ADVANCING CAPSULE ENDOSCOPY IN THE EXAMINATION OF THE UPPER GASTROINTESTINAL TRACT

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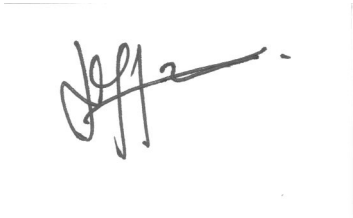
Dedicated to Min Hui

DECLARATION

This dissertation is the result of my own work and it has not been previously submitted, in part or whole, to any university of institution for any degree, diploma, or other qualification. I confirm that I shall abide by the University of Sheffield's regulations on plagiarism and that all written work shall be my own and will not have been PLAGIARISED from other paper-based or electronic sources. Where used, material gathered from other sources will be clearly cited in the text.



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Date: 20/07/2020

ABSTRACT

Advancements in capsule endoscopy technology allow it to image the upper gastrointestinal tract. Oesophagogastroduodenoscopy (OGD) is the gold standard examination, but it is often poorly tolerated and requires sedative premedication. This thesis examines how capsule endoscopy can improve the quality of an upper GI endoscopic examination.

The first study examines the rate of, and factors affecting missed cancer occurrence after conventional OGD. In this retrospective study, a total of 48 (7.7%) of 627 patients with oesophagogastric cancer had OGDs up to three years prior, which are considered missed opportunities to diagnose early neoplasia. Endoscopy sessions with missed cancer occurrence had at least one procedure more when compared to sessions where cancer was subsequently diagnosed or sessions where benign focal lesions were diagnosed.

In the next two studies, we examine the patients experience in a comparative study of tolerance and acceptability between magnet controlled capsule endoscopy (MACE) and conventional OGD (n=44) and transnasal endoscopy (TNE; n=16). By comparison to OGD in Chapter 4 and TNE in Chapter 5, patients were more accepting of and preferred MACE. Patients experienced significantly more distress (greater distress with higher median score) due to gagging (6 vs 1), choking (5 vs 1), abdominal bloating (2 vs 1), instrumentation (4 vs 1), discomfort during (5 vs 1) and after (2 vs 1) OGD when compared to MACE (all $p<0.0001$). Patients undergoing TNE were more distressed by gagging (1.5 vs 1, $p=0.03$), choking (3 vs 1, $p=0.001$), instrumentation (4.5 vs 1, $p=0.001$), discomfort during (5 vs 1, $p=0.001$) and after TNE (2 vs 1, $p=0.01$) by comparison to MACE.

A small bowel examination can be performed immediately after an upper GI MACE. It is hypothesised that laxative pre-procedure preparation may benefit small bowel mucosal visualisation, although likely to impact on tolerability and acceptance. The fourth study examines how to optimise an upper GI MACE examination to investigate

the small bowel. In advance of a small bowel capsule endoscopy, 186 patients were randomised to three pre-procedure preparation groups: clear fluids only or a single or split dose of polyethylene glycol (PEG) the examine the need for laxative pre-procedure medication. Split dose PEG improved distal small bowel mucosal views and overall adequacy of examination compared to clear fluids alone, although patients tolerated better and were more accepting of the later.

Acceptance of novel technology may be prohibited by cost. In the final study, we perform a cost minimisation analysis to examine how the cost of MACE compares to TNE and OGD, and examine in scenario analyses the potential effects of the COVID-19 pandemic and need for endoscopic biopsies on cost. We found that per procedure, MACE was most expensive (£329.40), followed by OGD (£121.67) and TNE (£90.10). As a result of the COVID-19 pandemic, the costs of OGD and TNE would rise by between 27% to 112% depending on changes in endoscopy capacity. In scenario analyses, cost parity between MACE and OGD could be reached if the price of single use capsule endoscopes fell by two thirds. If endoscopy capacity fell to 40%, cost parity could be reached if the price of capsule endoscopes fell by a third.

This thesis supports the use of MACE in the upper GI tract from the perspective of a superior patient experience compared to conventional OGD. Further improvements in imaging technology and reduction in cost of MACE will advance capsule endoscopy in the examination of the upper GI tract.

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PUBLICATIONS ARISING FROM THE BODY OF WORK PRESENTED IN THIS THESIS

The body of two chapters have been published and are reproduced in part (chapter 1) or in whole (chapter 3) with minor additions, explanations and references. Permission to include the publications in this thesis has been sought and approved by all named co-authors and publishers.

Mine and others contributions to each thesis chapter are summarised below:

Chapter 1: Tai FWD, Ching HL, Hale MF, McAlindon ME. Upper gastrointestinal endoscopy: can we cut the cord? Lancet Gastroenterol Hepatol. 2019;4(10):749-51.

Chapter 3: Tai FWD, Wray N, Sidhu R, Hopper A, McAlindon M. Factors associated with oesophagogastric cancers missed by gastroscopy: a case-control study. Frontline Gastroenterol. 2020;11(3):194-201.

I designed the study, collected data with the assistance of Nicholas Wray, analysed the data and wrote the manuscript.

Chapter 4: Professor McAlindon conceptualised the study and sought ethics approval. Hey Long Ching performed 18 of 44 MACE procedures. The remaining procedures, data collection, analysis and written manuscript (in submission) was undertaken by myself.

Chapter 5: I sought a substantial amendment for the study reported in Chapter 4, performed all MACE and TNE procedures, collected data, analysed and wrote the manuscript in submission.

Chapter 6: Professor McAlindon conceptualised the study, sought ethics approval and analysed capsule videos. With the assistance of Nicholas Wray, I co-ordinated the trial, collected and analysed data, and have written the chapter.

Chapter 7: I designed the study, collected and analysed data, and wrote the chapter.

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List of Abbreviations and Acronyms

AGP	Aerosol generating procedure	MM	Mark McAlindon
CAC	Computed assessment of cleansing	MRI	Magnetic resonance imaging
CE	Capsule endoscopy	NHS	National Health Service
CEU	Clinical effectiveness unit	NOGCA	National oesophagogastric cancer audit
CI	Confidence interval	NSAID	Non-steroidal antiinflammatory drugs
CMOS	Complementary metal oxide semiconductor	OAA	Overall adequacy of assessment
CONSORT	Consolidated Standards of Reporting Trials	OGD	Oesophagogastro duodenoscopy
COVID	Coronavirus disease	OR	Odds ratio
CT	Computed tomography	PEG	Poyethylene glycerol
ECS	Endoscopy concerns score	POUGIC	Post OGD upper GI cancer
EGC	Early gastric cancer	PPE	Personal protective equipment
EMR	Endoscopic mucosal resection	PREM	Patient reported experience measures
FPS	Frames per second	QE	Qualitative evaluation
FWDT	Foong Way David Tai	QI	Quantitative index
GI	Gastrointestinal	SB	small bowel
GTT	Gastric transit time	SBTT	Small bowel transit time
HADS	Hospital anxiety and depression score	SD	Standard deviation
IDA	Iron deficiency anaemia	SMT	Submucosal tumour
INR	International normalised ratio	SPSS	Statstical Product and Service Solutions
IPC	Infection prevention and control	TNE	Transnasal endoscopy
IQR	Interquartile range	TNM	Tumour Node Metastasis
JAG	Joint advisory group	UK	United Kingdom
LED	Light emitting diode	UPCQ	Universal patient centredness questionnaire
MACE	Magnet controlled capsule endoscopy	USA	United States of America

LIST OF APPENDICES

1 INTRODUCTION

Upper gastrointestinal (GI) endoscopy involves examining the upper gastrointestinal tract from the upper oesophagus to the second part of the duodenum. Conventional upper GI endoscopy, gastroscopy or oesophagogastroduodenoscopy (OGD) requires intubation of the upper oesophagus using a flexible endoscope which is achieved conventionally through the mouth, over the tongue and via the oropharynx. This gold-standard examination however can be uncomfortable and poorly tolerated amongst patients who often opt for conscious sedation. An alternative technique for examining the upper GI tract, like transnasal endoscopy (TNE) is less intrusive. TNE makes use of a thinner flexible endoscope which is passed into the oesophagus through the nasal passages and via the nasopharynx.

Capsule endoscopy differs from flexible endoscopy. A light emitting diode (LED) light source and image sensors powered by a battery contained within a pill transmits images wirelessly. Wireless capsule endoscopy (CE) has now been used to explore the small intestine for 20 years [1]. This routine examination of the small intestine has led to the adaptation of the capsule endoscopy platform towards other parts of the GI tract, such as the colon [2] and recently the upper GI tract. This thesis appraises the role of conventional flexible upper GI endoscopy and examines the impact of capsule endoscopy on the quality of care in upper GI endoscopy.

1.1 Conventional upper GI endoscopy

Conventional Oesophagogastroduodenoscopy (OGD) is the current gold-standard in endoscopic diagnosis of luminal upper GI disease. In symptomatic patients, OGD can help to differentiate between endoluminal disease from symptoms of dysmotility, neuroenteric and functional disorders. Common indications for OGD include symptoms of dyspepsia, a syndrome including upper abdominal discomfort, pain, bloating and heartburn, dysphagia, iron deficiency anaemia or weight loss. In the United Kingdom (UK) 0.8% of the population undergo OGD every year and this has seen a 40% increase in procedures performed in the last 10 years (Figure 1). One of the main roles of OGD is distinguishing benign from malignant disease. Up to 2% of patients are found to have oesophagogastric malignancy [3,4].

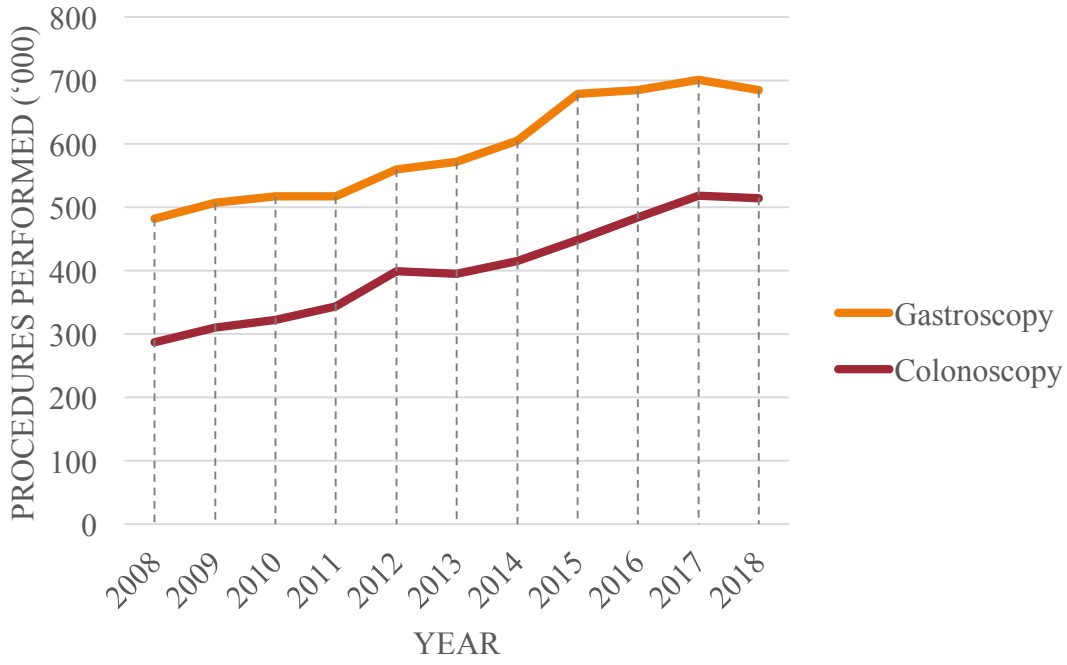


Figure 1: Number of OGD and colonoscopy procedures performed in the UK National Health Service (NHS) from 2008 to 2018

Depending on local incidence, OGD has also an evolving role in the surveillance for and screening of pre-malignant pathologies, which can give rise to oesophageal and gastric adenocarcinoma in the order of 0.2% per patient per annum.[5,6]

1.1.1 Oesophagogastric malignancy

There is a variation in the incidence of oesophagogastric (OG) malignancy worldwide. Oesophageal and gastric cancers overall are the 13th and 17th most common malignancy in the UK and are diagnosed in 0.7% of patients who present to primary care with alarm features [7,8]. Incidence of gastric adenocarcinoma is on the decline in the UK, however there is an increase in oesophageal adenocarcinoma due to an increasing prevalence of Barrett's oesophagus [9,10]. Both oesophageal and gastric cancers have poor prognoses in the UK. They present in the more advanced stages (TNM stage 3 and 4) in 75% [11,12] with up to a third of patients diagnosed after an emergency admission to secondary care. [13] Curative treatment is only suitable in a select 30-40%, with only 20% undergoing surgical treatment [14] and an overall 5-year survival rates of 15% and 20% respectively. [8]

In contrast, the incidence of gastric cancer is over 6 times greater in Japan than the UK with estimated age standardised incidence of 29.9 compared to 4.7 per 100,000 population in the UK [15]. In Japan, the high burden of gastric cancer and, in part, vigilant population based fluoroscopic and endoscopic screening have meant that over 50% of gastric cancers on diagnosis are confined within the mucosa or submucosa (Tumour Node Metastasis TNM stage 1a and 1b) [16]. Such early neoplasia is amenable to surgery or endoscopically organ preserving resection techniques which effectively cure early OG neoplasia with 10-year overall survival rates of 95% [17]. The success of health screening strategies depends on the performance of the screening tool, the incidence of disease, but also uptake of the screening test. Tests which are better accepted and tolerated by patients are more likely to be associated with greater uptake.[18] Less invasive methods of screening by comparison to conventional endoscopy are expected to be better accepted and therefore may support screening efforts for upper GI malignancies. Attempts at screening for Barrett's oesophagus using novel technologies

such as Cytosponge™ [a] have been well accepted by patients, [19] while transnasal endoscopy and oesophageal capsule endoscopy are preferred by patients than conventional OGD, [20,21] therefore may play a role in the prevention of oesophageal cancer.

1.1.2 Post OGD Upper GI Cancer: How gold is the gold standard?

Studies of patients diagnosed with OG malignancy have shown that there is a rate of missed cancer with gastroscopy. Fujita (1978) proposed that early gastric cancers (EGCs) have a superficial growth pattern where the majority of cells are on the surface of the gastric mucosa and spread laterally [22]. He proposed that the cellular doubling time of EGCs are estimated at 2-3 years, limited by the mechanical abrasion and desquamation of the epithelial wall when spreading laterally at its early stages. This is in contrast to the growth pattern of advancing cancers, which penetrate into the tissue, limited only by the supply of nutrients and oxygen, and therefore have a cellular doubling time amounting to months. It is believed therefore that an early (or advanced) gastric cancer seen on endoscopy would have been visible one year prior and potentially up to three years prior to endoscopic diagnosis

In Western populations, single centre studies [23-28] and pooled meta-analysis [4] report that between 5.3 and 13.9% of patients with OG malignancy have had a seemingly negative OGD within three years of OG cancer diagnosis and are termed Post-OGD Upper Gastrointestinal Cancers (POUGIC). These diagnoses are therefore considered to be potential missed diagnoses if the OGD was performed within one to three years, and definitely missed diagnoses when performed within one year of the diagnostic OGD [25].

Recent data from UK wide population based registry studies report oesophageal and gastric cancer are missed within the previous three years in 8.3% and 7.8% respectively

[a] The Cytosponge is an ingestible gelatine capsule containing a compressed mesh attached to a string. Five minutes after ingestion the capsule dissolves and the spherical mesh is retrieved back up the oesophagus collecting cytological samples along the length of the oesophagus for analysis.

[11,12]. Missed cancer occurrence are associated with the presence of alarm features [25,27], female gastric cancer patients under the age of 55 years [11] and early disease (TNM T 0/1 stage) at diagnosis [11,12]. In between 30 to 70% of POUGIC procedures, abnormalities have been described at the site of malignancy and therefore endoscopist (missing a lesion, not sampling a visible lesion or inadequate sampling) and histopathologists error could explain up to 70% of POUGICs [25,27]. The reasons for these 'errors' however are not entirely clear and subject to substantial discussion on how to improve the quality of OGDs and facilitate earlier detection OG cancer.

1.2 Factors affecting the quality of conventional OGD

What is a high-quality endoscopy? The three dimensions of quality of care are safety, clinical effectiveness and patient experience [29] and so a discussion about a high quality of endoscopy depends on perspective. From a clinical perspective a technically high-quality endoscopy can be considered one where *"patients receive an indicated procedure, correct and relevant diagnoses are recognized or excluded, any therapy provided is appropriate, and all steps that minimize risk have been taken."* [30]

On the other hand, a high-quality endoscopy can also be seen from the patients' perspective where a positive patient experience can be defined as one that involves the whole team getting to know the patient as an individual, tailoring their care accordingly, while building lasting relationships which enable patients to participate in their care [31]. In this section, we discuss the factors that affect the quality of upper GI endoscopy from both a technical and a patient experience perspective.

1.2.1 Factors which affect a technically high-quality OGD

Advancements in endoscopic imaging technology has led to optical near focus magnification and optical chromoendoscopy. With an ever-expanding arsenal of tools at our disposal there has been an appropriate interest to review the basics techniques in upper GI endoscopy and formalise quality measures around the world with a specific focus on improving the sensitivity of gastroscopy in pathology detection. [32-34]

1.2.1.1 Examination time

Studies have suggested that endoscopist performing procedures quickly increases the risk of missed pathology.[35,36] One retrospective study of neoplastic findings on OGD have suggested that endoscopists who performed procedures lasting over seven minutes have a threefold increase in detection of gastric neoplasia (OR 3.4; 95% CI 1.2 – 10.3) and were twice as likely to detect high risk lesions (OR 2.5; 95% CI 1.5 – 4.1) compared to quicker endoscopists [37]. An inspection time of more than 1 minute per centimetre (cm) of Barrett's oesophagus increases detection of high grade dysplasia and adenocarcinoma [36]. Similarly, colonoscopist who have a mean extubation time of greater than six minutes have been shown to detect a greater number of colorectal adenomas and cancers than their swifter counterparts [35]. Therefore, it is reasonable to conclude that longer procedure times can be a surrogate for a more thorough and detailed examination.

1.2.1.2 Endoscopist experience

It is logical however that the duration spent examining the upper GI tract is only as effective as the experience of the endoscopist in detecting pathology. Case series and population based studies have suggested lower rates of POUGIC associate with endoscopists with more than 10 years' endoscopy experience [38], medical (versus surgical) endoscopists [39] and procedures performed at specialist centres [40,41]. On the other hand, Teh et al. amongst others [25,41] have not found that endoscopist experience nor professional background (medical or surgical) contributed significantly to rates of POUGIC. Endoscopist experience is clearly associated with colonic polyp detection rate [42-44] and there is some evidence that it is associated with better diagnostic capability in OGD. Two studies have concluded that training and experience in gastroscopy does correlate with the ability to detect *Helicobacter pylori* infection and gastric intestinal metaplasia [45,46], both potentially premalignant conditions, requiring recognition of subtle endoscopic features. However, it is also likely that even with increasing experience or "seniority", without recognition of the importance of continuous personal and professional development and personal reflection, the nuances in detecting subtle neoplasia may be lost and result in a less accurate examination.

1.2.1.3 Patient co-operation and tolerance to OGD

That time spent inspecting the upper GI tract is one of the most important factors in the sensitivity of OGD, it makes sense that a distressed patient will limit ease of endoscopy and duration of inspection. Intravenous sedation can be used to augment patient tolerance to the procedure and benzodiazepines are the most commonly used non-dissociative class of sedative for which there are four recognised states of sedation. Minimal sedation is a mild anxiolytic and the patient is fully alert. A deeper, moderate or conscious, sedation is a state of sleepiness aroused by voice or light touch. Deep sedation is defined by a patient requiring painful stimuli to evoke a purposeful response, where otherwise spontaneous ventilation may often be inadequate. The use of moderate sedation is a satisfactory compromise and is widely considered to improve the quality of endoscopy, although most of the evidence relates to improvement in completion and adenoma detection rates in colonoscopy [47-49]. The use of sedation however does not seem to have an effect on the ease of OGD for the endoscopist [50-52], with pharyngeal local anaesthetic being most beneficial in improving technical adequacy by reducing patient retching. [53] However, there are no studies examining the effect of patient tolerance on pathology detection and few studies on the technical success of OGD. One study of unsedated patients suggested that after an examination time of 4 minutes a technically adequate examination could be achieved in 96%, and although 80% would repeat again unsedated, satisfactory tolerance was only reported in 61%. [54] Taken together therefore, where best practice suggests that inspection times should be increasing, it is likely to be at the cost of an acceptable patient experience. Patient acceptance may be improved with re-introduction of historical deeper sedation practices [55], but at the expense of patient safety, recovery time and costs. Nevertheless, a study of colonoscopy has suggested that more experienced endoscopists performed more comfortable procedures with less sedation use and a higher completion rate suggesting that technique and experience are also fundamentally important [56].

1.2.2 A high-quality upper GI endoscopy: a patient experience

Patient experience is the third pillar of quality of care, but less well understood in upper GI endoscopy. We consider here, the different measures of patient experience and then appraise the tolerance and acceptability of conventional OGD.

1.2.2.1 Measures of patient experience in endoscopy

The aim of understanding patient experience in endoscopy is to direct feedback towards promoting positive clinical practices. Measures of patient experience can help identify and contextualise factors associated with positive or negative experiences. The most common measure of the quality or experience in endoscopy care is patient satisfaction of the procedure [57]. Patients satisfaction are likely to occur if the healthcare encounter meets patients expectations with positive outcomes. [58,59] Meeting these expectations have been shown to result in positive health behaviours, improved clinical response and adherence to treatment [60,61] and accordingly, an unmet expectation is associated with lower satisfaction and weaker intentions to adhere to management.[62] In theory therefore, a patient with negative expectations but positive outcomes could be expected to have greater satisfaction than a patient with positive expectations and similarly positive outcomes. However, equally it may be that patients with positive expectations are more primed towards being satisfied with a positive outcome than those with negative expectations.[63] Patient satisfaction and willingness to repeat an endoscopy however are not synonymous measures of patient experience.[64] If the aim of examining patient experiences is to improve on the delivery of quality care, patient's expectations set too low or too high, may mean their satisfaction may be too insensitive to recognise deficiencies in their care. Therefore, patient acceptance or willingness to repeat an investigation would be a preferred indicator of future behaviour compared to satisfaction.

In an attempt to understand what influences patient acceptance, specific constructs related to endoscopy such as anxiety prior to endoscopy and adverse symptoms (of discomfort or pain) before, during and after the endoscopic procedures are commonly

measured. Patients experiences of endoscopy are however more comprehensive than just procedural tolerance [65] and endoscopists consistently overestimate the importance of adverse physical symptoms. [66,67]

Measures of patient acceptance in endoscopy, such as the Endoscopy Concerns Scale (ECS) score, were therefore devised to account for distresses peripheral to the tolerance of the procedure such as embarrassment, pre-procedure fasting, and intravenous cannulation; and to account for all stages of the healthcare encounter including pre-procedure preparation and post procedure care. [65] The content validity of PREM tools such as the ECS may be questioned. That most studies which examine patient experience are framed in the context of procedural tolerance is unsurprising. Tools like the ECS are often based on clinical, but less often patient opinion, and on self-perpetuating literature review. [57] Therefore understanding the aspects of a healthcare encounter that is valued by and importantly, framed by the patients can therefore more accurately reflect their experiences. The Universal Patient Centeredness Questionnaire (UPC-Q) is a patient reported experience measure (PREM) where patients determine up to three noteworthy aspects of the healthcare experience, rates their experience and ranks the aspects by their relative importance. [68] This patient generated index has been shown to have construct validity when compared to measures of experience, satisfaction and self-perceived health amongst hospital and psychiatric inpatients, and primary care outpatients, but has not been validated in hospital outpatient settings.

1.2.2.2 Patient experience of conventional OGD

The literature on patient experience is dominated by studies examining procedure tolerance. When asked, patients in fact prioritise the technical skill and personal manner of the endoscopist over control of discomfort. [66,69,70] Furthermore, less priority is given to waiting times prior to and on the day of the appointment, privacy and single sex environments. These findings are consistent in with both upper and lower GI endoscopy, with no difference amongst those undergoing with or without sedation[71].

During conventional OGD, discomfort and retching are often experienced due to the triggering of the gag-reflex as the endoscope stimulates the oro-pharynx. OGD is

feasible for many patients with topical oro-pharyngreal anaesthesia alone, however many highly motivated patients find OGD uncomfortable despite their willingness to repeat the OGD under the same conditions. [54] Pharyngeal sensitivity (defined as pharyngeal constriction with application of topical oropharyngeal anaesthetic), younger age and pre-procedural anxiety have been suggested to predict poor tolerance to unsedated OGD [54,72]. Sedation practices for diagnostic OGD vary considerably worldwide. Virtually all procedures are done under sedation in United States and Australia, but in less than a quarter of procedures in surveyed European countries. [73,74] In the United Kingdom, data from the National Endoscopy Database pilot suggest that in 2018, around 50% of patients opted for conscious sedation (personal communication: Dr Keith Siaw). Sedation may improve patient experience. In a meta-analysis of randomised control trials of moderate sedation in endoscopy, only 2 studies were identified examining the use of sedation against placebo in OGD. It showed that patients were over two-fold more likely to be satisfied with, and 25% more likely to be willing to repeat OGD with sedation compared to without. [55] A number of other studies have examined the effect of sedation on patient tolerance for OGD and broadly report that patient comfort is improved by use of sedation. [50,51,53,75] In the largest of these studies (340 patients), Ristikankare et al. (2004) report that midazolam significantly reduces the difficulty of intubation and discomfort experienced by the patient compared to placebo and control.

1.2.3 The safety of conventional OGD

Diagnostic OGD is safe and adverse events occur in between 0.01 – 0.5% of cases [76]. The majority are cardiopulmonary adverse events related to sedation and these occur in the order of 0.3% of sedated procedures. [77] Luminal perforation occurs in up to 0.04% of diagnostic procedures. [78] A recent study has suggested that up to 1% of patients undergoing OGD are treated for an infection within 30 days of OGD, five times greater than patients undergoing a non-invasive screening mammography. [79] Most of these infections were respiratory tract infections and 60% required hospitalisation.

