported outcome measurement instruments used in these trials were broken down into their component parts to identify additional outcomes. To ensure patients' perspectives were captured, a series of qualitative interviews exploring outcome prioritisation was undertaken to identify potentially important outcomes not identified in the systematic review[4]. A subsequent 'long list' of potentially important outcomes was compiled which underwent a process of rationalisation, prior to being presented to the stakeholder groups for prioritisation in stage 2.

The rationalisation process (appendix 2) was initiated through discussion within the study management group (SMG) to merge closely related items and map them against a taxonomy developed for COS[20]. This process was independently assessed by an external methodologist with extensive experience in COS development. The resulting 'short list' was

presented to stakeholder representatives (patients, surgeons, and oncology nurses) comprising the 'study advisory group' (SAG). The SAG was tasked with ratifying the process thus far, further merging of outcomes if required, developing plain language descriptions of the outcomes, and identifying additional outcomes which they believed had not yet been identified. Following this, the short-list of outcomes and corresponding plain language descriptions were presented to a patient group as part of a 'cognitive debriefing' exercise to ensure understanding and comprehensibility.

8.3.3.2 Stage 2 – Prioritising outcomes

8.3.3.2.1 International Delphi survey

To prioritise which items to include in the COS, we invited patients, surgeons, and oncology nurses to participate in an international, multi-language Delphi survey. The methodological approach used to translate the surveys and recruit participants have been previously described (see chapter 5). Although there is no formal sample size requirement for Delphi surveys, recruitment was facilitated with the support of a large network of professional bodies, patient groups and charities, to help ensure a representative spectrum of opinion was captured for each stakeholder group.

Participants were invited to score outcomes in terms of importance on a Likert-type scale of 1-9 (1-3; not important, 4-6; important, 7-9; critically important) in a two-round online Delphi survey. Participants were given the opportunity to add additional 'missing' outcomes, for consideration by participants in round 2. Suggested additional outcomes were considered by the SMG and independently reviewed by an external methodologist with experience of cancer-related surgical COS. The scores of each stakeholder group were collated and summarised separately to ensure an equal voice amongst stakeholder groups. Participants who had completed 50% of the first survey were included in the round 1 analysis and invited to participate in round 2. They were then presented with group scores (presented as score distribution charts) for each stakeholder group from round 1 and given the opportunity to reflect on the opinions of others before deciding whether to change their scores for each outcome in round 2. Those who changed scores between rounds were able to provide a reason for this (see chapter 7). After two rounds of voting, outcomes were categorised according to pre-determined criteria for inclusion in or exclusion from the core outcome set (COS). Those participants who had completed at least 50% of the survey in round two were included in the final analysis.

Any outcome scored as critically important (7-9) by more than 70% and not important (1-3) by less than 15% in all three stakeholder groups was categorised for inclusion. Any outcome scored as critically important (7-9) by less than 50% in all three stakeholder groups was categorised for exclusion. These criteria were adapted from established COS methodology[6]. Outcomes achieving any other combination of scores were categorised as not having

reached consensus (no consensus) and presented for further discussion at a consensus meeting.

8.3.3.2.2 Consensus meeting

Survey participants were invited to attend a consensus meeting in Manchester (UK) during March 2020. The aim of the meeting was to review the results of the Delphi survey and consider the outcomes for which no consensus was reached before finalising the COS. Participants could take part by attending the meeting venue in person, or through an online platform. The meeting was undertaken in English and chaired by a Clinical Academic from the SMG with experience in COS development and with no clinical expertise in the management of gastric cancer.

Following discussion, stakeholders were asked to score outcomes using the same criteria as was set out in the Delphi survey. Similarly, scores from each stakeholder group were considered separately to mitigate for imbalance in the numbers of each participant type. Turning Point software (Turning Technologies LLC, Youngstown, Ohio, OH, USA) was used to support voting at the venue and online simultaneously. Participants were also asked to complete an online voting form to mitigate against software malfunction. Outcomes reaching the original consensus criteria for inclusion in the final COS were to be added to those included from the Delphi survey.

8.3.4 Assessing Bias

To assess the impact of attrition bias between survey rounds, mean scores of participants completing both rounds of the Delphi survey were compared against those completing round 1 alone. Mean scores of those who took part in the Delphi survey but did not attend the consensus meeting were compared against the mean scores of those who attended to assess the degree to which consensus meeting participants were representative of those who participated in the survey. Both analyses were undertaken using a t-test to examine for statistically significant differences at the 0.05 level. Furthermore, the characteristics of stakeholders participating in both rounds were compared to those who only completed round 1. A descriptive analysis was undertaken, and the Chi squared test applied to examine for statistically significant differences at the 0.05 level.

8.3.5 Patient & Public involvement

A guiding principle of the GASTROS study was that patients' voices should be represented at each stage of the project. Patient representatives were integral with membership in the SAG and support from international charities. The dissemination of results from this study will be supported by a network of international charities and patient support groups.

8.3.6 Study registration and protocol

The GASTROS study was registered in the COMET database (http://www.comet-initiative.org/studies/details/764?result=true) prior to commencing. The study protocol has been described previously[5].

8.3.7 Ethical approvals and portfolio adoption

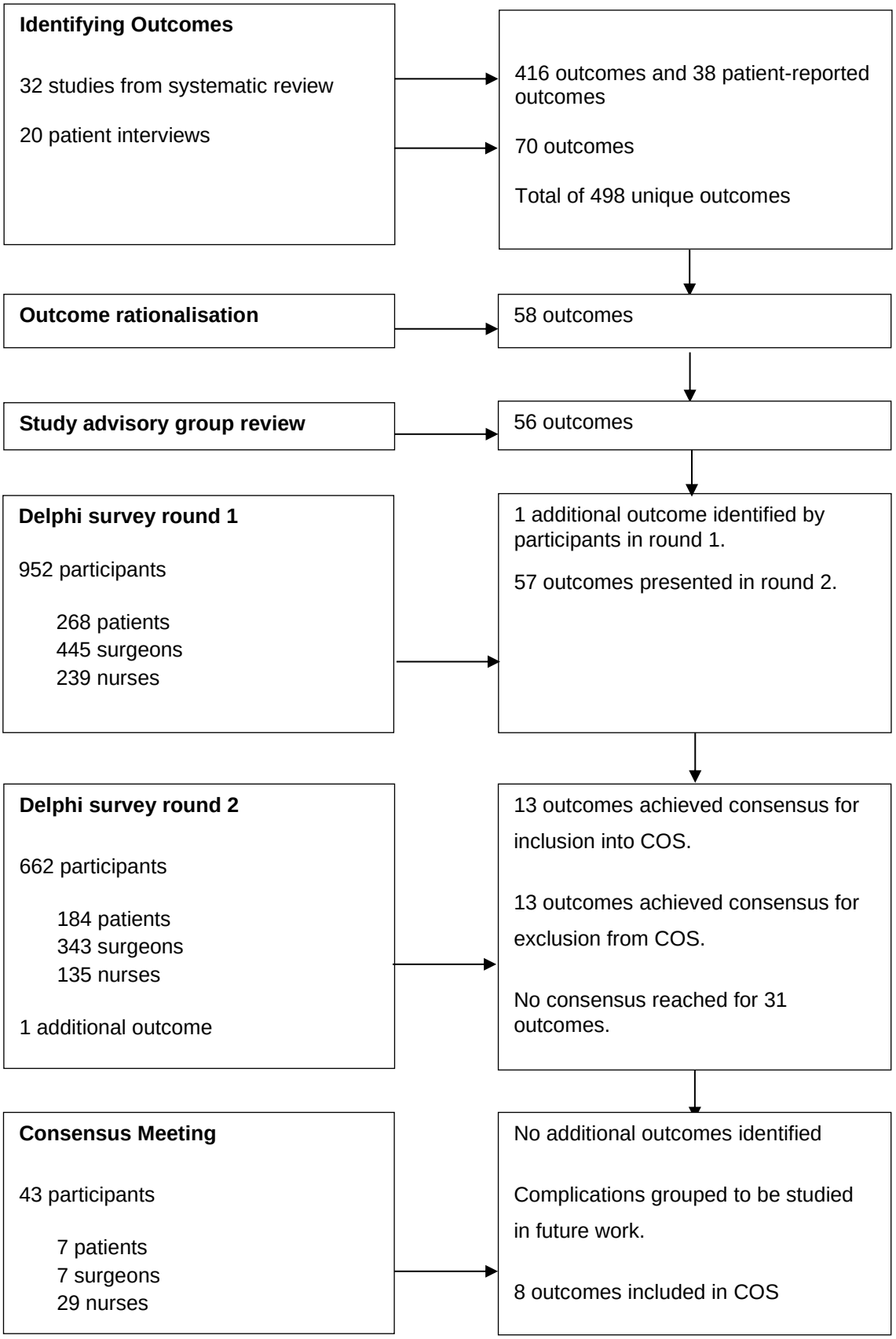
Ethical approvals were required for the qualitative patient interviews and international Delphi surveys. The qualitative interview study was given ethical approval by the National Research Ethics Service North West—Cheshire (11/NW/0739) and governance approvals by Central Manchester University Hospital NHS Foundation Trust. The Delphi survey was given ethical approval by the North West - Greater Manchester East Research Ethics Committee (18/NW/0347) and governance approvals by Manchester University Hospitals NHS Foundation Trust. Both the patient interviews and Delphi survey were adopted onto the National Institute for Health Research (NIHR) Clinical Research Network Portfolio (IDs 33312 and 38318). Ethical approval for international participants was sought and obtained locally by IWG collaborators.

8.4 Results

8.4.1 Overview

The results for each stage of the study are summarised in figure 2. The 498 outcomes identified from the systematic review, patient-reported outcome measures and patient interviews were rationalised by the SMG into 58 items which were presented to the SAG. The SAG merged ‘chyle leak’, ‘nutritional complications’, ‘respiratory function’, ‘surgical site infection’ and ‘time to ambulation’ into other existing outcomes. ‘Bleeding’, ‘anaesthetic complications’ and ‘destination on discharge’ were expanded or added as separate outcomes which meant that a total of 56 items were presented to participants in the Delphi survey (supplementary appendix 3).

Figure 8-2 Results from different stages of GASTROS study. *SMG = study management group. **SAG = study advisory group.



8.4.2 Delphi survey

A total of 1021 patients, surgeons and oncology nurses registered for the Delphi survey of whom 952 (268 patients, 445 surgeons, 239 nurses) from 55 countries across 6 continents fulfilled the criteria for inclusion in the round 1 analysis. Table 1 summarises the characteristics of those included in the analyses. Appendix 4 details the results of voting in both rounds. One additional outcome (duration of stay in an intensive care ward) suggested by participants in round 1 was presented in round 2 along with the original 56 outcomes for re-scoring (a total of 57 outcomes in round 2). Whilst other outcomes were suggested by participants in round 1, these were deemed by the SMG and external reviewer as either direct duplication of outcomes already included or not sufficiently unique that they warranted being presented separately (appendix 5). Scores from 662 participants in round 2 were included in the final analysis representing an attrition rate of 30%. Five hundred and fifty-seven (84%) participants changed the score of least one answer from round 1, with 191 (29%) participants changing a score to cross a boundary (e.g. from 1-3 to 4-6 or 7-9). A detailed analysis exploring the reasons for changing scores has been previously reported[18].

Consensus was reached to include 13 outcomes: **disease-free survival, disease-specific survival, surgery-related death, recurrence of cancer, completeness of tumour removal, overall quality of life, nutritional effects, all-cause complications, intra-operative complications, anaesthetic complications, anastomotic complications, multiple organ failure and bleeding**. Thirteen outcomes were categorised for exclusion, and no consensus was reached for 31 outcomes which were subsequently discussed at the consensus meeting. An analysis exploring the relationship between participant characteristics (e.g. regional and demographic differences) and their impact on how outcomes were scored has been previously reported (see chapter 6).

There was no statistically significant difference between the mean scores of participants completing both survey rounds and those completing round 1 only ($p=0.759$, mean difference 0.17, standard deviation 0.1, largest difference 0.4).

8.4.3 Consensus Meeting

Forty-three Delphi survey participants (7 patients, 29 surgeons, 7 nurses) attended the consensus meeting in person (18) or using the online platform (25). Fourteen countries from four continents (South America, North America, Europe, Asia) were represented. Six patients were from the UK with the seventh residing in the Netherlands. The difference in mean scores between consensus meeting participants and those completing round 2 of the survey was statistically significant ($p<0.0001$, mean difference 0.3, standard deviation 0.23, largest difference 1.16).

Table 8.1 Demographic characteristics of participants included in analysis of round 1 and 2 scores.

Stakeholder Group	Variable	Sub-Group	Total	Completed round 1 only (%)*	Completed both rounds (%)	p value
Patients	All	-	268	84	184	
	Age	<60		38 (45)	77 (42)	0.69
		>=60		46 (55)	107 (58)	
	Sex	Male		52 (62)	101 (55)	0.345
		Female		32 (38)	83 (45)	
	Region	West		53 (63)	113 (61)	0.185
		East		23 (27)	39 (21)	
		Other		8 (10)	32 (17)	
	Country income	HIC		53 (63)	113 (61)	0.792
		LMIC		31 (37)	71 (39)	
	Years since surgery	<1 year		15 (19)	30 (17)	0.656
		1 to 3 years		34 (44)	68 (39)	
		>3 years		29 (37)	75 (43)	
	Surgical approach	Open		70 (83)	145 (78)	0.850
		MIS		14 (17)	31 (22)	
	Type of surgery	Total		40 (49)	78 (44)	0.503
		Partial		42 (51)	98 (56)	
	Treatment Modality	Surgery alone		28 (34)	69 (39)	0.495
		Multimodal therapy		54 (66)	110 (61)	
Surgeons	All	-	445	102	343	
	Region	West		33 (32)	174 (51)	0.001
		East		53 (52)	109 (32)	
		Other		16 (16)	60 (17)	
	Country income	HIC		45 (44)	201 (57)	0.010
		LMIC		57 (56)	142 (43)	
	Surgeon experience	<50		21 (29)	70 (23)	0.450
		50-199		20 (27)	103 (34)	
		>200		32 (44)	127 (42)	
Nurses	All	-	239	104	135	
	Region	West		22 (21)	40 (30)	0.251
		East		57 (56)	61 (45)	
		Other		25 (24)	34 (25)	
	Country income	HIC		24 (23)	46 (34)	0.064
		LMIC		80 (77)	89 (66)	
	Nurse experience	0-5 years		59 (57)	59 (45)	0.056
		>5 years		44 (43)	73 (55)	

Table legend: HIC =high income country, LMIC = low- to middle-income country; MIS = minimally invasive surgery. *All percentages refer to the proportion of participants from each sub-group completing either round 1 or both rounds.

In preparation for the consensus meeting, the SMG reviewed and discussed the Delphi results. Out of the 13 outcomes that reached consensus to be included, 6 related to peri-operative complications. The SMG took the view that given the outcome 'all-cause complications' was voted for inclusion, by extension all complications would need to be measured and reported by researchers as a minimum. However, 14 complication-type outcomes from the list of 57 did not reach consensus for inclusion and a further two outcomes reached consensus for exclusion from the COS. The SMG decided to present this seemingly contradictory position at the consensus meeting for further discussion and voting on a desired final position.

After an interactive debate, participants were asked to vote for 1 of 5 propositions:

1. All complications to be individually reported as a minimum
2. All 'serious' (without defining the term 'serious') complications to be reported as a minimum
3. Outcomes meeting the criteria as 'core' as set out by the GASTROS study to be included
4. Unsure
5. Other options

The result of this 'live vote' was presented to participants who were given an opportunity for further discussion ahead of a final vote. The result of the second vote is shown in figure 3. Votes were split between options 1 and 2, with the lack of a clear consensus mandating the need for further work in this area. Consequently, all 'complication-type' outcomes were excluded from further discussion.

Non complication-type outcomes for which no consensus to include or exclude in the Delphi survey were then discussed. Results from the subsequent voting are presented in supplementary appendix 6. No further outcomes from this 'no consensus' group were sufficiently prioritised for addition to the final COS. The final COS is listed in table 2. Participants agreed that future work on complications, definitions and when outcomes should be reported should involve both patients and healthcare professionals.

8.4.4 Protocol deviations

Our original study protocol described a three-round Delphi survey. Based on emerging evidence at that time[21], several COS developers have demonstrated that consensus can be reached with a two-round survey, which was less resource and time-intensive. Consequently, we altered our approach and adopted a two-round Delphi survey in this study.

Figure 8-3. Results of voting on which complications should be reported in future trials.

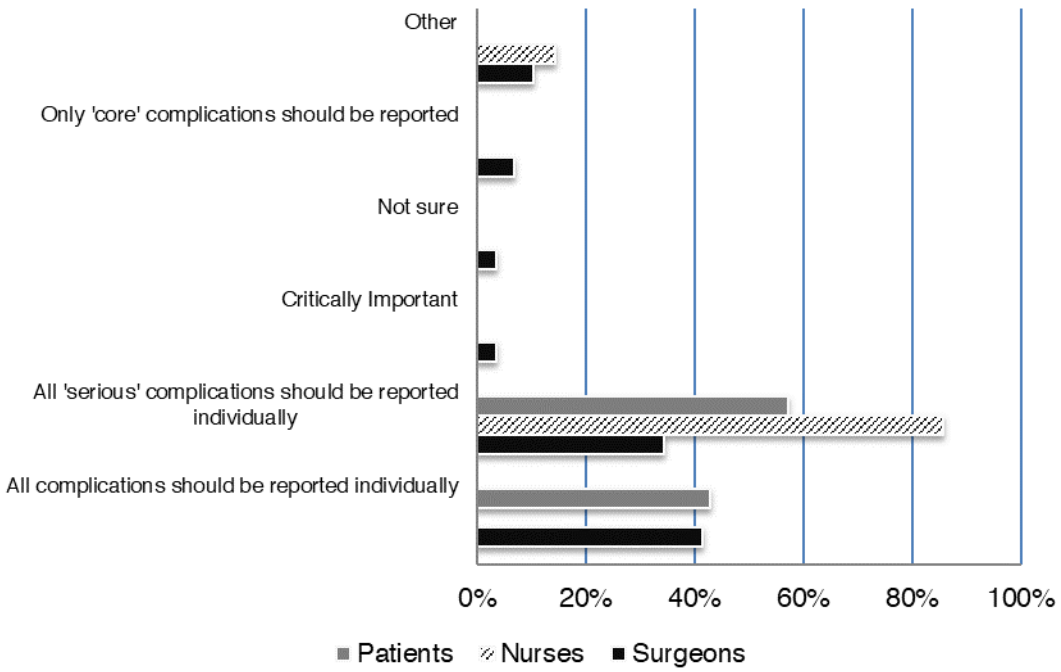


Table 8.2 Core outcome set for surgical trials in gastric cancer.

Surviving and controlling cancer	**Disease-free survival** ***Recurrence of cancer** **Disease-specific survival** **Surgery-related death** **Completeness of tumour removal**
Impacts of surgery	**Overall quality of life** **Nutritional Effects**
Complications	**'Serious' adverse events****

*The outcome 'recurrence of cancer' can be incorporated into the composite outcome 'disease-free survival'. It is shown here as it separately reached consensus as a core outcome.

**No consensus was reached with respect to which outcomes should be reported as a minimum. 'Serious' adverse events should be reported as a minimum whilst further work is undertaken in this area.

8.5 Discussion

The GASTROS study has developed the first COS for use in surgical trials for gastric cancer. This represents a significant step towards addressing the current challenges related to outcome reporting, evidence synthesis and research 'waste' in this field. Outcomes within the set were identified as critically important through an inclusive international consensus process involving patients and healthcare professionals. Our recommendation is that this COS be used for all future surgical trials in gastric cancer.

The primary scope of this COS is for use in clinical effectiveness trials. However, there are many additional applications. Knowledge of which outcomes are important to stakeholders will help healthcare services improve the design of registries and audits. We believe that this COS can be the catalyst which moves such initiatives away from solely collecting short-term data and focus on the long-term outcomes that are key to all stakeholders. Furthermore, understanding which outcomes are essential to patients can help shape pre-operative consultations and the development of information resources.

A COS can only achieve its stated aims if it is used by researchers. From the outset of the study, the SMG set out a clear strategy to ensure 'buy-in' by researchers and professional bodies. This resulted in broad international support and the development of a network which enabled the recruitment of over 1000 participants to the Delphi survey. These participants were well-balanced in terms of regional origins and personal or professional experience of gastric cancer. Furthermore, a strength of the study is that the methodology used is based on consensus guidelines and has been transparently reported in detail at each stage[5]. Researchers can therefore be reassured that the COS has been through a robust development process and is a valid framework on which to base their research regardless of where it takes place.

It should be emphasised that a COS is a minimum set of critically important outcomes. It does not limit trialists in their reporting of other outcomes of interest. Furthermore, we are aware that some grant-awarding bodies can make their own recommendations regarding which outcomes should be reported as a minimum. An example would be the recommendation to report 'overall survival' which was not prioritised through our consensus process[22]. As such, we recommend researchers ensure that additional outcomes selected in surgical trials for gastric cancer adequately reflect opinions of patients and clinicians in their region, as well as taking into consideration other funding requirements.

The study was unable to achieve agreement with respect to which complications should be included in the COS. The consensus meeting could not decide whether 'all complications' or only 'serious complications' should be reported as a minimum. However, the overwhelming majority voted for one or two of these options which will be the focus of future work in this area. Some clinicians held the view that it would be a mandatory requirement that all

adverse events should be recorded in effectiveness trials, and therefore by extension, all complications should be reported as a minimum. However, this standard is not reflected by trials in this field as was demonstrated by our systematic review on outcome reporting[3]. Others held the view that the minimum requirement was in fact 'serious' adverse events only. Patients similarly were split, but for reasons more reflective of their personal priorities. Another consideration in this debate is whether the sole purpose of a COS is to choose outcomes to report in trials or whether it also serves as the basis on which outcomes should be compared. If it is both, then it may be argued that complications which are low in incidence or have truly little impact on the patient should not be routinely reported as a minimum. Other surgical cancer-related COS have differed in their recommendations for the reporting of complications. Some have included only a small number of 'serious' or 'core' complication-related outcomes[23,24], whereas others have recommended the reporting of a broader collection of complications[25]. Based on discussions from the consensus meeting and the lack of agreement amongst other COS developers, our current recommendation is that all 'serious' adverse events should be reported as a minimum until this area is addressed further.