1.3 Less invasive alternatives in upper GI endoscopy

OGD is uncomfortable and although rare, is associated with significant risks of aspiration and infection. Less invasive alternatives in upper GI endoscopy, transnasal endoscopy (TNE) and capsule endoscopy are appraised in the following sections, with a detailed review on the advancements in capsule endoscopy and the clinical effectiveness of capsule endoscopy in the investigation of the upper GI tract.

1.3.1 Transnasal endoscopy

Transnasal endoscopy use is increasing worldwide. In Japan where enthusiasm for TNE originated, a third of outpatient clinics offer TNE outside of a formal endoscopy setting [80]. The use of an ultrathin diameter endoscope allows upper GI endoscopy to be performed through the nasal passages after dilatation and anaesthesia of the nasal passages with a topical decongestant and local anaesthetic (Figure 2). The benefit of this passage of insertion is that the nasopharynx avoids the gag-reflex triggered by afferent stimulation of structures supplied by the 9th cranial nerve within the oro-pharynx.

Figure 2: Standard gastroscope and ultra-thin transnasal gastroscope

A 11mm diameter standard gastroscope (left) compared to a 5.9mm ultra-thin transnasal gastroscope (right)

The technical performance of TNE is comparable to conventional OGD. The technical success rate of TNE with a less than 5.9mm diameter endoscope is 98% and in comparison, no different to OGD [21]. The diagnostic yield of Barrett's oesophagus and oesophageal varices are similar between the two modalities [81,82]. One study comparing high resolution OGD with TNE suggested TNE was inferior in detecting superficial gastric neoplasia [83]. Earlier generation transnasal endoscopes were challenged by less numerous optical fibre bundles and charged coupled device pixels resulting in insufficient mucosal illumination and image resolution of capacious areas of the stomach, for example at the fundus. However, follow up studies comparing new generation transnasal endoscopes with near focus magnification and narrow band imaging have since reported similar performances between ultrathin and conventional endoscopes. Transnasal passage however does mean there is additional risk of self-limiting epistaxis in between 2-5% [84-86] rising to 14% in 28 patients with significant bleeding diathesis (platelet count <50 and or INR >1.7) secondary to chronic liver disease [82].

Patients undergoing TNE find the experience highly acceptable with 85% willing to undergo TNE again the in future and 63% preferring TNE over OGD. [21] Further, the use of sedation with OGD does not affect preference between TNE and OGD. [21] Due to superior patient tolerance, TNE is usually performed without sedative premedication, thereby eliminating sedative related adverse events. The TNE procedure also seems to be less physiologically stressful with a smaller rise in pulse rate and systolic blood pressure during the procedure compared to OGD [87,88].

1.3.2 Capsule endoscopy

Capsule endoscopy is a non- invasive procedure where the GI tract is examined using a wireless pill sized capsule endoscope swallowed by the patient. Its principal components are a battery, an array of LEDs, an antennae and transmitter for wireless or electric field propagation of images, and an image sensor – most commonly a complementary metal oxide semiconductor (CMOS). Originally introduced in 2000 to image the small bowel, the first model (M2A capsule, Given Imaging, Yoqneam, Israel)

acquired two images per second and sent images wirelessly to a portable data recorder [1,89,90].

Although non-invasive, complications do occur with capsule endoscopy. Capsule retention occurs in about 1% when used for small bowel examinations, [91] more commonly when examining patients with suspected or established Crohn's disease. [92] Bronchial aspiration of capsules occur much less frequently. A review of case reports estimates that it occurred in 0.1% of patients at most, usually in men over 80 years of age. [93] However, devices were spontaneously expectorated by half the patients, and the remainder needed bronchoscopic removal with no fatalities reported.

1.3.2.1 The challenges of upper GI capsule endoscopy

In the tubular small bowel, video capsules are propelled passively by peristaltic movements in a relatively unidimensional plane. The capsules of around 25 x 10mm in dimension pass through a 25-30mm diameter small bowel and therefore have minimal side to side movement. Even when rotated at an angle away from the lumen, modern small bowel capsule endoscopes have a wide 150-170° field of view so the immediate mucosal surface is splayed up against peripheries of the optical dome with upcoming mucosa in the centre view.

The upper GI tract is made of three distinct areas, the oesophagus, stomach and duodenum, and each have their own challenges to visualise with a capsule endoscope. The stomach is a capacious hollow viscus with an unusual configuration, is collapsed in the fasted state and gravity dictates that a capsule rapidly locates to the dependent part. In contrast both the oesophagus and duodenum are tubular structures and while transit is relatively stable, the effects of gravity and peristalsis propel capsules quickly. It was recognised early that the rapid oesophageal transit of capsules (as fast as 20cm per second in the proximal oesophagus) along with a lack of orientation control of single sensor capsules meant that complete assessment of the oesophagus was unreliable [94,95]. The developments in capsule imaging technology have therefore had to simultaneously

address the challenges of negotiating the whole surface area of the stomach and potential rapid transit through oesophagus and duodenal bulb.

Advancements in capsule endoscopy imaging technology have resulted in measurable improvements. An increase in frame acquisition from two per second and an eight hour battery life in the PillCam SB2 (Given Imaging, Yoqneam, Israel) to 2-6 (variable rate) frames per second and a 12 hour battery in the PillCam SB3 (Given Imaging) resulted in an increased small bowel completion rate [96] and diagnostic yield for small bowel pathology [97]. When two image sensors, one at each end are used, improvements in the detection of small bowel lesions [98] and the ampulla of Vater [99] can also be demonstrated.

To date there have been several approaches to achieving a complete upper gastrointestinal tract examination with capsule endoscopy. Upper GI capsule endoscopy systems in clinical practice are described in Table 1. Key technological developments in imaging technology include improvements in battery life, optics and image sensor, along with external control of capsule endoscopes have been feasible due to addition of real time view and capsule endoscopes with magnetic inclusions. These developments are summarised in a timeline (Figure 3). Key clinical studies discussed in the following chapters comparing upper GI capsule endoscopy to conventional OGD are summarised in Table 2.

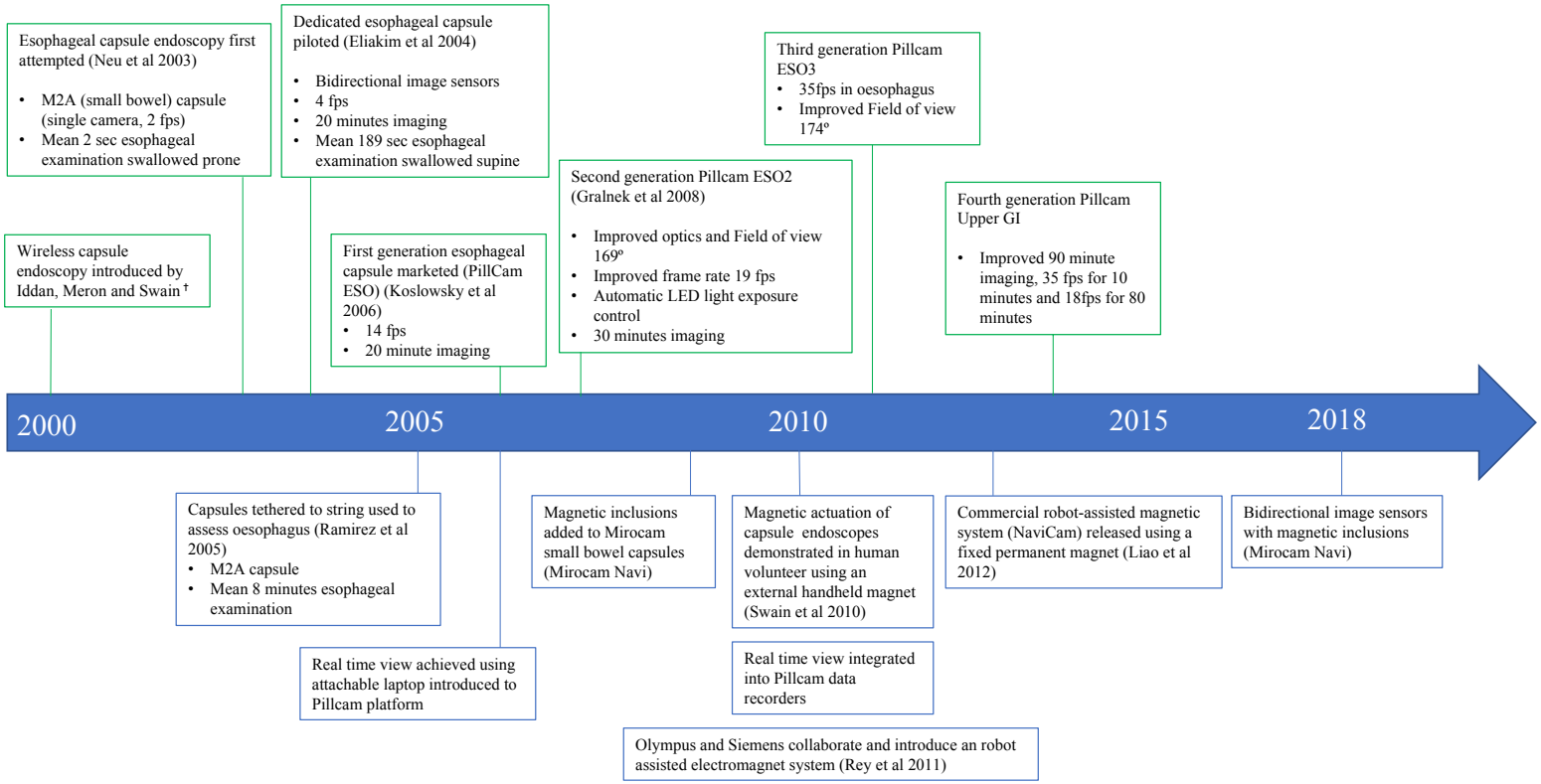


Figure 3: Key advances leading towards a wireless oesophagogastro duodenoscopy

† First human studies using wireless capsule endoscopy was reported in Nature in 2000 after collaboration between Paul Swain in UK and Gavriel Iddan, Gavriel Meron and Arkady Glukhovsky in Israel. Since then advancements in imaging technology in green and external control in blue (boxes above) have lead to the ability to image the upper gastrointestinal tract.

Table 1: Technical specifications for upper GI capsule endoscopes in the literature

	Image			Capsule			Control			
	Frame rate (fps)	Sensors / number of sensors	Resolution (pixels)	Field of view (degrees) / depth (mm)	Size (mm) / weight (g)	Battery life (hours)	Transmission	Type	Control	Field strength
Pillcam ESO	14	CMOS / 2	NR	140/ 0.1-30	11 x 26 / 2.9	0.33	RF	-	-	-
Pillcam ESO 2	19	CMOS / 2	256 x 256	169/ 0.1-30	11.4 x 26.4 / 2.9	0.5	RF	-	-	-
Pillcam ESO 3	35 / 18 *	CMOS / 2	256 x 256	172 / 0.1-30	11.6 x 31.5 / 2.9	0.5	RF	-	-	-
Pillcam UGI	35 / 18 *	CMOS / 2	256 x 256	172/ 0.1-30	11.6 x 32.3 / 2.9	1.5	RF	-	-	-
Mirocam MC-1000WM (Intromedic)	3	CMOS / 1	320 x 320	170/ 0-30	25 x 11 / 3.2	>11	EFP	Fixed	Handheld	0.2T
Olympus-Siemens MGCE	4	CCD / 2	NR	NR	31 x 11 / NR	0.5	RF	EM	Robot	100mT
Ankon Technologies AKT-1 NaviCam	2	CMOS / 1	480 x 480	>120 / 0-30	28 x 12 / 5	>8	RF	Fixed	Robot	200mT

*35 fps for the first 10 minutes and 18 fps for last 80 minutes. CMOS; complementary metal oxide semiconductor, CCD; charged coupled device, MGCE; Magnetic Guided Capsule Endoscope, RF; radiofrequency, EFP; electric field propagation, EM; electromagnet, mT; milliTesla, NR; not reported.

Table 2: Clinical studies comparing capsule endoscopy against conventional OGD

	Study			Outcomes					
	Reference	Type	Participant numbers, types and indications	Examination duration*	Landmark Views	SAE	Comparator	Tolerance and acceptability	Pathology detected
Oesophagus									
Pillcam ESO I + II (Medtronic)	Bhardwaj et al. (2009) [20]	Meta-analysis	618 patients, 9 studies, Screening and surveillance of Barrett's Oesophagus	Oesophageal transit time 1 – 1678s	NR	None reported	2 studies – histology and OGD, 2 studies histology only, 5 studies – OGD only	3 studies; all show majority preferred CE	Pooled specificity 86% and sensitivity 77% for Barrett's Oesophagus
	Lu et al. (2009) [100]	Meta-analysis	446 patients, 7 studies, Screening and surveillance of Oesophageal Varices	Oesophageal transit time 135 – 251s	NR	NR	Blinded OGD	NR	Overall pooled specificity 81% and sensitivity 86% for OV Screening OV patients only (4 studies; 106 patients) pooled specificity 55% and sensitivity 83%
Mirocam MC-1000WM (Intromedic)	Beg et al. (2018)[101]	Pathology enriched, blinded, self-controlled comparison	17 Barrett's oesophagus, 17 Oesophageal Varices, 16 healthy controls	3m (NR – 10m)	NR	None reported	Blinded OGD	Comfort VAS score CE vs OGD (1-10 least to most) 9.2 vs 6.7. 78% preferred CE to OGD, 22% no preference	Oesophageal varices – specificity 97% sensitivity 73% Barrett's Oesophagus - specificity 100% sensitivity 100%

(continued)	Reference	Type	Participants	Examination duration*	Landmark Views	SAE	Comparator	Tolerance and acceptability	Pathology detected
Stomach									
Mirocam MC-1000WM (Intromedic)	Ching et al. (2018) [102]	Blinded, self-controlled, single centre	50 Recurrent and refractory Iron deficiency anaemia	23m (1-60)	Landmark view of Oesophagus 90%, OGJ 53%, Cardia 96%, Fundus 98%, Greater curve 98%, Lesser curve 98%, Anterior body 98% Posterior body 98% Antrum 100% Pylorus 100% D1 100% D2 100%.	None reported	Blinded OGD	Median VAS score CE vs OGD (0-10; None – extreme) Pain 0 vs 2. Discomfort 0 vs 3 Distress 0 vs 3	n=63 significant findings, **22/63 CE and OGD** (16 Gastritis, 2 oesophagitis, one duodenal atrophy, one duodenitis, one angioectasia, one with bleeding in duodenum) **OGD only 12/63** (2 Gastritis, 2 oesophagitis, one angioectasia, one duodenitis, one duodenal ulcer) **CE only 33/63** (2 oesophagitis, 13 gastritis, 4 gastric ulcers, 6 angioectasia, 2 atrophy, 3 duodenitis, 2 duodenal ulcers, one with altered blood in stomach)
	Ching et al. (2019) [103]	Blinded, self-controlled, single centre	33 Upper GI bleeding	20m (NR)	Landmark view of Oesophagus 64%, OGJ 33%, Cardia 94%, Fundus 97%, Greater curve 97%, Lesser curve 97%, Anterior body 97% Posterior body 97% Pylorus 97%% D1 100% D2 100%.	None reported	Blinded OGD	Median VAS score CE vs OGD (0-10; None – extreme) Pain 0 vs 2. Discomfort 0 vs 3 Distress 0 vs 4	n=51 significant findings, **13/51 CE and OGD** (3 oesophageal varices, 3 erosive gastritis 3 gastric ulcers, 2 gastric varices, 3 duodenal ulcers and one with blood in lumen) **11/51 OGD only** (2 oesophageal varices, 2 erosive gastritis, one gastric ulcer, 2 angioectasia, 3 duodenal ulcers, one erosive duodenitis. **26/51 CE only** (one oesophageal varix, one oesophageal ulcer, 8 erosive gastritis, 2 angioectasia, 5 erosive duodenitis, 4 duodenal ulcers, one duodenal varix, 4 with blood in lumen.

(continued)		Type	Participants	Examination duration*	Landmark Views	SAE	Comparator	Tolerance and acceptability	Pathology detected
Stomach									
Olympus-Siemens MGCE	Rey et al. (2012) [104]	Blinded, self-controlled single centre	61 patients with indication for UGI examination	17m (10-26)	Complete view of Cardia 89%, Fundus 85%, Body 93%, Antrum 87%, Pylorus 89%	One patient vomited after ingestion of water	Blinded OGD	97% preferred CE	n=108 pathological findings, **63/108 OGD and CE** (44 gastritis/erosions, 8 polyps, 3 ulcers, 4 atrophy, 2 antral metaplasia and one external compression) **14/108 OGD only** (2 polyps, 2 angioectasias, 2 atrophy, 2 hypertrophic folds, 2 antral metaplasia, one gastritis, one bile reflux). **31/108 CE only** (11 polyps, 10 gastritis, 5 ulcers, 2 bleeding lesions, one metaplasia, one angioectasia, one hiatal hernia)
	Denzer et al. (2015) [105]	Blinded, self-controlled single centre	189 symptomatic patients	10m (10-11)	Complete view of Cardia, Fundus, Body, Antrum and Pylorus views ranging 93 -98% complete	None reported	Blinded OGD with propofol sedation	1.2 CE vs 1.7 OGD (Acceptability 1 – 10; excellent to very poor) 100% preferred CE	**Major lesions** (tumours, ulcers, angioectasias) specificity 94% sensitivity 62% **Minor lesions** (multiple and diffuse) FCGP - specificity 87% sensitivity 76% Gastritis - specificity 75% sensitivity 94% Atrophy - specificity 99% sensitivity 29%

(continued)		Type	Participants	Examination duration	Landmark Views	SAE	Comparator	Tolerance and acceptability	Pathology detected
Stomach									
Ankon Technologies AKT-1	Zou et al. (2015) [106]	Blinded, self-controlled, two centres	68 symptomatic patients	29m (8-53)	NA	None reported	Blinded OGD	NA	n=68 pathological findings, **OGD and CE 53/68** (34 erosions, 10 polyps, 4 mucosal protuberances, 3 atrophy, one external compression and one bleeding) **OGD only 7/68** (3 erosions, 2 ulcers, one atrophy and one mucosal protuberance) **CE only 8/68** (6 erosions, one polyp, one mucosal protuberance)
	Liao et al. (2016) [107]	Blinded, self-controlled, multi-centre	350 symptomatic patients	26m (20-33)	Good view (score 3/3) in Cardia 75% Fundus 73% Body 89% Incisura 92% Antrum 97% Pylorus 98%	One CE retrieved due to duodenal ulcer stenosis (1/350)	Blinded OGD	95.7% preferred CE, 1.1% preferred OGD 3.1% no preference	**Overall** gastric focal lesions specificity 95% sensitivity 90%, **Polyps** specificity 97% sensitivity 91% **Ulcer** specificity 100% sensitivity 90%, **Submucosal tumour** specificity 91% sensitivity 89% **Size** <5mm specificity 92% sensitivity 88%, >5mm specificity 88% sensitivity 92%

m; minutes, s; seconds, BO; Barretts Oesophagus, OV; oesophageal varices, VAS; Visual Analogue Score, NR; not reported, SAE; Serious adverse events * Examination duration reported as range or average (range)

1.3.2.2 Upper GI capsule endoscopy

A technologically advanced upper gastrointestinal capsule (Pillcam UGI; Medtronic Ltd, Dublin, Ireland) has two image sensors capturing as many as 35 images per second for 10 minutes and then 18 images per second for 80 minutes (Figure 4). It moves passively assisted by gravity and peristalsis within a pool of swallow water. It images simultaneously opposing walls in the stomach, as well as proximal and distal lumens in the oesophagus and duodenum. It is licensed to identify blood in patients with suspected upper gastrointestinal bleeding. In suspected upper GI bleeding, the live capsule view is superior to nasogastric aspiration in identifying blood in the upper GI tract, predicts high-risk endoscopic stigmata better than the Blatchford or pre-endoscopic Rockall scores and may be a cost-effective method of triaging upper GI bleeding in the emergency department [108-111].

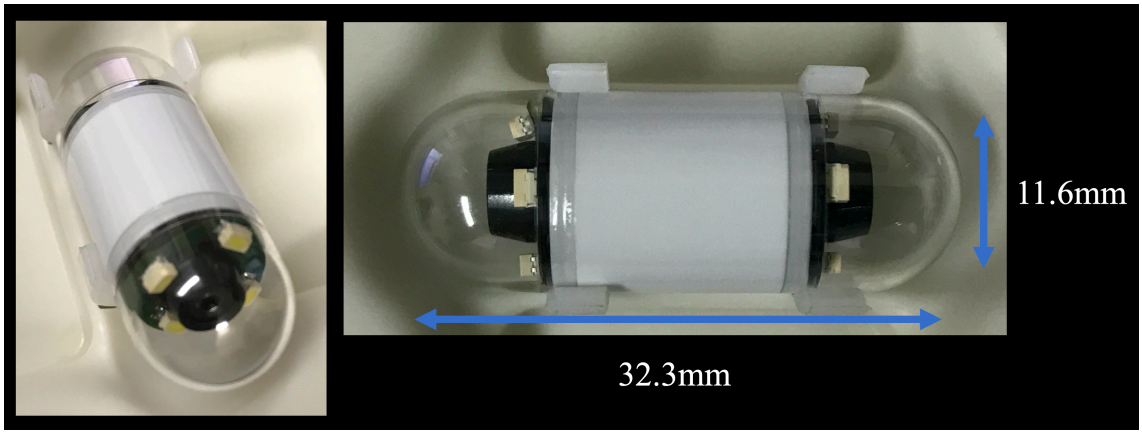


Figure 4: Pillcam Upper GI (UGI; Medtronic Ltd, Dublin, Ireland)

To achieve more complete views of the stomach, patients can adopt 9 different position changes in 90-degree intervals along lateral decubitus and recumbent (supine and prone) positions with and without a 30 degree tilt along the cranial-caudal axis. [112] This might be a relatively inexpensive approach: although a clinician would need to view and interpret the findings, no trained endoscopist or support staff are needed, no monitoring is necessary as sedation is not required and the equipment is disposable, therefore decontamination facilities are not needed. However, although excellent views were demonstrated throughout the distal oesophagus and stomach, entry into the

duodenum occurred in only 64% of cases and viewing of the video took a lengthy 48 minutes. No trials have yet compared the diagnostic yield or cost-effectiveness of this approach against conventional gastroscopy.

1.3.2.3 Magnet controlled capsule endoscopy

Control of the capsule endoscope is desirable. In particular, to stop capsule transit and image areas at risk of pathology such as the distal oesophagus, cardia and duodenal bulb, but also to translocate the capsule towards an area of interest. Active manipulation of the capsule endoscope can be achieved by external and internal actuation. Prototypes of capsules with internal actuation mechanisms (like motorised legs, fins and propellers) have been invented, but only external actuation devices, specifically those using magnetic fields have been subject to clinical trials. Experimental and pre-clinical approaches have been summarised elsewhere [113].

The addition of magnetic inclusions in capsule endoscopes allow manipulation of the capsule by an external magnet of varying sizes and types (Table 1). Swain and Keller first described the feasibility of magnet controlled capsule endoscopy (MACE) in the stomach and oesophagus using a handheld magnet and a real-time view platform [114,115]. Since then, the Mirocam Navi (Figure 5) has been shown to be equivalent to conventional gastroscopy in the detection of beads sewn into an *ex-vivo* porcine stomach in a blinded trial [116] and identified gastric landmarks in 94-100% of 26 human volunteers [117]. In the oesophagus the Mirocam Navi handheld magnet cannot translocate against gravity and peristalsis but can be held stationary for a 3 to 10 minute examination of the oesophagus in one study, [101] but less successfully in another. [102] In the stomach, while gastric landmarks can be identified in 95%, only relatively distant views of the proximal stomach can be visualised and gastric transit times was no different when controlled and when not. [102,117,118] It is believed this is due to a handheld magnets inherent lack of sensitive control and inability to overcome peristalsis.

Figure 5: Handheld Magnet controlled capsule endoscope

The Mirocam Navi (Intromedic, Seoul, Korea) system consists of a 1005g handheld magnetic 'hammer', a data recorder and a tablet computer

Sensitive but durable control of a magnetically assisted capsule endoscope relies on subtle alterations of the distance of the magnet from the capsule and rotation of the magnet head (which alters magnetic pole direction), which is difficult to achieve when suspending a handheld magnet of 1005 grams by hand above the abdominal wall for extended periods of time. Robot controlled MACE offers a more consistent and precise means of directing magnetic fields compared to handheld control, [119] with the key difference being the ability to control the direction and distance of the magnetic poles independently.

Two iterations of robot controlled MACE have been trialled using electromagnets [105] and fixed magnets [120]. The NaviCam by AnX Robotica Corp (Texas, USA) is a robot controlled MACE platform. Two joysticks are used by the endoscopist to control the polarity and distance of a fixed magnet attached from a 'C' arm hovering above a patient lying on a bed (Figure 6a). By altering polarity and position of the external magnet simultaneously, a combination of rotational (Figure 6d and e) and translational movements (Figure 6f) can be achieved while viewing the live video on the console (Figure 6b).

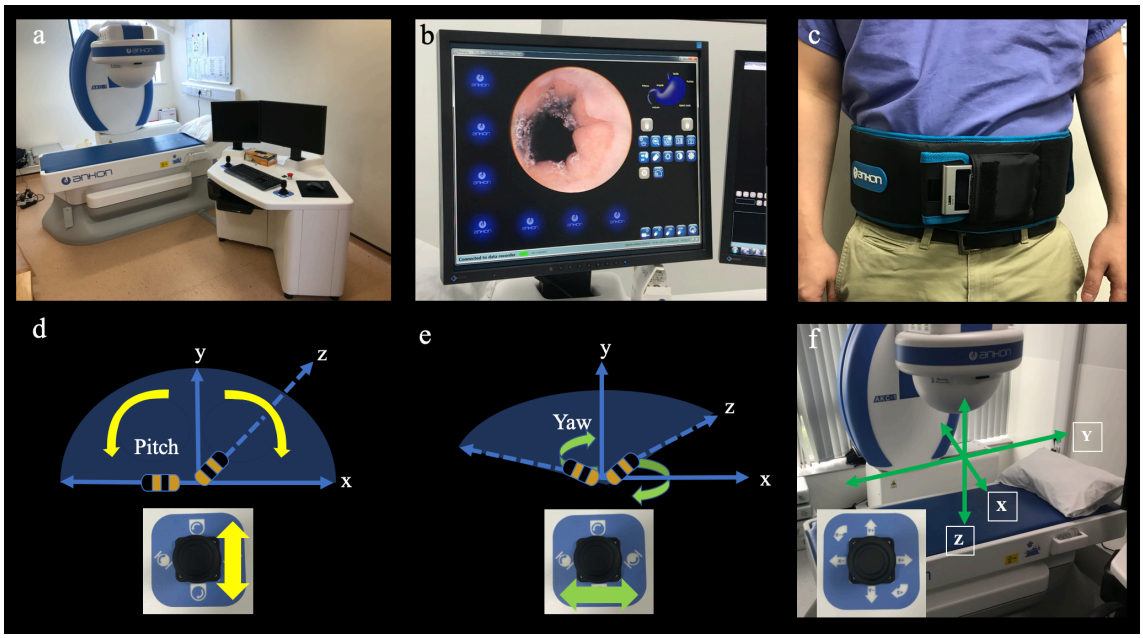


Figure 6: Robot controlled Magnet controlled capsule endoscopy

The Ankon Technologies NaviCam system consists of a) robot magnet platform with b) computer console for live view and c) wireless sensor belt and data recorder. The rotation of the capsule endoscope d) pitch and e) yaw, is controlled by moving the left joystick and capsule translocation achieved by movements of the magnet in the f) cranio caudal (Y axis), antero posterior (Z axis) and medio lateral (X axis) directions by controlling the right joystick.

This system has shown promise with widespread adoption in China. Using a combination of patient positions to more efficiently align magnetic fields with anatomical sites of interest and robot control of the external magnet, a comprehensive view of the stomach can be achieved in 93%. [121] After examination of the stomach, magnet assisted transpyloric transit can be achieved consistently with a significant reduction in capsule pyloric transit time (4.4 minutes) compared to unassisted by magnet with iv. domperidone only after 30 minutes (56.7 minutes, $p<0.001$). [122] Liao and collaborators report in a 350-patient multicentre study that capsule endoscopy had a 90.4% sensitivity compared to gastroscopy in the detection of gastric focal lesions irrespective of site or size of the lesion. [107] This large study supports the use of MACE in the stomach, however further studies should confirm these findings, which including studies of pathology detection in the oesophagus. No conclusions can therefore be made regarding the accuracy of MACE compared to OGD presently.

Recent reports however demonstrate the potential of this system in gastric cancer surveillance. In an uncontrolled operator blinded case series of superficial EGCs undergoing MACE prior to endoscopic resection, the size, site and morphology of 11 of 12 lesion were correctly identified [123]. Zhao and colleagues report in a multicentre study of 3,182 asymptomatic Chinese patients, seven (0.22%) patients diagnosed with gastric cancer. Mean procedure times were 14 minutes where 7 patients (0.74%) of patients above 50 were found to have gastric cancer [124]. These examination times are similar to the 15-20 minutes afforded to patients and endoscopist in the UK for conventional OGD which include, on average, up to 23 minutes to turn over the room between patients and administer conscious sedation where required. [125,126] Therefore, it is postulated that with training and experience, it is possible that such robot controlled MACE can examine similar volumes of patients to traditional OGD.

Finally, although a 1% capsule retention rate for small bowel capsule endoscopy is significant [91], no major adverse events have been reported following MACE, although experience of this technology is still limited. The study by Zhao et al (2018) is the largest series of upper GI MACE at present and no capsules were retained beyond four weeks. [93]

1.4 Improving clinical effectiveness of upper GI capsule endoscopy

Every capsule endoscope passes throughout the length of the GI tract and so the opportunity exists to image the entire GI tract in a single examination. Capsule endoscopes with two image sensors and adaptive frame rates can now image both the small and large bowel in its entirety in a single non-invasive examination in patients with suspected or established Crohn's disease. [127] In capsule endoscopy, meticulous bowel cleansing is important in ensuring adequate mucosal visualisation, more so than conventional endoscopy where suction and water irrigation can be used to clear debris and staining of the mucosa. With upper GI MACE, the opportunity now exists to examine the upper GI tract and the small bowel together. The potential benefit of such an examination and the anticipated pre-procedure preparation are discussed.

1.4.1 Anaemia and the role of panenteric capsule endoscopy

Iron deficiency anaemia (IDA) affects 2-5% of the adult population and accounts for between 4-13% of gastroenterology referrals as GI blood loss is considered the commonest cause in men and non-menstruating women. A single visit upper and lower endoscopic investigation is recommended because synchronous pathologies causing anaemia may occur in as many as 26% of cases. [128,129] The cause of anaemia is not identified by upper and lower GI tract investigation in 30% of cases and uncertainty exists as to whether minor pathologies which do not exhibit overt bleeding (such as oesophagitis, gastritis and colonic polyps) are the cause of anaemia. [130,131] Historically, pathology in the small bowel is considered to account for only 5% of all gastrointestinal causes of anaemia [132], however these were based on fluoroscopic examinations prior to the advent of capsule endoscopy. Capsule endoscopy can now detect flat vascular lesions such as angioectasias which were previously undetected by small bowel radiology and meta-analyses show significantly better diagnostic yields of capsule endoscopy compared to small bowel radiology (42% and 6%, respectively) in patients with IDA. [133] In patients with recurrent or refractory (as opposed to first presentation of) anaemia, capsule endoscopy studies show a diagnostic yield of small bowel pathology in 44% and 23% are due to angioectasias. [134]

Upper GI capsule endoscopy and in particular one with magnet control would allow for both an upper GI and small bowel investigation. In a study of 49 patients with recurrent or refractory anaemia undergoing both handheld upper GI MACE and conventional gastroscopy, 17 (34%) patients were deemed have a cause for their anaemia distal to D2 and out of reach of a conventional gastroscope [102]. However, 15 of these 17 patients also had a synchronous upper GI lesion (proximal to D2) known to be a cause of anaemia and so without a small bowel investigation 30% (15/49) may have been given an incorrect diagnosis for their anaemia. Whilst this high prevalence is specific to a cohort of patients who likely to be pathology enriched, it highlights a proof of concept that upper GI MACE can more effectively identify causes of anaemia because it

examines both the upper GI tract and small bowel. The most apparent cost of examining the small bowel after an upper GI MACE would be the inconvenience of fasting an additional 2 hours (until the capsule passes more distally into the small bowel) and continuing to wear the data recorder for 8 hours. The effectiveness of such an approach is dependent on the cleanliness of the upper GI tract where an overnight fast is usually sufficient, but also the small bowel, where there is evidence that bowel purgatives may help cleansing.

1.4.2 Bowel purgatives in small bowel capsule endoscopy

Bowel purgatives are used routinely in advance of colonic examinations and have been shown to improve examination completion and pathology detection. [135] Purgatives can also be used prior to small bowel capsule endoscopy as some studies suggest it can improve small bowel mucosal views. However, pre-procedure preparation with fasting and drinking of clear fluids the day before a small bowel capsule endoscopy or an upper GI capsule endoscopy is already well accepted by patients. After an upper GI MACE procedure, the small bowel can be examined as the capsule endoscope passes, therefore the effect of purgatives on small bowel cleansing and acceptability to patients prior to an upper GI MACE with small bowel examination is relevant.

Controlled studies which support the use of bowel purgatives report that polyethylene glycol (PEG) improves views [136-139] and even diagnostic yield in one study, [136] but larger studies dispute these findings. [140-142] The distal small bowel is most affected and mucosal views can be poor with no purgative preparation. [143] In most trials of small bowel cleansing, purgatives are consumed the evening before the procedure, however in ileocolonoscopy, it is well established that the terminal ileum and caecal views are improved with purgatives taken a few hours before the examination and studies splitting doses of purgatives have shown more superior cleansing and pathology detection. [135,144] The potential benefits of this approach may be better patient tolerance to the preparation and improvements in distal small bowel views.

2 HYPOTHESIS AND AIMS

NULL HYPOTHESIS: Capsule endoscopy does not advance the quality of the endoscopic examination of the upper gastrointestinal tract.

This body of work aims examine the role of capsule endoscopy in the endoscopic examination of the upper gastrointestinal tract, in particular, in advancing the quality of an upper gastrointestinal endoscopy. In Chapter 3, the clinical effectiveness of conventional OGD is examined by evaluating the rate of missed OG cancer occurring during conventional OGD and examining the factors which affect these occurrences. Capsule endoscopy is a less invasive examination than conventional OGD. In Chapter 4, the differences in patient experience of Magnet controlled capsule endoscopy (MACE) and conventional OGD are examined in a clinical trial of patients with dyspepsia. Yet, transnasal endoscopy is already better tolerated and accepted than conventional OGD. In Chapter 5, differences in patient experience of MACE and transnasal endoscopy are examined. Could the introduction of capsule endoscopy in upper GI endoscopy result in additional clinical benefit to the patient over flexible endoscopy? In Chapter 6, a randomised control trial of bowel purgatives in small bowel capsule endoscopy examines whether preparation with fasting and a clear liquid diet is an optimal method of examining the small bowel, or whether bowel purgatives are required. Finally, widespread adoption of capsule endoscopy in the upper GI tract will only be feasible where costs are controlled. In Chapter 7, a study of the economic impact of three upper GI endoscopic modalities: conventional OGD, TNE and MACE are examined.

3 FACTORS ASSOCIATED WITH UPPER GASTROINTESTINAL CANCERS MISSED BY GASTROSCOPY: A CASE CONTROL STUDY

3.1 Abstract

Introduction: Gastroscopy or Oesophagogastroduodenoscopy (OGD) is presumed to have missed oesophagogastric (OG) cancer if performed in the three years prior to diagnosis. Meta-analyses suggest that this occurs in 11% of OG cancer patients. We examine patient, endoscopist and service level factors that may affect rates of missed OG cancers in a case control study.

Methods: Cases of missed OG cancer were identified between January 2013 and December 2017 in Sheffield, UK. We examine the factors which affect missed cancer occurring during OGD procedures. Differences in use of sedative premedication, endoscopist experience and endoscopy service pressures were examined between procedures with missed cancer occurrence and two procedure controls: those on the same patients at which cancers were subsequently diagnosed and a group of procedures matched for endoscopist and location of lesion during which small benign focal lesions were identified.

Results: We identified 627 patients diagnosed with OG cancer and of these 48 (7.7%) had undergone gastroscopy in the preceding three years. Endoscopy lists where missed cancer procedures occurred contained a greater number of procedures compared to lists on which cancer diagnoses were subsequently made (OR 2.16, 95% CI 1.19 – 3.91) and when compared to lists during which benign small focal lesions were diagnosed (OR 1.25, 95% CI 1.02 – 1.52). The use of sedation, endoscopist profession and experience, or time of day of procedure were not associated with missed cancer occurrence during a procedure. Missed gastric cancer was more common in female patients (OR 3.0, 95% CI 1.32– 6.91). There were fewer cases of missed oesophageal cancer amongst those who were examined for dysphagia (OR 0.16, 95% CI 0.05 – 0.50), but more cases amongst those examined for anaemia (OR 5.36, 95% CI 1.87 – 15.41).

Conclusion: 7.7% of patients diagnosed with OG cancer could have been diagnosed and treated earlier. Our study suggests that endoscopy lists on which there are greater numbers of procedures may be associated with missed OG cancers.

3.2 Introduction

Oesophagogastroduodenoscopy (OGD) is the most common procedure performed in GI endoscopy units [145]. These OGDs are normal or yield benign pathology in the majority [146], however oesophagogastric (OG) cancers are diagnosed in between 1-2% and diagnostic yield has remained relatively static despite an over 40% increase in OGDs performed in the United Kingdom (UK) in the last 10 years (Figure 1).

It is well recognised that colorectal cancers may be diagnosed shortly after reportedly normal colonoscopy and a similar situation exists in OG cancer: between 5.3 and 13.9% of patients with OG malignancy in the Western population have had normal gastroscopies reported within the previous three years. [4,23-28] Reasons for missed cancers are unclear and the subject of much interest. In most cases pathology has been noted and these lesions might not have been sampled or inadequately sampled [4,27]. However up to 30% of procedures presumed to have missed cancers are reported as normal. [25,27] It is hypothesised therefore that this may be due to endoscopist experience and or poor patient tolerance.

Studies have suggested that performing procedures quickly increases the risk of missed pathology [35,36]. Endoscopist experience is clearly associated with colonic polyp detection rate [42-44] and there is some evidence that experience is associated with better diagnostic capability in OGD. [45,46] Service level factors such as endoscopy list composition and workload are often out of control of the endoscopist and may conceivably influence missed procedures owing to pressures of service provision and endoscopist fatigue. [147] Finally, while the use of sedation has been shown to improve completion rate in colonoscopy and potentially pathology detection, [48,148] it has only been shown to improve overall patient satisfaction and willingness to have a repeat OGDs [55]. Whether diagnostic quality of endoscopy improves with sedation is unknown.

In this case control study, we investigate whether endoscopist factors (procedural experience and professional background) or service level factors (number and types of

endoscopic procedures on endoscopy lists) and the use of sedative premedication associate with missed OG cancer occurrence.

3.3 Methods

Patients diagnosed with OG cancer between January 2013 and December 2017 were retrospectively identified from a local cancer database (Infoflex version 5, Chameleon Information Management Systems) for the population of Sheffield, UK using International Classification of Diseases (ICD) 15 and 16 codes. OGDs performed on these OG cancer patients between January 2010 and December 2017 at Sheffield Teaching Hospitals (Northern General Hospital and Royal Hallamshire Hospital) were reviewed to identify patients who have had procedures which are presumed to have missed cancer up to three years prior to diagnosis. Symptomatic patients investigated out with a surveillance procedure were included. Diagnoses made on asymptomatic patients in surveillance programmes and planned follow up endoscopies were excluded. Patient factors (gender, age, indication for procedure and anatomical location of cancer) was performed on the whole cohort of OG cancer patients.

A case control study of endoscopy procedures was then performed. The cases were the procedures where missed cancer was presumed to have occurred and they are compared to two control procedure groups. The first control comprised the procedures done on the same patients at their subsequent OGD which diagnosed cancer. However, endoscopists performing procedures presumed to have missed early cancer by definition would have missed small subtle lesions. Therefore, a second control group comprised select procedures at which small (<10mm) benign focal lesions were detected. These procedures were performed by the same endoscopist which performed the missed cancer procedure, on patients of the same age, gender and location of pathology (i.e. matched for endoscopist, patient and location of pathology).

Potential factors resulting in missed cancer occurrence examined were: use of sedation, professional background, training status and volume of OGD procedures of the examining endoscopist, endoscopy list size, procedure mix, time of day and position on

endoscopy list. Endoscopy session sizes are also examined by number of points, or procedure equivalents per session, as defined by the UK Joint Advisory Group (JAG) for GI endoscopy as 15 – 20 minute intervals per point. Trainee endoscopists were defined as those who were supervised during the procedure by UK Joint Advisory Group (JAG) certified independent endoscopists. The number of OGDs performed by an endoscopist between January 2008 and the procedure in question were divided by the months elapsed to measure endoscopists average monthly procedural volume.

This study was approved by the Clinical Effectiveness Unit at Sheffield Teaching Hospitals (CEU reference number 8301) and the University of Sheffield ethics review board (Reference number 018420). Data were analysed using SPSS (version 23.0, IBM, Armonk, USA). Continuous data are presented as mean (± standard deviation; SD) or median (interquartile range; IQR) and categorical variables and their difference are presented as a frequency (%) and Chi-Square (or exact) tests. Logistic regression was used to examine potential factors contributing to missed cancer procedures when compared to procedural controls. Significant values ($p<0.05$) are reported as odds ratios (OR) with 95% confidence intervals (CI).

3.4 Results

A total of 60214 OGDs were performed between January 2012 and December 2017 (Figure 1). We identified 627 patients diagnosed with oesophageal (50.9%) and gastric (48.8%) cancer during this period having excluded 45 cancers diagnosed on surveillance or follow up OGDs. Forty-eight patients with OG cancer (7.7%) had OGDs performed in the preceding three years and considered to have a missed cancer occurrence. These procedures were performed within one year in 2.9% and between one and three years in 4.8% prior to diagnosis (1.9% and 5.2% for oesophageal cancer and 3.9% and 4.6% for gastric cancer respectively). Oesophagogastric cancer and procedures at which missed cancer occurred represent 1.0% (627/60214) and 0.08% (48/60214) of all OGDs performed during the study period respectively.

Characteristics of patients with missed cancer occurrence were compared to the cohort of patients without missed cancer (n=578) in Table 3. There were more cases of missed gastric cancer in female patients (OR 3.0, 95% CI 1.32– 6.91) and potentially fewer cases amongst those who were examined for anaemia (OR 0.23, 95% CI 0.05 – 1.00). There were fewer cases of missed oesophageal cancer occurrence amongst those who were examined for dysphagia (OR 0.16, 95% CI 0.05 – 0.50), but more cases amongst those examined for anaemia (OR 5.36, 95% CI 1.87 – 15.41).

In a case control study, procedures with missed cancer occurrence were subsequently compared to two groups of control procedures (Figure 7). Three patients with missed cancer presented as upper GI bleeds requiring emergency endoscopy in theatres and were excluded from analysis. There was a median of 558 (IQR 635) days between the missed cancer occurrence (case) and OGDs diagnostic of cancer (control 1) with no difference in median times between those diagnosed with gastric and oesophageal cancers (p=0.09). Total number of procedures and procedure equivalents, number of OGDs on endoscopy lists and lists with OGDs only were associated with missed cancer occurrences when compared to procedures diagnostic of cancer (Table 4). The use of sedation, endoscopist experience or background, and time of day of procedure did not affect the outcome.

Procedures diagnostic of benign focal lesions (control 2) matched to the endoscopist performing the missed cancer procedure were identified in 44 of 45 patients. In one case, no suitable procedure was found within 3 months of missed cancer procedure and therefore excluded. In the oesophagus, these lesions were ulcers (n=4), submucosal lesions (n=2), polyps (n=5), nodules (n=5), a raised lesion (n=1), an erosion (n=1), an oesophageal varix with red spot (n=1) and an endoscopic mucosal resection (EMR) scar (n=1). In the stomach, these lesions were polyps (n=8), ulcers (n=4), erosions (n=5), nodules (n=2), angioectasias (n=2), a gastric varix with red sign (n=1), a healed gastric ulcer scar (n=1) and an EMR scar (n=1). These procedures were performed a median of 22 (IQR 125) days after the missed cancer procedure. Only total number of procedures (OR 1.25, 95% CI 1.02 – 1.52) and procedure equivalent points (OR 1.37 95% CI 1.04 – 1.79) on endoscopy lists were associated with a risk of missing cancer (Table 4).

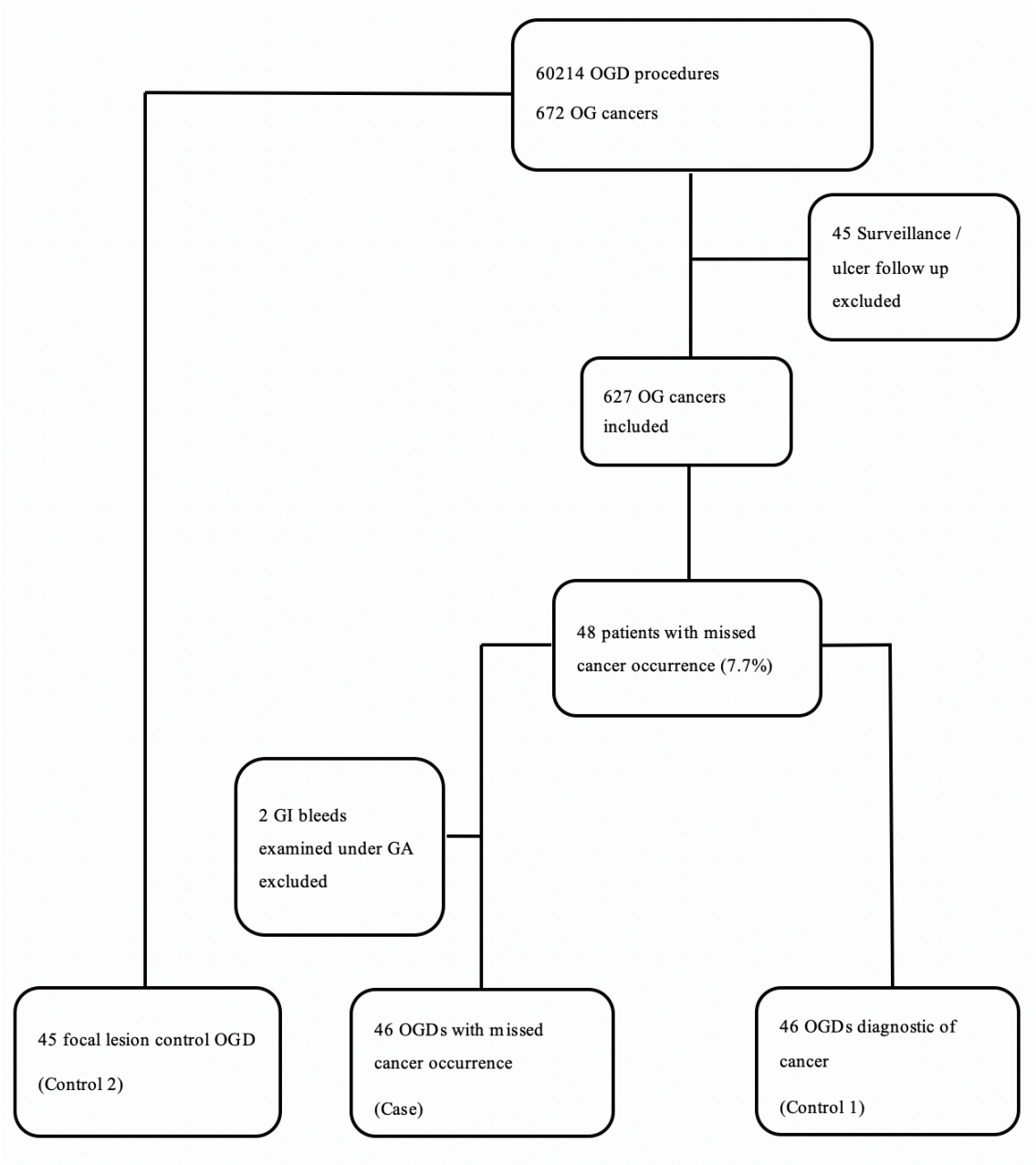


Figure 7: A study of missed OG cancer occurrence: selection of cases and control OGD procedures

OG oesophagogastric, GA general anaesthetic

Table 3: Comparison of oesophagogastric cancer patients with and without missed cancer procedures

	Overall	Oesophageal Cancer			Gastric Cancer		
		Not missed	Missed	p	Not missed	Missed	p
n (%)	627	319 (94.1)	20 (5.9)		305 (91.6)	28 (8.4)	
Age, mean (s.d)	72.1 (12.0)	70.9 (11.9)	74.3 (8.5)	0.22	73.7 (12.2)	71.8 (11.5)	0.45
Female gender, n (%)	446 (66.4)	92 (30.8)	6 (30.0)	0.94	97 (34.6)	16 (61.5)	0.01
Indication for gastroscopy, n (%)							
Dysphagia	236 (40.4)	172 (60.6)	4 (20.0)	0.001	55 (21.7)	5 (19.2)	0.77
Anaemia	96 (16.4)	21 (7.4)	6 (30.0)	0.005	67 (26.4)	2 (7.7)	0.03
Loss of weight	75 (12.8)	33 (11.6)	3 (15.0)	0.65	38 (15.0)	1 (3.8)	0.12
Dyspepsia	126 (21.6)	41 (14.4)	5 (25.0)	0.20	70 (27.6)	10 (38.5)	0.24
Vomiting	5 (0.9)	2 (0.7)	0 (0.0)	0.70	2 (0.8)	1 (3.8)	0.15
GI bleed	53 (9.1)	15 (5.3)	1 (5.0)	0.96	33 (13.0)	4 (15.4)	0.73
Imaging abnormality	51 (8.2)	19 (6.4)	1 (5.0)	-	28 (10.0)	3 (11.5)	-

(continued)	**Overall**	**Oesophageal Cancer**			**Gastric Cancer**		
		Not missed	Missed	p	Not missed	Missed	p
Location of cancer, n (%)							
Oesophagus (C15.x)				0.45			
Upper	11 (3.4)	10 (3.1)	1 (5.0)				
Middle	61 (19.1)	55 (18.4)	6 (30.0)				
Lower	204 (63.9)	192 (64.2)	12 (60.0)				
Unspecified	43 (13.5)	42 (14.0)	1 (5.0)				
Gastric (C16.x)							0.76
Cardia	87 (28.4)				77 (27.5)	10 (38.5)	
Fundus	17 (5.6)				15 (5.4)	2 (7.7)	
Body	75 (24.5)				69 (24.6)	6 (23.1)	
Antrum	48 (15.7)				45 (16.1)	3 (11.5)	
Pylorus	18 (5.9)				18 (6.4)	0 (0.0)	
Unspecified	41 (13.4)				38 (13.6)	3 (11.5)	

Comparison of age, gender and indication and location of cancer between oesophagogastric cancer patients with missed cancer occurrence and without.