The term 'serious' was purposefully not defined at the consensus meeting so as not to remove focus from the discussions. Others have already attempted to define this; the Gastrectomy Complications Consensus Group (GCCG) is a collaboration of European surgeons who have prioritised a list of 27 clearly-defined complications which should be reported as a minimum in research, audits and registries[26]. They sought consensus through a Delphi process, although their methodology differs to the GASTROS study in that patients and non-European healthcare professionals did not participate. Currently, it is the only substantial work available in this field addressing the reporting of complications and will undoubtedly contribute to, and shape, our future work.

Defining outcomes is an area which deserves further consideration. Our approach was to use plain language descriptions to define outcomes presented in the Delphi survey and consensus meetings. These were developed with the support of our SAG and an independent patient group. This was necessary to ensure patients were engaged throughout the study and made translations easier. We acknowledge that these may not be adequately detailed for use in trials and more work is required with researchers and patients to address this for the outcomes included in the COS. Substantial work has already been undertaken by the StEP-COMPAC (Standardised Endpoints in Perioperative Medicine-Core Outcome Measures in Perioperative and Anaesthetic Care) group to identify available definitions for outcomes from several systematic reviews[27–30]. The group have sought consensus from clinicians to arrive at definitions for numerous outcomes including some included in our COS (e.g. disease-free survival and cancer-specific survival). As with the GCCG complication list, this process did not involve patients which was contrary to the recommendation made by the

GASTROS consensus meeting. Standardising definitions for outcomes included in this COS will form part of stage 3 of the GASTROS study.

Identifying which outcomes to measure is the first step in standardising outcome reporting in this field. Whilst many outcomes in the COS are 'event'-type outcomes (e.g. complications, survival and recurrence), some are 'composite' outcomes which require the use of an instrument to measure (e.g. quality of life and nutritional outcomes). There is currently no standardised approach to measuring these outcomes[31–33] and selecting the best tools to measure these outcomes requires a robust methodological approach similar to the one employed in this study[34,35]. Whilst this will form the basis of future work for our group (stage 3), much of this can be undertaken in collaboration with other closely aligned disciplines where there is significant overlap (e.g. surgery for oesophageal cancer).

There are limitations to our study which require discussion. It could be argued that given the multi-modal nature of treatment for gastric cancer, the COS would be more relevant if it incorporated all therapies including chemotherapy, radiotherapy and endotherapy. However, at the time that GASTROS was conceived, there were 24 ongoing surgical trials planning to recruit 11,000 patients for whom non-surgical related outcomes would not be applicable or relevant. Our preference would be to collaborate with gastroenterological, clinical and medical oncology colleagues to develop endotherapy, chemotherapy and radiotherapy 'modules' which could be appended to our COS, as necessary. These could be developed alongside several disciplines that use similar endotherapy, chemotherapy or radiotherapy approaches.

Every effort was taken to establish collaborators in regions with a high incidence of gastric cancer and translate the Delphi survey into the local language . Despite making early contact with clinicians and societies in Japan and South Korea, we were unable to recruit representatives to the IWG which meant that the Delphi survey could not be translated into Japanese and Korean. The timing of support from Japanese and Korean collaborators meant that their participation was through the English language Delphi survey which likely impacted on our recruitment of patients from these countries. Nonetheless, an exploratory analysis of the Delphi survey results suggested that 'Eastern' patients did not prioritise outcomes differently to their 'Western' counterparts (see chapter 6). However, this assumes that East Asian patient priorities are similar and does not account for cultural differences within this region. As we have discussed above, we recommend that researchers work with patients as partners to determine additional outcomes which are locally important at the trial design phase.

Another consideration relates to the type of stakeholder groups which were recruited to the study. This decision was discussed extensively by the SMG and SAG and agreed prior to the commencement of the study. It was agreed to limit participation to patients, nurses and surgeons as this represented a balance of a broad spectrum of opinion but ensured that the

study's coordination and data analysis was manageable. It should be acknowledged that other groups, such as care-givers, allied health professionals, regulators, policy-makers and grant awarding bodies, will also provide valuable opinion. Inclusion of these groups will be considered in future stages of the GASTROS study and when the COS is reviewed.

The consensus meeting was held in English, limiting participants to English-speakers only. Whilst there was a broad spectrum of international representation from the surgeon group, this was not mirrored by the patient or nurse stakeholders who were primarily UK-based. Furthermore, there was a statistically significant difference in the mean Delphi survey scores of those who attended the consensus meeting compared to those who did not. These factors may have influenced the discussions of the outcomes for which no consensus was reached in the Delphi. That said, the difference in mean scores was in fact very small (mean difference 0.3, largest difference 1.16) and no further outcomes were added following discussions, supporting the validity of the Delphi process which recruited widely in terms of regional origin and other demographic characteristics across all three stakeholder groups.

8.5.1 Conclusion

A core outcome set, based on the priorities of international patients and healthcare professionals, has been developed for surgical trials in gastric cancer. Subsequent utilisation of this COS in all surgical trials of gastric cancer will help to standardise the reporting of critically important outcomes and facilitate evidence synthesis in this field. Further work is required to address the reporting of complications and identify accompanying outcome measurement instruments for the COS.

8.6 References

1. Etemadi A, Safiri S, Sepanlou SG, et al. The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol. 2020;5(1):42-54. doi:10.1016/S2468-1253(19)30328-0

2. Johnston FM, Beckman M. Updates on Management of Gastric Cancer. Curr Oncol Rep. 2019;21(8):1-9. doi:10.1007/s11912-019-0820-4

3. Alkhaffaf B, Blazeby JM, Williamson PR, Bruce IA, Glenny A-M. Reporting of outcomes in gastric cancer surgery trials: a systematic review. BMJ Open. 2018;8(10):e021796. doi:10.1136/BMJOPEN-2018-021796

4. Alkhaffaf B, Blazeby JM, Bruce IA, Morris RL. Patient priorities in relation to surgery for gastric cancer: qualitative interviews with gastric cancer surgery patients to inform the development of a core outcome set. BMJ Open. 2020;10(2):e034782. doi:10.1136/bmjopen-2019-034782

5. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study). Trials. 2017;18(1):370. doi:10.1186/s13063-017-2100-7

6. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(S3):280. doi:10.1186/s13063-017-1978-4

7. Gargon E, Gorst SL, Harman NL, Smith V, Matvienko-Sikar K, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 4th annual update to a systematic review of core outcome sets for research. Gillies K, ed. PLoS One. 2018;13(12):e0209869. doi:10.1371/journal.pone.0209869

8. Gargon E, Gorst SL, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 5th annual update to a systematic review of core outcome sets for research. Naudet F, ed. PLoS One. 2019;14(12):e0225980. doi:10.1371/journal.pone.0225980

9. Davis K, Gorst SL, Harman N, et al. Choosing important health outcomes for comparative effectiveness research: An updated systematic review and involvement of low and middle income countries. Scherer RW, ed. PLoS One. 2018;13(2):e0190695. doi:10.1371/journal.pone.0190695

10. Gorst SL, Gargon E, Clarke M, Smith V, Williamson PR. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and Identification of Gaps. Scherer RW, ed. PLoS One. 2016;11(12):e0168403. doi:10.1371/journal.pone.0168403

11. 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. Garattini S, ed. PLoS One. 2016;11(1):e0146444. doi:10.1371/journal.pone.0146444

12. Gargon E, Gurung B, Medley N, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: A Systematic Review. Scherer RW, ed. PLoS One. 2014;9(6):e99111. doi:10.1371/journal.pone.0099111

13. Blencowe NS, Strong S, McNair AGK, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg. 2012;255(4):658-666. doi:10.1097/SLA.0b013e3182480a6a

14. Fish R, Sanders C, Adams R, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. lancet Gastroenterol Hepatol. 2018;3(12):865-873. doi:10.1016/S2468-1253(18)30264-4

15. McNair AGK, Whistance RN, Forsythe RO, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLoS Med. 2016;13(8). doi:10.1371/journal.pmed.1002071

16. Chan WL, Lam KO, Lee VHF, et al. Gastric Cancer – From Aetiology to Management: Differences Between the East and the West. Clin Oncol. 2019;31(8):570-577. doi:10.1016/j.clon.2019.05.012

17. Yamamoto M, Rashid OM, Wong J. Surgical management of gastric cancer: The East vs. West perspective. J Gastrointest Oncol. 2015;6(1):79-88. doi:10.3978/j.issn.2078-6891.2014.097

18. Fish R, MacLennan S, Alkhaffaf B, Williamson PR. “Vicarious thinking” was a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results. J Clin Epidemiol. 2020;128:118-129. doi:10.1016/j.jclinepi.2020.09.028

19. Kirkham JJ, Gorst S, Altman DG, et al. COS-STAR: a reporting guideline for studies developing core outcome sets (protocol). Trials. 2015;16(1):373. doi:10.1186/s13063-015-0913-9

20. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84-92. doi:10.1016/j.jclinepi.2017.12.020

21. Brookes ST, Macefield RC, Williamson PR, 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(1):409. doi:10.1186/s13063-016-1479-x

22. Cole A, Cubi-Molla P, Pollard J, et al. Making Outcome-Based Payment a Reality in the NHS Making Outcome-Based Payment a Reality in the NHS 2 Reference.; 2019.

23. Avery KNL, Chalmers KA, Brookes ST, et al. Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. Ann Surg. March 2017:1. doi:10.1097/SLA.0000000000002204

24. McNair AGK, Whistance RN, Forsythe RO, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLOS Med. 2016;13(8):e1002071. doi:10.1371/journal.pmed.1002071

25. Potter S, Holcombe C, Ward JA, Blazeby JM. Development of a core outcome set for research and audit studies in reconstructive breast surgery. Br J Surg. 2015;102(11):1360-1371. doi:10.1002/bjs.9883

26. Baiocchi GL, Giacopuzzi S, Marrelli D, et al. International consensus on a complications list after gastrectomy for cancer. Gastric Cancer. 2019;22(1):172-189. doi:10.1007/s10120-018-0839-5

27. Haller G, Bampoe S, Cook T, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: clinical indicators. Br J Anaesth. 2019;123(2):228-237. doi:10.1016/j.bja.2019.04.041

28. Barnes J, Hunter J, Harris S, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: infection and sepsis. Br J Anaesth. 2019;122(4):500-508. doi:10.1016/j.bja.2019.01.009

29. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. Br J Anaesth. 2018;120(5). doi:10.1016/j.bja.2018.02.007

30. Buggy DJ, Freeman J, Johnson MZ, et al. Systematic review and consensus definitions for standardised endpoints in perioperative medicine: postoperative cancer outcomes. Br J Anaesth. 2018. doi:10.1016/j.bja.2018.03.020

31. Son YG, Kwon IG, Ryu SW. Assessment of nutritional status in laparoscopic gastrectomy for gastric cancer. Transl Gastroenterol Hepatol. 2017;2(OCT). doi:10.21037/tgh.2017.09.08

32. Shan B, Shan L, Morris D, Golani S, Saxena A. Systematic review on quality of life outcomes after gastrectomy for gastric carcinoma. J Gastrointest Oncol. 2015;6(5):544-560. doi:10.3978/j.issn.2078-6891.2015.046

33. Ryu SW, Kim IH. Comparison of different nutritional assessments in detecting malnutrition among gastric cancer patients. World J Gastroenterol. 2010;16(26):3310-3317. doi:10.3748/wjg.v16.i26.3310

34. Prinsen CAC, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a “Core Outcome Set” – a practical guideline. Trials. 2016;17(1):449. doi:10.1186/s13063-016-1555-2

35. Terwee CB, Mokkink LB, Knol DL, Ostelo RWJG, Bouter LM, De Vet HCW. Rating the methodological quality in systematic reviews of studies on measurement properties: A scoring system for the COSMIN checklist. Qual Life Res. 2012;21(4):651-657. doi:10.1007/s11136-011-9960-1

8.7 Appendices

8.7.1 Appendix 1. Core Outcome Set-STandards for Reporting: The COS-STAR Statement.

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM	Page
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper reports the development of a COS	258
Abstract	1b	Provide a structured summary	259
INTRODUCTION			
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.	260
	2b	Describe the specific objectives with reference to developing a COS.	260
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.	261
	3b	Describe the intervention(s) covered by the COS.	261
	3c	Describe the setting(s) in which the COS is to be applied.	261
METHODS			
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.	265
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.	262

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM	Page
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.	262
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).	263
Consensus Process	7	Describe how the consensus process was undertaken.	263
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.	263
Consensus Definition	9a	Describe the consensus definition.	263
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.	264
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.	265
RESULTS			
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.	269
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.	267
Outcomes	13a	List all outcomes considered at the start of the consensus process.	Appendix 2
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.	267
COS	14	List the outcomes in the final COS.	270

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM	Page
DISCUSSION			
Limitations	15	Discuss any limitations in the COS development process.	273
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.	274
OTHER INFORMATION			
Funding	17	Describe sources of funding/role of funders.	Disclosures
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.	Disclosures

8.7.2 Appendix 2. Rationalisation of outcomes from to original source by study management group. The ‘source’ column refers to where the outcome was identified: Interviews (qualitative interviews), Trials (systematic review of trials), PROs (domains from Patient-Reported Outcome measurement instruments).

Source	**Original Verbatim Outcome**	**Outcome**	**Outcome Area**	**Outcome Domain**
Interviews	Anaesthetic Complications	Adverse drug reaction	Adverse events	Adverse events/effects
Interviews	Epidural Related Complications	Adverse drug reaction	Adverse events	Adverse events/effects
Interviews	Hallucinations	Adverse drug reaction	Adverse events	Adverse events/effects
Interviews	Medication-related complications	Adverse drug reaction	Adverse events	Adverse events/effects
Interviews	Medication-related complications	Adverse drug reaction	Adverse events	Adverse events/effects
Interviews	Bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Interviews	Perforated bowel	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Interviews	Cardiac Complications	Cardiac complications	Physiological/Clinical	Cardiac Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Ability to have adjuvant chemotherapy	Ability to have adjuvant chemotherapy	Life Impact	Delivery of care
Interviews	Complete Excision of Cancer	Completeness of tumour resection	Life Impact	Delivery of care
Interviews	Excision of Lymph Nodes	Completeness of tumour resection	Life Impact	Delivery of care
Interviews	Need for splenectomy	Completeness of tumour resection	Life Impact	Delivery of care
Interviews	Operative time	Duration of surgery	Life Impact	Delivery of care
Interviews	Wound Size	Wound size	Life Impact	Delivery of care
Interviews	Body Image	Mental Health	Life Impact	Emotional functioning/wellbeing
Interviews	Insomnia	Mental Health	Life Impact	Emotional functioning/wellbeing

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Psychological impact	Mental Health	Life Impact	Emotional functioning/wellbeing
Interviews	Weight Loss	Mental Health	Life Impact	Emotional functioning/wellbeing
Interviews	Anastomotic Leak	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Anastomotic Stricture	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Belching	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Constipation	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Diarrhoea	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Dumping	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Gastrointestinal problems	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Gastrointestinal symptoms	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Nausea + Vomiting	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Reflux	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Adhesional	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Intestinal complications	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Small bowel obstruction	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Interviews	Time to start Eating and drinking	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Fatigue	Fatigue	Physiological/Clinical	General Outcomes
Interviews	Cramps	Pain	Physiological/Clinical	General Outcomes
Interviews	Long Term Pain	Pain	Physiological/Clinical	General Outcomes
Interviews	Pain	Pain	Physiological/Clinical	General Outcomes
Interviews	Post-op Pain	Pain	Physiological/Clinical	General Outcomes
Interviews	Overall QoL	Overall Quality of Life	Life Impact	Global Quality of Life
Interviews	Length of Stay Following Surgery	Duration of hospital stay	Resource Use	Hospital
Interviews	Re-Admission to Hospital	Readmission to hospital	Resource Use	Hospital
Interviews	B12 Deficiency	Nutritional complications	Physiological/Clinical	Metabolism and nutrition outcomes
Interviews	Eating & Drinking	Nutritional complications	Physiological/Clinical	Metabolism and nutrition outcomes
Interviews	Necessity of long-term feeding	Nutritional complications	Physiological/Clinical	Metabolism and nutrition outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Curing Cancer	Disease free survival	Death	Mortality/Survival
Interviews	Survival	Overall survival	Death	Mortality/Survival
Interviews	Post-operative Death	Surgery-related death	Death	Mortality/Survival
Interviews	Intra-operative Death	Surgery-related death	Death	Mortality/Survival
Interviews	Peri-operative death	Surgery-related death	Death	Mortality/Survival
Interviews	Hernia	Need for additional procedure	Resource Use	Need for intervention
Interviews	Need for future interventions	Need for additional procedure	Resource Use	Need for intervention
Interviews	Need for reintervention	Need for additional procedure	Resource Use	Need for intervention
Interviews	Re-Intervention	Need for additional procedure	Resource Use	Need for intervention

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Re-operation	Need for additional procedure	Resource Use	Need for intervention
Interviews	Recurrence of Cancer	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Interviews	Exercising	Social life and relationships	Life Impact	Physical Functioning
Interviews	Peripheral Oedema	Time to ambulation	Life Impact	Physical Functioning
Interviews	Post-op Mobility	Time to ambulation	Life Impact	Physical Functioning
Interviews	Catheter related complications	Urinary complications	Physiological/Clinical	Renal and urinary outcomes
Interviews	Pleural Effusion	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Interviews	Pneumonia	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Interviews	Pneumothorax	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Respiratory complications	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Interviews	Normal Activities Affected	Activities of daily living and work/employment	Life Impact	Role functioning
Interviews	Returning to normal function	Activities of daily living and work/employment	Life Impact	Role functioning
Interviews	Returning to normality	Activities of daily living and work/employment	Life Impact	Role functioning
Interviews	Working	Activities of daily living and work/employment	Life Impact	Role functioning
Interviews	Wound Complications	Other Wound Complication	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Interviews	Interacting with Others	Social life and relationships	Life Impact	Social functioning
Interviews	Reliance on Others	Social life and relationships	Life Impact	Social functioning

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Interviews	Cerebro-vascular complications	Cerebrovascular complications	Physiological/Clinical	Vascular Outcomes
PROs	Problems with concentration and memory (cognitive function)	Cognitive Functioning	Life Impact	Cognitive Functioning
PROs	Spiritual or faith issues	Spiritual or faith issues	Life Impact	Cognitive Functioning
PROs	Problems with weight	Mental Health	Life Impact	Emotional functioning/wellbeing
PROs	Feeling in control of weight and appearance	Mental Health	Life Impact	Emotional functioning/wellbeing
PROs	Feeling satisfied/confident with one's body	Mental Health	Life Impact	Emotional functioning/wellbeing
PROs	Problems with anxiety	Mental health	Life Impact	Emotional functioning/wellbeing
PROs	Problems with depression	Mental health	Life Impact	Emotional functioning/wellbeing