Table 4: Factors affecting missed cancer occurrence: a study of cases and two controls

	Case: Procedures with missed cancer occurrence	Control 1: Procedures which diagnosed cancer		Control 2: Benign focal lesions	
		OR (95% CI)		OR (95% CI)	
n	45	45		44	
Xylocaine	45 (100)	44 (97.8)	-	44 (100.0)	-
Sedation n, (%)	11 (24.4)	19 (42.2)	2.26 (0.92 - 5.56)	10 (22.7)	1.1 (0.43 – 3.02)
Endoscopist, n (%)					
Gastroenterologist	27 (62.8)	27 (62.8)	Reference		
Surgeon	10 (23.3)	14 (32.6)	0.71 (0.27 - 1.89)		
Other (Nurse / Radiologist / GP)	6 (14.0)	2 (4.7)	3.00 (0.56 - 16.21)		
Performed by trainee	7 (16.3)	7 (16.3)	1.00 (0.32 - 3.14)		
Mean OGDs performed per month, (s.d)	26 (20.5)	25 (15.7)	1.00 (0.98 - 1.03)		

(continued)	**Case: Procedures with missed cancer occurrence**	**Control 1: Procedures which diagnosed cancer**		**Control 2: Benign focal lesions**	
		OR (95% CI)		OR (95% CI)	
Endoscopy List					
Procedures per list, mean (s.d)	8.5 (2.0)	7.1 (2.0)	1.42 (1.13 - 1.78)*	7.4 (2.5)	1.25 (1.02 - 1.52)*
Procedure equivalents or points per list, mean (s.d)	9.4 (1.4)	8.2 (1.7)	1.64 (1.2 - 2.22)*	8.5 (2.0)	1.37 (1.04 – 1.79)*
Gastroscopies per list n, (%)	7.6 (3.2)	5.9 (3.0)	1.19 (1.03 - 1.36)*	6.5 (3.2)	1.11 (0.97 - 1.26)
Gastroscopy only lists n, (%)	29 (64.4)	19 (42.8)	2.48 (1.06 - 5.80)*	27 (61.4)	1.27 (0.51 - 2.91)
Sigmoidoscopies per list, median (range)	0 (0 - 4)	0 (0-3)	0.84 (0.50 - 1.42)	0 (0 - 2)	1.45 (0.72 - 2.92)
Colonoscopies per list, median, (range)	0 (0 - 4)	0 (0-3)	0.90 (0.63 - 1.27)	0 (0 - 4)	0.95 (0.68 - 1.31)
Therapeutic procedures per list, median (range)	0 (0 - 3)	0 (0-6)	0.66 (0.36 - 1.21)	0 (0 - 2)	0.85 (0.38 - 1.88)
List with therapies n, (%)	5 (11.1)	10 (22.2)	0.44 (0.14 - 1.40)	10 (22.7)	0.34 (0.10 - 1.18)
Time of day (PM or evening) n, (%)	25 (55.6)	26 (57.8)	0.91 (0.39 - 2.10)	17 (38.6)	1.91 (0.82 - 4.45)
Last procedure on list n,(%)	5 (11.1)	1 (2.2)	5.50 (0.62 – 49.11)	4 (9.1)	1.28 (0.32 – 5.13)
Latter half of list n,(%)	34 (75.6)	34 (75.6)	1.00 (0.38 – 2.61)	37 (84.1)	0.64 (0.22 – 1.88)

Procedures with missed cancer occurrence (cases) compared to procedures diagnostic of cancer (control 1) and matched procedures at which benign focal lesions were identified (control 2). Odd ratios (OR) and 95% confidence intervals (CI) case procedures compared to two control groups. * $p<0.05$

3.5 Discussion

Of 627 patients diagnosed with OG cancer, 48 (7.7%) had undergone OGDs in the previous three years at which 5.9% of oesophageal and 8.4% of gastric cancers were presumed to have been missed. UK population cohort studies from the National Oesophagogastric Cancer audit (NOGCA) report 7.8% and 8.3% of oesophageal and gastric cancers are missed respectively [11,12]. That we excluded cancers diagnosed on asymptomatic patients in surveillance programs, may explain our lower rate of missed oesophageal cancer occurrence. Gastric cancers were missed more commonly in female patients. Oesophageal and gastric cancers were missed less commonly when OGDs were performed for dysphagia and anaemia respectively. NOGCA data in the UK report similar gender differences in missed gastric cancer occurrence [11]. Further, they reported that lower proportions of advanced cancers (T3/4 stage) were associated with missed oesophageal [12] and gastric [11] cancers at diagnosis. This is consistent with our finding that missed oesophageal and gastric cancer occurrence was less commonly associated with OGDs performed for alarm symptoms, as if OG cancers manifests symptomatically, they are more likely to be advanced in nature. [149,150]. We found that amongst patients with oesophageal cancer, a missed procedure was more likely if indicated for anaemia. An explanation may be that endoscopists may not exercise the same index of suspicion to oesophageal lesions in OGDs indicated for anaemia in comparison to dysphagia. However, whether or not the cause of the anaemia at the time of missed cancer OGD was related to occult oesophageal malignancy is uncertain.

In this case control study, OGDs with missed cancer occurrence were compared to two control groups of procedures. Increasing numbers of procedures on endoscopy lists were associated with missed cancers when compared to both control groups where cancer, and benign focal lesions were detected respectively. Endoscopy lists with procedures where missed cancer had occurred had on average an additional procedure compared to lists where cancer or focal lesions were diagnosed. Use of sedation, endoscopist professional background or procedural experience, time of day or when the procedure was performed and types of procedures on list did not affect the outcome.

By using the latter procedures at which cancer was diagnosed, we controlled for patient factors (age, gender and anatomical location of cancer) and examined endoscopist and service factors which could be contributing to cases of missed OG cancer. However, it could be argued that the size of the lesion could be the primary determinant of whether or not cancer was detected. Therefore, to control for the size of the lesion and endoscopist ability, a second control group of procedures performed by the same endoscopist who missed cancer and furthermore diagnostic of benign (<10mm) focal lesions were compared with procedures with missed cancer occurrence. The actual size of the missed lesions cannot be known but reasonable to assume they were 10mm or less in size [22].

The reasons for the suggested relationship between missed cancer occurrence and greater numbers of procedures on endoscopy lists can be considered a few ways. The sensitivity of endoscopic procedures relates to inspection time. [35-37] Teh and collaborators (2015) have shown that endoscopists with procedure times of more than seven minutes had an over two-fold (OR 2.50; 95% CI 1.52 – 4.12) diagnostic yield of high risk lesions and an over threefold yield of gastric neoplasia (OR 3.42; 95% CI 1.25 –10.38) than those performing shorter examinations. [37] Increasing workload may also be due to fatigue. In a survey of colonoscopy practice in the USA, 7% of respondents reported that increasingly populated endoscopy sessions have resulted in conscious reductions in examination times [147]. Colorectal adenoma detection and examination times have also been shown to fall by 7% and 20% respectively by the end of the day in another study [151]. It is therefore conceivable that increasing workload and fatigue have a negative impact on endoscopists examination times or thoroughness of examination in the upper GI tract.

Although 35% of missed cancer occurrences were on lists with lower GI procedures, there is no association between presence of lower GI or therapeutic procedures and missed OG cancer occurrences on endoscopy lists. Diagnostic OGDs are quicker examinations to perform than colonoscopies and so endoscopy sessions with only OGDs would have more procedures. That over 60% of cases of missed cancer occurred on lists with only OGDs, and that the number of procedure equivalent points per session also associated with missed cancer occurrence may suggest that it is the number of

procedures performed per list, rather than the overall workload from longer or more complex procedures that negatively affect outcome. In fact, it is the activity between procedures which takes most of the time during an endoscopy list: the turnaround time, defined as time between the extubation of one patient and intubation of the next [152,153]. In the UK, Bryce et al. (2018) reported that in a single centre across 43 endoscopy lists and 169 patients, mean turnaround time per patient was 20.8 minutes [152]. In Ontario, Canada where conscious sedation is used routinely, the patients spend on average a total of 23 minutes in the endoscopy room before and after the procedure [125]. A further increase in endoscopy activity might be achieved by improving workflow efficiencies, thereby reducing turnaround time, without having a negative impact on examination time. However, Edmondson et al. (2016) reported a similar turnaround time of 20 minutes even after implementing a nurse-led consent and intravenous cannulation, and with the peak effect of the sedative midazolam being between 3-4 minutes after administration [154], it may be that patient and physician preference for intravenous sedation may limit peri-procedural time efficiencies. In that using sedative medication takes additional time, our data did not find a beneficial effect of using intravenous sedation on outcome. However, there is likely a lack of power in this study to demonstrate an association between miss cancer occurrence and use of sedation. Studies of less invasive upper GI endoscopic modalities such as transnasal endoscopy (TNE) and magnet controlled capsule endoscopy (MACE) have been suggested to be better tolerated than conventional OGD and importantly, mean examination times reported to be longer [87,107]. It would therefore be important to further examine the association between use of sedation, its impact on patient tolerance, adequacy of views (which may be affected by patient intolerance), examination times and ultimately pathology detection.

Our data failed to demonstrate any association between professional background and training grade with missed cancer occurrences. This would be consistent with studies which report that endoscopist experience, when measured by number of years' experience, did not affect sensitivity of OGD to detect early gastric cancer [41] and further, inconclusive differences in missed cancer occurrence between medical and non-medical endoscopists.[39]. We were unable to show that trainee status or experience were associated with missed OG cancer occurrence. This is in contrast to the study of Teh et al. who found that trainee grade endoscopists (with procedural independence) were

more likely to miss high-risk lesions at gastroscopies than staff grade endoscopists. The difference may be explained by the fact that trainees in our study performed all gastroscopies under the direct supervision of an accredited endoscopist which may augment the diagnostic yield of the trainee. Two further studies concluded that training and experience correlated with the ability to detect endoscopic evidence of *Helicobacter pylori* infection and gastric intestinal metaplasia [45,46]. It seems more likely, that expertise, based on training and experience, is the main determinant of high quality gastroscopies, rather than professional background or procedural volume *per se*. Structured training programs such as the interactive web-based Barrett's Oesophagus Related Neoplasia project have shown that web-based modules can improve endoscopists ability to detect and delineate dysplastic areas within videos of Barrett's oesophagus segments over the course of four sets of 20 training videos with tailored mandatory feedback. These improvements were independent of whether the participant was a gastroenterology trainee, a junior or senior gastroenterologist (with less than or more than 5 years board certified experience respectively) [155]. Finally, our study did not demonstrate an association between time of day of procedure and missed cancer. Colorectal adenoma detection rates have been shown to decline as time passes in the day suggesting that endoscopist fatigue and attention span may affect performance [156,157]. However, our study is likely not large enough to adequately address this question.

There are limitations to the study. The number of cases were small and it cannot be certain that all had visible lesions at the time of the initial non-diagnostic procedure. Procedures presumed to have missed cancer were rare with one occurring every 1250 procedures during our 5-year study period. A case control design was therefore selected to examine factors which were more peripheral to the case of missed cancer occurrence, for example, endoscopy list size and case mix during which the miss cancer procedure occurred. This means however, we cannot be certain of the differences in endoscopy list size in procedures which did not have an OG cancer diagnosis. Endoscopy examination times were not available and further research is needed to determine if this is affected by number of procedures on a list. Consecutive cases of OG cancer were included, however some have been missed if procedures were performed out of area, in the private sector on in cases where radiological imaging in patients was sufficient for

pragmatic patient management. Nevertheless, these cases are likely to be low given a similar rate of missed cancers found in this and other studies. [4,11,12]

The implications of this study on service delivery are important. They suggest that endoscopy lists with more procedures are associated with a risk of missing OG cancer. British and European guidance recommend documenting examination times [32,33] and this study supports this measure to ensure that pressures of service delivery does not result in shorter examination times. On the other hand, the turnaround time between conventional endoscopic procedures are relatively constant and likely vary insofar as the additional time required when offering sedation [125,152,153]. A non-invasive examination such as MACE therefore may allow for longer examination times if better tolerated by patients, and within the same timeframe if turnaround time is reduced in the absence of a need for sedation, monitoring and endoscope reprocessing.

4 A COMPARATIVE STUDY OF PATIENT TOLERANCE AND ACCEPTABILITY OF MAGNET ASSISTED CAPSULE ENDOSCOPY AND CONVENTIONAL GASTROSCOPY IN DYSPEPSIA

4.1 Abstract

Introduction: Gastroscopy or Oesophagogastroduodenoscopy (OGD) is commonly performed to investigate dyspepsia, but oropharyngeal intubation can cause patient distress. These reactions may be attenuated following the administration of intravenous sedatives or by the use of non-invasive alternatives. In this study, patient tolerance and acceptability of OGD have been compared with magnet-controlled capsule endoscopy (MACE).

Methods: A self-controlled blinded comparison of OGD and MACE in the investigation of dyspepsia was performed. Factors affecting patient tolerance and acceptability were examined using the Endoscopy concerns scale (ECS) and a patient generated index, the Universal Patient Centredness Questionnaire (UPC-Q).

Results: Forty-four patients undertook MACE followed by OGD. Pre-procedure ECS scores were higher before OGD (39 vs 26, $p<0.0001$) than MACE suggesting OGD results in more distress to patients than MACE in anticipation of endoscopy. Patients experienced significantly more distress (median score) due to gagging (6 vs 1, $p<0.0001$), choking (5 vs 1, $p<0.0001$), abdominal bloating (2 vs 1, $p<0.0001$), instrumentation (4 vs 1, $p<0.0001$), discomfort during (5 vs 1, $p<0.0001$) and after (2 vs 1, $p<0.0001$) OGD when compared to MACE. All of patients found MACE acceptable compared to 64% with OGD. ECS scores were significantly higher after OGD (34 vs 11, $p<0.0001$) and UPC-Q score was lower for OGD (50 vs 98, $p<0.0001$) compared to MACE, both supporting superior acceptance of MACE over OGD. If given a choice, all patients preferred MACE to OGD. If there was a 50% chance of requiring an OGD after MACE for tissue samples, 83% patients would still choose MACE as the first procedure. Two-thirds of endoscopic findings are detected by both MACE and OGD.

Conclusion: MACE is better tolerated, accepted and preferred by patients than OGD and most patients would prefer MACE first even if OGD was required to obtain biopsies.

4.2 Introduction

Gastroscopy or Oesophagogastroduodenoscopy (OGD) is an uncomfortable procedure and many patients require intravenous sedation or general anaesthesia which may, therefore, require planning and reorganisation of routines at work and home. Adverse events occur in up to 1 in 200 OGDs and 60% are cardiopulmonary events and often related to sedation. [76,158] It is, therefore, understandable that patients may delay seeking medical advice for symptoms due to fear of investigation. [159] The recent COVID-19 pandemic has prompted consideration of the risks of transmission of microbial agents to endoscopy staff by aerosol-generating procedures such as OGD. [160] These concerns underlie a continuing search for less invasive upper GI investigative tools which are effective, safe, simple to perform and acceptable to patients.

Capsule endoscopy does not involve intubation by the endoscopist but rather patient directed swallowing of the imaging device. Developments include magnetic control of the capsule which can be moved and rotated in a stream of swallowed water to achieve gastric visualisation. Studies suggest that patients find magnet-controlled capsule endoscopy (MACE) more comfortable than, [102,103] and preferable to OGD. [105,107]

Other than studies of procedural tolerance or satisfaction, understanding of patients' OGD experience is limited [57]. In this study, we have performed a detailed comparison of tolerance of OGD and MACE. It is well recognised that procedural tolerance is only one of several factors which affect acceptability of a test and the overall patient experience. Therefore, we have also compared acceptability and assessed the broader experience of each investigative pathway using the Endoscopy Concerns Scale (ECS) [65] and the Universal Patient Centredness Questionnaire (UPC-Q), [68] a patient-reported experience measure.

4.3 Methods

4.3.1 Subjects

Patients between the ages of 18 and 80 years of age referred to Sheffield Teaching Hospitals (Sheffield, UK) for the endoscopic investigation of dyspepsia as per National Institute of Clinical Excellence guidance (CG184) were invited to join the study [161]. Patients with implanted metallic devices or prostheses were excluded. Contraindications to capsule endoscopy included a history of dysphagia, Crohn's disease, small bowel resection or previous abdominopelvic irradiation and long term (over six months) daily consumption of a non-steroidal anti-inflammatory drug (NSAID).

4.3.2 Interventions

Patients were offered the choice of OGD (with or without sedation) or transnasal endoscopy (TNE). Procedures were described to the patients verbally and in standardised hospital information leaflets provided as part of routine clinical practice. Those who agreed to participate in the study of OGD were also asked to have MACE in the two weeks preceding their OGD and included in this study.

MACE was performed using the NaviCam (AnX Robotica Corp, Texas, USA). The system comprises two joysticks which control the polarity and proximity of an external magnet suspended on a robot arm above the patient recumbent on an examination couch. Examinations were performed by two endoscopist trained in the technique in Shanghai, China. Prior to the examination, patients swallowed 80mg simethicone (Infacol, Teva, Castleford, UK) in 100mls of water and followed a series of position changes to wash the stomach. Immediately before swallowing the capsule, patients drank between 500 to 1000mls of water to distend the stomach. [162] The capsule endoscope (AKEM-11SW; AnX Robotica Corp, Texas, USA) was ingested in the left lateral decubitus position. The operation of the MACE and examination of the stomach is described elsewhere [163]. MACE was considered incomplete and patients excluded

from the study if there was undigested food in the stomach, the procedure time was less than 10 minutes or there were prolonged periods of signal loss.

OGD (GIF-H260 or GIF-H290, Olympus Corp, Tokyo, Japan or EC34-i10F, Pentax Corp, Tokyo, Japan) was performed within two weeks of MACE by a JAG accredited endoscopist blinded to the findings of MACE. Patients were given 6 sprays of oropharyngeal topical anaesthesia (10% Xylocaine, 10mg per spray; Aspen Pharma Trading Ltd, London, UK) with or without conscious sedation according to normal practice.

4.3.3 Data collection and analysis

Tolerance, acceptability and preference questionnaire

Pre-procedure

Knowledge of what patients anticipate in advance of their investigative experience is necessary to understand their health seeking behaviour and compliance. Prior to each examination patients are asked to score on a visual analogue scale (1-10: not at all to extremely) their anxiety, as well as 13 aspects causing concern related to telling friends about, fasting and discomfort prior to, the test; intravenous cannulation, instrumentation (defined as insertion of flexible endoscope or swallowing the capsule), expressions of emotions, the endoscopist seeing food in the stomach during the test and feelings of gagging, choking, vomiting, bloating, discomfort during the test. [65] Summation of each of these 13 aspects scores was used as a measure of how acceptable the patient regarded the test in advance of the procedure (pre-procedure Endoscopy concerns scale (ECS) scores between 13-130: most to least acceptable).

Post-procedure

Four measures of patient acceptance and preference were collected after the procedure:

1) An ECS questionnaire scoring 10 of the 13 items described earlier quantified their actual experience. The three pre-procedural items (concerns related to telling friends about, fasting and discomfort prior to, the test) were not repeated. Items are summated to provide a measure of acceptability in light of their actual experience (post procedure ECS: 10-100).

2) Patients were asked to consider three scenarios: whether or not they would undergo the test again or advise a friend to do the same in similar medical circumstances or have the test as a screen for cancer in five years' time. A patient was regarded as finding the test acceptable if they answered in the affirmative to all three questions.

3) The UPC-Q assesses and compares patients' individual experience of each form of endoscopy. [68] Each patient was asked to identify three aspects of the overall pathway which was most important to them and rank the level of importance of the three aspects relative to each other by dividing a total of six points between the aspects. They were then asked to rate their experience of each aspect (1-5: poor to excellent). The overall UPC-Q score (0-100: least to most acceptable) was obtained using the following equation (where A_1, A_2 and A_3 are the three aspects of the pathway chosen by each patient):

$$UPC\text{-}Q\ score = (Grade\ A_1 \times Rate\ A_1/6) + (Grade\ A_2 \times Rate\ A_2/6) + (Grade\ A_3 \times Rate\ A_3/6) \times 25$$

Aspects of the care pathway listed as important to patients were categorised according to whether their subject matter related to communication, procedural tolerance or aftercare, test accuracy or results.

4) Patients are asked to express a preference between tests. Where histological assessment is warranted after MACE, a second conventional endoscopy is required and therefore may affect patients' initial preference. Patients are asked a series of questions designed to examine preference for the primary diagnostic test based on an increasing probability of requiring a second procedure to obtain biopsies.

Baseline characteristics and endoscopic findings

Patient age, gender, previous experience with endoscopy, and Hospital Anxiety and Depression scale (HADS) scores were collected prior to examination. HADS was used to diagnose anxiety (trait) and depression if patients scored over eight on a 21-point scale as previously described. [164,165] During OGD the use of sedation, video recordings of the procedure and examination findings are collected. During MACE examination findings are documented with images. MACE and OGD findings are compared against an unblinded review of OGD and MACE videos in parallel to identify each finding. Time spent examining overall, in the oesophagus and stomach were compared (excluding biopsies, and including both phases of intubation and extubation for conventional OGD).

4.3.4 Outcome measures

The primary outcomes of the study were to determine aspects of endoscopy which cause distress to patients and to compare these individual aspects, overall acceptability and global experience of OGD and MACE. A secondary outcome was an analysis of how the need for a second procedure to obtain biopsies after MACE affected patients' choice of their primary investigation and to compare endoscopic findings between modalities.

4.3.5 Statistical methods

Advice was sought from the Statistical Services Unit at the University of Sheffield. A sample of 44 patients would have 90% power to detect a difference in mean distress scores of 1 between MACE and OGD, assuming a standard deviation of the differences of 2, using a paired t-test with a 0.05 two-sided significant level.

SPSS Statistics for Macintosh, Version 24.0.0 (IBM Corp, New York, USA) was used for statistical analysis. Parametric and non-parametric continuous data is presented as mean and standard deviation (SD) or median and interquartile range (IQR) respectively. Normality of data is determined by an insignificant Shapiro-Wilk test. Non-parametric paired differences in central tendencies were examined using Wilcoxon signed rank tests. Unpaired differences were examined using Mann Whitney U or Kruskal-Wallis H test. Categorical data is presented as number and percentages: n (%), and McNemar test was used to compare paired dichotomous variables. Construct validity of the UPC-Q was examined by correlation of convergent and discriminant factors. Statistical significance is defined as $p<0.05$.

4.3.6 Ethics

This study was approved and conducted in accordance with the ethical standards of the South Central – Berkshire B Research Ethics Committee (16/SC/0606. ClinicalTrials.gov NCT03420729), and the 1964 declaration of Helsinki and its later amendments.

4.4 Results

4.4.1 Participants

Recruitment towards this study comparing OGD and MACE is part of a larger study involving, in addition, a cohort of patient who opted for TNE (reported in Chapter 5). A total of 111 patients were approached and 108 were confirmed eligible. A patient with dysphagia, a metallic heart valve and long-term NSAID use were ineligible. Of 108 patients invited to participate, 69 completed the study (36 patients declined and three

agreed to do so but failed to attend their appointments) of which 47 opted for OGD

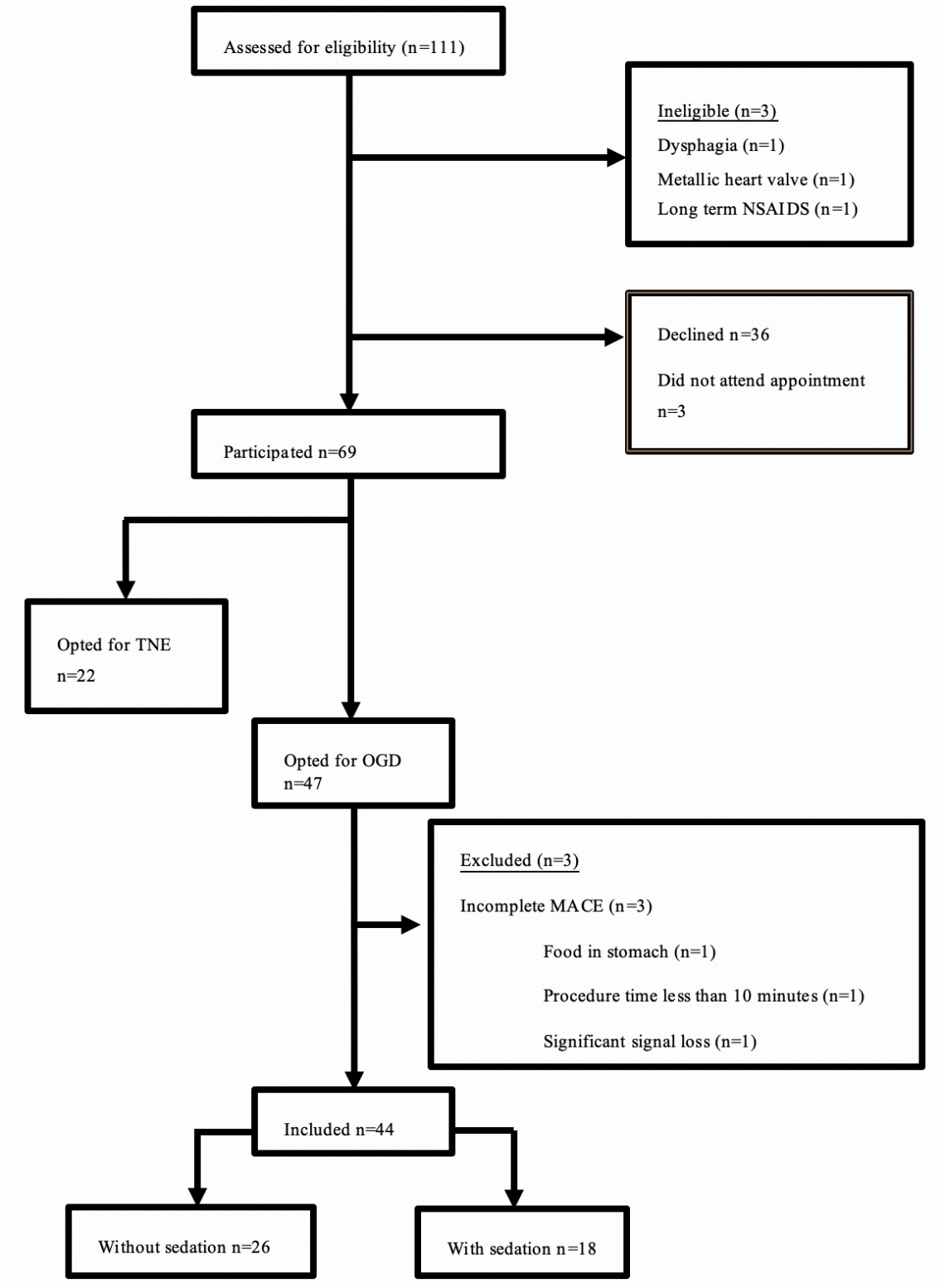


Figure 8). The majority of patients who declined to participate did not want to undergo clinically unnecessary examinations.

MACE was successful in 44 patients (91.7%) and OGD in all patients. MACE was unsuccessful in three patients due to undigested food in the stomach (n=1), a procedure time of less than 10 minutes (n=1) and prolonged periods of signal loss (n=1). The median age of included patients was 53 (IQR 31), were female in 66% (n=27), had previous experience of OGD in 41% (n=18) and opted for conscious sedation in 41% (n=18) with a median dose of midazolam and fentanyl of 2mg (range 1.5 - 4) and 50mcg (range 25 - 75). Median (IQR) HADS anxiety score was 5 (8) with 29% (n=12) having an anxiety trait (score >8).

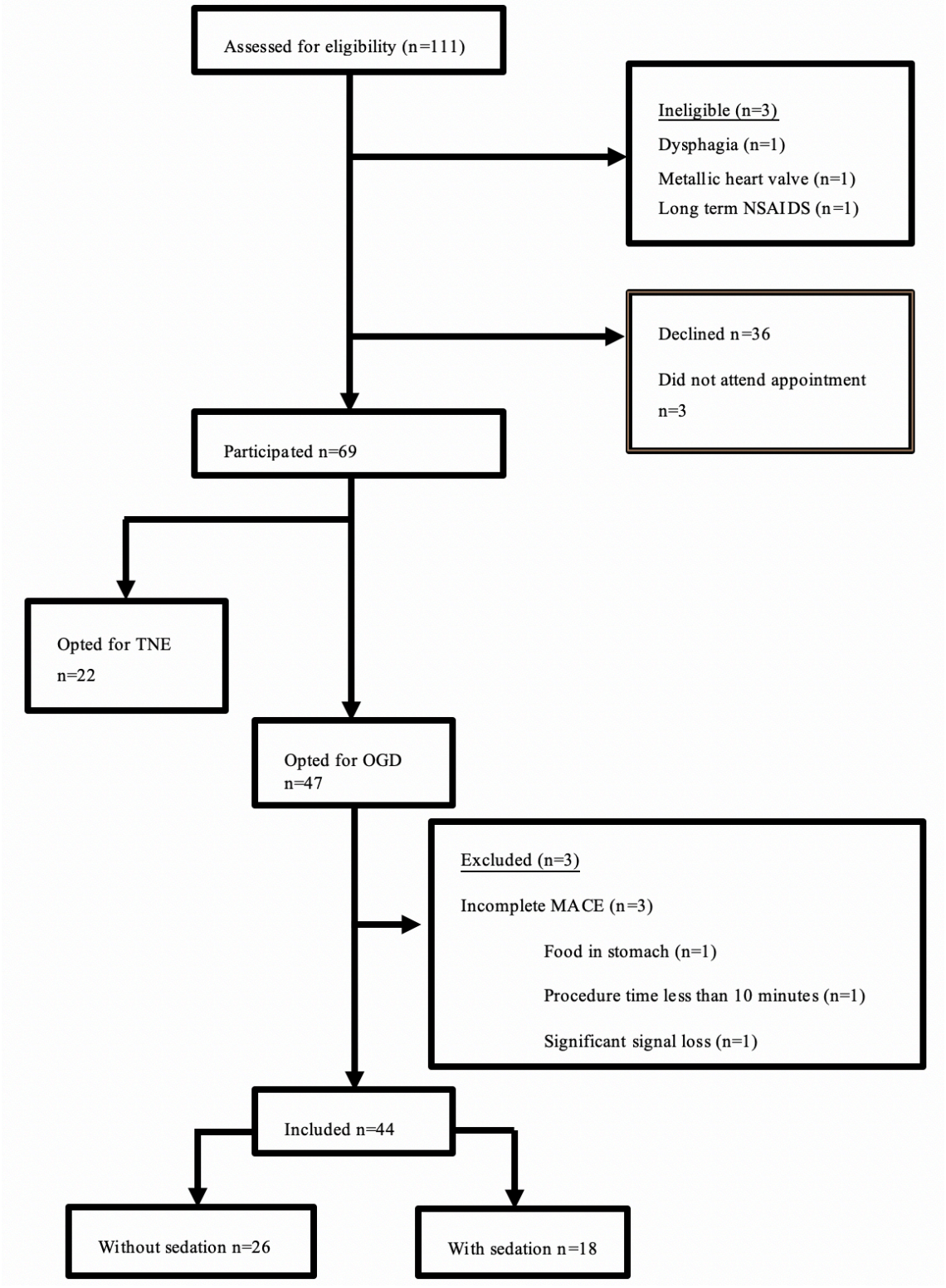


Figure 8: Patients who opted for OGD in a comparison of patient experience of OGD and MACE

4.4.2 Patient anxiety and anticipatory concerns of OGD and MACE

Prior to their procedure, patients were more anxious about having OGD than MACE, with median state anxiety scores of 5 and 2 ($p<0.0001$; Table 5a). Trait anxiety scores (HADS) correlated with state anxiety scores prior to OGD ($r=0.42$ $p=0.004$) and MACE ($r=0.55$, $p<0.0001$). Median pre-procedure ECS scores were higher before OGD (39 vs 26, $p<0.0001$) than MACE. What caused most distress (median score) prior to OGD were concerns about procedure related factors: the process of intubation (5 vs 3, $p<0.0001$), gagging (5 vs 2, $p<0.0001$), choking (5 vs. 2, $p<0.0001$), vomiting (4 vs 1, $p=0.001$) and discomfort (5 vs 2, $p<0.0001$); by comparison, discussing the procedure with friends and relatives, fasting pre-procedure, the anticipation of the need for intravenous cannulation, displays of emotions and the endoscopist seeing food in the stomach caused negligible distress (Table 5a). No differences were seen in the pre-procedure ECS ($p=0.28$) and state anxiety ($p=0.95$) scores between those who have and those who have not experienced OGD before.

4.4.3 Patient tolerance and factors causing distress during OGD and MACE

After their procedure, patients reported experiencing significantly more distress (median score) due to gagging (6 vs 1, $p<0.0001$), choking (5 vs 1, $p<0.0001$), abdominal bloating (2 vs 1, $p<0.0001$), instrumentation (4 vs 1, $p<0.0001$), discomfort during (5 vs 1, $p<0.0001$) and after (2 vs 1, $p<0.0001$) OGD when compared to MACE (Table 5b). Amongst the patients undergoing OGD with sedation, MACE was still significantly better tolerated than sedated OGD (Table 6). Patients correctly anticipated which factors related to OGD caused them distress. No differences were found in distress caused in anticipation of OGD and actual experience of OGD (Table 7). All factors related to MACE caused significantly less distress than anticipated.

4.4.4 Acceptability and patient related experience of OGD and MACE

Median post procedure ECS scores were significantly higher after OGD (34 vs 11, $p<0.0001$) compared to MACE. UPC-Q score was lower for OGD (50 vs 98, $p<0.0001$) than MACE. Amongst the patients undergoing OGD with sedation, MACE was significantly better accepted than sedated OGD (Table 6). As defined by affirmative answers to all three questions regarding preparedness to undergo the same test again to investigate symptoms or screen for cancer or recommend the test to a friend, 64% and 100% of patients found OGD and MACE acceptable.

The UPC-Q was completed appropriately by 95% (n=42). Aspects of care deemed important by patients can broadly be divided into the following categories: procedural tolerance (including drinking the water, swallowing the capsule, test discomfort and duration), staff communication (including information about, and progress of, the test), procedural aftercare and recovery (including a comfortable environment and adverse effects), test results, test accuracy and other matters. The importance of each aspects of care and comparisons between OGD and MACE are illustrated and captioned in Figure 9.

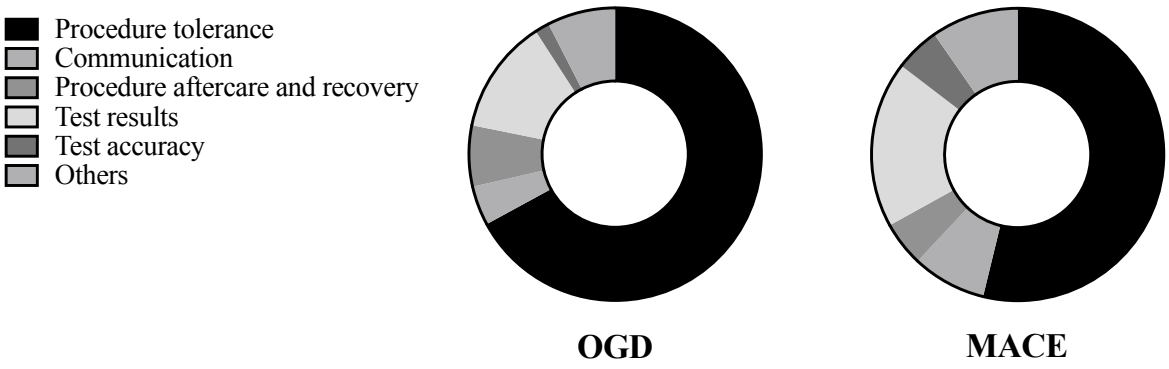


Figure 9: Aspects of care important to patients undergoing OGD and MACE generated by the UPC Questionnaire.

Six points were allocated by 42 patients each to aspects of care pathway deemed important after each procedure. There was a greater percentage of a total 252 allocated points towards procedure tolerance after OGD than MACE (67.1% and 54.0%, p=0.003) suggesting that procedure tolerance was significantly more important after OGD than MACE. No differences were found in staff communication (4.4% and 4.1%, p=0.68), procedure aftercare and recovery (6.7% and 4.1%, p=0.71), test results (12.7% and 14.4%, p=0.07), test accuracy (1.6% and 2.9%, p=0.17) and other concerns (7.5% and 8.8%, p=0.13).

4.4.5 Patient preference between OGD and MACE

When asked to express a preference for one or other test, all patients preferred MACE to OGD. If tissue biopsies were necessary (therefore requiring flexible endoscopy as a second test) after MACE and the chance of requiring biopsies was 1 in 20, 1 in 10, 1 in 5, 1 in 4 or 1 in 2, 100%, 100%, 94%, 94% and 83% would prefer MACE followed by OGD (rather than a single OGD test).

4.4.6 Performance characteristics of UPC-Q and ECS

The UPC-Q correlated with post procedure ECS after both MACE ($r = -0.32$ $p=0.01$) and gastroscopy ($r = -0.40$ $p=0.002$) demonstrating convergent validity, but not with pre-procedure ECS ($p=0.49$ and $p=0.29$) nor state anxiety scores ($p= 0.25$ and $p=0.26$) providing some evidence of discriminant validity as well.

4.4.7 Endoscopic findings

Twenty-three patients were included in the analysis of endoscopic findings [b]. Magnetic transpyloric steering of the capsule into the duodendum occurred in 47.8% (11/23). The mean (SD) examination time of MACE and OGD are 40.1 (2.9) and 4.9 (0.5) minutes ($p<0.0001$) with significantly more time spent examining the stomach with MACE (38.7 (2.9) vs. 3.0 (0.3) minutes, $p<0.0001$) but similar time examining the oesophagus (1.3 (0.5) vs. 0.9 (0.1) minutes, $p=0.43$). No serious adverse events occurred after MACE nor OGD.

There was agreement in findings between MACE and OGD in 65% (15/23) of patients (Table 8). Eight patients (35%) had normal examinations on both MACE and OGD.

[b] The first initial 18 patients did not have OGD video recordings as amendments for ethics proposals and recording equipment were pending. Three patients had incomplete video recordings owing to technical problems.

Thirty endoscopic findings were found in total: 66% of findings (20/30) were seen by both MACE and OGD, 16.7% (5/30) by MACE alone and 16.7% (5/30) by OGD alone. Endoscopic images of findings on MACE and OGD for each finding is detailed in Figure 10 (Cases 2, 4, 5 and 8), Figure 11 (Cases 9-12), Figure 5 (Cases 16-18), Figure 13 (Cases 20 and 21) and Figure 14 (Cases 22 and 23).

Table 5: Distress caused in anticipation of and by actual experience of OGD compared to MACE

	a) Pre-procedure anticipation			b) Patient experience		
	OGD	MACE	p	OGD	MACE	p
Telling friends/colleagues about test	1 (0)	1 (3)	0.01			
Fasting	1 (1)	1 (2)	0.15			
Discomfort prior to procedure	1 (1)	1 (2)	<0.0001			
Gagging	5 (4)	2 (5)	<0.0001	6 (6)	1 (0)	<0.0001
Choking	5 (2)	2 (5)	0.05	5 (6)	1 (0)	<0.0001
Bloating	2 (2)	2 (4)	0.001	2 (4)	1 (0)	0.08
Vomiting	4 (2)	1 (6)	0.19	1 (3)	1 (0)	<0.0001
Doctor seeing food in stomach	1 (0)	1 (0)	0.002	1 (0)	1 (0)	0.79
Displaying emotions during the test	1 (1)	1 (3)	<0.0001	1 (4)	1 (0)	<0.0001
Instrumentation	5 (4)	3 (5)	0.03	4 (7)	1 (1)	<0.0001
Intravenous catheter	1 (1)	1 (3)	0.12	1 (1)	1 (0)	0.001
Discomfort during procedure	5 (3)	2 (6)	<0.0001	5 (5)	1 (0)	<0.0001
Discomfort after procedure	2 (2)	2 (4)	0.04	2 (4)	1 (0)	<0.0001
Pre procedure anxiety	5 (5)	2 (2)	<0.0001			
Pre procedure ECS	39 (41)	26 (7)	<0.0001			
Post procedure ECS				34 (32)	11 (1)	<0.0001
UPC-Q				50 (50)	98 (25)	<0.0001

Pairwise comparison of pre-procedure anxiety and pre- and post- procedure distress (1 – 10: Least to most) scores; pre- (13-130: Most to least acceptable) and post- (10-100) procedure endoscopic concern scale (ECS) score and universal patient centredness questionnaire (UPC-Q) scores (least to most acceptable: 0-100) between OGD and MACE reported as a median (IQR).

Table 6: Patient experience in those undergoing OGD with sedation compared to MACE

	Patient experience		
	OGD (with sedation)	MACE	p
Gagging	6 (6)	1 (0)	0.001
Choking	4 (5)	1 (0)	0.001
Bloating	1 (2)	1 (0)	0.17
Vomiting	1 (2)	1 (0)	0.04
Doctor seeing food in stomach	1 (0)	1 (0)	1.00
Displaying emotions during the test	1 (4)	1 (0)	0.04
Instrumentation	3 (5)	1 (1)	0.008
Intravenous catheter	2 (3)	1 (0)	0.005
Discomfort during procedure	4 (6)	1 (0)	0.001
Discomfort after procedure	2 (3)	1 (0)	0.005
Post procedure ECS	25 (26)	10.5 (2)	<0.0001
UPC-Q	54 (52)	100 (19)	0.003

Pairwise comparison of distress scores (1 – 10: Least to most distressing), post- procedure endoscopic concern scale (ECS) score (10-100: Most to least acceptable) and universal patient centredness questionnaire (UPC-Q) score (Least to most acceptable: 0-100) between OGD with sedation and MACE reported as median (IQR).

Table 7: Comparison of patient expectation and experience during OGD and MACE

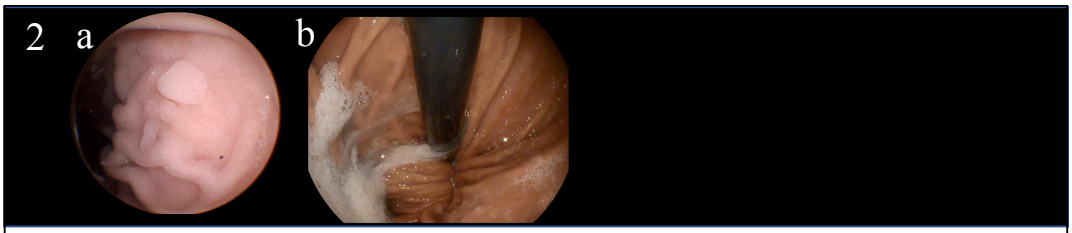
	OGD			MACE		
	Expectation	Experience	p	Expectation	Experience	p
Gagging	5 (5)	6 (6)	0.22	2 (4)	1 (0)	<0.0001
Choking	5 (5)	5 (6)	0.85	2 (2)	1 (0)	<0.0001
Bloating	2 (4)	2 (4)	0.79	2 (2)	1 (0)	0.002
Vomiting	4 (6)	1 (3)	0.08	1 (2)	1 (0)	<0.0001
Doctor seeing food in stomach	1 (0)	1(0)	0.34	1 (0)	1 (0)	0.04
Displaying emotions during the test	1 (3)	1 (4)	0.49	1 (1)	1 (0)	0.002
Instrumentation	5 (5)	4 (7)	0.16	3 (4)	1 (1)	<0.0001
Intravenous catheter	1 (3)	1 (1)	0.04	1 (1)	1 (0)	<0.0001
Discomfort during procedure	5 (6)	5 (5)	0.92	2 (3)	1 (0)	<0.0001
Discomfort after procedure	2 (4)	2 (4)	0.72	2 (2)	1 (0)	<0.0001

Paired comparison of distress scores (1 – 10: Least to most) cause in anticipation of and actual experience of OGD and MACE reported as median (IQR)

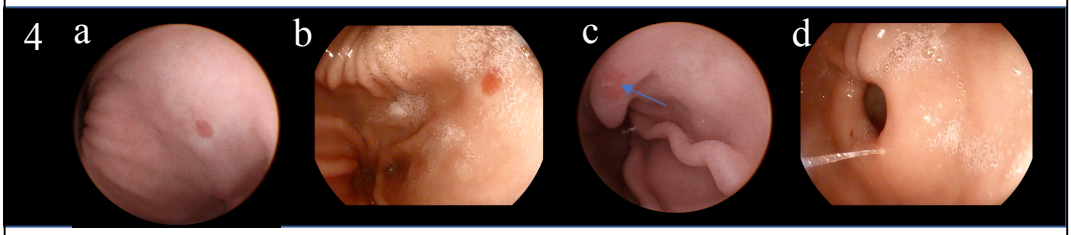
Table 8: Comparison of findings in 23 patients with dyspepsia investigated with MACE and OGD.

Case	MACE and OGD	MACE only	OGD only
1	Normal		
2		Fundal polyp	
3	Normal		
4	Antral angioectasia	Antral erosion	
5		(antral bulge)§	Oesophagitis
6	Normal		
7	Normal		
8	Prepyloric erosion x2		
9	D2 Angioectasia		
10	Antral gastritis*	Prepyloric erosion	
11	Antral erosion and fundal polyp†		
12			Pyloric erosion
13	Normal		
14	Normal		
15	Normal		
16	Oesophagitis* and Fundal polyp†		
17	Duodenditis		
18	Antral erosions		Duodenitis
19	Normal		
20	Oesophagitis*	Fundal polyp	Hiatus hernia, duodenitis
21	Fundal polyp x2†, Antral gastritis		
22	Oesophagitis*, cluster of polyps on lower posterior body of stomach		
23	Antral gastritis, multiple >20 flat polyps on body of stomach, hiatus hernia	Linear ulcer along lesser curve	

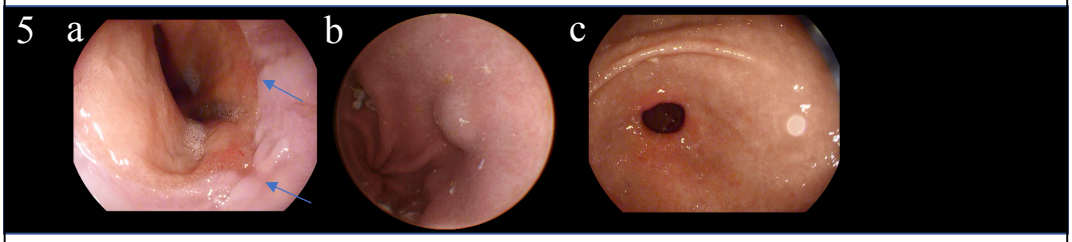
*Not seen on live MACE examination, but seen on retrospective review of capsule video. †not seen on initial blinded review of OGD videos, but seen in retrospect after unblinding. §Antral bulge not seen on OGD



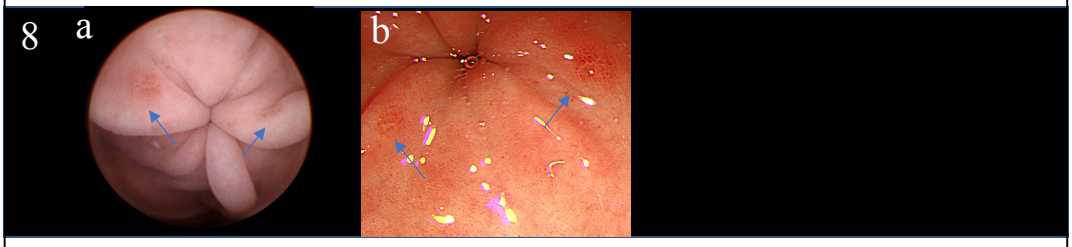
Case 2: Fundal polyp. a) Polyp seen on MACE but not OGD. b) Best view of the fundus seen during OGD with a much retching.



Case 4: Antral angioectasia and antral erosion. a) Angioectasia seen on MACE and b) on OGD; c) Antral erosion seen on MACE but not on OGD. d) Best view of antrum on OGD

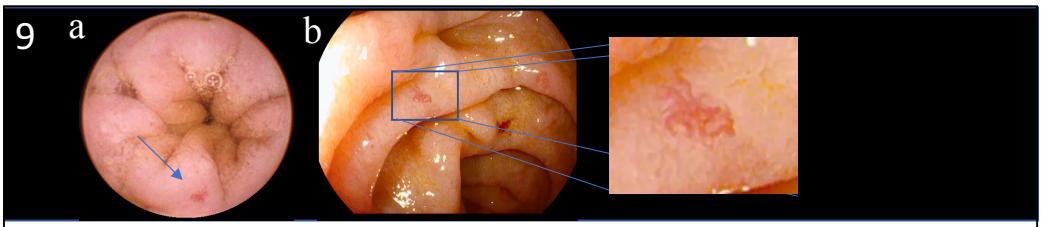


Case 5: Oesophagitis Grade A. a) Oesophagitis seen on OGD but not seen on MACE. b) submucosal bulge seen in pylorus on MACE, but not on OGD. c) Antrum view on OGD shows the mucosa is flat suggesting the finding on MACE is a false positive

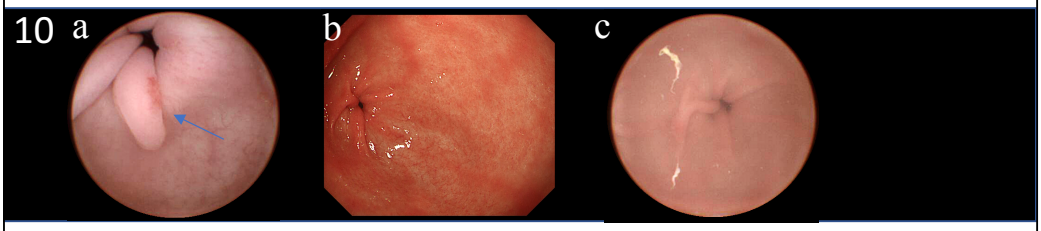


Case 8: Two pyloric erosions. a) Erosions seen on MACE and b) OGD

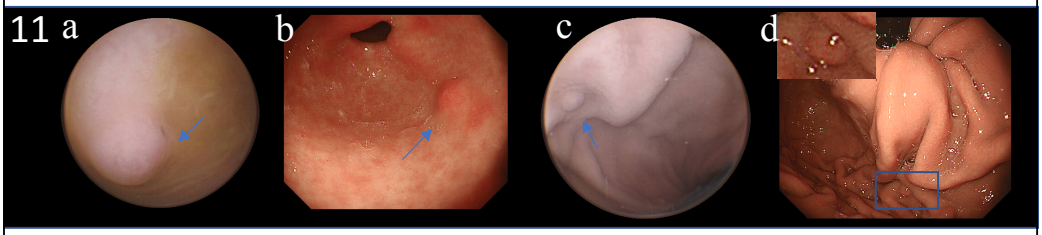
Figure 10: Endoscopic images of cases 2, 4, 5 and 8



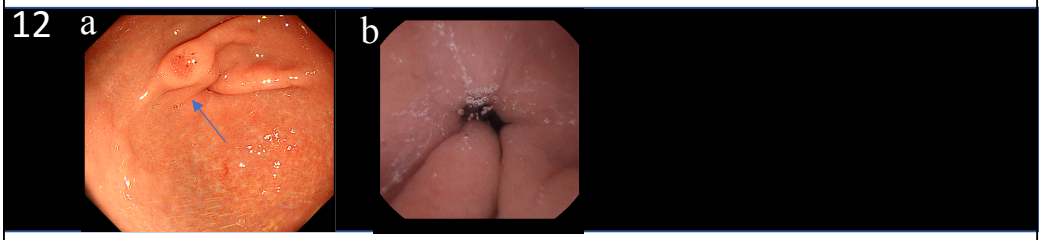
Case 9: Second part of duodenum angioectasia. a) Angioectasia seen on MACE and b) OGD.



Case 10: Antral erosive gastritis. a) Solitary erosion seen on MACE but not on OGD. b) Antral linear erythema seen on OGD but more subtly seen on c) MACE in retrospect after unblinding.

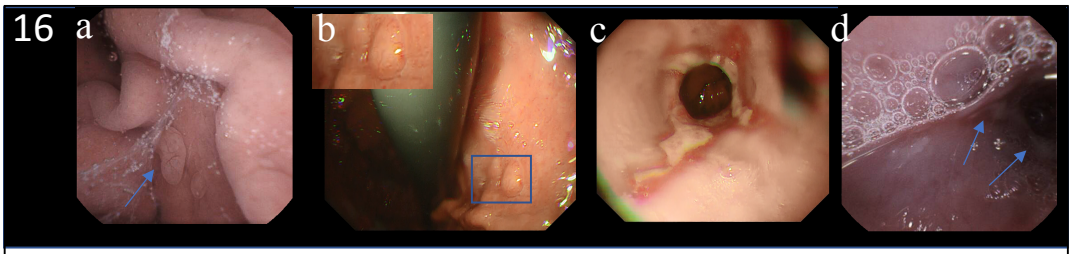


Case 11: Antral nodular erosion and small polyp. a) Antral nodular erosion seen on MACE and b) OGD; c) Subtle fundal polyp seen on MACE and on d) OGD in retrospect after unblinding.