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
PROs	Problems with changes in general mood	Mental health	Life Impact	Emotional functioning/wellbeing
PROs	Money worries due to loss of earnings (finances)	Mental health	Life Impact	Emotional functioning/wellbeing
PROs	Able to eat/drink more easily (dysphagia)	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Able to swallow without pain (odynophagia)	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Able to enjoy healthy/balanced eating pattern	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with acid indigestion/heartburn including at night (reflux)	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with regurgitation and/or vomiting	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Belching, bloating or gas (flatulence)	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
PROs	Problems choking when eating/drinking	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with appetite loss	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with sense of taste	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Sudden dizziness, sweating and/or feeling drained after eating (dumping)	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with feeling sick (nausea)	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with diarrhoea, including frequent bowel movements	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with weak voice/hoarseness	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with constipation	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
PROs	Problems with coughing	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with a dry mouth	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
PROs	Problems with tiredness (fatigue)	Fatigue	Physiological/Clinical	General Outcomes
PROs	Problems with general pain/discomfort	Pain	Physiological/Clinical	General Outcomes
PROs	Overall quality of life	Overall Quality of Life	Life Impact	Global Quality of Life
PROs	Having good general health	Physical health	Life Impact	Perceived health status
PROs	Able to carry out usual activities	Activities of daily living	Life Impact	Physical Functioning
PROs	Able to participate/enjoy physical activities	Activities of daily living	Life Impact	Physical Functioning
PROs	Problems with sleeping	Insomnia	Life Impact	Physical Functioning
PROs	Interested in and able to enjoy sex	Social life and relationships	Life Impact	Physical Functioning
PROs	Feeling out of breath/difficulties breathing (dyspnoea)	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
PROs	Problems with hair loss	Hair Loss	Physiological/Clinical	Skin and subcutaneous tissue outcomes
PROs	Problems eating socially	Ability to eat socially	Life Impact	Social Functioning
PROs	Able to have relationships with friends	Social life and relationships	Life Impact	Social Functioning
PROs	Able to have relationships with family members	Social life and relationships	Life Impact	Social Functioning
Trials	Adverse drug reaction	Adverse drug reaction	Adverse Events	Adverse events/effects
Trials	Complications number of	Any Complications	Adverse Events	Adverse events/effects
Trials	Early surgical complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Hospital morbidity	Any Complications	Adverse Events	Adverse events/effects
Trials	Any complication	Any Complications	Adverse Events	Adverse events/effects
Trials	Complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Morbidity	Any Complications	Adverse Events	Adverse events/effects
Trials	Morbidity rate	Any Complications	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Number of patients with complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Operative morbidity	Any Complications	Adverse Events	Adverse events/effects
Trials	Overall complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Overall morbidity	Any Complications	Adverse Events	Adverse events/effects
Trials	Overall Post-operative complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Peri-operative complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Post-operative complications	Any Complications	Adverse Events	Adverse events/effects
Trials	Post-operative morbidity	Any Complications	Adverse Events	Adverse events/effects
Trials	post-operative surgical parameters	Any Complications	Adverse Events	Adverse events/effects
Trials	Post-operative symptoms	Any Complications	Adverse Events	Adverse events/effects
Trials	Procedure-related morbidity and mortality	Any Complications	Adverse Events	Adverse events/effects
Trials	Total complications	Any Complications	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Total morbidity	Any Complications	Adverse Events	Adverse events/effects
Trials	Colonic perforation	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Gastrointestinal injury	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Iatrogenic spleen injury	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	idiopathic small bowel perforation	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Pancreatic injury	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Pancreatitis traumatic	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Splenic injury	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Thermal injury	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Trocar related injury	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Recurrent laryngeal nerve palsy	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Splenic artery pseudoaneurysm	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Allogenic blood transfusion	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Amount of blood transfused	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Bleeding abdominal	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Blood transfusion	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Blood transfusion volume	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Gastrointestinal bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Haemorrhage	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Hb	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	intra-abdominal bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Intraluminal bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Intraoperative blood transfusion	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	intraoperative major bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	intraperitoneal haemorrhage	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Need for blood transfusion	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Peritoneal haemorrhage	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Post-operative bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Post-operative drain discharge	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Post-operative hemorrhage	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Transfusion	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Transfusions received	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Upper gastro-intestinal haemorrhage	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Amount of bleeding	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Amount of blood loss	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Blood loss	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Estimated blood loss	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Intraoperative blood loss	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Mean blood loss	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Operative blood loss	Organ, vascular and/or nerve injury	Adverse Events	Adverse events/effects
Trials	Surgical complications	Surgical complications	Adverse Events	Adverse events/effects
Trials	Surgical risk	Surgical complications	Adverse Events	Adverse events/effects
Trials	Intraoperative complications	Surgical complications	Adverse Events	Adverse events/effects
Trials	Chyle leakage	Chyle leak	Physiological/Clinical	Blood and lymphatic system outcomes
Trials	Chylous drainage	Chyle leak	Physiological/Clinical	Blood and lymphatic system outcomes
Trials	Chylous leakage	Chyle leak	Physiological/Clinical	Blood and lymphatic system outcomes
Trials	Chylous lymphorrhea	Chyle leak	Physiological/Clinical	Blood and lymphatic system outcomes
Trials	Lymphatic leakage	Chyle leak	Physiological/Clinical	Blood and lymphatic system outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Lymphorrhoea	Chyle leak	Physiological/Clinical	Blood and lymphatic system outcomes
Trials	Atrial fibrillation	Cardiac complications	Physiological/Clinical	Cardiac Outcomes
Trials	Cardiac complications	Cardiac complications	Physiological/Clinical	Cardiac Outcomes
Trials	Cardiac failure	Cardiac complications	Physiological/Clinical	Cardiac Outcomes
Trials	Cardiocirculatory	Cardiac complications	Physiological/Clinical	Cardiac Outcomes
Trials	Myocardial infarction	Cardiac complications	Physiological/Clinical	Cardiac Outcomes
Trials	R0 resection	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Radicality R0	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Radicality R1	Completeness of tumour resection	Life Impact	Delivery of Care

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Residual Tumour	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Residual tumour R0	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Residual tumour R1/2	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Residual tumour R1/2	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Clear margin distance	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Distal resection margin	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Proximal margin positive/negative	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Proximal resection margin	Completeness of tumour resection	Life Impact	Delivery of Care

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Resection line involvement - distal	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Resection line involvement - proximal	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Length of lesser curvature of resected stomach	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Length of lesser curvature of resected stomach	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Length of resection on greater curve	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Length of resection on lesser curve	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Dissected Lymph nodes - mediastinal	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Dissected Lymph nodes - para-aortic	Completeness of tumour resection	Life Impact	Delivery of Care

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Number of lymph nodes dissected or resected or retrieved	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Number of lymph nodes removed N1 group	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Number of lymph nodes removed N2 group	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Number of lymph nodes removed N3 group	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Number of lymph nodes removed N4 group	Completeness of tumour resection	Life Impact	Delivery of Care
Trials	Conversion to open surgery	Conversion to Open Surgery	Life Impact	Delivery of Care
Trials	Open conversion	Conversion to Open Surgery	Life Impact	Delivery of Care
Trials	Open conversion rate	Conversion to Open Surgery	Life Impact	Delivery of Care

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Duration of surgery	Duration of Surgery	Life Impact	Delivery of Care
Trials	Mean operating time	Duration of Surgery	Life Impact	Delivery of Care
Trials	Operative time	Duration of Surgery	Life Impact	Delivery of Care
Trials	Surgical time	Duration of Surgery	Life Impact	Delivery of Care
Trials	Time for operation	Duration of Surgery	Life Impact	Delivery of Care
Trials	length of incision	Wound size	Life Impact	Delivery of Care
Trials	Length of laparotomy incision	Wound size	Life Impact	Delivery of Care
Trials	Length of longest wound	Wound size	Life Impact	Delivery of Care
Trials	Main wound size (cm)	Wound size	Life Impact	Delivery of Care
Trials	Size of wound	Wound size	Life Impact	Delivery of Care
Trials	Total length (of wound)	Wound size	Life Impact	Delivery of Care
Trials	Wound length (cm)	Wound size	Life Impact	Delivery of Care

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Medical cost	Cost	Resource Use	Economic
Trials	Post-operative glucose tolerance	Endocrine complications	Physiological/Clinical	Endocrine outcomes
Trials	endocrine complications	Endocrine complications	Physiological/Clinical	Endocrine outcomes
Trials	endocrine events	Endocrine complications	Physiological/Clinical	Endocrine outcomes
Trials	Metabolic complications	Endocrine complications	Physiological/Clinical	Endocrine outcomes
Trials	Anastomosis failure	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic dehiscence	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic leak	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic leakage from GJ	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic leakage from OJ	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic leakage type 1	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic leakage type 2	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Leakage	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Minor leakage	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Esophagus and remnant stomach infarction	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Gastric remnant necrosis	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Duodenal leak	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Duodenal stump leak	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Duodenal stump leakage	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic bleeding	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Bleeding from anastomosis	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomosis stricture	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Anastomotic stenosis	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Stenosis	Anastomotic complications	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Delayed gastric emptying	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Delayed gastric emptying without obstruction	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Gastric atonia	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Gastroparesis	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Stasis	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Rate of reinsertion of NG tube	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Diarrhoea	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Prolonged diarrhea	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Severe diarrhoea	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Dumping syndrome	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Early dumping syndrome	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Hiccups	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Nausea	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Reflux oesophagitis	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Vomiting	Gastrointestinal functional problems	Physiological/Clinical	Gastrointestinal outcomes
Trials	Malabsorption	Nutritional complications	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Severe feeding problem requiring prolonged hyperalimentation	Nutritional complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Abdominal distention	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Acute enteritis	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Gastrointestinal complications	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Enterocutaneous fistula	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Enterocutaneous fistulas	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Intestinal fistula	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Intestinal ischaemia	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Afferent loop syndrome	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	A-loop syndrome	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Bowel obstruction	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Bowel obstruction/ileus	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Ileus mechanical	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Ileus adhesive	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	intestinal obstruction	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Small-bowel obstruction	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Ileus	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Ileus paralytic	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Ileus prolonged	Other gastrointestinal complications	Physiological/Clinical	Gastrointestinal outcomes
Trials	Days till first flatus	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Days to first flatus	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Days to sips of water	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Eating	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	First eating (post-operative day)	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	First flatus	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	First flatus (post-operative day)	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Food intake	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Progression of oral intake	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time of first flatus/index of peristalsis recovery	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to first flatus	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to first flatus (days)	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to first liquid intake	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Time to first soft diet uptake	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to flatus (postoperative days)	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to food intake	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to liquid diet	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to sips of water	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time to start oral intake (days)	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time until removal of the naso-gastric tube	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes
Trials	Time until start of meals	Return of Gastro-Intestinal function	Physiological/Clinical	Gastrointestinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Multiple organ failure	Multiple organ failure	Physiological/Clinical	General Outcomes
Trials	Body weight (kg)	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Decrease in body weight	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Decrease of body weight 1 month after the operation	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Lean body mass	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Nutritional Status	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Prealbumin (gm/dL)	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Serum Albumin	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Total body weight	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Total protein	Nutritional status	Physiological/Clinical	General Outcomes
Trials	Degree of pain	Pain	Physiological/Clinical	General Outcomes
Trials	Pain	Pain	Physiological/Clinical	General Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Post-operative Pain	Pain	Physiological/Clinical	General Outcomes
Trials	Post-operative pain	Pain	Physiological/Clinical	General Outcomes
Trials	Residual pain at day 7	Pain	Physiological/Clinical	General Outcomes
Trials	Body temperature exceeding 37 ° C (days)	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	Fever	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	CK	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	CRP	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	CRP 3 days after surgery	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	Days of fever	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	Fever	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	IL-6	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	Immediate postoperative inflammatory and immune responses	Surgical stress response	Physiological/Clinical	General Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Immunological response after surgery	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	Immunological response to surgery	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	Surgical stress response	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	WBC (/mm3)	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	WCC	Surgical stress response	Physiological/Clinical	General Outcomes
Trials	QoL	Overall Quality of Life	Life Impact	Global Quality of Life
Trials	Overall satisfaction	Overall Quality of Life	Life Impact	Global Quality of Life
Trials	Cholecystitis	Gallbladder-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Cholecystitis acute	Gallbladder-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Cholecystitis requiring percutaneous drainage	Gallbladder-related complications	Physiological/Clinical	Hepatobiliary Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Presence of gallstones	Gallbladder-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Drug-induced hepatitis	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Hepatic complications	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Hepatic failure	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Liver dysfunction	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Transient LFT abnormality	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Blood urea nitrogen	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	LFT	Hepatic complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Pancreatitis	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Pancreatitis acute	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Pancreatitis edematous	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Pancreatitis severe	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Pancreas-related complications	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Abdominal drainage	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Amylase level in drainage fluid	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Minor discharge of pancreatic juice	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Pancreatic fistula	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Pancreatic leak	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Pancreatic leakage	Pancreas-related complications	Physiological/Clinical	Hepatobiliary Outcomes
Trials	Days of hospitalization	Duration of hospital stay	Resource Use	Hospital
Trials	Duration of hospital stay	Duration of hospital stay	Resource Use	Hospital
Trials	Duration of post-operative hospital stay	Duration of hospital stay	Resource Use	Hospital
Trials	Readmission	Readmission to hospital	Resource Use	Hospital
Trials	Abdominal abscess	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Abdominal liquid accumulation	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Abscess intra-abdominal	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Abscess subphrenic	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Abscesses Intra-abdominal	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Ascites	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Fluid collection	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Fluid collection/abscesses	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Intra-abdominal collections	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	intra-abdominal infection	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Major abdominal infections	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes
Trials	Prolonged retention of intra-abdominal fluid	Abdominal collection	Physiological/Clinical	Infection and infestation outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Infection	Other Infection	Physiological/Clinical	Infection and infestation outcomes
Trials	Herpes zoster	Other Infection	Physiological/Clinical	Infection and infestation outcomes
Trials	Viral infection	Other Infection	Physiological/Clinical	Infection and infestation outcomes
Trials	Mediastinitis	Other Infection	Physiological/Clinical	Infection and infestation outcomes
Trials	Septic complications	Other Infection	Physiological/Clinical	Infection and infestation outcomes
Trials	Systemic infections	Other Infection	Physiological/Clinical	Infection and infestation outcomes
Trials	Disease free survival	Disease free survival	Death	Mortality/Survival
Trials	Disease free survival 4-year	Disease free survival	Death	Mortality/Survival
Trials	Disease free survival 5-year	Disease free survival	Death	Mortality/Survival

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Recurrence-free survival	Disease free survival	Death	Mortality/Survival
Trials	Relapse-free survival	Disease free survival	Death	Mortality/Survival
Trials	Death from gastric cancer as a cause	Disease specific survival	Death	Mortality/Survival
Trials	Disease specific survival	Disease specific survival	Death	Mortality/Survival
Trials	Disease specific survival 5-year	Disease specific survival	Death	Mortality/Survival
Trials	Gastric cancer related deaths	Disease specific survival	Death	Mortality/Survival
Trials	Overall survival	Overall survival	Death	Mortality/Survival
Trials	Overall survival 10-year	Overall survival	Death	Mortality/Survival
Trials	Overall survival 3-year	Overall survival	Death	Mortality/Survival
Trials	Overall survival 5-year	Overall survival	Death	Mortality/Survival
Trials	Overall survival 6-year	Overall survival	Death	Mortality/Survival
Trials	Overall survival 7-year	Overall survival	Death	Mortality/Survival

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Survival 11-year	Overall survival	Death	Mortality/Survival
Trials	Survival 5-year	Overall survival	Death	Mortality/Survival
Trials	Survival Period	Overall survival	Death	Mortality/Survival
Trials	Death	Surgery-related death	Death	Mortality/Survival
Trials	Death from a post-operative complication	Surgery-related death	Death	Mortality/Survival
Trials	Death from all causes	Surgery-related death	Death	Mortality/Survival
Trials	Hospital death	Surgery-related death	Death	Mortality/Survival
Trials	Hospital mortality	Surgery-related death	Death	Mortality/Survival
Trials	In-hospital mortality	Surgery-related death	Death	Mortality/Survival
Trials	Mortality	Surgery-related death	Death	Mortality/Survival
Trials	Mortality from all causes	Surgery-related death	Death	Mortality/Survival
Trials	Mortality not related to surgery	Surgery-related death	Death	Mortality/Survival

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Operative death	Surgery-related death	Death	Mortality/Survival
Trials	Operative mortality	Surgery-related death	Death	Mortality/Survival
Trials	Post-operative death	Surgery-related death	Death	Mortality/Survival
Trials	Post-operative mortality	Surgery-related death	Death	Mortality/Survival
Trials	Post-operative survival	Surgery-related death	Death	Mortality/Survival
Trials	Treatment related deaths	Surgery-related death	Death	Mortality/Survival
Trials	Re-laparotomy	Need for additional procedure	Resource Use	Need for intervention
Trials	Re-operation	Need for additional procedure	Resource Use	Need for intervention
Trials	Re-operation details	Need for additional procedure	Resource Use	Need for intervention
Trials	Return to theatre	Need for additional procedure	Resource Use	Need for intervention

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	4-day post-operative use of analgesics	Need for analgesia	Resource Use	Need for intervention
Trials	Dose of analgesic (mg)	Need for analgesia	Resource Use	Need for intervention
Trials	Duration of pain control	Need for analgesia	Resource Use	Need for intervention
Trials	Frequency of analgesics injection	Need for analgesia	Resource Use	Need for intervention
Trials	Frequency of injection given according to analgesic requests	Need for analgesia	Resource Use	Need for intervention
Trials	Pain control	Need for analgesia	Resource Use	Need for intervention
Trials	Post-operative analgesia	Need for analgesia	Resource Use	Need for intervention
Trials	Time to removal of epidural anesthesia (days)	Need for analgesia	Resource Use	Need for intervention
Trials	Times analgesic given	Need for analgesia	Resource Use	Need for intervention
Trials	Times of pain rescue	Need for analgesia	Resource Use	Need for intervention
Trials	Total amount of analgesics infused (mL)	Need for analgesia	Resource Use	Need for intervention

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Cumulative risk of recurrence	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	Cumulative risk of relapse	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	Disease recurrence rate	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	port site metastasis	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	Recurrence	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	Recurrence patterns	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	Recurrent disease	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms
Trials	Tumor recurrence	Recurrence of cancer	Physiological/Clinical	Outcomes related to neoplasms

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	First walking (post-operative day)	Time to ambulation	Life Impact	Physical functioning
Trials	Number of days to get out of bed	Time to ambulation	Life Impact	Physical functioning
Trials	Recovery of Physical Activity	Time to ambulation	Life Impact	Physical functioning
Trials	Time to ambulation	Time to ambulation	Life Impact	Physical functioning
Trials	Walking	Time to ambulation	Life Impact	Physical functioning
Trials	Post-operative psychosis	Post-operative psychosis	Physiological/Clinical	Psychiatric Outcomes
Trials	Renal complications	Renal complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Renal failure	Renal complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Acute urinary retention	Urinary complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Catheter-induced sepsis	Urinary complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Urinary complications	Urinary complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Urinary retention	Urinary complications	Physiological/Clinical	Renal and urinary outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Urinary tract complications	Urinary complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Urinary tract infection	Urinary complications	Physiological/Clinical	Renal and urinary outcomes
Trials	Hypercapnia	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Atelectasis	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Atelectasis or pleural effusion	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Bronchopneumonia	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Bronchoscopic toilet	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Cardiopulmonary disease	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	empyema thoracis	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Lung Infection	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Major cardiorespiratory incidents	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Minor patchy pulmonary collapse	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Minor pulmonary atelectasis	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pleural	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pleural effusion	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pleural fluid	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Pneumonia	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Post-operative respiratory care	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Post-operative respiratory function	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pulmonary	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pulmonary complications	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pulmonary edema	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pulmonary infection	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pyothorax	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Respirator use after surgery	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Respiratory complications	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Respiratory failure	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Thoracic effusion requiring thoracic drainage	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Tracheotomy	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Tube tracheotomy	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	ARDS	Pulmonary complications	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	FEV1(L)	Respiratory function	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	FEVC(L)	Respiratory function	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Pulmonary function	Respiratory function	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	SaO2	Respiratory function	Physiological/Clinical	Respiratory, thoracic and mediastinal outcomes
Trials	Wound complications	Other Wound Complication	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound haematoma	Other Wound Complication	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound problem	Other Wound Complication	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound seroma	Other Wound Complication	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Incision fat liquefaction	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Incision infection	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound abscess	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound dehiscence	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound evisceration	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound infection	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Wound infection/dehiscence	Wound Infection	Physiological/Clinical	Skin and subcutaneous tissue outcomes
Trials	Cerebrovascular	Cerebrovascular complications	Physiological/Clinical	Vascular Outcomes
Trials	Transient ischemic attack	Cerebrovascular complications	Physiological/Clinical	Vascular Outcomes

Source	Original Verbatim Outcome	Outcome	Outcome Area	Outcome Domain
Trials	Arteriosclerosis obliterans of the leg	Thromboembolic complications	Physiological/Clinical	Vascular Outcomes
Trials	Deep vein thrombosis	Thromboembolic complications	Physiological/Clinical	Vascular Outcomes
Trials	Pulmonary embolism	Thromboembolic complications	Physiological/Clinical	Vascular Outcomes
Trials	Thromboembolic complications	Thromboembolic complications	Physiological/Clinical	Vascular Outcomes
Trials	Uncomplicated calf vein thrombosis	Thromboembolic complications	Physiological/Clinical	Vascular Outcomes

8.7.3 Appendix 3. Final outcomes presented to participants in round 1 of the Delphi survey

Outcome	**Plain language description**	**Domain Area**
1. Disease-free survival	How long someone is alive without cancer returning.	Outcomes Related to Death
2. Dying from stomach cancer	Dying from stomach cancer. This does not include dying from treatment for stomach cancer.	Outcomes Related to Death
3. Dying from any cause	Dying from any cause. This includes dying from treatment for stomach cancer.	Outcomes Related to Death
4. Surgery-related death	Dying as a direct consequence of surgery	Outcomes Related to Death
5. Cardiac complications	Complications related to the heart, such as a heart attack or abnormal heart rhythms.	Physiological & Clinical Outcomes
6. Endocrine complications	Complications related to the body's hormones, such as developing diabetes.	Physiological & Clinical Outcomes
7. Anastomotic complications	Complications related to surgical joins made as a result of removing	Physiological & Clinical Outcomes

	stomach cancer.	
8. Gastro-intestinal functional problems	Symptoms related to how the digestive system works, including those which may become problematic months after discharge from hospital.	Physiological & Clinical Outcomes
9. Bowel Complications	Problems with the bowel, such as those which occur while still in hospital (not including anastomotic complications).	Physiological & Clinical Outcomes
10. Time to recommencing oral intake	The time taken for a patient's bowel function to return after surgery, such that they can start eating and drinking again.	Physiological & Clinical Outcomes
11. Fatigue	Feeling of tiredness.	Physiological & Clinical Outcomes
12. Multiple organ failure	A severe complication which leads to several organs (such as the heart or lungs) not functioning properly.	Physiological & Clinical Outcomes
13. Pain		Physiological & Clinical Outcomes
14. Surgical Stress Response	The body's response to the stress of surgery.	Physiological & Clinical Outcomes

15. Gallbladder complications	Complications related to the gallbladder.	Physiological & Clinical Outcomes
16. Hepatic Complications	Complications related to the liver.	Physiological & Clinical Outcomes
17. Pancreatic Complications	Complications related to the pancreas.	Physiological & Clinical Outcomes
18. Abdominal Collection	Fluid or infections in the abdomen.	Physiological & Clinical Outcomes
19. Other infections	General infections which are not related to the abdomen, lungs or wounds.	Physiological & Clinical Outcomes
20. Nutritional Effects	The extent to which the body can consume and use the nutrients needed to function properly.	Physiological & Clinical Outcomes
21. Recurrence of Cancer	The chances of the cancer coming back.	Physiological & Clinical Outcomes
22. Renal complications	Complications related to the kidneys, such as kidney failure.	Physiological & Clinical Outcomes
23. Urinary complications	Complications related to the bladder and urinary tract, such as a urinary infection.	Physiological & Clinical Outcomes

24. Post-operative psychosis	A temporary altered mental state after surgery which includes not being able to tell what is or isn't real.	Physiological & Clinical Outcomes
25. Respiratory complications	Complications such as a chest infection, a collapsed lung or fluid on the lungs.	Physiological & Clinical Outcomes
26. Wound complications	Problems with the surgical incisions, including infection and problems with healing.	Physiological & Clinical Outcomes
27. Cerebro-vascular complications	Complications such as strokes and mini-strokes.	Physiological & Clinical Outcomes
28. Thrombo-embolic complications	Complications such as blood-clots in the legs and lungs.	Physiological & Clinical Outcomes
29. Bleeding	Blood loss as a result of surgery	Physiological & Clinical Outcomes
30. Ability to undertake physical activities	Ability to undertake day-to-day activities including exercise	Life Impact
31. Insomnia	Problems with sleeping.	Life Impact
32. Impact on sexual function	The effect of surgery on a patient's sexual activity.	Life Impact

33. Ability to eat socially	Ability to eat with friends and family.	Life Impact
34. Ability to interact socially	The ability to have relationships with family and friends.	Life Impact
35. Impact of surgery on social and work roles	The effect of surgery on being able to work and caring for others.	Life Impact
36. Impact on mental health	The effect of surgery on a patient's psychological well-being.	Life Impact
37. Impact on Physical Appearance	The effect of surgery on a patient's physical appearance	Life Impact
38. Impact on cognitive functioning	The effect of surgery on concentration and memory.	Life Impact
39. Impact on spirituality or faith	The effect of surgery on a patient's spirituality or faith.	Life Impact
40. Overall quality of life	An overall measure of how a person's general wellbeing has been affected by surgery.	Life Impact
41. Impact on perception of physical health	How healthy a patient believes they are following surgery.	Life Impact
42. Ability to complete treatment	Being well enough to complete all aspects of treatment, such as	Life Impact

pathway.	chemotherapy and/or radiotherapy following surgery.	
43. Completeness of tumour removal	Ensuring that the tumour has been surgically removed.	Life Impact
44. Conversion to open surgery	The surgical team having to unexpectedly change the approach from a minimally invasive (laparoscopic or key-hole) operation to a traditional open approach, usually involving a larger incision.	Life Impact
45. Duration of surgery	The length of time taken to perform the surgery.	Life Impact
46. Wound size	The size of the wound or wounds needed to perform the surgery.	Life Impact
47. Cost	The overall cost of surgery.	Resource Use
48. Duration of hospital stay	How long a patient stays in hospital.	Resource Use
49. Readmission to hospital	Whether a patient needs to return to hospital after being discharged following surgery.	Resource Use
50. Destination on Discharge	The location where a patient is discharged to from hospital.	Resource Use

51. Need for an additional intervention.	Unexpected additional procedures or surgeries which may be required.	Resource Use
52. Need for pain relief	The need for a patient to take or be given pain relief after surgery.	Resource Use
53. Duration of stay in an intensive care ward*	How long a patient requires in a critical care or high dependency	Resource Use
54. Adverse drug reaction	Complications related to medications.	Adverse Events
55. All-cause complications	Any complication which may arise after surgery.	Adverse Events
56. Intra-operative complications	Complications which occur during surgery such as accidental injury to an organ.	Adverse Events
57. Anaesthetic complications	Complications specifically related to anaesthesia.	Adverse Events

- This additional outcome was identified in round 1 and presented to participants in round 2.