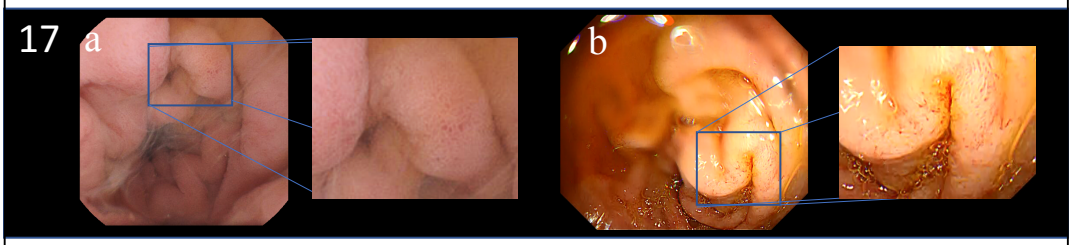


Case 8: Solitary pre-pyloric erosion. a) Pre-pyloric erosion seen on OGD but not on MACE. b) MACE view of pylorus.

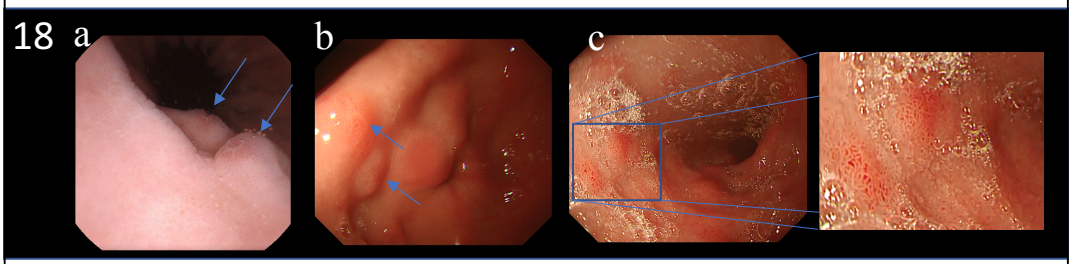
Figure 11: Endoscopic images of cases 9 - 12



Case 16: Fundal polyp and Oesophagitis grade D. a) Fundal polyp seen on MACE and on b) OGD in retrospect after unblinding. c) Oesophagitis seen on OGD but not on MACE initially. d) On retrospective review of MACE, one image has the tips of the ulcerated oesophagus (blue arrows).

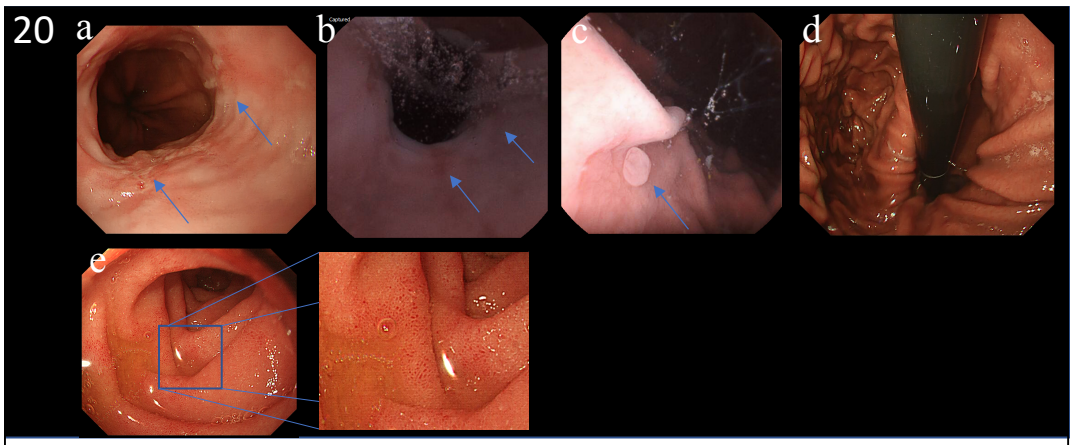


Case 17: Duodenitis. a) Patches of red tipped and oedematous villi seen on MACE and b) on OGD

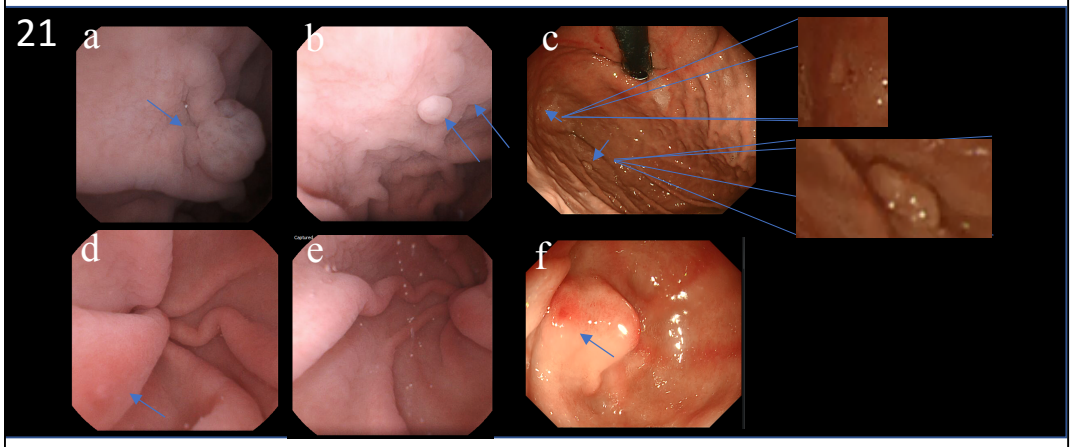


Case 18: Two pre-pyloric erosions and duodenitis. a) Pre-pyloric erosions seen on MACE and b) OGD; c) Duodenitis seen on OGD. The capsule did not record into the small bowel – guided transpyloric passage was attempted but failed and patient did not want to keep data recorder on.

Figure 12: Endoscopic images of cases 16 – 18

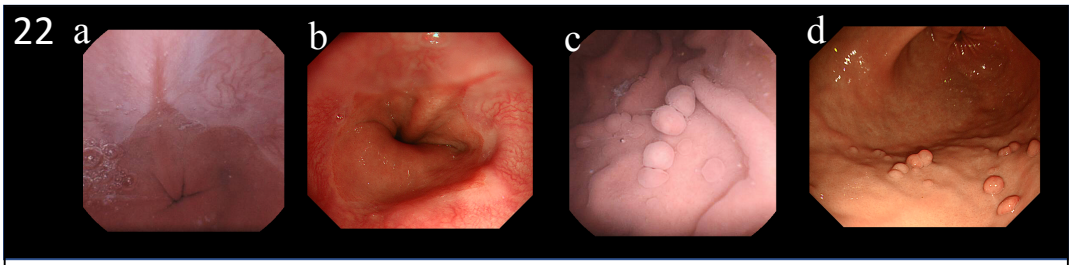


Case 20: Oesophagitis grade B, hiatus hernia, fundal polyp and duodenitis. a) Oesophagitis seen on OGD but not live MACE. b) On retrospective review of MACE video, tips of oesophagitis can be seen (blue arrows). c) Fundal polyp seen on MACE but not OGD. d) Best view of fundus on OGD shows significant hiatal hernia but poor distension of fundus. Hiatal hernia not seen on MACE. e) Duodenitis seen on OGD. The capsule did not record into the small bowel – guided transpyloric passage was attempted but failed and patient did not want to keep data recorder on.

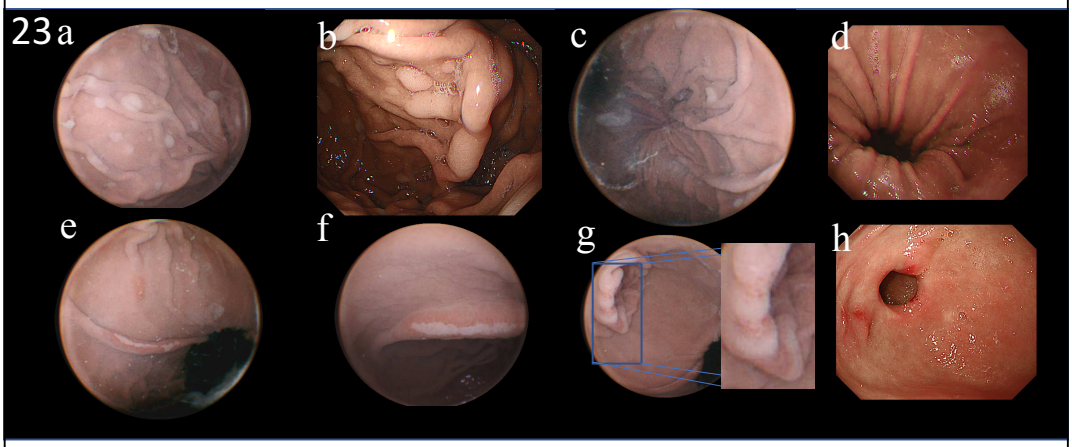


Case 21: Two fundal polyps and antral erosive gastritis. a) Bigger and b) smaller fundal polyp seen on MACE. c) Both polyp seen on OGD in the distance after unblinding. d) A single erosion and e) linear erythema seen on MACE. f) OGD shows erosion (blue arrow) and linear erythema.

Figure 13: Endoscopic images of cases 20 and 21



Case 22: Oesophagitis grade A and a cluster of gastric polyps. a) Oesophagitis seen on MACE and on b) OGD. c) A cluster of polyps on the lower posterior body of stomach seen on c) MACE and d) OGD



Case 23: Multiple flat polyps, large hiatus hernia, Cameron ulcer and antral gastritis. a) multiple pale flat polyps scattered along body of stomach seen on MACE and b) OGD. c) Converging gastric folds seen on MACE and d) OGD suggesting a hiatus hernia. e) A linear ulcer that tracks down a single fold along the length of the lesser curve to the f) antrum seen on MACE. This ulcer was not seen on OGD. This is likely a Cameron ulcer associated with the large hiatus hernia. g) Linear erythema seen on MACE and h) on OGD.

Figure 14: Endoscopic images of cases 22 and 23

4.5 Discussion

The anticipation of an OGD causes significantly more distress in comparison to MACE as evidenced by higher pre-procedure ECS scores. In advance of OGD, concerns causing most distress were related to procedural tolerance (intubation, feelings of gagging, choking and discomfort during OGD) and these matched by patients' actual experience. This may explain in part why OGD causes considerable patient anxiety but significantly less so prior to MACE. Patients' actual experience favours MACE over OGD by some margin and by all measures, including specific aspects of procedural tolerance, acceptability (including both patient-related experience measures: UPC-Q and post procedure ECS score) and preference. The majority of patients would prefer two procedures, MACE followed by OGD rather than a single OGD, even if there was a 50% chance of requiring flexible endoscopy as a second test to obtain biopsies for histological assessment.

OGD is the accepted gold standard in upper GI investigation, however, about 10% of early cancers are missed at initial OGD. [4] Upper GI lesions have been identified during push enteroscopy [166] and capsule endoscopy [167] and are presumed to have been missed by prior OGD. Furthermore, recent studies of MACE using a handheld or robot controlled magnet suggest at least diagnostic equivalence with OGD. [102,103,107] In these studies, both MACE and OGD missed pathologies. This is consistent with the finding of this study where a third of endoscopic findings were only seen with one modality. Although both MACE and OGD detected 25 of 30 endoscopic findings each, suggesting similar performance, this study is not powered to examine differences in diagnostic yield in a general population of dyspeptic patients where a low yield of pathology is expected.

Pathologies in this study were graded independently at the MACE examination and at the conventional OGD procedure. Each finding was then confirmed on an unblinded review of the MACE and OGD videos read in parallel. Interestingly, in four cases of fundal polyps detected on MACE but not OGD, the polyps could be seen in the fundus from a distance on OGD videos in retrospect (Case 11, 16 and 21: Table 8). That the mean examination time of OGDs was 4.9 minutes, and falls short of the 7 minutes now

expected by endoscopists, may explain why pathology may have been missed on OGD [32,33]. However, small gastric polyps are mostly inconsequential in patients with dyspepsia and therefore this discrepancy may reflect a reporting bias of the conventional endoscopist. On the other hand, a longer examination time with MACE may have contributed to an increased detection in gastric pathology. There were cases of a missed polyp in the fundus (case 2) and a Cameron's ulcer along the lesser curve (case 23) which were clearly identified by MACE, but not identified on OGD due to imperfect distension and mucosal inspection. It could be further hypothesised that when the upper GI tract is distended with water some pathologies are more apparent than when inflated with air which is seemingly less physiological. For example one study found that gastric antral vascular ectasia were commonly detected amongst anaemic patients during small bowel capsule endoscopy, but missed on initial OGD. [168].

Early studies of handheld MACE have suggested that while distant views were achieved in the majority [117], detailed views were difficult to achieve in the upper stomach. In a large 350-patient multicentre study of patients undergoing both robot MACE and conventional OGD, MACE was equally capable in detecting focal gastric lesions irrespective of size or location with an overall 90% sensitivity and 94% specificity compared to OGD. The manoeuvrability of capsule endoscopes using a robot MACE system in the stomach is therefore felt therefore to be an improvement over the handheld device, although comparative studies between MACE systems are lacking.

In contrast to Asian countries, where gastric cancer is more prevalent, in the west there is an increasing incidence of Barrett's oesophagus and oesophageal adenocarcinoma and therefore the adoption of upper GI capsule endoscopy in Western populations is likely to be limited by its ability to detect oesophageal pathology [9]. Our initial experience of oesophageal examination using the robot MACE system has been disappointing. Although the amount of time spent examining the oesophagus was no different between MACE and OGD, three cases of oesophagitis were missed by MACE and in two seen on one or two frames briefly when unblinded. This is possibly because the capsule endoscope has only a unidirectional image sensor and if by chance held facing away from the gastrooesophageal junction, it would miss pathology. Handheld MACE systems such as the Mirocam Navi seem more capable in holding the capsule in

the lower oesophagus with a mean oesophageal examination time of 3.1 minutes [169], likely due to closer apposition of the magnet to the chest wall. Other techniques such as tethering the capsule endoscope to a detachable string are being re-examined and have the additional advantage of a controlled examination of the upper and middle oesophagus, [170] although more technologically advanced capsules with higher image capture rates and bidirectional image sensors are likely to be more tolerable and acceptable to patients. [112] Finally, a controlled transpyloric transit rate in less than half of cases is disappointing and would explain why duodenal pathology was occasionally missed. With the benefit of more experience and practice, it is possible to achieve transpyloric passage in all cases within 4.4 minutes in a series of 107 patients [122].

Along with clinical effectiveness, patient experience is a further pillar in quality of care and the primary focus of this study. [171] Studies of patient experience of endoscopy have focused on procedural tolerance and satisfaction. [57,171] This study has shown that over a third of patients volunteered concerns were unrelated to their procedural tolerance. That test results are important to patients is unsurprising, but many also expressed an interest in the overall investigative pathway, the detail (like sensations experienced) and duration of the test. Patients valued a comfortable environment during recovery and information about potential adverse effects.

A measure of satisfaction is unidimensional and conveys patients' overall contentedness with their experience, but in contrast to patient-related experience measures (PREMs), does not encompass all aspects of care nor discriminate which aspects are important. [172] Patient experience may affect compliance with investigation and participation in screening programmes and therefore services responsive to feedback can improve patient outcomes.[71,172] Therefore we chose to use two PREMs, the ECS and UPC-Q. The ECS comprised aspects of patient concerns before, during and after endoscopy, and the score derived was shown to demonstrate good internal consistency and construct validity and to correlate with patients' acceptance of OGD.[65] The UPC-Q is a patient-generated index based on each individual's concerns, priorities and experiences and serves to examine patient acceptability of a healthcare experience beyond the constraints set by an endoscopy paradigm. It performs reliably and correlates well against known measures of patient satisfaction in other in- and out-patient settings.[68]

That it correlates with the ECS in this study, an experience score designed for endoscopic practice, suggests that the UPC-Q could be used as a patient-related experience measure in this setting. However, one of the main limitations of this study is that the ECS has not been validated in MACE, and some question have been adapted without evidence of validity. No PREM has yet been developed specifically for capsule endoscopy. The ECS was developed based on patient reports and literature review of conventional endoscopy, but not by more systematic qualitative interviews of patients experiences of endoscopies. Therefore, the content validity of the ECS tool even with conventional endoscopy could also be questioned. At present no better tool exists, and therefore it is possible that the measures may bias towards better tolerance and acceptance of MACE. This is because the conventional distresses to intubational endoscopy, such as gagging and feelings of choking may not apply to such a degree that is important to patients.

Our results are consistent with previous studies of tolerance and preference for capsule endoscopy over OGD. [101-105,107] Patients are thought to formulate a notion of satisfaction by comparing their expectation with actual experience. [173] Our patients accurately anticipated the unpleasant aspects of OGD, yet only 64% of patients regarded it as acceptable and it performed comparatively poorly in the UPC-Q. Patients MACE experience was universally better than anticipated compared to 76% of patients who reported feeling more distressed than anticipated in at least one domain after OGD.[c] This would explain why patients place a greater ranking of importance to procedural tolerance after OGD than MACE.

Our study contrasts with the 95% acceptability rate of OGD identified in the study of Condon et al. [65] where all patients were sedated. The use of conscious sedation for OGD had a disappointing impact in this study. However, systematic review and meta-analysis showed that compared to no sedation, use of midazolam alone only improves

[c] Patients who reported a worse experience than anticipated distress in at least one of 10 post-procedure measures of distress: 0/44 for MACE and 32/44 for OGD

patient satisfaction and willingness to repeat the procedure (not any aspect of tolerance nor overall experience) [55], and at mean doses of 4.8-10.3 mg, far greater than would be used in current practice. That patients may not always feel 'conscious' sedation is adequate may explain the move towards anaesthetist-directed sedation using propofol in the USA. [77]

Studies which examine the diagnostic yield of upper GI capsule endoscopy technology and OGD perform MACE prior to OGD to ensure biopsy defects are not mistaken as false positives on MACE [104]. As in our study, when patients act as their own controls, exposing patients to MACE prior to OGD might cause bias in their responses to tolerance and acceptability. It is likely that acceptability is defined by the context in which it is assessed, and the experience of a non-invasive alternative in this study prior to OGD may have adversely affected the acceptability of OGD. Future prospective trials of patient experience should consider this exposure bias and randomisation of order of procedure could be considered.

This study demonstrates patient's preference for MACE over OGD even where biopsies and subsequent OGD are required. However, the present study does not consider patients preferences informed with information regarding the accuracy of the investigations. We show in Chapter 3 that the miss cancer occurrence rate is 1 in 1250 OGD procedures. Liao et al. (2015) show that the sensitivity of MACE to detect focal gastric lesions is 90.4% by comparison to OGD. [107] Our anecdotal experience suggests the current iteration of MACE performs poorly in the oesophagus, however no adequately powered studies yet examine the accuracy of MACE in the oesophagus. When patients are not informed about the accuracy of the procedures, our UPC-Q data suggests that test accuracy is ranked as a priority by 1.6% and 2.7% of those undergoing OGD and MACE respectively (p=0.17). It is expected however that informing patients that MACE likely performs poorer than OGD, the gold standard, would negatively influence their acceptance of MACE and ultimately preference between OGD and MACE.

The ability to obtain biopsies remains an important advantage of OGD. It has been previously found that whilst 84% of 500 patients having OGD to investigate dyspepsia

had biopsies taken, they contributed to management in only 16% beyond empirical treatment with proton pump inhibitors or *Helicobacter pylori* 'test and treat' strategies. [174] If however, lesions are seen requiring biopsies, this study suggest that patients are willing to return for a gastroscopy and prefer to have a MACE examinations initially. The utility and cost effectiveness of this approach in upper GI endoscopy should be further examined. Finally, in recent times, it is increasingly recognised that aerosols generated by retching increase the risk of transmitting COVD-19 to endoscopy staff and patients. [160] This could be mitigated by the use of MACE where oro-pharyngeal reactions are typically absent when swallowing the capsule endoscope.

5 A COMPARATIVE STUDY OF PATIENT TOLERANCE AND ACCEPTABILITY OF MAGNET CONTROLLED CAPSULE ENDOSCOPY AND TRANSNASAL ENDOSCOPY IN DYSPEPSIA

5.1 Abstract

Introduction: Transnasal endoscopy (TNE) is a less invasive and better tolerated upper GI examination than conventional per oral Oesophagogastroduodenoscopy (OGD). Where an already less invasive alternative exists, the benefits of capsule endoscopy in the upper GI tract should be examined. In this study, patient tolerance and acceptability of OGD and transnasal endoscopy (TNE) have been compared with magnet-controlled capsule endoscopy (MACE).

Methods: A self-controlled unblinded comparison of MACE and TNE in the investigation of patients with dyspepsia was performed. Factors affecting patient tolerance and acceptability were examined using two patient reported experience measures, the Endoscopy concerns scale (ECS) and Universal Patient Centredness Questionnaire (UPC-Q).

Results: Pre-procedure ECS scores were higher before TNE (42 and 32, p=0.04) than MACE. Patients were more distressed (median scores) by gagging (1.5 vs 1, p=0.03), choking (3 vs 1, p=0.001), instrumentation (4.5 vs 1, p=0.001), discomfort during (5 vs 1, p=0.001) and after (2 vs 1, p=0.01) TNE compared to MACE. All and 94% of patients found MACE and TNE acceptable respectively. However, UPC-Q score was lower (75 vs 88, p=0.007) and post procedure ECS higher (25 vs 10.5; p=0.001) for TNE than MACE suggesting MACE is better accepted than TNE. MACE would be preferred by 64% of patients even if TNE was subsequently recommended to obtain biopsies.

Conclusion: Overall discomfort and instrumentation are the main causes of patient distress during TNE and tolerance and patient experience favoured MACE. Patients prefer MACE to TNE, even if a further TNE is required after MACE for biopsies in 50% of cases.

5.2 Introduction

Transnasal endoscopy (TNE) involves the intubation of an ultrathin endoscope through the nasal passages to examine the upper GI tract. It is less invasive, better tolerated and accepted by patients than conventional oesophagogastroduodenoscopy (OGD). [21,80] Studies suggest that in the diagnoses of oesophageal disease, TNE is equivalent to conventional OGD. [81,82] There is a self-limiting risk of epistaxis in up to 5%. However because of superior patient tolerance most cases are performed without conscious sedation and therefore its cardiovascular risks. [76]

Capsule endoscopy may be less invasive still. A single study has described that oesophageal capsule endoscopy is more comfortable and preferred by patients compared to transnasal oesophagoscopy in the examination of Barrett's oesophagus. [175] Capsule endoscopy however is unable to take mucosal biopsies which is the main advantage of flexible endoscopes, ones including TNE. Where a less invasive and better tolerated upper GI investigation already exists, the relative benefits of capsule endoscopy should be explored. A more detailed understanding of patients' experience with TNE and studies comparing patient tolerance and acceptability of MACE and TNE are lacking. [57]

We compare the broader experience of MACE and TNE using two patient-related experience measures (PREMs), the Endoscopy Concerns Scale (ECS) and the Universal Patient Centredness Questionnaire (UPCQ), as well as examine patient preference between MACE and TNE. [65,68]

5.3 Methods

5.3.1 Subjects

The recruitment for this study is part of a larger study of previously described in Chapter 4. The subjects included in this study are similar to that described in section 4.3.1 (on page 48) with the exception that patients with contraindications to TNE were not eligible for participation in this study. This included patients with a bleeding diathesis (such as those on Warfarin or have chronic liver disease), a history of nasal polyps, previous nasal surgery or a deviated nasal septum.

5.3.2 Interventions

Patients were offered the choice of OGD (with or without sedation) or transnasal endoscopy (TNE). Procedures were described to the patients verbally and in standardised hospital information leaflets provided as part of routine clinical practice. Those who agreed to participate in the study of TNE were also asked to have MACE in the two weeks preceding their TNE and included in this study. The MACE procedure was performed as described previously in section 4.3.2 (on page 48). TNE was performed after MACE on the same day by FWDT who was unblinded to the findings of MACE. Patients were prepared with 5 sprays (1 ml) of 5% lidocaine/ 0.5% phenyephrine nasal spray (Alliance Healthcare Ltd, Surrey, UK) per nostril 15 minutes prior to procedure followed by 6 sprays of topical local anaesthetic spray (10% Xylocaine, 10mg per spray; Aspen Pharma Trading Ltd, London, UK) immediately prior to TNE (GIF-XP290N, Olympus Corp, Tokyo, Japan).

5.3.3 Data collection and analysis

Data collection and analysis of pre-procedure and post-procedure measures of acceptability and procedural tolerance measures were performed in this study as described in Chapter 4 (section 4.3.3, on page 49). Briefly, measures of acceptability include pre-procedure anxiety, the 13 anticipated aspects causing distress (and summated pre- and post-procedure ECS scores), the UPC-Q patient generated index, the assessment of acceptability based on three scenarios (undergoing the test again, advising a friend to undergo the test or having the test as a screen for cancer) and preference between MACE and TNE. Patient tolerance was measured using aspects causing distress experienced by patient during the examination. Aspects important to patients which were generated and ranked in the UPC-Q were categorised and degree of importance quantified.

5.3.4 Outcome measures

The primary outcomes were to determine aspects of endoscopy which caused distress to patients and to compare these individual aspects, overall acceptability and experience of MACE compared to TNE

5.3.5 Statistical methods

Advice was sought from the Statistical Services Unit at the University of Sheffield. A sample of 44 per group would have a 90% power to detect a difference in distress scores of 1 between MACE and flexible endoscopy assuming a standard deviation of 2 using a paired t-test with a 0.05 two-sided significance level. A sample of 48 patients

would allow for an *a priori* interim analysis to be performed after 16 transnasal gastroscopies which would have a 90% power to detect a difference in mean distress score of 2 and satisfy the requirements of full power. [d]

SPSS Statistics for Macintosh, Version 24.0.0 (IBM Corp, New York, USA) was used for statistical analysis. Parametric and non-parametric continuous data is presented as mean and standard deviation (SD) or median and interquartile range (IQR) respectively. Non-parametric paired differences in central tendencies were examined using Wilcoxon signed rank tests. Unpaired differences were examined using Mann Whitney U or Kruskal-Wallis H test. Categorical data is presented as number and percentages: n (%), and McNemar test was used to compare paired dichotomous variables. Statistical significance is defined as $p<0.05$.

5.3.6 Ethics

This study was approved and conducted in accordance with the ethical standards of the South Central – Berkshire B Research Ethics Committee (16/SC/0606. ClinicalTrials.gov NCT03420729), and the 1964 declaration of Helsinki and its later amendments.

[d] This study design was considered due to a limited supply of capsule endoscopes supplied for research purposes. It was decided that should the primary outcome not be reached that a further supply of capsules could be considered, therefore necessary to design a study which allowed for an interim analysis.

5.4 Results

5.4.1 Participants

Recruitment towards this study comparing TNE and MACE is part of a larger study involving, in addition, a larger cohort of patients who opted for OGD (reported in Chapter 4). A total of 111 patients were approached and 108 were confirmed eligible. A patient with dysphagia, a metallic heart valve and long-term NSAID use were ineligible. Of 108 patients invited to participate, 69 completed the study (36 patients declined and three agreed to do so but failed to attend their appointments) of which 22 opted for TNE (Figure 15).

MACE was successful in 16 (72%) and TNE in 21 (96%) of patients. MACE was unsuccessful in 5 due to undigested food in the stomach (n=1), a procedure time of less than 10 minutes (n=3) and prolonged periods of signal loss (n=1) and TNE unsuccessful in one due to failure to intubate either nostril. The median age of included patients was 52.5 (IQR 27), were female in 56% (n=9), had previous experience of conventional OGD in 13% (n=2) but none had previous experience of TNE. Median (IQR) HADS anxiety score was 2 (6) with 27% (n=3) having an anxious trait (HADS anxiety score >8).

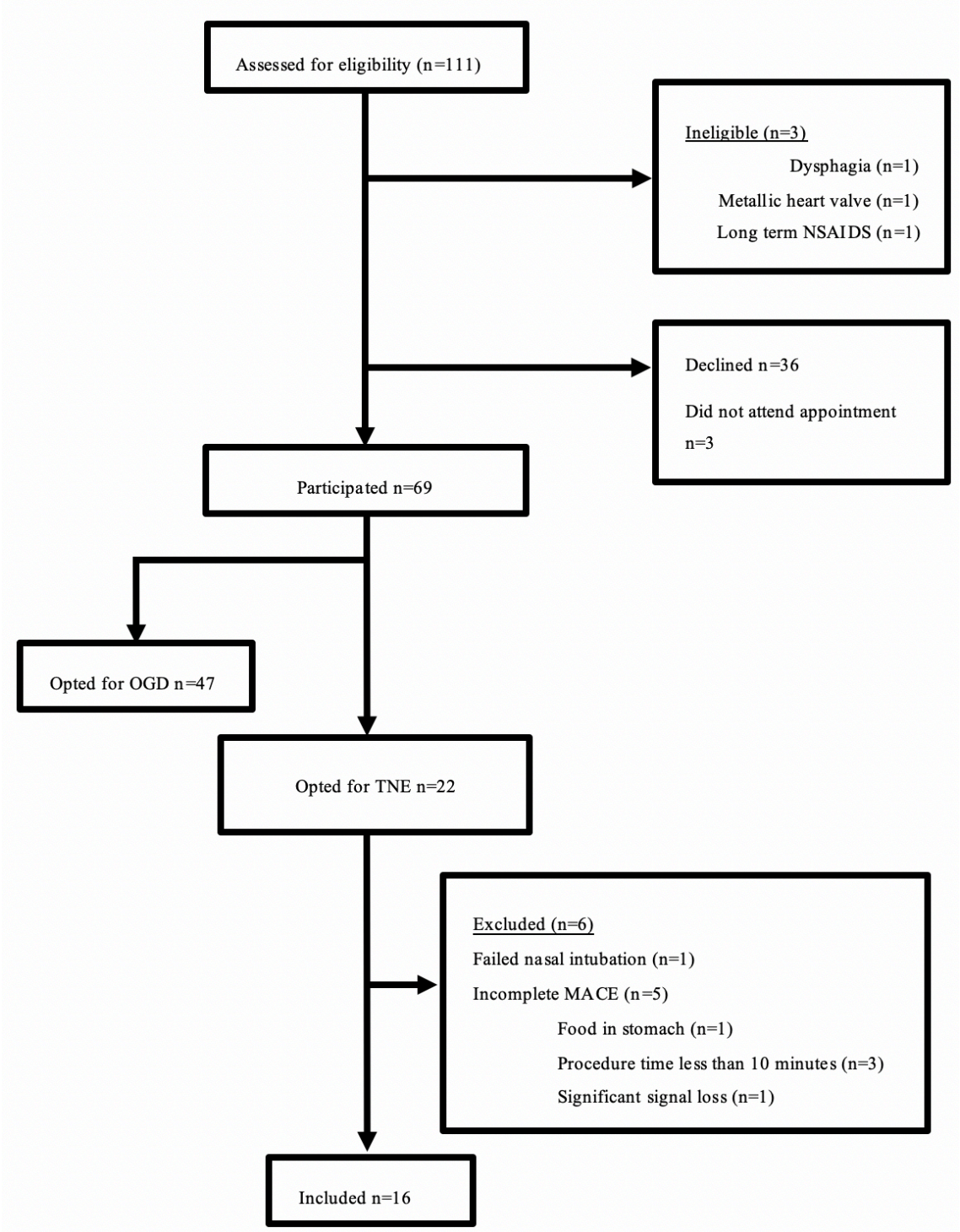


Figure 15: Patients who opted for TNE in a comparison of patient tolerance and acceptability of TNE and MACE

5.4.2 Patient anxiety, anticipatory concerns and views on acceptability of MACE and TNE

Before the procedure, patients were no more anxious about having TNE than MACE with median (IQR) state anxiety scores of 4.5 (5) and 4 (4) respectively (p=0.57). Median pre-procedure ECS scores were higher before TNE (42 vs 32, p=0.04; Table 9a) than MACE. Median distress scores were significantly more in anticipation of TNE than MACE when patients anticipated instrumentation (7.5 vs. 2.5, p=0.008) and procedural discomfort (6.5 vs. 3, p=0.005; Table 9a).

5.4.3 Patient tolerance and factors causing distress during TNE and MACE

After their procedure, patients reported experiencing significantly more distress (median score) due to gagging (1.5 vs 1, p=0.03), choking (3 vs 1, p=0.001), instrumentation (4.5 vs 1, p=0.001), discomfort during (5 vs 1, p=0.001) and after (2 vs 1, p=0.01) TNE compared to MACE (Table 9b). Patients experienced significantly less distress from instrumentation and feelings of choking during TNE than anticipated (Table 10). With the exception of abdominal bloating, patients experienced less distress related to all factors affecting procedural tolerance (gagging, choking, discomfort, instrumentation) during MACE than anticipated.

5.4.4 Acceptability and patient related experience of TNE and MACE

Median post procedure ECS scores were significantly higher after TNE (25 vs 10.5, p=0.001) compared to MACE. UPC-Q score was lower after TNE (75 vs 88, p=0.007) than MACE (Table 9b). As defined by affirmative answers to all three questions regarding preparedness to undergo the same test again or recommend the test or undergo as screening procedure, 100% and 94% (15/16) of patients found MACE and TNE acceptable. When given a choice 94% (15/16) preferred MACE to TNE.

The UPC-Q was completed appropriately by 94% (n=15). Aspects of care deemed important by patients can broadly be divided into the following categories: procedural tolerance (including drinking the water, swallowing the capsule, test discomfort and duration), staff communication (including information about, and progress of, the test),

procedural aftercare and recovery (including a comfortable environment and adverse effects), test results, test accuracy and other matters. The importance of each aspects of care and comparisons between TNE and MACE are illustrated and captioned in Figure 16.

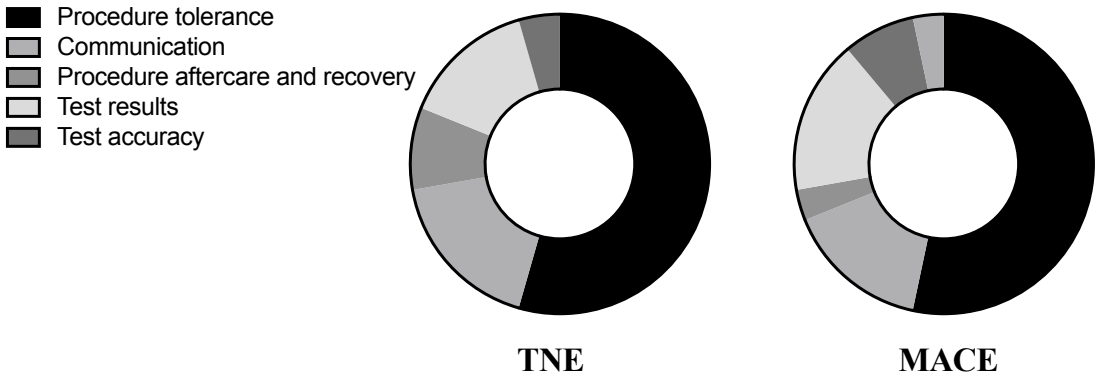


Figure 16: Aspects of care important to patients undergoing TNE and MACE generated by the UPC Questionnaire.

Six points were allocated by 15 patients each (totalling to 90 points) to aspects of care pathway deemed important after each procedure. Patients apportioned points for procedure tolerance (TNE 54.4% and MACE 53.3%, p=0.89), staff communication (17.8% and 15.6%, p=0.69), procedure aftercare and recovery (8.9% and 3.3%, p=0.12), test results (14.4% and 16.7%, p=0.17), test accuracy (4.4% and 7.8%, p=0.87) and other concerns (0.0% and 3.3%) similarly between TNE and MACE.

5.4.5 Effect of the need to obtain mucosal biopsies on patient test preference

If tissue biopsies were necessary, therefore requiring TNE as a second test after MACE and the chance of requiring biopsies was 1 in 20, 1 in 10, 1 in 5, 1 in 4 or 1 in 2, 94%, 94%, 81%, 75% and 63% would prefer MACE followed by TNE respectively.

Table 9: Distress caused in anticipation of and by actual experience of TNE compared to MACE

	a) Pre-procedure anticipation			b) Patient experience		
	TNE	MACE	p	TNE	MACE	p
Telling friends/colleagues about test	1 (1)	1 (2)	0.89			
Fasting	1.5 (3)	1.5 (3)	0.16			
Discomfort prior to procedure	1 (1)	1 (2)	0.88			
Gagging	3 (5)	3.5 (6)	0.94	1.5 (2)	1(0)	0.03
Choking	3 (5)	3.5 (6)	0.14	1.5 (2)	1(0)	0.02
Bloating	1 (1)	2 (2)	0.13	1 (3)	1(1)	0.86
Vomiting	1.5 (1)	1 (3)	1.00	1 (0)	1(0)	0.66
Doctor seeing food in stomach	1 (0)	1 (0)	0.34	1 (0)	1(0)	0.16
Displaying emotions during the test	1 (1)	1 (3)	0.08	1 (1)	1(0)	0.24
Instrumentation	7.5 (4)	2.5 (3)	0.008	4.5 (4)	1(0)	0.001
Intravenous catheter	1 (1)	1 (2)	0.93	1 (0)	1(0)	0.29
Discomfort during procedure	6.5 (3)	3 (4)	0.005	5 (5)	1(0)	0.001
Discomfort after procedure	4 (3)	3 (5)	0.40	2 (3)	1(0)	0.01
Pre procedure anxiety	4.5 (5)	4 (4)	0.57			
Pre procedure ECS	45 (25)	32 (19)	0.04			
Post procedure ECS				25 (15)	10.5 (5)	0.001
UPC-Q				75 (67)	88 (37)	0.007

Pairwise comparison of pre-procedure anxiety and pre- and post- procedure distress (1 – 10: Least to most) scores; pre- (13-130: Most to least acceptable) and post- (10-100) procedure endoscopic concern scale (ECS) score and universal patient centredness questionnaire (UPC-Q) scores (least to most acceptable: 0-100) between TNE and MACE reported as a median (IQR).

Table 10: Comparison of patient expectation and experience during TNE and MACE

	TNE			MACE		
	Expectation	Experience	p	Expectation	Experience	p
Gagging	3 (6)	1.5 (2)	0.10	3.5 (5)	1 (0)	0.003
Choking	3 (6)	1.5 (2)	0.05	3.5 (5)	1 (0)	0.004
Bloating	1 (2)	1 (3)	0.10	2 (2)	1 (1)	0.08
Vomiting	1.5 (3)	1 (0)	0.08	1 (1)	1 (0)	0.04
Doctor seeing food in stomach	1 (0)	1 (0)	0.31	1 (0)	1 (0)	0.32
Displaying emotions during the test	1 (3)	1 (1)	0.23	1 (1)	1 (0)	0.06
Instrumentation	7.5 (3)	4.5 (4)	0.04	2.5 (4)	1 (0)	0.008
Intravenous catheter	1 (2)	1 (0)	0.40	1 (1)	1 (0)	0.06
Discomfort during procedure	6.5 (4)	5 (5)	0.14	3 (3)	1 (0)	0.002
Discomfort after procedure	4 (4)	2 (3)	0.09	3 (3)	1 (0)	0.002

Paired comparison of distress scores (1 – 10: Least to most) cause in anticipation of and actual experience of OGD and MACE reported as median (IQR)

5.5 Discussion

Transnasal endoscopy and MACE are both well accepted by patients. Prior to procedures, there were no differences in anxiety levels and participants were marginally more accepting of MACE than TNE as evidence by higher pre-procedure ECS scores. Prior to endoscopies, patients were more distressed in anticipation of instrumentation of the nostril and discomfort of the TNE procedure than swallowing a capsule endoscope and the discomfort of MACE. Their actual experience mirrored this with significantly more distress during instrumentation and discomfort of TNE, but also, minimal but significantly greater distress caused by gagging and choking with TNE compared to MACE. Patients were marginally more accepting of MACE than TNE by both patient-reported experience measures (PREMs), the ECS and UPC-Q but furthermore 94% preferred MACE over TNE and 64% of patients would prefer MACE followed by TNE rather than a single TNE test if biopsies were required in 50% of the cases.

Patients experienced less distress than anticipated during both procedures: due to choking and instrumentation with TNE, and by most measures of tolerance with MACE and this would explain the high acceptability of both procedures. Procedural tolerance, although not the only aspect important to patients experience, was the most important aspect with over 50% of volunteered concerns. This study reports significantly more discomfort during TNE than MACE. In particular, this interim analysis after 16 transnasal endoscopy patients revealed a mean difference in the primary endpoint, the discomfort score of 4.1 (95% CI 2.5 – 5.6, $p<0.0001$) favouring MACE and satisfying an *a priori* condition for full power in detecting at least a difference of 2 points between modalities. Therefore, the trial was concluded at this point.

The concept of discomfort is broad and in endoscopy encompasses more specifically unpleasant sensations. Studies which compare patient experience of TNE to conventional OGD report overall better acceptance of TNE [21] and less desire for sedation during future procedures [176,177]. Nevertheless, consistent with the findings of

this study, they all report minimal but discernible degrees of discomfort [177], with gagging [87], choking [178,179] and retching [176] in patients undergoing TNE. In one study 23% of patients undergoing TNE experienced minimal gagging [87]. Nasal intubation was distressing amongst the participants of this study. This may be because the endoscopists experience of TNE was limited to 30 procedures at the end of the trial and further experience would have been desirable prior to starting the trial. On the other hand, nasal intubation, despite the appropriate pre-procedure medication, can be painful and cause distress. In a study by Preiss and collaborators, nasal intubation was significantly more painful and cause more choking than oral intubation, both when using the same 5.9mm ultrathin scope. [180] Broadly the literature suggests that TNE can be distressing during nasal intubation due to nasal pain and in contrast, whilst conventional oral intubation is not painful *per se*, causes discomfort due to gagging. It may be expected therefore that a less invasive investigation (than per oral OGD), but still ultimately requiring the passage and manipulation of a flexible endoscope through a lumen, to cause more distress on instrumentation and during the procedure than one that is non-invasive and does not involve endoscope manipulation in the traditional way.

The focus of this study was on patient tolerance and acceptability and with this in mind methodology should be discussed. This was a non-blinded study, both interventions performed by the same endoscopist, and therefore not designed to examine differences in pathology detection. However, even in comparing patient experience the study suffers from performance bias due to the interventions being performed by the same unblinded endoscopist. Furthermore, as previously suggest in Chapter 4 (section 4.5 on page 70), because patient act as their own controls, always performing MACE prior to TNE may affect patient's expectations and negatively impact acceptability of TNE, especially amongst the majority (88%) of patients in the study who have not experienced upper GI endoscopy before. Therefore, randomisation of which intervention occurred first would have been more ideal. The impact of these effects however is thought to be small. Acceptability favours MACE, although the differences in the ECS and UPC-Q scores between MACE and TNE are minimal in this small study of 16 patients, so it is possible that a more experienced endoscopist, randomisation and blinding may result in no differences in acceptability between MACE and TNE, but

unlikely to make TNE more acceptable or preferable than MACE. It may, however result in more patients opting for TNE directly rather than MACE followed by TNE with increasing probabilities of requiring biopsies. Nevertheless, 15 of 16 patients would repeat the TNE again, recommend to a friend under the same conditions and undergo as a screening test, in spite of the distresses of intubation and procedural discomfort.

6 THE EFFECT OF POLYETHYLENE GLYCOL PURGATIVES IN SMALL BOWEL CAPSULE ENDOSCOPY

6.1 Abstract

Introduction: Capsule endoscopy can examine both the upper GI tract and small bowel with the same device. The role of bowel purgatives in advance of a small bowel capsule endoscopy is contentious and therefore the pre-procedure preparation for a MACE examination for an examination of both the upper GI tract and small bowel is yet to be defined. We examine the benefit of polyethylene glycol (PEG) prior to a small bowel examination and further the role of different timing interventions of the PEG laxative.

Methods: A randomised control trial of a single 2 litre dose, a split dose (1 litre the evening before and 1 litre the morning of the procedure) of PEG and a clear liquid diet only was performed. We examined a computed assessment of cleansing (CAC), a reviewer assessment of cleansing and further the tolerability and acceptability of pre-procedure interventions

Results: A total of 186 (85%) of recruited patients were analysed. There were no differences in the CAC scores between the intervention groups. However, there was a significantly greater reviewer assessed quantitative index in the fourth quartile of the small bowel between PEG and clear fluids (8.4 vs 7.7 p=0.006), in particular when PEG was administered as a split dose (8.5; p=0.01). Furthermore, overall adequacy of assessment was significantly greater with PEG interventions than clear liquid diet only (single 91.4%, split 91.5% vs clear liquid diet 72.9%, p=0.005). However, patients better tolerated (0-4: completely intolerable to completely tolerable) a clear liquid diet (3.7) compared to a single dose (3.0) and split dose (2.8) of PEG (both $p<0.0001$ vs. clear liquid diet) and were more accepting of a clear liquid diet (95.9%) than single (87.5%) and split (77.6%) dose of PEG (p=0.03).

Conclusion: Pre-procedure PEG laxatives given on the morning of the procedure improve distal small bowel mucosal views. However, patients better tolerate and are more accepting of a clear liquid diet only compared to pre-procedure PEG laxatives.

6.2 Introduction

Turbid fluid and digestive residue overlying the small bowel mucosal surface result in inadequate examinations and repeat investigations due to the potential for missed diagnoses during capsule endoscopy. Historically, a clear liquid diet and a 12 hour fast was the recommended pre-procedure preparation for small bowel capsule endoscopy [181]. This is similar to and adequate preparation for upper GI capsule endoscopy. [162] Bowel purgatives are used routinely in advance of colonic examinations and have been shown to improve examination completion and pathology detection. [135] It is well established that terminal ileum and right colon views are improved with purgatives taken a few hours before the examination and splitting doses of purgatives have shown more superior cleansing and pathology detection. [135,144] It is not clear however, whether purgatives prior to capsule endoscopy augment small bowel mucosal views. [182,183]. Controlled studies which support the use of purgatives report that Polyethylene glycol (PEG) improves views [136-139] and even diagnostic yield in one study [136], but larger studies dispute these findings.[140-142]

Robot controlled MACE has the advantage of investigating the small bowel beyond the reach of a conventional endoscope in the same examination as the upper GI examination. To achieve this, pre-procedure bowel preparation suitable for both the upper GI tract and small bowel would need to be defined. We examine the additional benefit of using PEG laxative in the small bowel over a clear liquid diet and 12 hour fast. Furthermore, we examine the effect of two different dose timings, a single and a split dose of PEG laxative.

6.3 Methods

6.3.1 Patient selection and randomisation

Patients undergoing a small bowel capsule endoscopy were invited to join the trial from the outpatient department of Sheffield Teaching Hospitals NHS Foundation Trust. Written consent was obtained by the requesting physician and confirmed by a member of the small bowel capsule endoscopy team over the phone prior to randomisation. Participants were randomised to one of three treatment groups: Split dose polyethylene glycol (PEG), Single dose PEG and clear liquid only. A central online randomizer application (Randomizer for Clinical Trial, Medsharing, France) using variable size permuted blocks of 6 and 9 were used. After randomisation, the patient was sent detailed written instructions by a team of capsule endoscopy specialist nurses.

6.3.2 Interventions and procedure

Common to all participants, patients were advised to stop iron supplements for 5 days prior, and to fast after a light breakfast and lunch the day before the examination. They were encouraged to drink at least 2 litres of only clear fluid during the course of the day before the examination. Patients randomised to the clear liquid arm were given no further instructions. Patients randomised to an intervention arm were provided with PEG (Klean-prep 69 grams per litre, Norgine, Middlesex, UK) and if randomised to the split dose PEG arm, were instructed to consume 1 litre of PEG solution at 7 pm the day before, and again at 6am on the day of the procedure. If randomised to the single dose PEG arm, patients were instructed to consume 2 litres of PEG solution at 6 am on the day of the examination.

Patients on the day of the examination completed a post preparation questionnaire (Appendix 5). This contained questions regarding the amount of laxative consumed (where appropriate: none, some, most or all of it), overall tolerance of the pre-procedure

preparation (completely intolerable to completely tolerable: score 0-4), tolerance of 7 factors (bloating, dizziness, nausea, vomiting, abdominal pain, poor sleep and bad taste, completely intolerable to completely tolerable: score 0-4) and willingness to repeat the examination with the same pre-procedure preparation.

Patients ingested 80mg simethicone (Infacol, Teva, Castleford, UK) in 100mls of water 10 minutes before swallowing the capsule endoscope as per standard protocol. The capsule is swallowed at 9 am and after transpyloric passage is confirmed on the real-time monitor, the patient is instructed to abstain from fluids for 2 hours and food for 4 hours. As per standard protocol, intramuscular metoclopramide 10mg is given after 1 hour if the capsule endoscope is still within the stomach. Upon completion, video data is downloaded on the Pillcam Reader (Medtronic, Minneapolis, USA), read and reported in a standard fashion. At trial completion, the cases were pseudoanonymised by deidentifying cases on the Pillcam Reader platform prior to analysis.

6.3.3 Outcomes

The primary outcome of this study was cleanliness of the small bowel preparation assessed by the computed assessment of cleanliness (CAC) score. Secondary outcomes include the effect of the intervention on a reviewer assessment of cleansing, gastric and small bowel capsule transit time, the examination findings and patient tolerance and acceptance of pre-procedure preparation.

6.3.4 Analysis

Tissue colour bars were extracted by taking a screenshot (Snipping Tool, Microsoft, Redmond, USA). A computed assessment of cleanliness (CAC) score is generated by measuring ratios of red and green channel intensities on the tissue colour bar produced by Pillcam Reader software with each examination. This CAC method, previously

described by Van Weyenberg et al. (2011), produces a score between 0 and 10 with a higher score representing better visualisation.[184] Analyses were examined overall and individually by small bowel quartiles (divided by time) to assess the effect of the intervention on different segments of the small bowel. Red and green channel intensities (0-255: least to most intense) were measured (Photoshop CC 2017 v1.1, Adobe Inc, California, USA) and CAC calculated using the following formula:

$$CAC\ score = (Red\ channel\ intensity / Green\ channel\ intensity) -1 \times 10$$

Figure 17a and b show a worked example and representative images of bowel cleanliness and their corresponding CAC values respectively. The CAC score calculations were performed by one blinded examiner (FWDT).

Each case was further reviewed by an expert (MM) blinded to the findings specifically to assess bowel cleansing (Table 11). The five elements which impair mucosal views were assessed in each of the four quartiles. The percentage mucosa visualised, fluid and debris, bubbles, bile/chyme staining and brightness were scored out of two (severe, moderate and minimal/mild impairment: 0-2) and summated to derive a quantitative index (QI; scored 0-10, higher score represents superior cleansing). A qualitative evaluation (QE; Poor, Fair, Good and Excellent) and overall assessment adequacy (OAA; adequate or inadequate) were also scored. This methodology for quantitative and qualitative assessment of cleansing in the small bowel was conceived and validated by Brotz et al (2009) and has been used in the conception and validation of the CAC score by Van Weyenberg et al (2011).

Owing to the Coronavirus 2019 pandemic, a pragmatic decision was made to perform an interim analysis of this study for the purposes of this doctoral thesis as the trial was temporarily suspended in March 2020.