8.7.4 Appendix 4a. Results of voting after round 1 of the Delphi survey

	Patients			Surgeons			Nurses		
Outcome	**% not important**	**% important**	**% critically important**	**% not important**	**% important**	**% critically important**	**% not important**	**% important**	**% critically important**
1. Disease-free survival	1.9	13.5	84.6	0.5	5.4	94.1	4.3	18.7	77.0
2. Dying from stomach cancer	2.8	11.8	85.4	0.0	6.8	93.2	2.2	15.9	81.9
3. Dying from any cause	8.1	27.8	64.1	5.0	30.1	64.8	5.6	34.2	60.2
4. Surgery-related death	4.8	13.2	82.0	1.1	5.9	93.0	3.5	20.3	76.2
5. Cardiac complications	8.3	29.4	62.3	5.5	45.5	49.0	4.7	34.9	60.4
6. Endocrine complications	10.9	37.7	51.5	14.0	61.9	24.1	6.0	45.7	48.3
7. Anastomotic complications	5.8	19.8	74.5	0.5	4.8	94.7	1.3	16.6	82.1
8. Gastro-intestinal functional problems	3.0	22.4	74.5	2.1	24.7	73.3	0.0	26.8	73.2
9. Bowel Complications	3.8	22.8	73.4	2.1	32.3	65.6	1.7	30.6	67.7

10. Time to recommencing oral intake	7.3	35.8	56.9	5.5	37.3	57.3	4.2	30.9	64.8
11. Fatigue	13.4	35.6	51.0	11.6	58.2	30.1	12.3	49.8	37.9
12. Multiple organ failure	6.9	13.0	80.1	3.4	21.9	74.7	3.9	21.0	75.1
13. Pain	13.0	30.7	56.3	3.9	41.8	54.3	3.0	27.7	69.4
14. Surgical Stress Response	12.1	39.3	48.6	7.8	47.7	44.5	4.3	39.1	56.7
15. Gallbladder complications	9.3	35.4	55.3	14.4	47.9	37.7	6.9	47.2	45.9
16. Hepatic Complications	8.2	28.8	63.0	10.3	49.1	40.6	4.3	43.3	52.4
17. Pancreatic Complications	8.2	24.2	67.6	5.7	35.7	58.6	3.5	40.3	56.3
18. Abdominal Collection	8.0	23.5	68.5	2.5	28.3	69.2	1.3	29.2	69.5
19. Other infections	9.4	30.7	59.8	4.8	41.8	53.4	3.4	31.4	65.3
20. Nutritional Effects	4.2	26.5	69.3	1.8	27.8	70.4	2.6	24.7	72.8
21. Recurrence of Cancer	5.0	4.6	90.4	0.0	4.1	95.9	0.9	15.4	83.8
22. Renal complications	7.3	25.6	67.1	7.5	54.6	37.9	3.9	42.2	53.9

23. Urinary complications	8.8	31.3	59.8	14.1	60.6	25.3	6.0	51.7	42.2
24. Post-operative psychosis	15.0	39.7	45.3	16.6	55.6	27.8	6.8	47.7	45.5
25. Respiratory complications	8.3	23.8	67.9	2.3	38.3	59.5	2.1	28.9	68.9
26. Wound complications	16.0	30.1	53.9	3.0	36.0	61.0	3.8	31.1	65.1
27. Cerebro-vascular complications	8.6	20.2	71.2	7.3	49.2	43.5	5.1	37.2	57.7
28. Thrombo-embolic complications	8.9	16.9	74.2	3.2	36.3	60.5	3.0	30.2	66.8
29. Bleeding	8.9	24.2	66.9	1.6	15.8	82.6	0.4	18.7	80.9
30. Ability to undertake physical activities	3.8	37.6	58.6	2.3	34.0	63.7	2.2	33.9	63.9
31. Insomnia	19.7	44.0	36.3	15.5	60.9	23.6	7.0	47.6	45.4
32. Impact on sexual function	21.8	41.5	36.7	16.7	57.4	25.8	14.9	56.1	28.9
33. Ability to eat socially	11.8	40.3	47.9	10.2	41.6	48.1	11.0	43.6	45.4
34. Ability to interact socially	13.3	37.3	49.4	10.2	45.2	44.5	8.8	44.5	46.7
35. Impact of surgery on social and work roles	7.3	33.7	59.0	6.8	40.7	52.6	5.3	38.6	56.1

36. Impact on mental health	8.5	26.9	64.6	7.4	47.9	44.7	4.0	33.9	62.1
37. Impact on Physical Appearance	24.7	42.2	33.1	15.8	56.7	27.4	12.3	45.8	41.9
38. Impact on cognitive functioning	10.0	29.3	60.6	11.1	49.4	39.4	8.3	44.3	47.4
39. Impact on spirituality or faith	36.9	33.3	29.8	29.8	52.1	18.1	20.5	53.3	26.2
40. Overall quality of life	4.9	23.2	71.9	1.2	18.1	80.7	2.6	26.2	71.2
41. Impact on perception of physical health	4.2	41.6	54.2	7.7	47.4	44.9	4.4	38.2	57.5
42. Ability to complete treatment pathway.	3.8	16.9	79.2	4.4	24.0	71.6	2.6	31.1	66.2
43. Completeness of tumour removal	3.8	4.2	92.0	0.2	5.1	94.7	0.9	14.5	84.6
44. Conversion to open surgery	23.0	24.3	52.7	11.0	29.2	59.8	6.2	32.2	61.7
45. Duration of surgery	28.2	27.5	44.3	9.5	40.9	49.5	7.5	38.3	54.2
46. Wound size	35.4	31.5	33.1	21.3	50.0	28.7	10.6	48.0	41.4
47. Cost	22.0	40.4	37.6	4.7	43.8	51.5	8.3	41.7	50.0
48. Duration of hospital stay	18.1	47.3	34.6	2.6	37.0	60.5	2.6	34.5	62.9

49. Readmission to hospital	16.3	36.4	47.3	1.4	20.3	78.3	3.5	25.8	70.7
50. Destination on Discharge	25.8	41.0	33.2	13.6	45.9	40.5	16.6	47.6	35.8
51. Need for an additional intervention.	11.8	32.5	55.7	4.0	24.8	71.2	5.2	40.9	53.9
52. Need for pain relief	15.4	32.8	51.7	4.0	40.9	55.1	4.4	28.8	66.8
53. Duration of stay in an intensive care ward	Added after round 1								
54. Adverse drug reaction	8.9	27.1	64.0	8.2	51.0	40.8	3.9	34.9	61.1
55. All-cause complications	5.1	20.0	74.9	1.4	23.8	74.8	1.3	25.0	73.7
56. Intra-operative complications	7.6	17.1	75.3	0.5	10.2	89.3	0.9	14.4	84.7
57. Anaesthetic complications	11.0	18.5	70.5	2.6	30.3	67.1	2.2	21.1	76.7

8.7.5 Appendix 4b. Results of voting after round 2 of the Delphi survey

	Patients			Surgeons			Nurses			
Outcome	**% not important**	**% important**	**% critically important**	**% not important**	**% important**	**% critically important**	**% not important**	**% important**	**% critically important**	**Delphi consensus**
1. Disease-free survival	3.4	11.2	85.4	0.0	2.3	97.7	0.7	14.1	85.2	IN
2. Dying from stomach cancer	2.3	11.4	86.4	0.0	3.5	96.5	1.5	18.5	80.0	IN
3. Dying from any cause	5.8	27.5	66.7	2.6	31.9	65.5	5.2	31.3	63.4	NO CONSENSUS
4. Surgery-related death	2.9	13.1	84.0	0.9	2.3	96.8	3.7	18.7	77.6	IN
5. Cardiac complications	5.7	34.7	59.7	3.5	53.1	43.4	4.4	36.3	59.3	NO CONSENSUS
6. Endocrine complications	8.0	47.1	44.8	9.9	74.0	16.1	7.4	51.1	41.5	OUT
7. Anastomotic complications	2.8	20.5	76.7	0.3	4.4	95.3	0.0	15.6	84.4	IN
8. Gastro-intestinal functional problems	3.3	23.9	72.8	1.2	23.9	74.9	0.0	30.4	69.6	NO CONSENSUS
9. Bowel Complications	3.3	24.9	71.8	1.5	37.6	60.9	2.2	37.8	60.0	NO

										CONSENSUS
10. Time to recommencing oral intake	7.7	43.7	48.6	4.4	39.4	56.3	6.7	33.3	60.0	NO CONSENSUS
11. Fatigue	13.1	46.4	40.4	9.1	62.9	28.1	8.1	60.7	31.1	OUT
12. Multiple organ failure	3.4	10.2	86.4	1.5	17.3	81.3	1.5	18.7	79.9	IN
13. Pain	12.7	33.1	54.1	1.7	42.6	55.7	3.7	37.0	59.3	NO CONSENSUS
14. Surgical Stress Response	9.7	49.1	41.1	7.0	50.3	42.7	6.0	52.6	41.4	OUT
15. Gallbladder complications	8.2	38.6	53.2	16.7	52.9	30.4	6.8	53.8	39.4	NO CONSENSUS
16. Hepatic Complications	4.6	32.9	62.4	9.3	56.6	34.1	3.0	49.6	47.4	NO CONSENSUS
17. Pancreatic Complications	5.2	24.4	70.3	5.5	36.4	58.0	2.2	47.0	50.7	NO CONSENSUS
18. Abdominal Collection	2.9	25.6	71.5	2.6	24.0	73.4	2.2	31.9	65.9	NO CONSENSUS
19. Other infections	6.3	35.6	58.0	2.6	46.9	50.4	3.0	35.8	61.2	NO CONSENSUS

20. Nutritional Effects	2.7	23.5	73.8	0.9	26.3	72.8	2.2	23.0	74.8	IN
21. Recurrence of Cancer	2.8	5.0	92.2	0.3	2.1	97.7	0.8	11.3	88.0	IN
22. Renal complications	5.3	24.7	70.0	5.3	61.4	33.3	3.8	45.9	50.4	NO CONSENSUS
23. Urinary complications	5.8	36.0	58.1	13.2	69.9	17.0	7.4	64.4	28.1	NO CONSENSUS
24. Post-operative psychosis	12.2	48.8	39.0	14.6	63.6	21.9	5.2	60.0	34.8	OUT
25. Respiratory complications	5.1	25.4	69.5	1.2	32.4	66.5	2.2	29.6	68.1	NO CONSENSUS
26. Wound complications	11.7	35.8	52.5	2.0	38.2	59.8	2.2	30.4	67.4	NO CONSENSUS
27. Cerebro-vascular complications	4.7	17.6	77.6	5.5	51.9	42.6	3.7	42.2	54.1	NO CONSENSUS
28. Thrombo-embolic complications	5.2	18.0	76.7	2.6	33.2	64.1	3.7	31.1	65.2	NO CONSENSUS
29. Bleeding	5.2	22.5	72.3	1.2	11.4	87.5	3.0	16.3	80.7	IN
30. Ability to undertake physical activities	2.2	37.4	60.4	1.5	32.1	66.5	3.0	40.7	56.3	NO CONSENSUS

31. Insomnia	20.3	47.3	32.4	14.0	68.8	17.2	8.1	57.0	34.8	OUT
32. Impact on sexual function	23.0	46.0	31.0	14.6	67.0	18.4	10.4	66.7	23.0	OUT
33. Ability to eat socially	11.5	46.2	42.3	6.1	52.8	41.1	9.6	50.4	40.0	OUT
34. Ability to interact socially	13.2	40.7	46.2	8.2	50.1	41.7	9.6	51.9	38.5	OUT
35. Impact of surgery on social and work roles	8.2	40.7	51.1	4.7	43.3	52.0	5.9	45.9	48.1	NO CONSENSUS
36. Impact on mental health	5.5	35.7	58.8	5.9	51.3	42.8	3.7	41.8	54.5	NO CONSENSUS
37. Impact on Physical Appearance	23.6	53.8	22.5	13.5	70.5	16.1	12.6	58.5	28.9	OUT
38. Impact on cognitive functioning	9.0	33.1	57.9	7.1	58.5	34.4	6.7	55.6	37.8	NO CONSENSUS
39. Impact on spirituality or faith	39.5	41.3	19.2	31.6	58.1	10.3	20.7	62.2	17.0	OUT
40. Overall quality of life	3.9	22.1	74.0	0.6	12.9	86.5	3.0	26.7	70.4	IN
41. Impact on perception of physical health	5.0	42.8	52.2	4.4	52.9	42.7	6.0	41.8	52.2	NO CONSENSUS
42. Ability to complete treatment pathway.	3.9	16.3	79.8	0.6	20.8	78.6	3.0	31.1	65.9	NO CONSENSUS

43. Completeness of tumour removal	2.2	5.0	92.8	0.0	2.6	97.4	0.0	12.7	87.3	IN
44. Conversion to open surgery	20.4	28.4	51.2	10.9	30.6	58.5	6.1	30.3	63.6	NO CONSENSUS
45. Duration of surgery	29.2	30.9	39.9	9.1	47.1	43.9	6.7	38.1	55.2	NO CONSENSUS
46. Wound size	37.0	38.7	24.3	22.5	58.2	19.3	10.4	55.2	34.3	OUT
47. Cost	20.9	52.3	26.7	5.3	49.6	45.2	11.9	45.9	42.2	OUT
48. Duration of hospital stay	20.0	51.1	28.9	2.6	40.6	56.7	3.0	36.8	60.2	NO CONSENSUS
49. Readmission to hospital	15.1	35.2	49.7	0.9	20.2	78.9	0.8	29.3	69.9	NO CONSENSUS
50. Destination on Discharge	25.0	46.7	28.3	9.9	55.8	34.2	18.0	51.1	30.8	OUT
51. Need for an additional intervention.	10.2	33.9	55.9	1.5	23.1	75.4	5.2	38.1	56.7	NO CONSENSUS
52. Need for pain relief	14.5	35.2	50.3	2.9	42.7	54.4	3.8	27.8	68.4	NO CONSENSUS
53. Duration of stay in an intensive care ward	2.9	32.9	64.1	1.2	43.2	55.7	2.3	35.2	62.5	NO CONSENSUS

54. Adverse drug reaction	6.7	26.3	67.0	8.2	55.3	36.5	6.2	36.2	57.7	NO CONSENSUS
55. All-cause complications	3.9	20.2	75.8	1.2	17.6	81.2	1.5	20.6	77.9	IN
56. Intra-operative complications	6.3	13.1	80.6	0.3	8.2	91.5	0.0	14.6	85.4	IN
57. Anaesthetic complications	7.4	17.7	74.9	1.5	28.0	70.5	2.4	19.7	78.0	IN

8.7.6 Appendix 5. Suggested 'additional' outcomes from round 1 Delphi survey participants to consider for presentation in round 2. *These suggestions were grouped into one outcome -'duration of stay in an intensive care ward'. **SMG= study management group.

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
*Critical care utilisation	New outcome	N/A	Include	Include	**Include**
*Duration of ICU Admission	New outcome	N/A	Include	Include	**Include**
*Intensive Care duration	New outcome	N/A	Include	Include	**Include**
Adverse effect on patients spouse; how they cope	Ambiguous term	N/A	Exclude	Exclude	Exclude
Family support	Ambiguous term	N/A	Exclude	Exclude	Exclude
Positive?	Ambiguous term	N/A	Exclude	Exclude	Exclude
Reviews	Ambiguous term	N/A	Exclude	Exclude	Exclude
Access route for surgery (ex open; laparoscopic; robotic)	Not an outcome	N/A	Exclude	Exclude	Exclude
Adherence to trial protocol	Not an outcome	N/A	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Being fully informed as regard to the disease	Not an outcome	N/A	Exclude	Exclude	Exclude
Blocking of plexus via endoscopic ultrasound	Not an outcome	N/A	Exclude	Exclude	Exclude
Compliance of the surgery	Not an outcome	N/A	Exclude	Exclude	Exclude
cTNM	Not an outcome	N/A	Exclude	Exclude	Exclude
Finding of CTM positive to pre-neoadivative exploratory laparoscopy	Not an outcome	N/A	Exclude	Exclude	Exclude
Gastric resection (distal gastrectomy, total gastrectomy, proximal gastrectomy)	Not an outcome	N/A	Exclude	Exclude	Exclude
General health/performance status before treatment	Not an outcome	N/A	Exclude	Exclude	Exclude
Geographical location of study	Not an outcome	N/A	Exclude	Exclude	Exclude
Importance of endoscopic follow-up	Not an outcome	N/A	Exclude	Exclude	Exclude
Laparoscopic-endoscopic procedures (LECS)	Not an outcome	N/A	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Learning curve for procedure / surgeon experience	Not an outcome	N/A	Exclude	Exclude	Exclude
Number of patients receiving Neo-adjuvant therapy	Not an outcome	N/A	Exclude	Exclude	Exclude
Number of patients undergoing bi-directional chemotherapy during surgery	Not an outcome	N/A	Exclude	Exclude	Exclude
Number of patients undergoing HIPEC hyperthermic intraperitoneal chemotherapy	Not an outcome	N/A	Exclude	Exclude	Exclude
Operator qualification experience	Not an outcome	N/A	Exclude	Exclude	Exclude
Organ-preserving operations in gastric cancer surgery	Not an outcome	N/A	Exclude	Exclude	Exclude
Percentage of Stomach Removed	Not an outcome	N/A	Exclude	Exclude	Exclude
Possibility to participate in special study or experimental treatment (eg immunotherapy)	Not an outcome	N/A	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Post operative advice & support	Not an outcome	N/A	Exclude	Exclude	Exclude
Post treatment monitoring (scans; blood tests; endoscopy; etc).	Not an outcome	N/A	Exclude	Exclude	Exclude
Pre-surgical considerations such as dental treatment not possible when on Apixaban	Not an outcome	N/A	Exclude	Exclude	Exclude
Reconstruction method (Bi I, Bi II, ROUX-Y)	Not an outcome	N/A	Exclude	Exclude	Exclude
Simultaneous treatment of liver metastases	Not an outcome	N/A	Exclude	Exclude	Exclude
Surgical approach	Not an outcome	N/A	Exclude	Exclude	Exclude
T is important that a hospital takes care of the patient from the beginning to the end and that all the tests are done in the hospital and do not leave the patient at the mercy of the cup !!!!!!	Not an outcome	N/A	Exclude	Exclude	Exclude
The most important thing is the patient's trust to the doctor and the team	Not an outcome	N/A	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Time from first symptom to time of medical consultation	Not an outcome	N/A	Exclude	Exclude	Exclude
Travel time to treatment center	Not an outcome	N/A	Exclude	Exclude	Exclude
Tumour histology	Not an outcome	N/A	Exclude	Exclude	Exclude
Tumour site	Not an outcome	N/A	Exclude	Exclude	Exclude
Use of drainage	Not an outcome	N/A	Exclude	Exclude	Exclude
Complications of adjuvant treatment	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude
Complications of neoadjuvant treatment	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude
Comprehensive treatment	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude
Hospitalization satisfaction, patient hospitalization experience	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Neoadjuvant versus adjuvant chemotherapy (perioperative complications; DFS; OS)	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude
Neoadjuvant/adjuvant modality treatment	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude
Patient satisfaction	Not an outcome related to surgery	N/A	Exclude	Exclude	Exclude
(Duodeno)gastro-esophageal reflux	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Ability to eat (rather than just socially)	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Ability to perform physical activity/sports	Outcome already presented in round 1	Ability to undertake physical activities	Exclude	Exclude	Exclude
Ability to resume eating to get enough calories to maintain a healthy life	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Amount of ingested meal compared to before gastrectomy	Outcome already presented in round 1	Multiple	Exclude	Exclude	Exclude
Anemia	Outcome already presented in round 1	Bleeding	Exclude	Exclude	Exclude
Anorexia	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
BMI	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Body shape(weight change)	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Change in body weight	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Changes of body weight 1;3;6;12 months after gastrectomy	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Degree of radical cure (palliative, radical)	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Details of neo-adjuvant chemotherapy	Outcome already presented in round 1	Ability to complete treatment pathway.	Exclude	Exclude	Exclude
Development of dumping syndrome	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Difference of postgastrectomy diet (english; continental; korean; chinese)	Outcome already presented in round 1	Multiple	Exclude	Exclude	Exclude
Discomfort; calmness ; panic	Outcome already presented in round 1	Pain	Exclude	Exclude	Exclude
Drainage withdrawal day	Outcome already presented in round 1	Multiple	Exclude	Exclude	Exclude
Dumping syndrome	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Dumping syndrome - impact on day-to-day functioning	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Dumping years after surgery	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Early and late dumping	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Early dumping abdominal symptoms	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Early dumping general symptoms	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Eating	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Effect of treatment on memory	Outcome already presented in round 1	Impact on cognitive functioning	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Effect of treatment on relationship	Outcome already presented in round 1	Ability to interact socially	Exclude	Exclude	Exclude
Effects of alcohol consumption	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Effects of fizzy drinks	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Effects on metabolic diseases such as hypertension, diabetes, and gout	Outcome already presented in round 1	Multiple	Exclude	Exclude	Exclude
Exocrine complications e.g. Pancreatic insufficiency	Outcome already presented in round 1	Pancreas complications	Exclude	Exclude	Exclude
Fatigue	Outcome already presented in round 1	Fatigue	Exclude	Exclude	Exclude
Functional outcome related to different type of reconstruction after gastrectomy	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Gain a useful life to provide for dependants & self or lose life in the attempt	Outcome already presented in round 1	Impact of surgery on social and work roles	Exclude	Exclude	Exclude
Hematologic complications (mainly anemia)	Outcome already presented in round 1	Bleeding	Exclude	Exclude	Exclude
Household income	Outcome already presented in round 1	Impact of surgery on social and work roles	Exclude	Exclude	Exclude
How your body responded after the surgery.	Outcome already presented in round 1	Surgical Stress Response	Exclude	Exclude	Exclude
Impact of dumping syndrome	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Impact of treatment on weight	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
In hospital mortality	Outcome already presented in round 1	Surgery-related death	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Incidence of bile acid malabsorption	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Incidence of small intestinal bacterial overgrowth	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Ingested amount of food per day	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Late dumping symptoms	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Length of absenteeism from work	Outcome already presented in round 1	Impact of surgery on social and work roles	Exclude	Exclude	Exclude
Length of Recovery time	Outcome already presented in round 1	Duration of Hospital Stay	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Life or death decisions/risks are vitally important. Quality of life effects if only temporary are important to be aware of; but not so important. Those side effects of surgery which are going to be permanent are also critically important for the patient to know about and the level of risk. They can then make an informed decision and be more mentally prepared for the process as it unfolds and also be able to manage their conditions in the longer term.	Outcome already presented in round 1	Overall Quality of Life	Exclude	Exclude	Exclude
Lost of the job	Outcome already presented in round 1	Impact of surgery on social and work roles	Exclude	Exclude	Exclude
Lost of the partner	Outcome already presented in round 1	Ability to interact socially - The ability to have relationships with family and friends.	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Lymph node cleaning range (D1, D2, D2+, D3)	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
More about nutritional outcome	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Multivisceral resection	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Muscle function (physical activity)	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Nausea	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Nausea and vomiting	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Need for a dietitian after discharge	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Need for supplementary feeding	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
No appetite	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Number of patients receiving Adjuvant therapy	Outcome already presented in round 1	Ability to complete treatment pathway.	Exclude	Exclude	Exclude
Number of resected lymph nodes	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Nutritional condition improving measures (e.g., PE)	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Nutritional support by endoscopy (probes, prostheses, dilatations)	Outcome already presented in round 1	Need for an additional intervention.	Exclude	Exclude	Exclude
Operation time	Outcome already presented in round 1	Duration of surgery	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Other treatments after surgery	Outcome already presented in round 1	Ability to complete treatment pathway.	Exclude	Exclude	Exclude
Overall survival e disease free survival post HIPEC	Outcome already presented in round 1	Overall survival	Exclude	Exclude	Exclude
Palliative resection	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Patients with peritoneal recurrence of post-HIPEC gastric cancer	Outcome already presented in round 1	Recurrence of Cancer	Exclude	Exclude	Exclude
Percentage weight-loss.	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Permanent pain after treatment	Outcome already presented in round 1	Pain	Exclude	Exclude	Exclude
Post op histology	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Post operative inability to eat normally. Weight loss and further care needed.	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Postoperative considerations and post-treatment planning and programs.	Outcome already presented in round 1	Ability to complete treatment pathway.	Exclude	Exclude	Exclude
Postprandial fullness	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Post-surgical nutrition	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Prevalence of dumping syndrome	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
pTNM	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Quality of resection specimen and pathology outcomes	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Quality of surgery	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Realisation of how life would change after the operation	Outcome already presented in round 1	Overall Quality of Life	Exclude	Exclude	Exclude
Recurrence place (liver vs peritoneum vs lymph node vs lungs vs others)	Outcome already presented in round 1	Recurrence of Cancer	Exclude	Exclude	Exclude
Regurgitation	Outcome already presented in round 1	Gastro-intestinal functional problems	Exclude	Exclude	Exclude
Reoperation cause	Outcome already presented in round 1	Need for an additional intervention.	Exclude	Exclude	Exclude
Restoration of bowel function	Outcome already presented in round 1	Time to recommencing oral intake	Exclude	Exclude	Exclude
Retinal sac resection (complete, incomplete, unremoved)	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Sarcopenia	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Severity of various symptoms after gastrectomy	Outcome already presented in round 1	Multiple	Exclude	Exclude	Exclude
Site of recurrence	Outcome already presented in round 1	Recurrence of Cancer	Exclude	Exclude	Exclude
Start of liquid intake	Outcome already presented in round 1	Time to recommencing oral intake	Exclude	Exclude	Exclude
Start of solid diet	Outcome already presented in round 1	Time to recommencing oral intake	Exclude	Exclude	Exclude
Sweeping lymph node group	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude
Sweeping the number of lymph nodes	Outcome already presented in round 1	Completeness of tumour removal	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
Time of recurrence	Outcome already presented in round 1	Recurrence of Cancer	Exclude	Exclude	Exclude
Time spent in the hospital (surgery+chemo+artificial nutrition+palliative etc. Etc.)	Outcome already presented in round 1	Duration of Hospital Stay	Exclude	Exclude	Exclude
Time to and percentage of patients with chemotherapy initiation	Outcome already presented in round 1	Ability to complete treatment pathway.	Exclude	Exclude	Exclude
Time to mobilization	Outcome already presented in round 1	Ability to undertake physical activities	Exclude	Exclude	Exclude
Tiredness just after mild efforts it's really considerable; I have a limited autonomy during the day	Outcome already presented in round 1	Fatigue	Exclude	Exclude	Exclude
Weight loss	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude
Weight loss after surgery	Outcome already presented in round 1	Nutritional Effects	Exclude	Exclude	Exclude

Suggestion by Delphi participant (verbatim and translated)	**Reason for inclusion or exclusion**	**Which Domain is this already included in?**	**SMG** Decision**	**Reviewer Decision**	**Final Decision**
12 month survival	Relates to how or when an outcome is measured	N/A	Exclude	Exclude	Exclude
90 day survival	Relates to how or when an outcome is measured	N/A	Exclude	Exclude	Exclude
PROMS at 3,6&12 months	Relates to how or when an outcome is measured	N/A	Exclude	Exclude	Exclude

8.7.7 Appendix 6. Results from the GASTROS Consensus meeting.

Results from the GASTROS Consensus meeting held on Sunday the 8th of March 2020.

Participant information

- 43 participants (7 patients ,7 nurses, 29 surgeons)
- 14 countries (4 continents – South America, North America, Europe, Asia).
    - 1 patient from Netherlands (remainder from UK)
    - 1 nurse from Belgium (remainder from UK)
- 18 in Manchester; 25 online
- 40 participants were present throughout the entire day. Three left halfway through the meeting (2 from the venue and 1 online).
    - 21 online had intermittent technical problems with voting app but made a note of their votes and supplied them on an online form with 24 hours of the meeting.

Complications

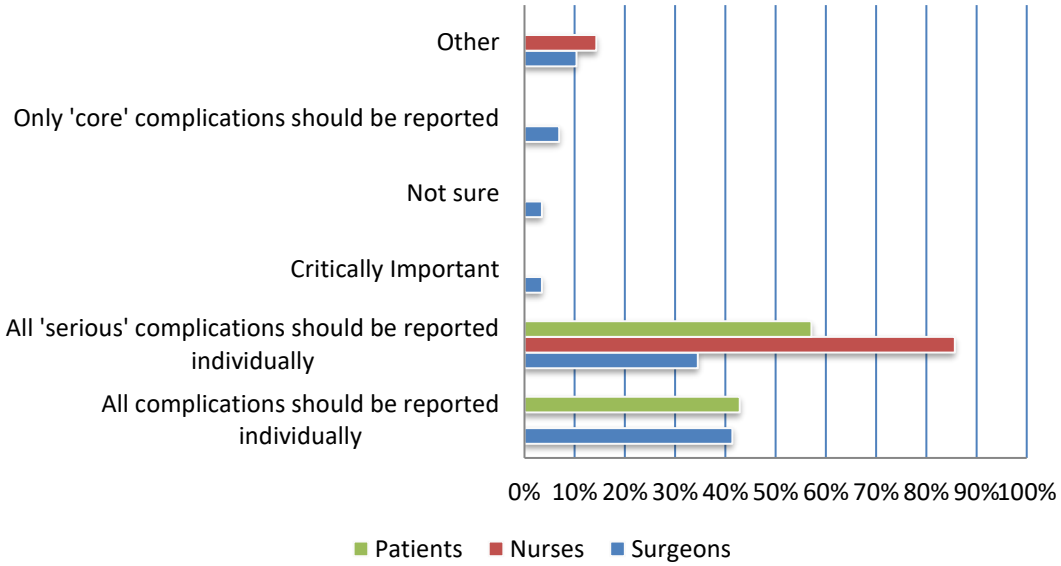
The first session discussed how complications should be reported. This was required because ‘all-cause complications’ had reached consensus to include in the core outcome set based on the Delphi survey, whilst some complications were excluded. To record ‘all-cause’ complications, all complications must be recorded as a minimum. To clarify this potential disparity, participants were asked to discuss different options and vote on their preference. After two rounds of voting, there was no clear consensus how complications should be reported. This has identified the need for further work on this topic. For the manuscript, the term ‘complications’ will be used and qualified by explaining that more work is required.

The remaining outcomes were discussed and rated by participants. No further outcomes were added to the core outcome set. The following charts illustrate how participants voted during the meeting.

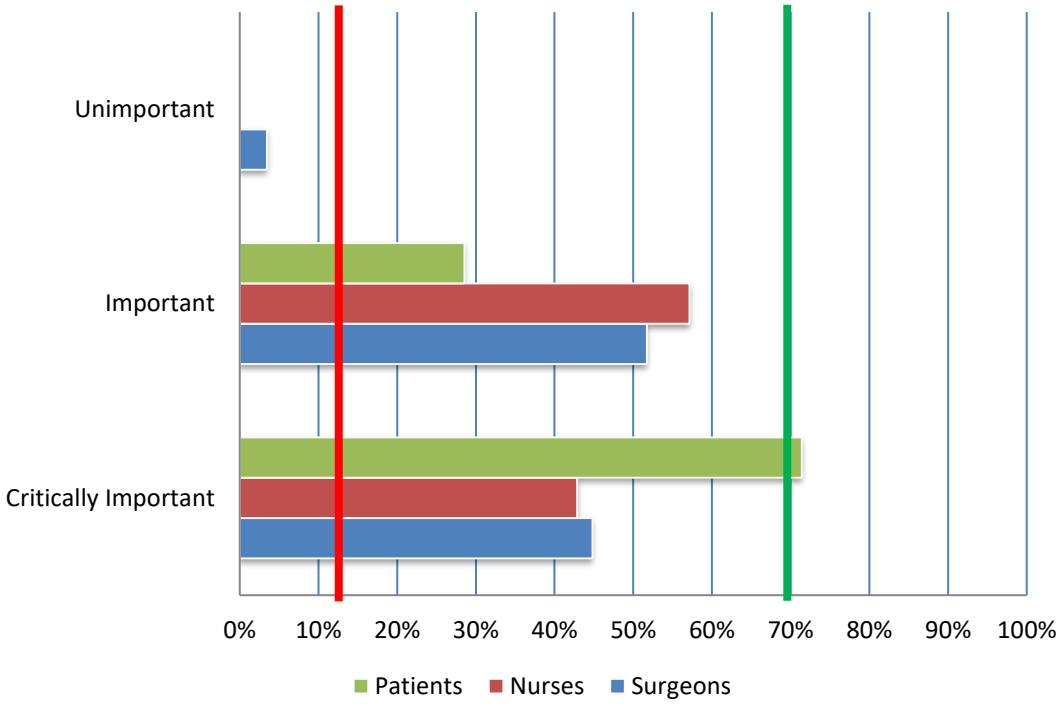
Definitions

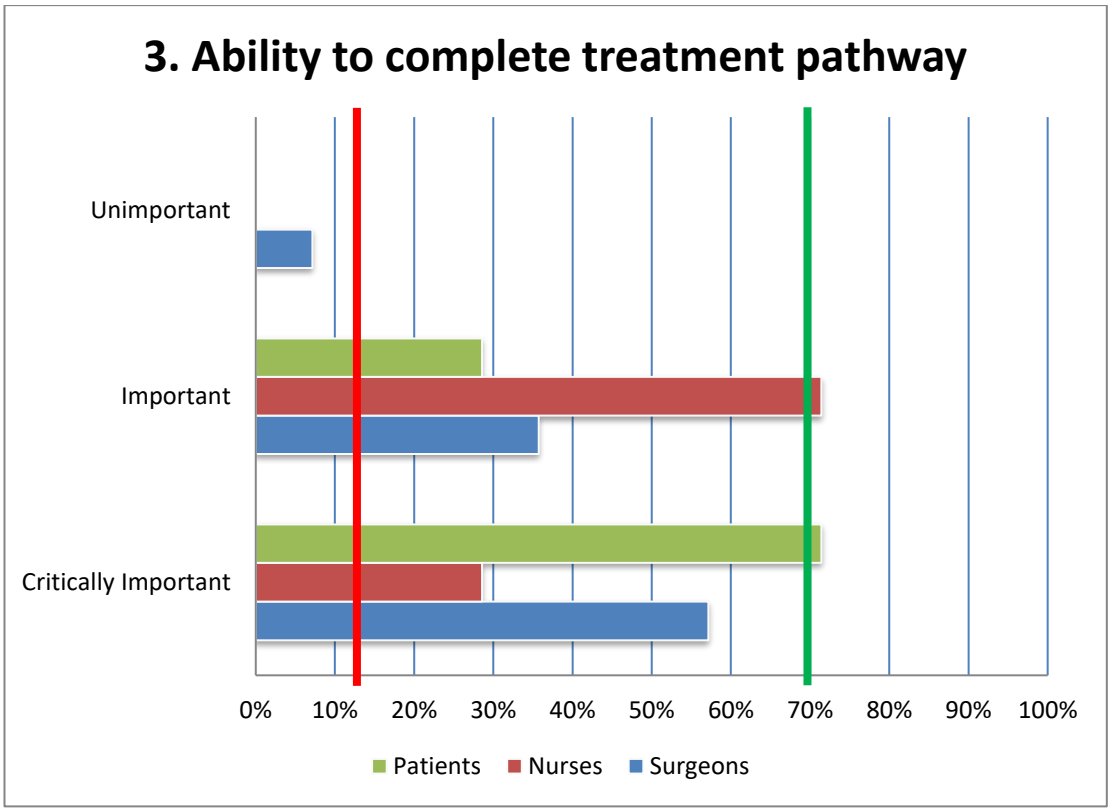
Participants were asked how definitions should be finalised. The majority of participants agreed that this should be a process which involves both healthcare professionals and patients.

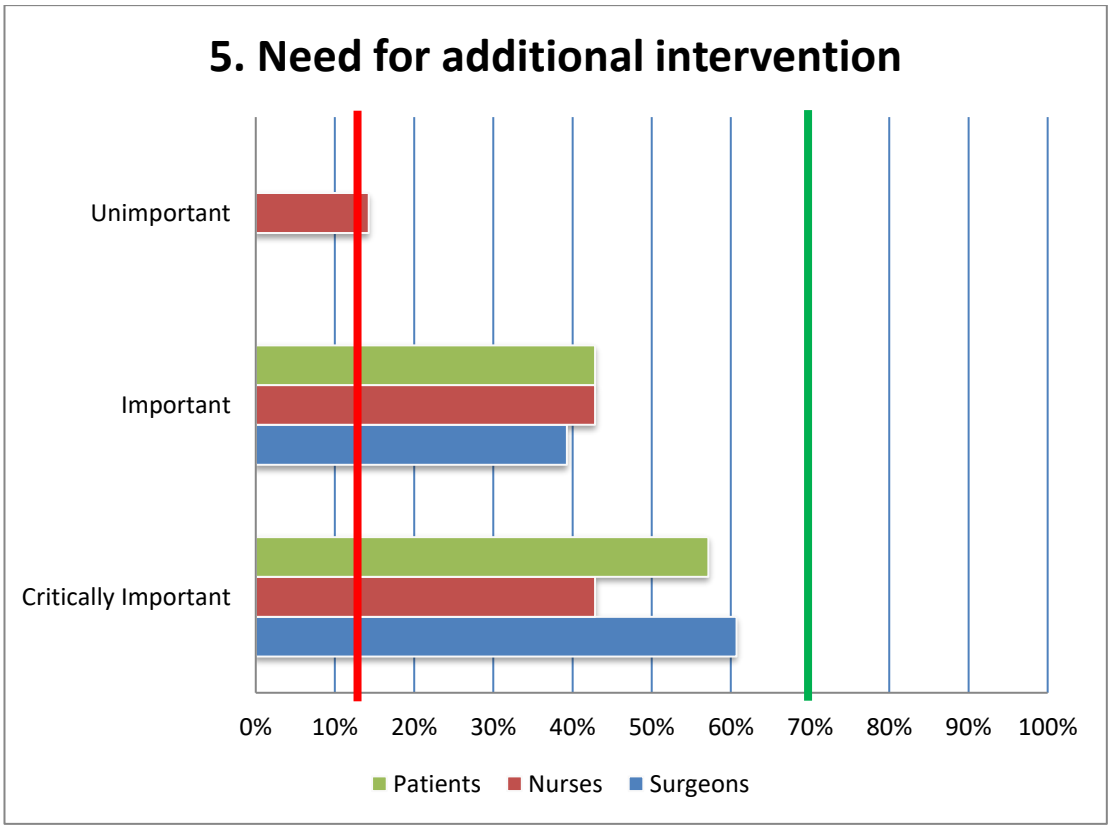
Which complications should be reported?

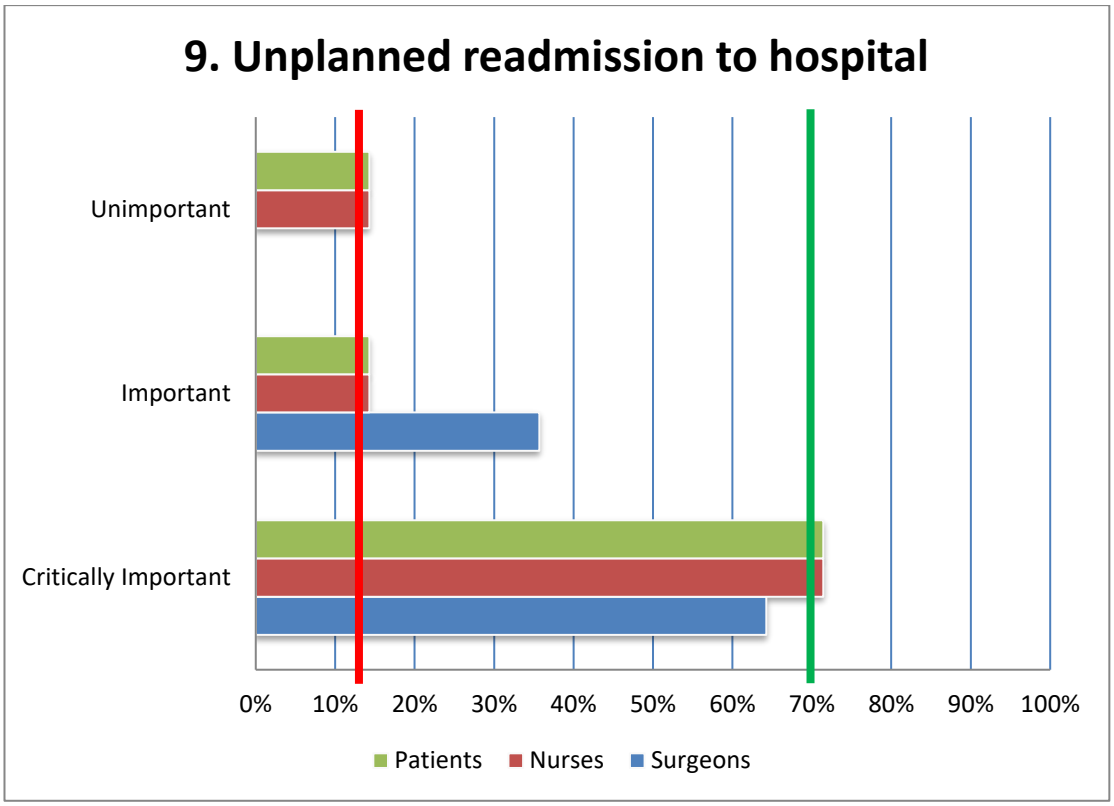


1. Gastro-intestinal functional problems




3. Ability to complete treatment pathway
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients
Nurses
Surgeons


5. Need for additional intervention
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients
Nurses
Surgeons


9. Unplanned readmission to hospital
Unimportant
Important
Critically Important
0%
10%
20%
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Patients
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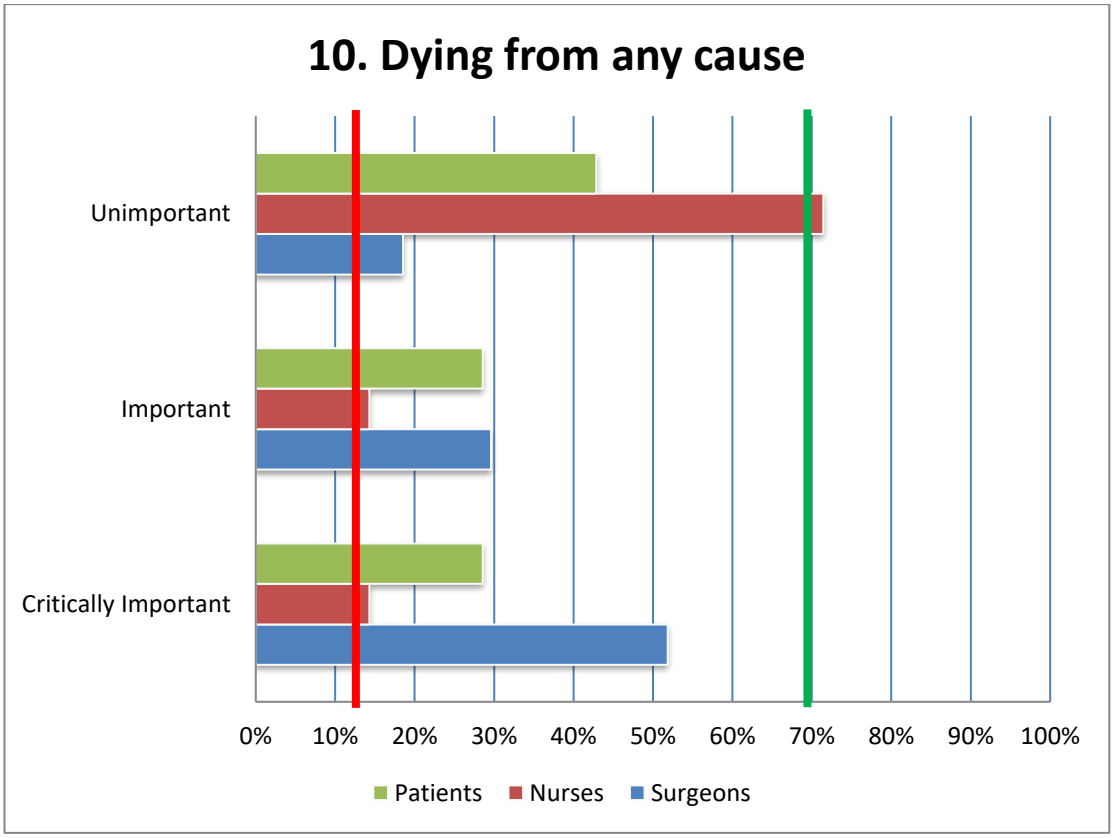
10. Dying from any cause
Unimportant
Important
Critically Important
0%
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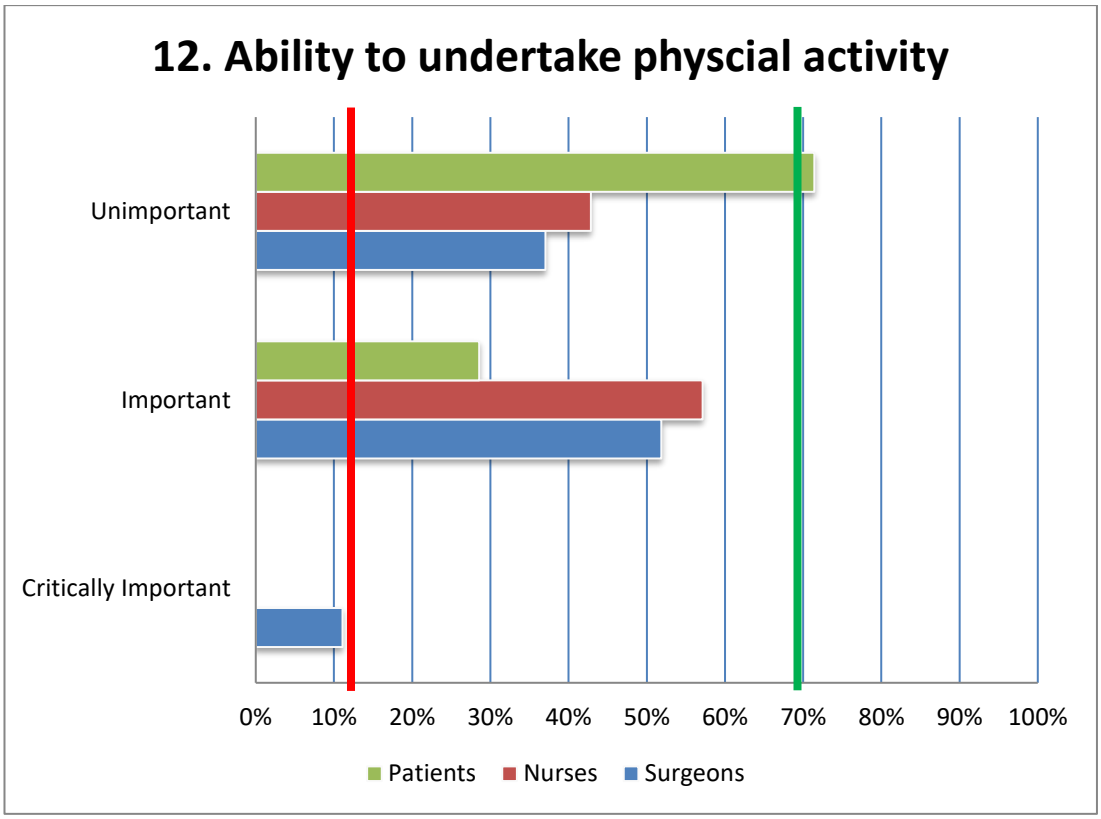
Patients
Nurses
Surgeons


12. Ability to undertake physcial activity
Unimportant
Important
Critically Important
0%
10%
20%
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80%
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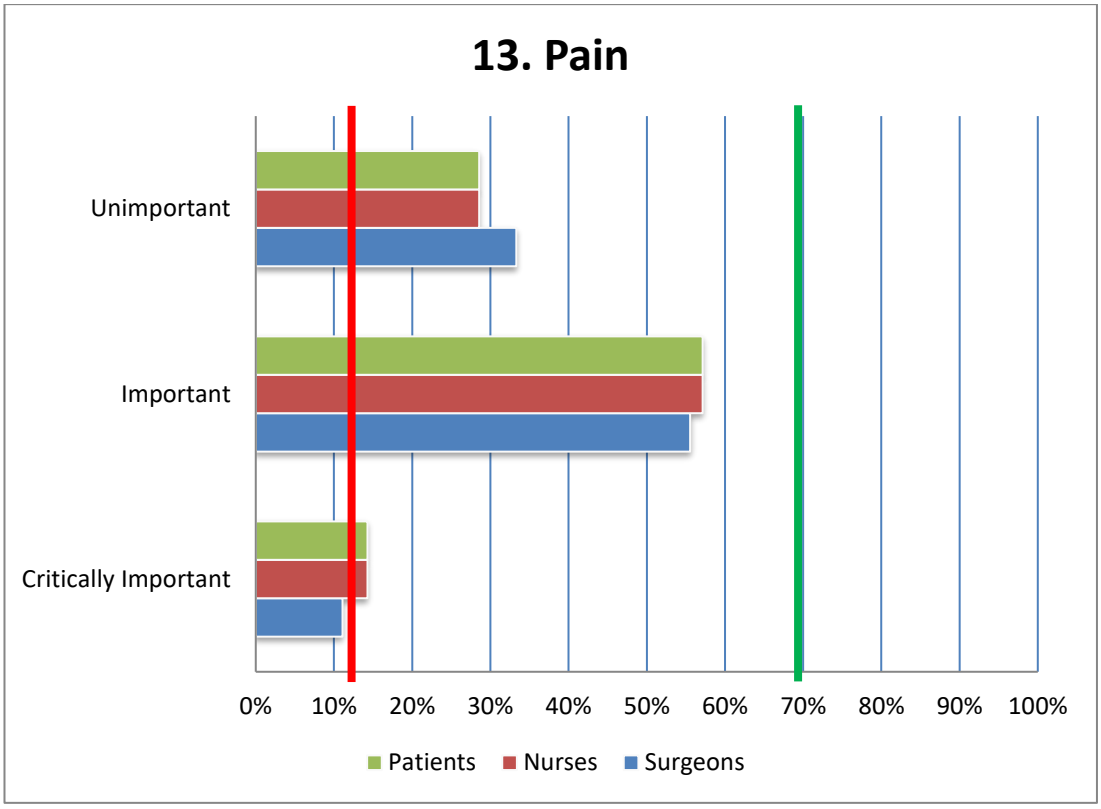
Patients
Nurses
Surgeons


13. Pain
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
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80%
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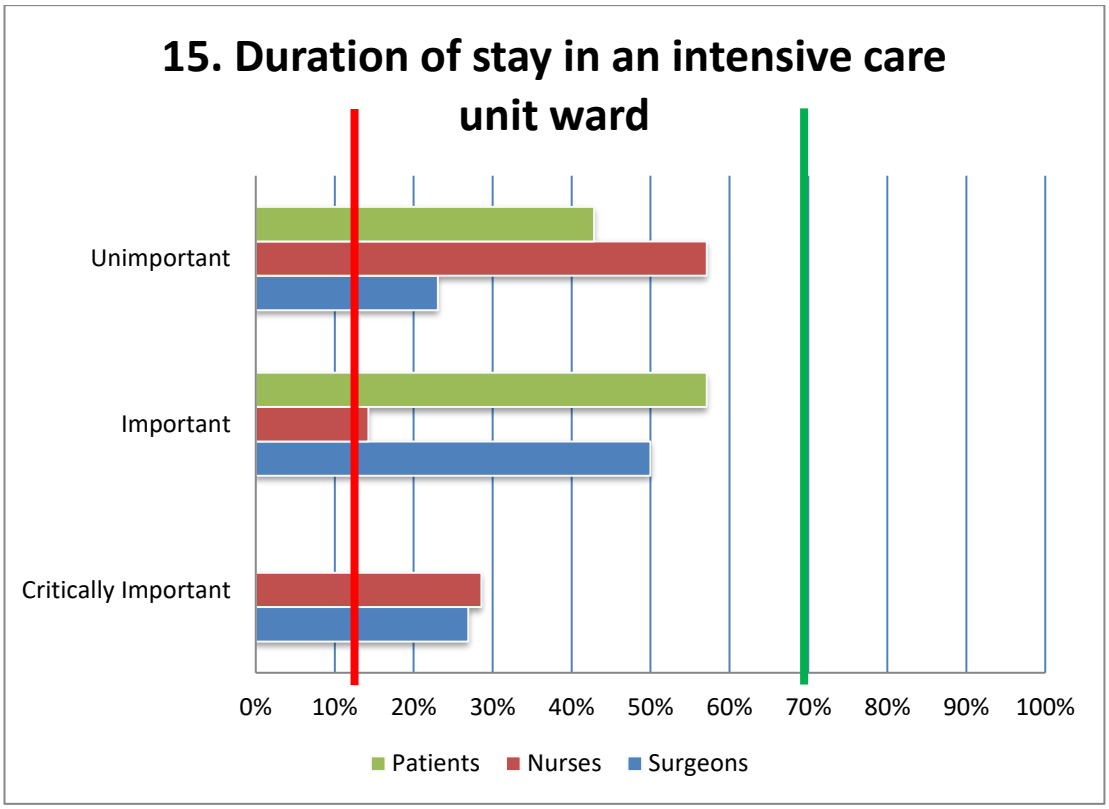
100%
Patients
Nurses
Surgeons


15. Duration of stay in an intensive care unit ward
Unimportant
Important
Critically Important
0%
10%
20%
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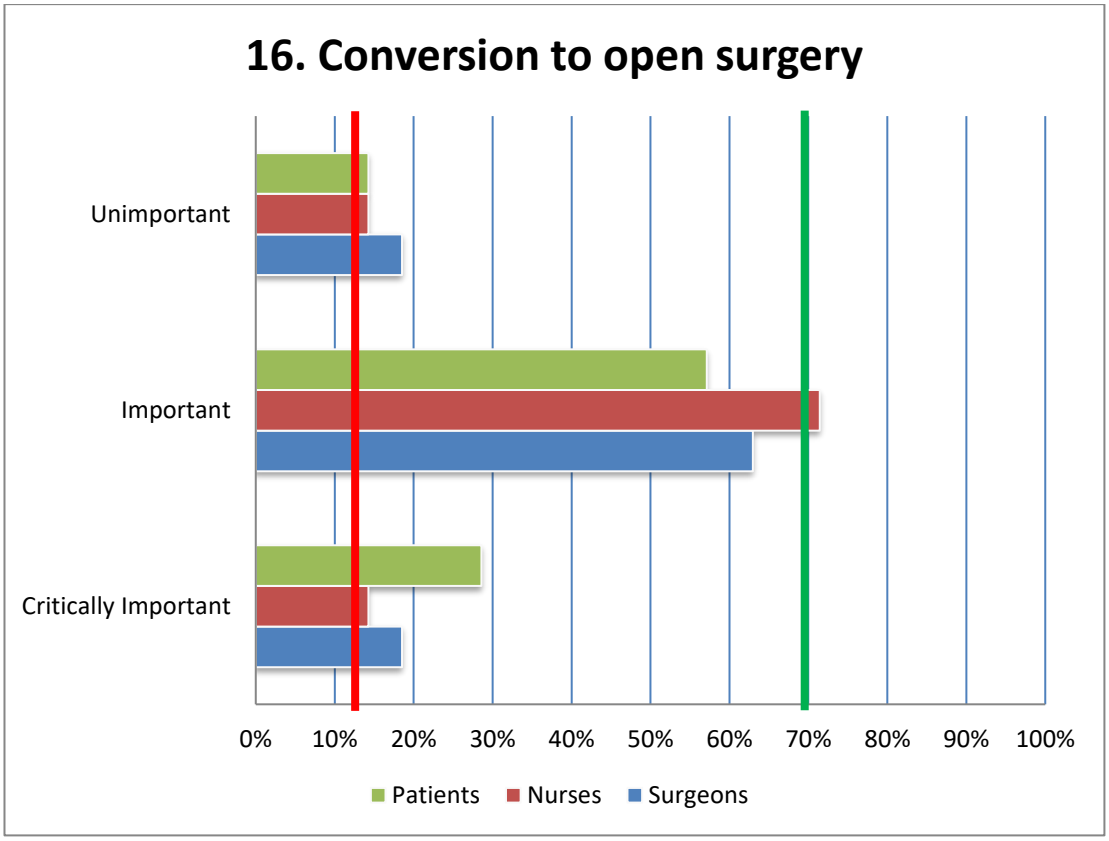
80%
90%
100%
Patients
Nurses
Surgeons


16. Conversion to open surgery
Unimportant
Important
Critically Important
0%
10%
20%
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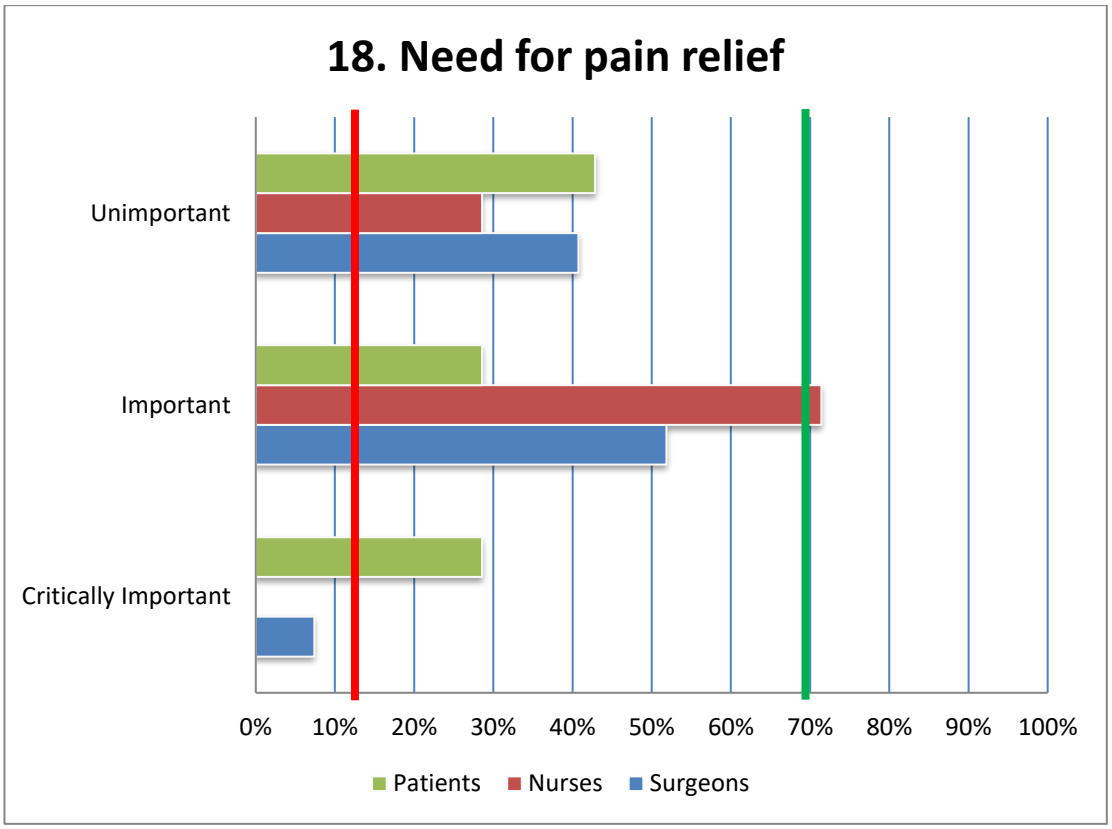
Patients
Nurses
Surgeons


18. Need for pain relief
Unimportant
Important
Critically Important
0%
10%
20%
30%
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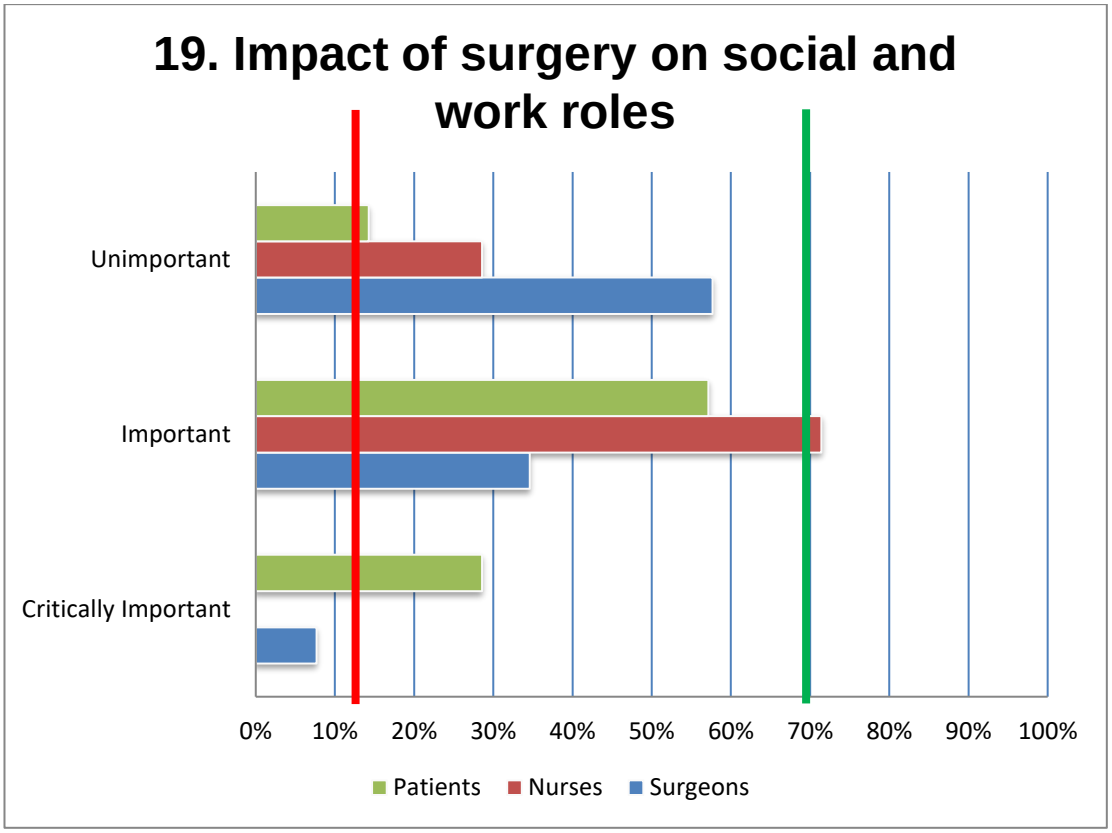
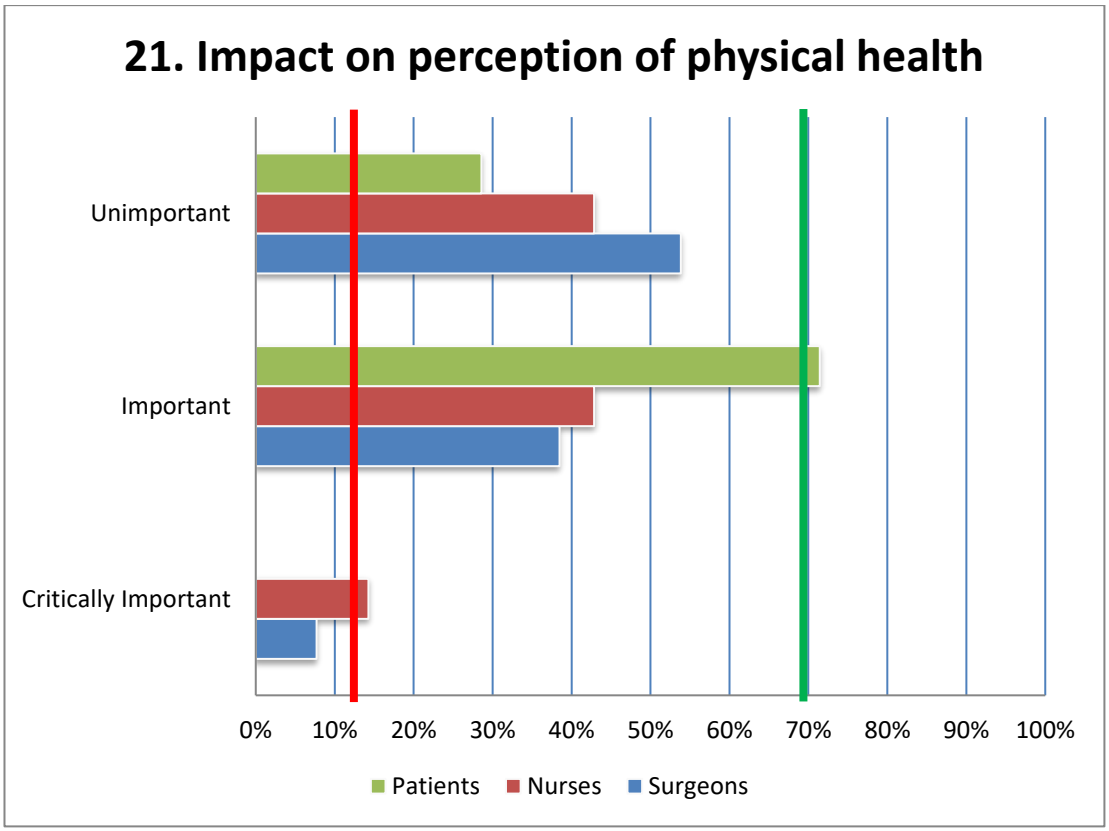
Patients
Nurses
Surgeons


19. Impact of surgery on social and work roles
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients
Nurses
Surgeons


21. Impact on perception of physical health
Unimportant
Important
Critically Important
0%
10%
20%
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40%
50%
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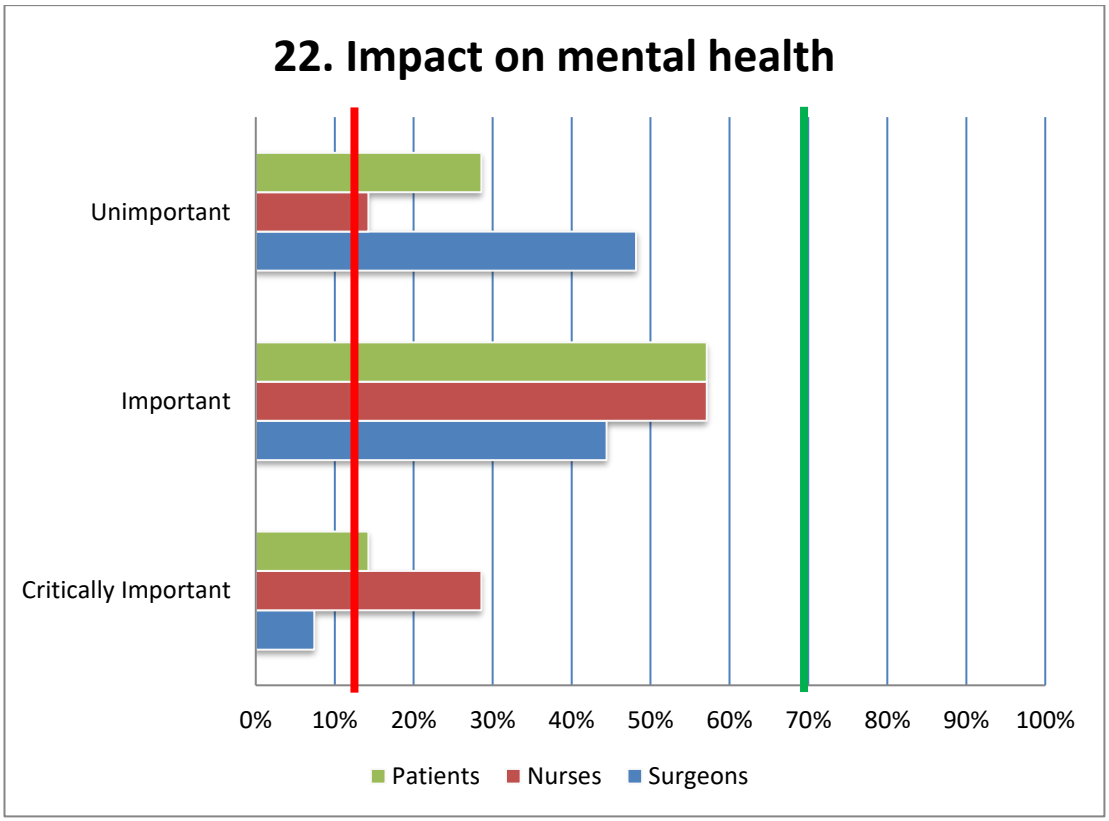
90%
100%
Patients
Nurses
Surgeons


22. Impact on mental health
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
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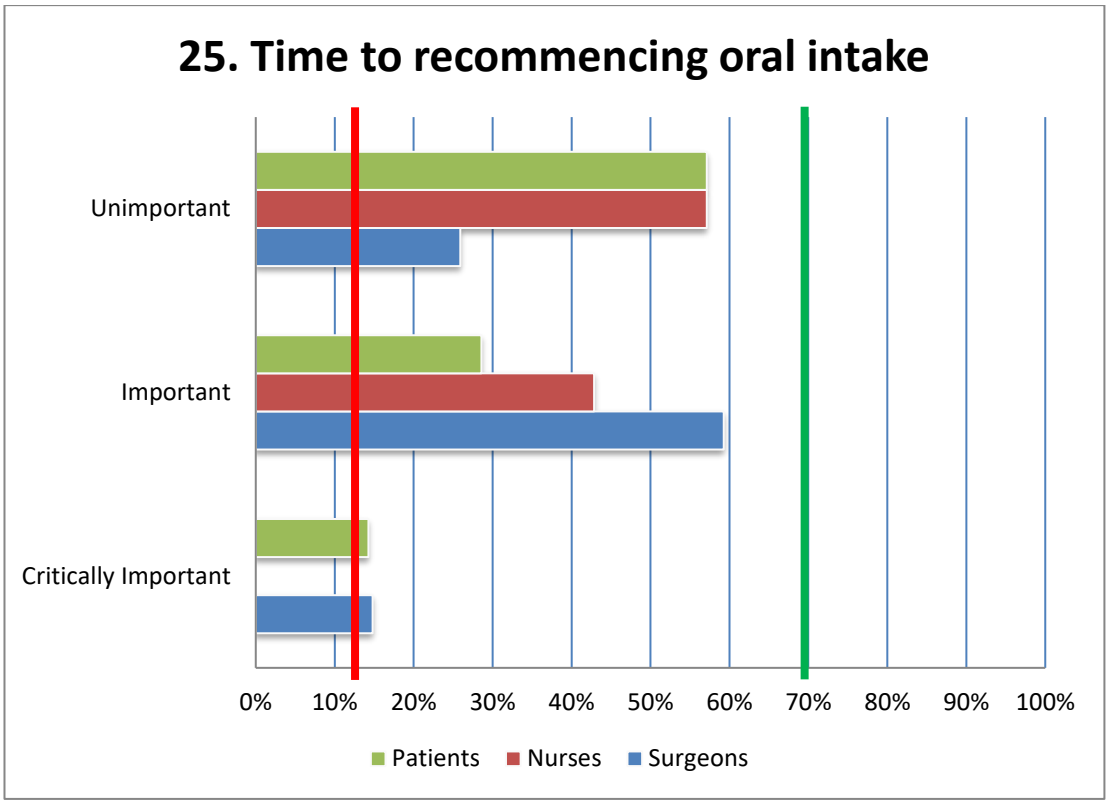
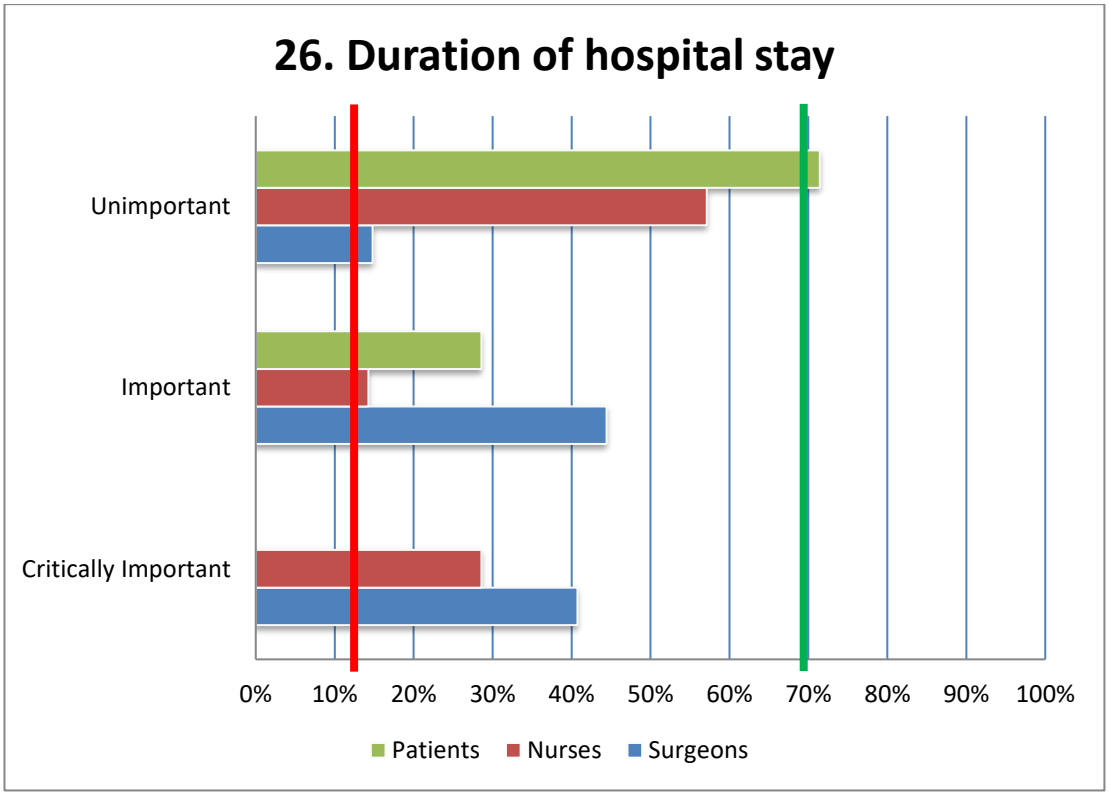
90%
100%
Patients
Nurses
Surgeons


25. Time to recommencing oral intake
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients
Nurses
Surgeons


26. Duration of hospital stay
Unimportant
Important
Critically Important
0%
10%
20%
30%
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90%
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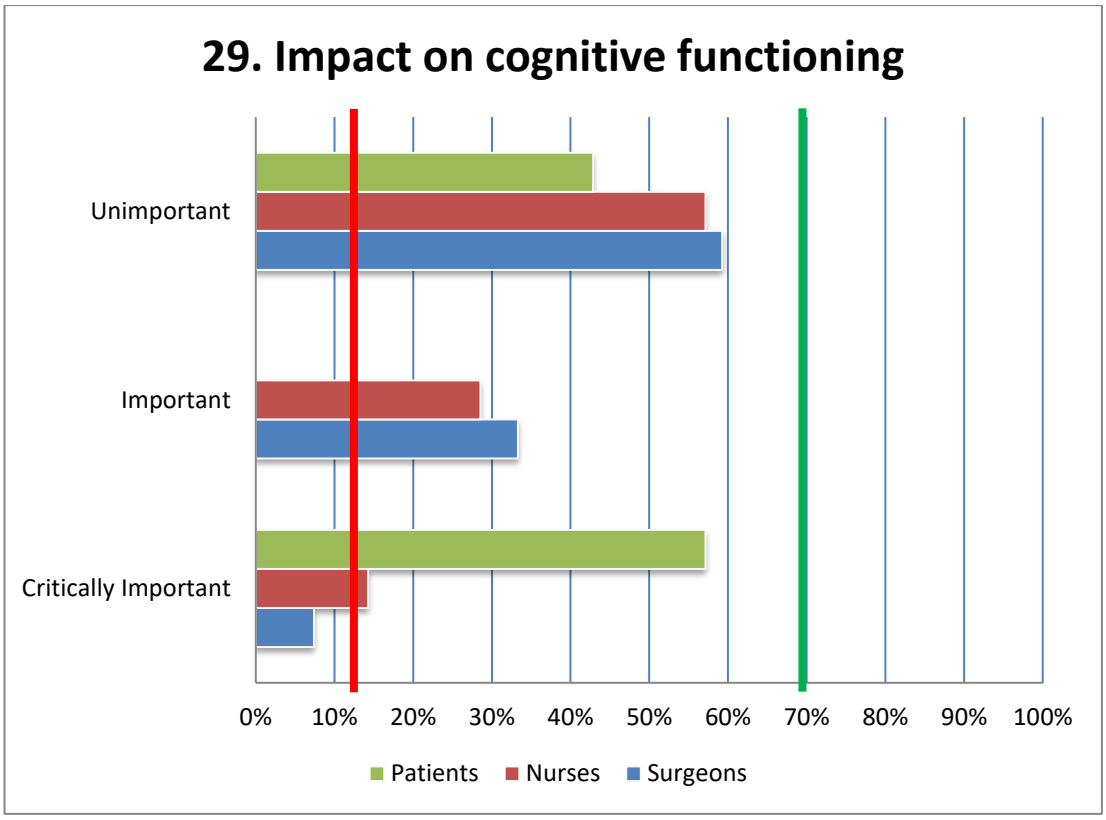
Patients
Nurses
Surgeons


29. Impact on cognitive functioning
Unimportant
Important
Critically Important
0%
10%
20%
30%
40%
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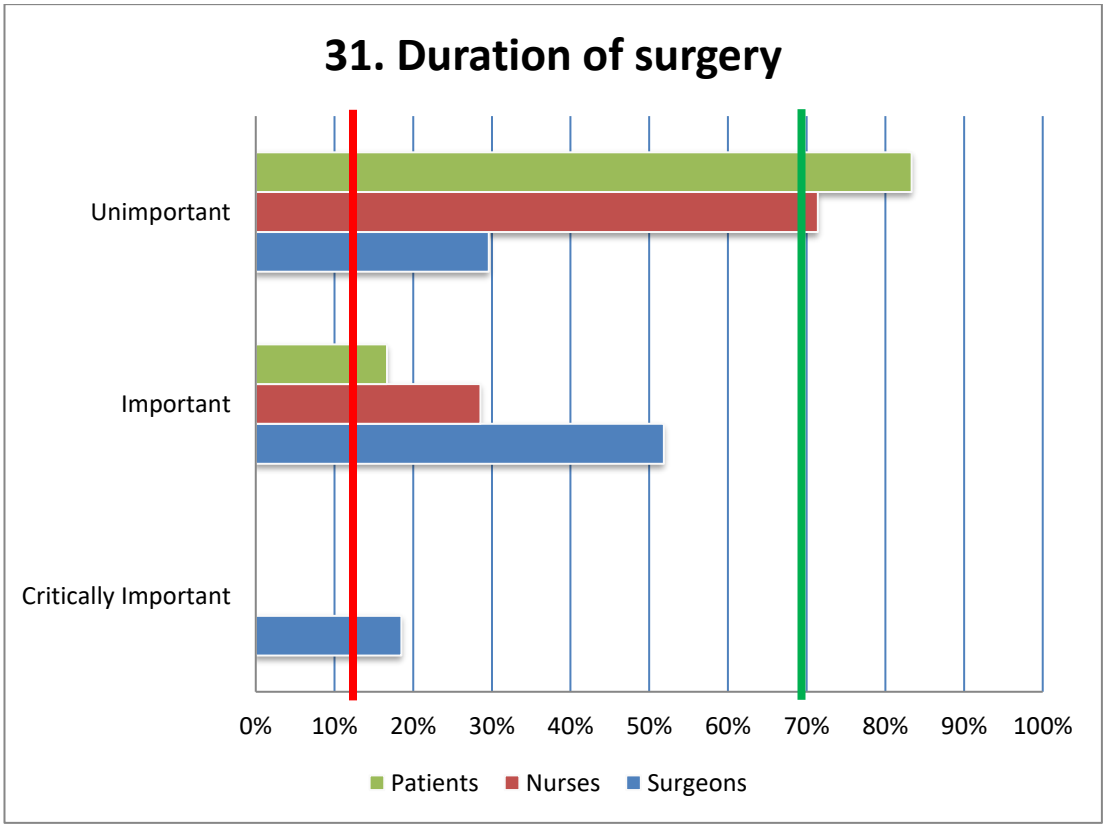
100%
Patients
Nurses
Surgeons


31. Duration of surgery
Unimportant
Important
Critically Important
0%
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30%
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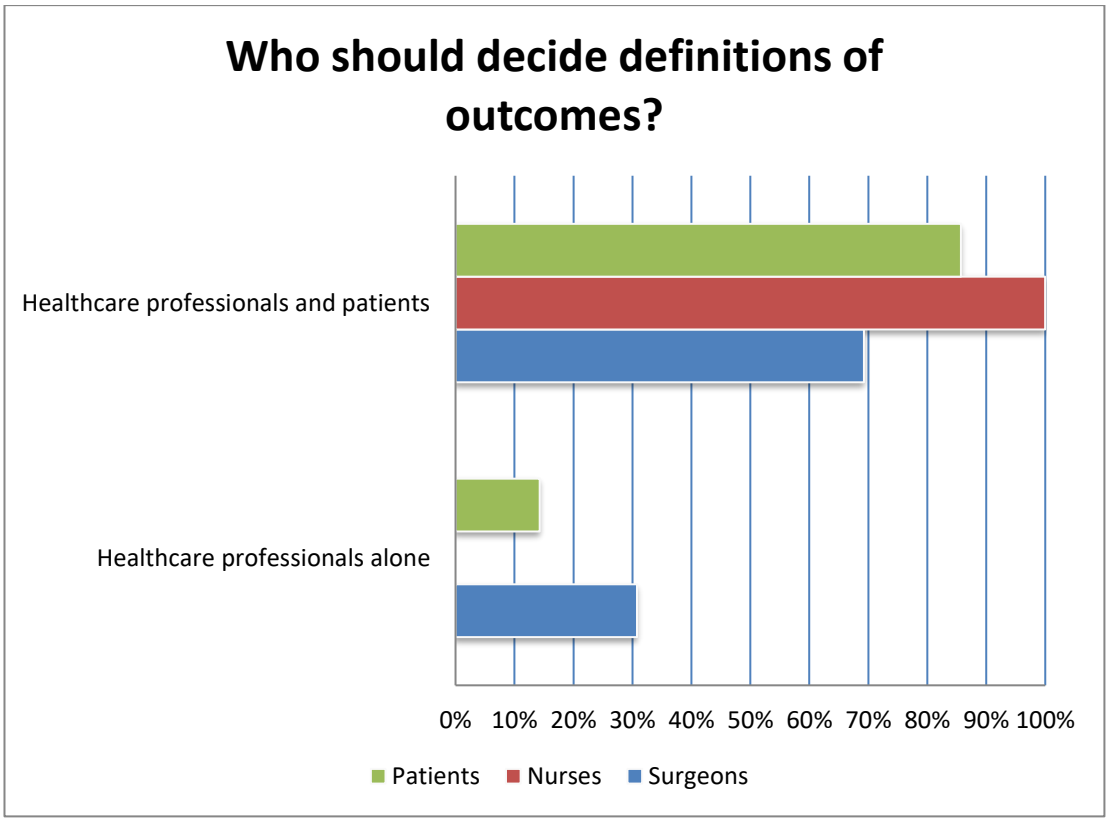
90%
100%
Patients
Nurses
Surgeons


Who should decide definitions of outcomes?
Healthcare professionals and patients
Healthcare professionals alone
0%
10%
20%
30%
40%
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60%
70%
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90%
100%
Patients
Nurses
Surgeons

9 Discussion

Author

Bilal Alkhaffaf.

9.1 Introduction

The following chapter summarises the main findings from this doctoral thesis, details the study's contributions to the field, and considers its main limitations. In addition, planned future work related to this area is discussed.

9.2 Core Outcome Sets in Cancer Surgery

This study is the first to develop a core outcome set (COS) for surgical effectiveness trials in gastric cancer. However, there have been a number of other COS in the wider field of cancer surgery, specifically in oesophageal, colorectal, prostate and oropharyngeal cancer[1–4]. A further group has established a core set of 'patient-reported outcomes' in relation to pancreatic cancer surgery studies although did not address other outcomes which may be of importance[5]. The methodological approaches used (summarised in table 1) were broadly similar and mirrored those used in this present study for gastric cancer surgery; namely the identification of potentially important outcomes through a systematic review and patient interviews, followed by a consensus process to prioritise outcomes into a COS. All studies ensured that key stakeholder opinion was sought, including that of patients and healthcare workers although only the gastric cancer COS sought opinion from international patient stakeholders in the Delphi survey.

With respect to the selection of core outcomes (summarised in table 2), there were further similarities. Different aspects of survival or recurrence were a frequent theme alongside surgery-related mortality and measures of the degree of oncological resection. Equally, the reporting of overall quality of life or at the very least outcomes which impact on quality of life featured in all studies. Whilst each COS included outcomes related to complications, as one may expect, the types of complications varied reflecting differences in interventions, anatomical location and their subsequent impact on patients. These comparisons are important as they will inform other studies in the field of cancer surgery of the likely outcome areas that may be included. Furthermore, it will strengthen the case for COS developers to identify areas of common interest on which they can work collaboratively, such as the identification of appropriate outcome measurement instruments. This is discussed further below.

Table 9.1 Methodological approaches adopted by core outcome set developers for effectiveness trials in cancer surgery

	Gastric Cancer[6]	**Oesophageal Cancer**[1]	**Colorectal Cancer**[2]	**Prostate Cancer**[3]	**Oropharyngeal Cancer**[4]
Stakeholders	• Patients • Healthcare workers	• Patients • Healthcare workers	• Patients • Healthcare workers	• Patients • Healthcare workers	• Patients • Healthcare workers
Systematic review	Yes	Yes	Yes	Yes	Yes
Patient interviews	Yes	Yes	Yes	Yes	Yes
Delphi survey	Yes	Yes	Yes	Yes	Yes
Consensus meeting	Yes	Yes	Yes	Yes	No
International Participation	• Delphi survey • Consensus meeting	• No	• No	• Delphi survey (healthcare workers only)	• Interviews • Delphi survey (healthcare workers only)

Table 9.2 Outcomes included in core outcomes sets for effectiveness trials in cancer surgery.

	Gastric Cancer[6]	**Oesophageal Cancer**[1]	**Colorectal Cancer**[2]	**Prostate Cancer**[3]	**Oropharyngeal Cancer**[4]
Surviving & Controlling Cancer		• Overall survival	• Long-term survival	• Death from any cause	
	• Disease-free survival			• Disease progression	
	• Disease-specific survival			• Death from prostate cancer	• Disease-specific survival
	• Recurrence of cancer		• Cancer recurrence	• Distant disease recurrence/metastases • Local disease recurrence	• Distant metastatic Control • Local Control • Regional Control
	• Surgery-related death	• In-hospital mortality	• Perioperative survival	• Perioperative deaths	• Death related to treatment
	• Completeness of tumour removal	• Inoperability	• Resection margins	• Positive surgical margin	
				• Need for salvage therapy	

Adverse Events	• Serious adverse events	• Conduit necrosis and anastomotic leak • The need for another operation related to their primary esophageal cancer resection surgery • Respiratory complications	• Anastomotic leak • Surgical site infection • Stoma rates and complications • Conversion to open operation (where appropriate)	• Thromboembolic disease • Bothersome or symptomatic urethral or anastomotic stricture	• Interventions for the management of treatment related morbidity
Impacts of Surgery	• Overall quality of life	• Overall quality of life	• Physical function • Sexual function	• Overall quality of life • Sexual function	• Health-related quality of life
	• Nutritional effects	• Severe nutritional problems • The ability to eat and drink			• Dysphagia
	•	• Problems with acid indigestion or heartburn	• Faecal incontinence • Faecal urgency	• Bowel function • Faecal incontinence • Stress incontinence Urinary function	

9.3 Main Findings

During this study, the views of international stakeholders from high, middle and low-income countries across all 6 continents were considered using a rigorous and transparently reported methodology adapted from established principles in the field[7]. The main findings included:

- The heterogeneity of outcome reporting in this field
- Patient priorities in relation to outcome reporting
- Methodological considerations for COS development (discussed separately)

The primary benefits of the COS will be to guide researchers in selecting outcomes they should measure and report as a minimum. Standardising the reporting of outcomes will facilitate data synthesis, improving the quality of evidence and thereby leading to improvements in patient care. The COS will likely have other benefits; it will guide those developing regional, national and international audits in selecting outcomes which should be measured. Additionally, understanding the priorities of patients will guide clinical consultations and inform the development of patient information material for use during the consent process ahead of surgery.

The systematic review of previous trials demonstrated significant heterogeneity in outcome selection and reporting in the field of gastric cancer surgery. Whilst similar findings have been mirrored across numerous clinical specialties[8–10], this is the first time that such inconsistencies have been highlighted in the field of gastric cancer surgery. In addition to the findings from the patient interviews in chapter 4, the review highlighted the need for greater standardisation of outcome reporting and consideration of important perspectives such as those of patients. Ultimately, patients are the ones with 'lived experience' and stand to gain the most out of research, so it is imperative that their rich insights are taken into account.

9.4 Methodological contributions

This doctoral thesis was able to explore key methodological areas that future COS developers may benefit from, including:

- Methods to optimise the translation of Delphi surveys
- Extending international collaboration for COS development
- The role of stakeholders in their contributions to Delphi studies
- The importance of Delphi surveys compared to single round surveys in consensus-seeking processes

Chapter 5 examines how COS studies have attempted to facilitate international participation in their design, with particular emphasis on translating Delphi surveys. It can be argued that to truly consider a COS study 'international', stakeholder opinion from multiple geographical regions may be necessary. This was especially important in the case of gastric cancer given the worldwide burden of

the disease. Furthermore, it could be said that to a gain representative international opinion which does not exclude potentially important or varied viewpoints, Delphi surveys should be translated into local languages. Chapter 5 identified that current approaches to translating surveys for used in international COS were heterogenous and not based on robust methodology. Using this COS as a case study, an approach adapted from international guidelines was developed to translate Delphi surveys for use in COS. Furthermore, nine key considerations to facilitate international Delphi survey participation were described. This chapter is the first to address this topic in relation to COS and sets out an easily replicable step-by-step guide which resulted in nearly 1000 participants from across 6 continents participating in the GASTROS Delphi survey.

Chapter 6 contributes to the understanding of how participants should be selected and grouped in Delphi surveys used to develop COS. The limited previous work in this field[11,12] has suggested that there is significant variation in how healthcare professionals prioritise outcome selection. However, the analysis from the GASTROS Delphi survey suggests that once these healthcare professionals are separated into their disciplines (e.g. surgeons and oncology nurses), there appears to be little variation in opinion, even when taking account of differences in geographical location or clinical experience. This finding supports this study's approach to group surgeons and nurses separately and may inform the design of other COS developers when deciding how to organise stakeholders. Furthermore, whilst the GASTROS Delphi survey was able to recruit a significant number of participants, the analysis in chapter 6 suggests that this may not be necessary as long as study teams can demonstrate that stakeholders are appropriately representative of their respective group. Indeed, these findings will also inform the approach taken in future work related to the GASTROS study when developing outcome definitions and identifying appropriate measurement instruments.

Delphi surveys have become a widely adopted method of seeking consensus in COS development[13]. However, it may be argued that a single questionnaire which is less resource intensive and quicker to complete may yield similar results. Chapter 7 presents a collaboration between the GASTROS study and two other COS in the fields of anal and prostate cancer. This work was the first to examine the degree of score changes between Delphi survey rounds and the reasons for this. Key drivers for changing scores were identified, including 'time to reflect' and 'vicarious thinking' facilitated by seeing the scores of other participants in previous rounds. Being able to change scores led to more outcomes reaching consensus in round 2 compared to round 1. The findings from this study support the use of Delphi surveys over single questionnaires when seeking consensus in the context of COS development.

9.5 Limitations

Limitations have been previously discussed in each chapter; however, the following section summarises the study's main limitations. The scope of the COS focussed on surgical trials for gastric cancer. It may be argued that given the recent development of multi-modal treatments for gastric cancer, a COS which incorporates outcomes relating to adjuvant therapies (e.g. chemotherapy) and

endoscopic treatments is required. However, for many patients, neither chemotherapy nor endoscopy are used which may render some outcomes included in a 'multi-modal' COS irrelevant. Furthermore, at the time of developing the study design, there were more than twenty trials examining operative approaches to gastric cancer supporting the need for a surgical-focused COS. As is described further in the 'future work' section, this potential limitation could be mitigated through the development of chemotherapy or endoscopy-related COS to supplement the surgical COS developed in this study.

Whilst a strength of this study was its ability to recruit a broad range of international participants from both high and low-to-middle income countries, there was a notable absence of Japanese and Korean patients from the Delphi cohort. South Korea and Japan have one of the highest incidences of gastric cancer worldwide and patient representation from these regions was important[14]. Despite attempts to engage with collaborators during an early stage of the study design, support was initially not forthcoming limiting the study team's ability to translate the survey in the local languages and establish recruitment. By the time significant support materialised, Japanese and Korean participants were limited to using English language versions of the survey which, in practical terms, restricted participation to surgeons only. However, as previously described, the analysis in chapter 6 identified little variation within stakeholder groups even when geographical or economic (e.g. high income and low-middle income countries) differences were considered. Furthermore, COS present minimum reporting standards and do not restrict researchers reporting other outcomes which they may deem important to stakeholders in their regions. Taking this into consideration, a key suggestion from chapter 6 was that researchers may wish to undertake additional work with stakeholders (including patients) during the design phase of their trials to ensure that outcomes which may be regionally important but not included in this COS are reported.

Another consideration relates to the type of stakeholder groups which were recruited to the study. This decision was discussed extensively by the SMG and SAG and agreed prior to the commencement of the study. It was agreed to limit participation to patients, nurses and surgeons as this represented a balance of a broad spectrum of opinion but ensured that the study's coordination and data analysis was manageable. It should be acknowledged that other groups, such as care-givers, allied health professionals, regulators, policy-makers and grant awarding bodies, will also provide valuable opinion. Inclusion of these groups will be considered in future stages of the GASTROS study and when the COS is reviewed (see below).

Finally, the consensus meeting was unable to make recommendations regarding how complications should be reported in the COS. This highlights the inherent challenges of seeking consensus in this setting and suggests that with respect to COS, there are circumstances where additional approaches may need to be employed. The main difference in opinion was whether to report 'all' or only 'serious' complications. By extension, there was agreement by all that at the very least, serious complications should be reported as a minimum until further work to develop this area is undertaken with the support of patients and healthcare professionals.

9.6 Future work and collaborations

The design of this study has resulted in the development of an extensive network of international healthcare professionals and patient groups with a common purpose to improve the reporting of outcomes in the field of gastric cancer surgery. This network will support future work in this area so that it can continue to be undertaken collaboratively and on the principles of inclusivity and key stakeholder participation. The following section describes the next stages of related work, including that which is already underway. Some of this work will be undertaken under the banner of the COUGAR group (Core outcomes in upper gastrointestinal audit and research – www.cougargroup.org). Established by the author, COUGAR will focus on the study and reporting of core outcomes in upper gastrointestinal audit and research. It aims to achieve these objectives by promoting and building on methodological research in this field and by undertaking collaborative research which focuses on the reporting of core outcomes.

In the wider context, there are several emerging voices in the field of COS development. In addition to COMET (Core Outcome Measures in Effectiveness Trials - www.COMET-initiative.org), groups such as ICHOM (International Consortium for Health Outcomes Measurement – www.ichom.org) and regulatory bodies such as the FDA (USA Food and Drug Administration – www.fda.gov) have advocated for the development of COS. Collaborative approaches between some of these groups has already begun (The Red Hat group[15]) which will be essential as the field evolves.

9.6.1 Reporting complications

Further work is required to determine which complications should be reported in future trials. As described, this will focus mainly on whether all complications should be reported, or whether the minimum requirements will be to report ‘serious’ outcomes. The consensus meeting recommended that this work should involve both patients and healthcare professionals. Furthermore, agreement has been secured that this work will be supported by the Gastrectomy Complications Consensus Group (www.gastrodata.org) who have previously standardised the reporting of complications amongst surgeons in this field[16].

9.6.2 Finalising definitions and establishing ‘how’ to measure outcomes

Plain language definitions of outcomes presented to participants in the Delphi survey and consensus meeting were developed by the study management and study advisory groups. This aimed to ensure that meanings were not lost during translations and to reduce the risk of patients not engaging fully with the process. It is accepted that these definitions may not be sufficiently detailed to be used in a clinical trial setting, and as such further work will be required in this area. Significant efforts to standardise definitions has already been undertaken by the Standardised Endpoints in Perioperative Medicine (StEP) group with which the author has collaborated[17–20]. Much of this will be relevant to the outcomes included in this COS.

The initial aim was to develop an accompanying measurement instrument set to supplement the COS. The methodological principles guiding this aspect of work are still in an early phase of evolution compared to those guiding COS development. Identifying appropriate outcome measurement instruments to accompany a COS in gastric cancer surgery would likely constitute sufficient work for a PhD study in and of itself. Furthermore, it became apparent that developing an international COS of this nature would present opportunities to examine methodological considerations that had not previously been studied in detail. This would provide the opportunity to demonstrate 'independent though' and sufficient material to meet the requirements of a PhD study. Consequently, understanding how outcomes should be measured will form a significant part of future work, by which point there will be greater clarity regarding some of the approaches that will need to be employed.

Understanding 'how' outcomes should be measured will enable researchers to select appropriate and reliable measurement instruments and further aid evidence synthesis in this field. Whilst for several outcomes the measurement is binary (e.g. recurrence of cancer - yes or no), some outcomes (e.g. nutritional outcomes and quality of life) are a composite of several elements and require multiple or complex scales to reliably measure. Plans are already under way to nest research examining how best to measure nutritional outcomes in a cohort study of patients undergoing gastrectomy for which the author is the lead collaborator. With respect to 'quality of life', much of what is measured is common across different diseases and disciplines. As described above, there is therefore significant scope for collaboration with other COS developers here. The methodology for identifying measurement instruments has not been as extensively studied in comparison to approaches to develop COS. It is likely that there will also be a need for collaborative working by COS developers in this regard with groups such as COMET and COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments – www.COSMIN.nl).

Establishing the time points at which to measure outcomes is also an essential consideration. Chapter 3 identified that this was an area of outcome reporting which was not standardised. Whilst a recent consensus study has been completed recommending the reporting of gastrectomy complications at 30 and 90 days[16], this work was not without its limitations and will require additional development. Furthermore, there is no consensus with respect to timepoints at which other core outcomes such as quality of life, recurrence, survival or nutritional outcomes should be reported. The author plans to address this alongside the identification of outcome measurement instruments.

9.6.3 Uptake and review of the COS

Once a COS is finalised, the next step is ensuring that it is used by trialists and researchers so that the benefits described can be realised. Embedded in the early stages of this study was a strategy to encourage 'buy-in' from a broad range of clinicians and researchers including those with a track record of leading trials in this field. Such individuals were selected to become members of the International Working Group (IWG) and consequently the study was able to find support from numerous international societies and patient groups. Furthermore, the broad range of international stakeholder opinion which was considered aimed to reassure researchers that the final COS was

externally valid and relevant to their study cohorts. The degree to which COS are being adopted is an area of study being undertaken by the COMET Initiative whose work has highlighted the significant role that grant-awarding bodies can have in the uptake of COS[21]. Other groups, notably in the field of women's health research (www.crown-initiative.org), have successfully engaged scientific journal Editors in promoting the value of COS. In practical terms, ensuring that the gastric cancer surgery COS is implemented by trialists will require active promotion and careful monitoring.

Part of the remit of the newly formed COUGAR group will be to promote the gastric cancer COS and ensure that outputs arising from it are widely disseminated amongst researchers, societies and patient groups. Furthermore, ensuring that the COS remains relevant and up to date is vital. Whilst there is no established timeframe before which a COS should be reviewed, the author believes that a review in five years' time is appropriate. As of the 1st of September 2020, www.ClinicalTrials.gov contained 10 surgical trials for gastric cancer registered as 'not yet recruiting' with most planning to be completed by December 2025. Therefore, this period of 5 years should provide sufficient opportunity for the COS study findings to be shared, researchers to begin using the COS and feedback on its use to be gathered. Additionally, none of these trials intend to use radically new types of surgical intervention which would have warranted earlier review of the COS.

9.6.4 Related therapy COS

To extend the benefits of this COS to research which incorporates adjuvant or alternative therapies, it will be vital to develop a COS 'module' which considers outcomes related to chemotherapy and endoscopic resection. Such COS may be undertaken in collaboration across clinical specialities, although there will be disease-specific outcomes that will need to be considered. This will form part of the future working plans of the COUGAR group.

9.6.5 'Meta-COS'

The review at the beginning of this chapter has highlighted the significant overlap and differences between COS within the field of cancer surgery. The GASTROS study has also demonstrated the significant time and financial resource that is required to develop a robust COS. One approach to mitigate these challenges is to develop a broader 'meta-COS' which can be applied to several specialities. A study group has already been established to develop this research area further in which the author is a lead collaborator.

9.7 Final Summary

A COS for surgical trials in gastric cancer has been developed with international patients and healthcare professionals. It is recommended that disease-free survival, disease-specific survival, surgery-related death, recurrence, completeness of tumour removal, overall quality of life, nutritional effects, and complications are reported as a minimum by all future trials in this field. Key methodological considerations for COS developers have been described which may support work in other fields.

9.8 References

1. Avery KNL, Chalmers KA, Brookes ST, et al. Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. Ann Surg. March 2017:1. doi:10.1097/SLA.0000000000002204

2. McNair AGK, Whistance RN, Forsythe RO, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLOS Med. 2016;13(8):e1002071. doi:10.1371/journal.pmed.1002071

3. MacLennan S, Williamson PR, Bekema H, et al. A core outcome set for localised prostate cancer effectiveness trials. BJU Int. 2017;120(5):E64-E79. doi:10.1111/bju.13854

4. Waters AMÍ. A core outcome set for clinical trials in oropharyngeal cancer - The University of Liverpool Repository. https://livrepository.liverpool.ac.uk/3022643/. Published 2017. Accessed September 13, 2020.

5. Van Rijssen LB, Gerritsen A, Henselmans I, et al. Core Set of Patient-reported Outcomes in Pancreatic Cancer (COPRAC): An International Delphi Study among Patients and Health Care Providers. Ann Surg. 2019;270(1):158-164. doi:10.1097/SLA.0000000000002633

6. Alkhaffaf B, Glenny A-M, Blazeby JM, Williamson P, Bruce IA. Standardising the Reporting of Outcomes in Gastric Cancer Surgery Trials: Protocol for the Development of a Core Outcome Set and Accompanying Outcome Measurement Instrument Set (The GASTROS Study). Trials. 2017;18(1):370. doi:10.1186/s13063-017-2100-7

7. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. Trials. 2017;18(S3):280. doi:10.1186/s13063-017-1978-4

8. Blencowe NS, Strong S, McNair AGK, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg. 2012;255(4):658-666. doi:10.1097/SLA.0b013e3182480a6a

9. Fish R, Sanders C, Ryan N, der Veer S Van, Renehan AG, Williamson PR. Systematic review of outcome measures following chemoradiotherapy for the treatment of anal cancer (CORMAC). Color Dis. 2018;20(5):371-382. doi:10.1111/codi.14103

10. Whistance RN, Forsythe RO, McNair AGK, et al. A systematic review of outcome reporting in colorectal cancer surgery. Colorectal Dis. 2013;15(10):e548-60. doi:10.1111/codi.12378

11. Potter S, Brookes ST, Holcombe C, Ward JA, Blazeby JM. Exploring methods the for selection and integration of stakeholder views in the development of core outcome sets: A case study in reconstructive breast surgery. Trials. 2016;17(1):1-11. doi:10.1186/s13063-016-1591-y

12. Coulman KD, Howes N, Hopkins J, et al. A Comparison of Health Professionals' and Patients' Views of the Importance of Outcomes of Bariatric Surgery. Obes Surg. 2016;26(11):2738-2746. doi:10.1007/s11695-016-2186-0

13. Biggane AM, Brading L, Ravaud P, Young B, Williamson PR. Survey indicated that core outcome set development is increasingly including patients, being conducted internationally and using Delphi surveys. Trials. 2018;19(1):113. doi:10.1186/s13063-018-2493-y

14. Etemadi A, Safiri S, Sepanlou SG, et al. The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol. 2020;5(1):42-54. doi:10.1016/S2468-1253(19)30328-0

15. Gargon E, Rhonda Facile, Robby Nieuwlaat J, Schmitt, Holger Schunemann, Lee Simon,

Allison Tong, Jonathan Craig, Caroline Terwee, Peter Tugwell, Sean Tunis PW. The Red Hat Group: an initiative to promote broader uptake of core outcome sets through the healthcare research ecosystem. https://www.comet-initiative.org/UploadedDocuments/06fb6f06-6ce1-42e5-98c2-92fb3b9afb33-RHG EQUATOR_REWARD 2020.pdf. Accessed December 21, 2020.

16. Baiocchi GL, Giacopuzzi S, Marrelli D, et al. International consensus on a complications list after gastrectomy for cancer. Gastric Cancer. 2019;22(1):172-189. doi:10.1007/s10120-018-0839-5

17. Haller G, Bampoe S, Cook T, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: clinical indicators. Br J Anaesth. 2019;123(2):228-237. doi:10.1016/j.bja.2019.04.041

18. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. Br J Anaesth. 2018;120(5). doi:10.1016/j.bja.2018.02.007

19. Buggy DJ, Freeman J, Johnson MZ, et al. Systematic review and consensus definitions for standardised endpoints in perioperative medicine: postoperative cancer outcomes. Br J Anaesth. 2018. doi:10.1016/j.bja.2018.03.020

20. Barnes J, Hunter J, Harris S, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: infection and sepsis. Br J Anaesth. 2019;122(4):500-508. doi:10.1016/j.bja.2019.01.009

21. Hughes KL, Kirkham JJ, Clarke M, Williamson PR. Assessing the impact of a research funder's recommendation to consider core outcome sets. Derrick GE, ed. PLoS One. 2019;14(9):e0222418. doi:10.1371/journal.pone.0222418