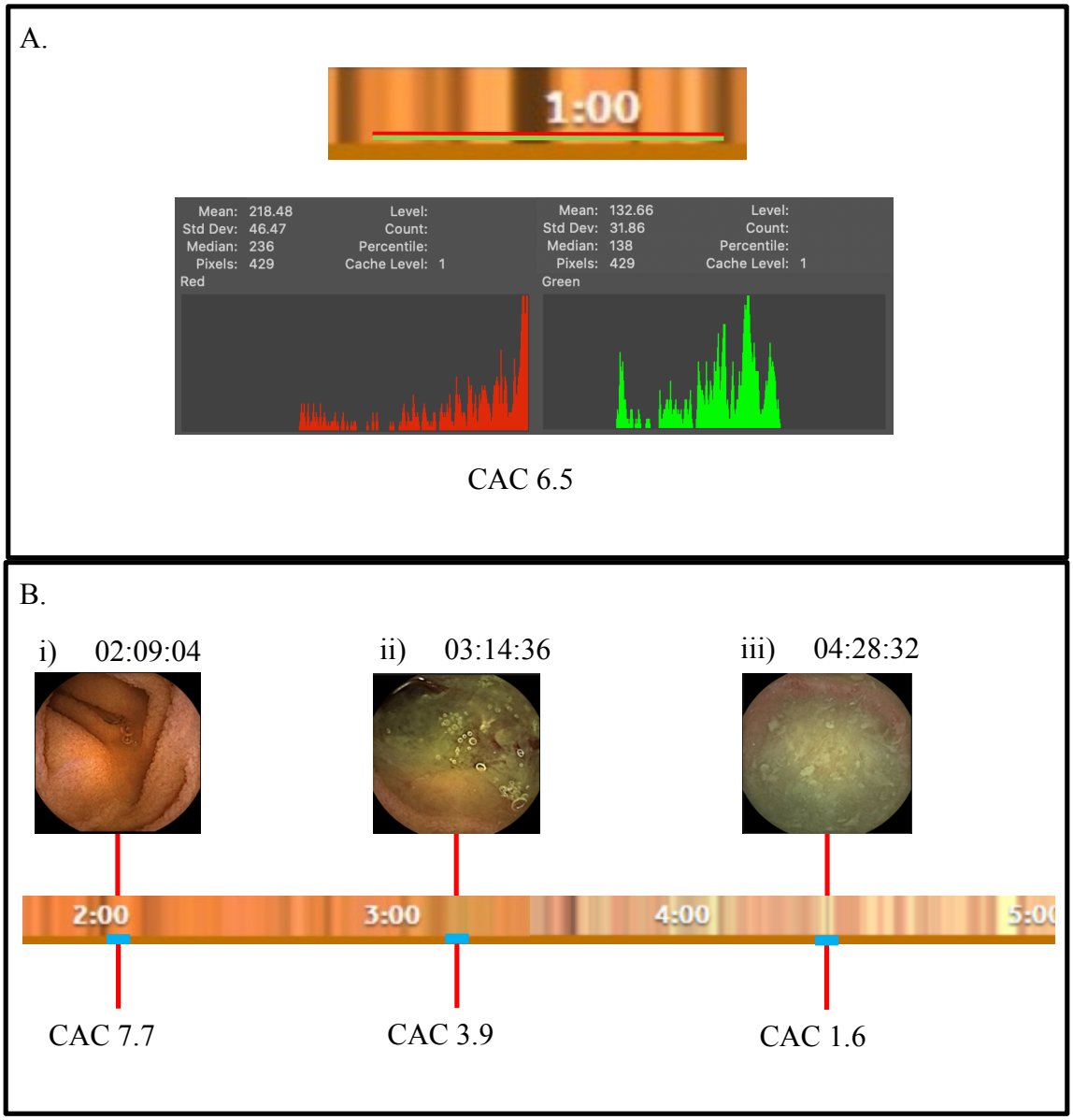


Figure 17: Computed assessment of cleansing adopted from van Weyenberg et al. (2011).

a) Worked example of a single quartile. Histograms of red and green channel intensities of the highlighted portion of the colour bar as measured in Adobe Photoshop CC. The ratio of mean intensities of red (218.5) and green (132.7) are used calculate the CAC score (6.5). b) Representative small bowel cleanliness and the segment (blue bar) of tissue colour bar used to calculate the CAC score for the corresponding segments. i) Shows excellent small bowel cleanliness, ii) and iii) deteriorating bowel cleanliness.

Table 11: Blinded reviewer assessment of bowel cleansing using the Quantitative index, Qualitative evaluation and Overall adequacy of assessment

Adopted from Brotz et al. (2009)

Quantitative index (QI)

Total score: 0 - 10, higher scores = superior cleansing

Elements

Percentage of mucosa visualised*

Fluid and debris

Bubbles

Bile/chyme staining

Brightness

Score per element

2 = Minimal / Mild impairment

1 = Moderate impairment

0 = Severe impairment

Qualitative evaluation (QE)

Excellent: Visualisation of ≥90% of mucosa; no, or minimal, fluid and debris, bubbles, and bile/chyme staining; No, or minimal reduction of brightness

Good: Visualisation of ≥90% of mucosa; mild fluid and debris, bubbles, and bile/chyme staining; mildly reduced brightness

Fair: Visualisation of <90% of mucosa; moderate fluid and debris, bubbles, and bile/chyme staining; moderately reduced brightness

Poor: Visualisation of <80% of mucosa; excessive fluid and debris, bubbles, and bile/chyme staining; Severely reduced brightness

Overall assessment of adequacy (OAA)

Adequate

Inadequate

* Severe <80% = 0, moderate 80-89% = 1, minimal/mild ≥90% =2

6.3.5 Statistics

Sample size calculation

Advice was sought from the University of Sheffield Mathematics and Statistics resource centre. A sample of 101 patients per arm will have a 90% power to detect a mean difference of 0.5 points at a 0.025 two tailed significance level between either interventions and the control arm. A randomized study of bowel purgatives showed a within group standard deviation of around one point [140], therefore with this assumption a mean difference of 0.5 points is a moderate effect. Assuming at 15% withdrawal rate 115 patients will be recruited to each group and it is estimated that 230 patients will be recruited from Sheffield and 115 patients from Ontario[e].

Statistical analysis

Continuous variables are presented as mean (SD) and compared using unpaired T-test or one-way analysis of variance (ANOVA) to compare differences between arms. Where differences between arms exist, Bonferroni's post hoc correction is used to examine differences within groups. Categorical variables are presented as n, % and examined between groups using Chi Square (and Fisher's exact test where appropriate). Statistical significance is set at the 0.05 level.

6.3.6 Ethics

This study sponsored by Sheffield Teaching Hospitals and approved and conducted in accordance with the ethical standards of the Yorkshire & The Humber - South

[e] This study is part of a larger multicentre study with a centre in Ontario, Canada.

Yorkshire Research Ethics Committee (17/YH/0359, ClinicalTrials.gov NCT03351972), and the 1964 declaration of Helsinki and its later amendments.

6.4 Results

6.4.1 Recruitment

Between the 13th of December 2017 and 27th of February 2020, 220 patients were enrolled and randomised into this study. Patient flow through the study is illustrated in Figure 18. Thirty-four patients (10.9%) were withdrawn from the study for withdrawal of consent for trial (n=6), refusing investigation (n=6), referrer cancelling the investigation (n=2), being unable to swallow patency device (n=3), failure of passage of patency device (n=3), not attending the capsule endoscopy appointment (n=7), using a non-Pillcam SB capsule endoscope (n=5) and at the discretion of the PI (n=2; detailed in Figure 18). There was no difference in proportion of patients who did not receive the interventions (p=0.07).

There were 186 patients who successfully completed the small bowel capsule endoscopy (Table 12). There were 5 incomplete examinations (n=1 capsule remained in the stomach, n=4 capsules did not reach the caecum), 4 examinations with significant loss of signal and one study with data corruption, resulting in a complete small bowel examination in 177 (95.1%) and a complete CAC analysis in 176 patients (94.6%). Indications for capsule endoscopy include suspected small bowel bleeding (n=39), abdominal symptoms (n=83), assessment of established Crohn's disease (n=27), assessment of coeliac disease (n=31) and other (n=6).

6.4.2 Assessment of cleansing

The mean overall CAC score for clear fluids (5.5) was no different to PEG overall (5.6, p=0.52), nor single (5.6) or split dose (5.7, group p=0.73) PEG interventions (Table 13). The mean overall reviewer assessed quantitative index (QI)

for PEG overall was marginally higher than clear fluids only (mean difference 0.3, p=0.05), but no differences found between clear fluids and different timing interventions of PEG (clear fluids: vs. split p=0.04, vs. single p=0.65; Table 13). In the fourth (distal) quartile, there was however a significantly higher QI with PEG laxatives overall (mean difference 0.7, p=0.006), favouring a split dose prep (vs. clear fluid only mean difference 0.8 p=0.01), and a significantly better QE (good or excellent visualisation) with PEG overall (77.8% vs. 59.3% p=0.01). There were no differences in the mean QI and the proportion of QE marked as good or excellent between clear fluids and PEG overall nor amongst single or split doses interventions within the first three small bowel quartiles. No differences were found with respect to cleanliness scores between single and split doses by all measures of cleanliness and across all quartiles. Overall proportion of adequately cleansed examinations was significantly greater with PEG overall (OR 4.0 95% CI 1.7 – 9.5) compared to clear fluids (Table 13). All but one inadequate examination had inadequacies in the fourth quartile.

6.4.3 Transit time and diagnostic yield

Mean gastric and small bowel transit time were no different between clear fluid (35 and 243 mins respectively) and PEG overall (41 and 215 mins, p=0.31 and 0.06 respectively) nor between clear fluids and individual timing interventions (group p=0.50 and 0.14 respectively; Table 13). No differences in proportion of patients with abnormal findings were found between clear fluids and PEG overall (p=0.88), nor between clear fluids and individual timing interventions (group p=0.28; Table 13)

6.4.4 Patient tolerance and acceptability

Tolerance questionnaire data was complete in 157 patients (84.4%; Clear fluids n=56, Split n=53, Single n=48) and summarised in Table 14. There were no differences in questionnaire completion rates between interventions. Of 101 patients who were allocated to PEG laxatives, 82 (81.2%), 14 (13.9%) and 5 (5.0%) patients consumed all, most and some of the PEG solution. There was no difference in the reported consumption of the PEG solution between the split and single dose arms

(p=0.71). Clear fluid only was significantly more tolerable (mean score 3.7) than PEG overall (mean difference -0.8, p<0.0001) and when compared to both PEG timing interventions (mean difference vs. split dose -1.0, p<0.0001 and single dose -0.7, p<0.0001). Abdominal bloating and bad taste cause by PEG laxatives were significantly less tolerable than clear fluids only (Table 14). No differences were seen in overall tolerance between split and single dose PEG interventions (p=0.86). More patients were willing to repeat a small bowel capsule endoscopy with clear fluids alone (96.3%) than split dose PEG (77.6%; p=0.02).

6.4.5 Performance of quantitative and qualitative scores

There was a moderate positive correlation (Spearmans rho) between the CAC and QI scores overall (r=0.56), in the first (r=0.42), second (r=0.53), third (r=0.46) and fourth quartile (r=0.52; all p<0.0001). Adequate small bowel examinations (n=150) had a significantly greater overall mean CAC (mean difference 1.0, 95% CI 0.5 – 1.5) and QI (mean difference 1.7 95% CI 1.4 – 2.0) than inadequate examinations (n=26) (p<0.0001).

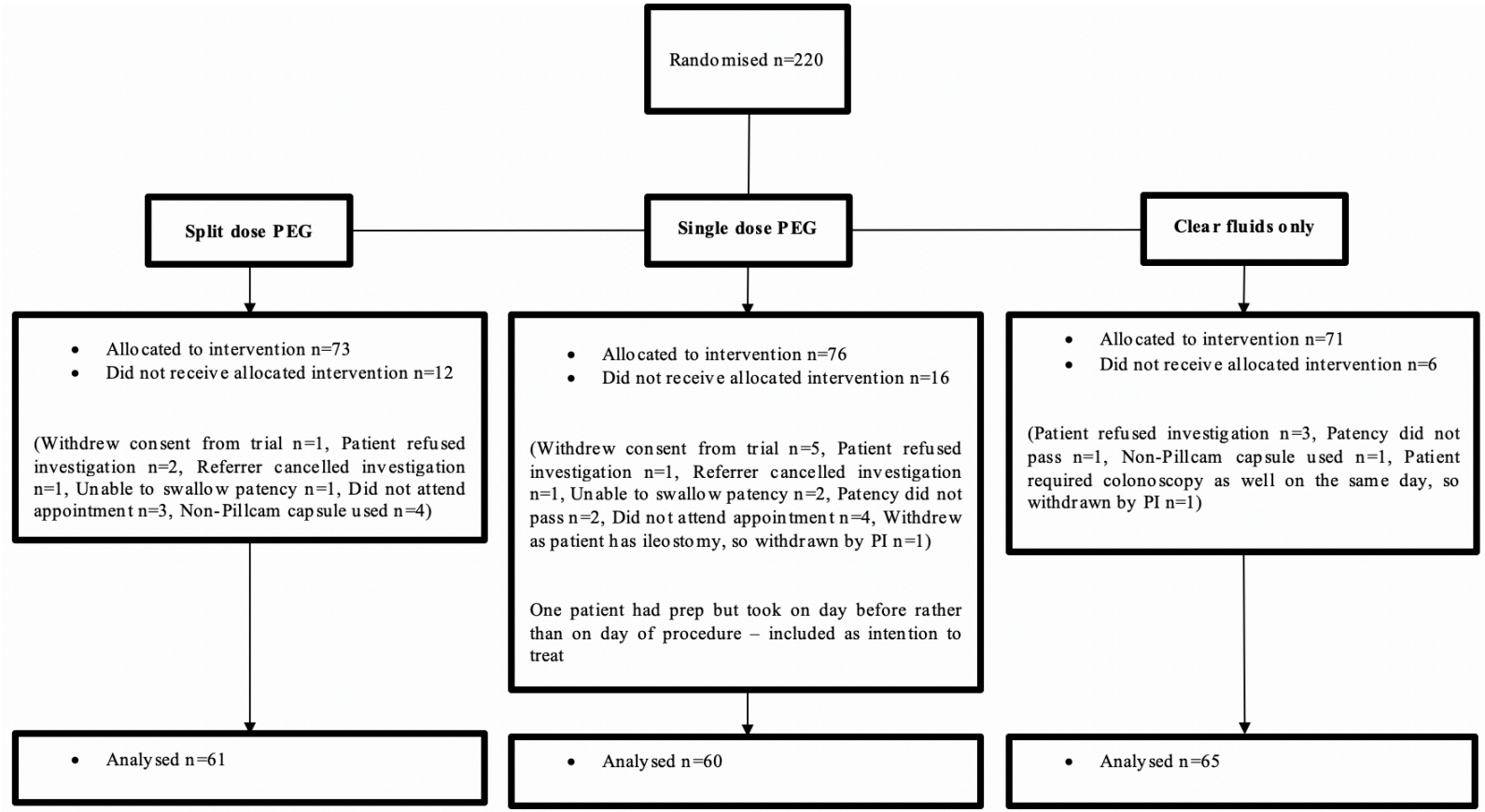


Figure 18: CONSORT diagram outlining patient flow through the trial

PEG Polyethylene glycol, PI Principal investigator

Table 12: Baseline characteristics of patients completing trial

	All patients	Clear liquid only	PEG overall	PEG by dose timing		p value Clear liquid vs.	
				Single	Split	PEG overall	by PEG timing†
n	186	65	121	60	61		
Age, years (sd)	47.1 (17.1)	49.3 (17.8)	46.0 (16.6)	44.6 (15.7)	47.4 (17.5)	0.23	0.31
Female gender, n (%)	117 (62.9)	38 (58.5)	79 (65.3)	40 (67.8)	38 (62.3)	0.43	0.58
Indication, n (%)						0.97	0.89
Suspected small bowel bleeding	39 (21.0)	13 (20.0)	26 (21.5)	10 (16.7)	16 (26.2)		
Abdominal pain or diarrhoea	83 (44.6)	28 (43.1)	55 (45.5)	30 (50.0)	25 (41.0)		
Assessment of established Crohn's disease	27 (14.5)	11 (16.9)	16 (13.2)	8 (13.3)	8 (13.1)		
Assessment of Coeliac disease	31 (16.7)	11 (16.9)	20 (16.5)	9 (15.0)	11 (18.0)		
Other	6 (3.2)	2 (3.1)	4 (3.3)	3 (5.0)	1 (1.6)		
Patency assessment, n (%)	74 (39.8)	28 (43.1)	46 (38.0)	19 (31.7)	27 (44.3)	0.53	0.29
SBCE completion, n (%)	177 (95.1)*	60 (92.3)	118 (98.3)	58 (98.3)	60 (98.4)	0.34	0.49

Age, gender, indication of small bowel capsule endoscopy (SBCE), need for patency assessment and SBCE completion rates. †group differences one way-ANOVA or Z-test of column proportions. *one patient corrupt data file excluded.

Table 13: Computed and reviewer assessment of cleansing, capsule transit times and diagnostic yield using PEG and dose timing interventions

	All patients	Clear liquid only	PEG overall	PEG by dose timing		p value Clear liquid vs.	
				Single	Split	PEG overall	by PEG timing†
n	176	59	117	58	59		
CAC overall, mean (sd)	5.6 (0.9)	5.5 (1.0)	5.6 (0.8)	5.6 (0.7)	5.7 (0.9)	0.52	0.73
First Quartile	6.0 (0.9)	6.1 (0.9)	6.0 (1.0)	6.0 (0.9)	6.0 (1.0)	0.50	0.80
Second Quartile	5.7 (0.9)	5.8 (0.9)	5.7 (0.9)	5.6 (0.8)	5.7 (1.0)	0.60	0.71
Third Quartile	5.6 (1.0)	5.5 (1.3)	5.6 (0.9)	5.5 (0.9)	5.7 (0.9)	0.60	0.54
Fourth Quartile	5.2 (1.2)	5.0 (1.6)	5.3 (1.0)	5.4 (1.0)	5.3 (1.0)	0.10	0.14
Quantitative Index, mean (sd)	8.9 (0.9)	8.7 (1.0)	9.0 (0.8)	8.9 (0.8)	9.1 (0.8)	0.05	0.04
First Quartile	9.2 (1.0)	9.1 (1.1)	9.3 (1.0)	9.2 (1.0)	9.4 (1.0)	0.26	0.30
Second Quartile	9.2 (1.1)	9.1 (1.2)	9.3 (1.1)	9.2 (1.1)	9.4 (1.0)	0.19	0.22
Third Quartile	8.9 (1.4)	8.8 (1.5)	9.0 (1.4)	8.9 (1.5)	9.2 (1.2)	0.44	0.39
Fourth Quartile	8.2 (1.4)	7.7 (1.6)*	8.4 (1.3)	8.4 (1.3)	8.5 (1.4)*	0.006	0.01

Continued	**All patients**	**Clear liquid only**	**PEG overall**	**PEG by dose timing**		**p value** Clear liquid vs.	
				Single	Split	PEG overall	by PEG timing†
Qualitative Evaluation, n Good/Excellent (%)							
First Quartile	165 (93.8)	55 (93.2)	110 (94.0)	54 (93.1)	56 (94.9)	1.0	0.90
Second Quartile	166 (94.3)	54 (91.5)	112 (95.7)	54 (93.1)	58 (98.3)	0.31	0.25
Third Quartile	146 (83.0)	45 (76.3)	101 (86.3)	49 (84.5)	52 (88.1)	0.14	0.21
Fourth Quartile	126 (71.6)	35 (59.3)	91 (77.8)	58 (79.3)	45 (76.3)	0.01	0.04
Overall adequacy of assessment, n(%)	150 (85.2)	43 (72.9)^*	107 (91.5)	53 (91.4)^	54 (91.5)*	0.003	0.005
First Quartile	175 (99.4)	59 (100)	116 (99.1)	58 (100)	58 (98.3)	1.0	0.37
Second Quartile	174 (98.9)	58 (98.3)	116 (99.1)	58 (100)	58 (98.3)	1.0	0.60
Third Quartile	168 (95.5)	57 (96.6)	111 (94.9)	54 (93.1)	57 (96.6)	0.72	0.58
Fourth Quartile	151 (85.8)	43 (72.9)^*	108 (92.3)	54 (93.1)^	54 (91.5)*	0.001	0.002
GTT, min (sd)	39 (37)	35 (32)	41 (39)	43 (37)	39 (41)	0.31	0.50
SBTT, min (sd)	225 (95)	243 (85)	215 (99)	209 (92)	221 (105)	0.06	0.14

Continued	All patients	Clear liquid only	PEG overall	PEG by dose timing		p value Clear liquid vs.	
				Single	Split	PEG overall	by PEG timing†
Findings, n abnormal (%)	79 (44.9)	25 (42.4)	54 (46.2)	32 (55.9)	22 (36.2)		
Significant findings	42 (23.9)	13 (22.0)	29 (24.8)	17 (28.8)	12 (20.7)	0.91	0.45
Coeliac disease	25 (14.2)	8 (13.6)	17 (14.5)	8 (13.6)	9 (15.5)		
Crohns disease	10 (5.7)	3 (5.1)	7 (6.0)	4 (6.8)	3 (5.2)		
Blood	2 (1.1)	1 (1.7)	1 (0.9)	1 (1.7)	0 (0.0)		
Polyp / SMT	4 (2.3)	1 (1.7)	3 (2.6)	3 (5.1)	0 (0.0)		
Significant angioectasia[a]	2 (1.1)	0 (0.0)	2 (1.7)	0 (0.0)	2 (3.4)		
Insignificant findings	37 (21.0)	12 (20.3)	25 (21.4)	16 (27.1)	9 (15.5)		
Benign	26 (14.8)	10 (16.9)	16 (13.7)	12 (20.3)	5 (8.6)		
Non-specific inflammation	10 (5.7)	2 (3.4)	8 (6.8)	4 (6.8)	4 (6.9)		

Small bowel computed assessment of cleansing (CAC, score 0-10: higher representing better cleansing), reviewer assessed Quantitative Index (QI; 0-10: higher representing better cleansing), Qualitative evaluation and Overall adequacy of assessment of bowel cleansing, gastric transit time (GTT), small bowel transit time (SBTT) and examination findings of PEG overall and by timing intervention vs. clear fluid only. †group differences one way-ANOVA or Z-test of column proportions: * / ^ significant between group differences after Bonferroni's correction $p<0.016$ [a] One angioectasia and one arteriovenous malformation seen as significant in contrast to 9/27 insignificant small non-bleeding angioectasia listed as benign. SMT Submucosal tumour, GTT Gastric transit time, SBTT small bowel transit time, PEG polyethylene glycol, sd standard deviation

Table 14: Patient tolerance and acceptance of PEG laxative compared to a clear liquid diet only

	All patients	Clear liquid only	PEG overall	PEG by dose timing		p value Clear liquid vs.	
				Single	Split	PEG overall	PEG by timing†
n	149	50	99	48	51		
Overall tolerance	3.2 (1.0)	3.7 (0.5)*^	2.9 (1.1)	3.0 (1.0)*	2.8 (1.2)^	<0.0001	<0.0001
Abdominal bloating	3.5 (0.9)	3.7 (0.7)*^	3.3 (1.0)	3.4 (0.9)*	3.2 (1.0)^	0.004	0.017
Dizziness	3.8 (0.5)	3.8 (0.6)	3.8 (0.5)	3.8 (0.5)	3.8 (0.5)	0.86	0.97
Nausea	3.4 (0.8)	3.7 (0.6)*	3.3 (0.8)	3.3 (0.8)*	3.3 (0.9)	0.001	0.006
Vomiting	3.9 (0.5)	4.0 (0.3)	3.8 (0.5)	3.8 (0.6)	3.8 (0.5)	0.07	0.32
Pain	3.6 (0.8)	3.8 (0.5)^	3.4 (0.8)	3.5 (0.8)	3.4 (0.9)^	<0.0001	0.004
Poor sleep	3.4 (1.0)	3.5 (0.8)	3.3 (1.0)	3.5 (1.0)	3.2 (1.0)	0.35	0.23
Bad taste	3.1 (1.2)	3.9 (0.4)*^	2.7 (1.2)	2.7 (1.1)*	2.7 (1.3)^	<0.0001	<0.0001
Would be willing to repeat with same preparation, n Yes (%)	127 (87.0)§	47 (95.9)*	80 (82.5)	42 (87.5)	38 (77.6)*	0.03	0.03

Overall and seven different factors affecting tolerance to pre-procedure preparation. Tolerance scores ranged from completely intolerable to completely tolerable (0 – 4: higher representing better tolerance) †group differences one way-ANOVA or Z-test of column proportions: * / ^ significant between group differences after Bonferroni's correction p<0.016. §3 patients with missing responses. PEG polyethylene glycol, sd standard deviation

6.5 Discussion

In this preliminary reporting of a randomised control trial of the use of PEG laxatives administered as a split dose or as a single dose on the day of the procedure, we show no difference in the computed assessment of cleansing (CAC) scores between patients who have had clear liquids only pre-procedure preparation and PEG laxative. However, on blinded reviewer assessment, the overall adequacy of bowel cleansing was significantly greater with both single and split dose PEG compared to clear liquids only, mostly due to the adequacy of the fourth (distal) quartile cleansing. This corroborates a better cleansing score with PEG laxatives, using both the quantitative index (QI) and qualitative assessment (QA) scores, in particular with a split dose dosing regime in the distal small bowel. We show that patients tolerate better, and are more accepting of clear liquids than PEG laxative pre-procedure with no difference in patient tolerance between a split and single dose preparation.

Views of the distal small bowel are most affected during small bowel capsule endoscopy [143] and this study would support this view with worse bowel cleansing in the distal compared to proximal quartiles in all intervention groups and by all measures of bowel cleanliness. A systematic review and meta-analysis in 2016 on the whole extent of the literature on laxatives in small bowel cleansing supported the use of laxatives in improving small bowel views [183]. Controlled studies which support the use of PEG report that 2 litres (compared to 1 or 4 litres) is optimal in improving views [136,137,185], however recent larger studies show no clear benefit of PEG laxatives over clear liquids only. [140-142] In fact, by using a reviewer assessed five-point ordinal scale (0-5: inadequate to excellent cleanliness), Hookey et al (2017) report clear fluids only resulted in cleaner small bowel overall compared to PEG taken the evening before the procedure. Our preliminary analysis supports the view that PEG laxatives do improve small bowel cleansing, particularly in the distal small bowel. We believe the discrepancy in bowel cleansing between ours and others can be explained by a difference in the timing of the preparations. In our study, all patients randomised to a

PEG group had at least 1 litre of PEG (as split dose or 2 litres at 6am as a single dose) on the morning of the procedure.

In advance of ileocolonoscopy, there is a precedent in using a split dose of PEG laxative and it is accepted that such timing results in superior cleansing and pathology detection compared to a single dose the evening before the procedure, particularly in the proximal segments (right colon and terminal ileum). [144,186] In most trials of small bowel cleansing however, purgatives are consumed in the day before the procedure, including the larger negative studies [140-142]. In two small studies, administration of PEG as a split dose (the evening before the procedure and on the day of the procedure) offered some benefit over a single dose of PEG the evening before the procedure [187] and clear fluids [143]. It is therefore hypothesised that the cleansing, particularly in the distal small bowel, is due to the dose of PEG taken on the morning, hours before the procedure.

Of interest, although this analysis is underpowered by a third, our preliminary results might suggest that for cleansing of the distal most quartile, split dose PEG is more effective than clear fluids only. No differences in cleanliness as measured by QI or QE, were seen between a split and single dose, and single dose and clear fluids. This would be consistent with one previous study which compared a single 2 litre PEG dose in the evening before versus on the morning of the capsule endoscopy which showed no difference in mucosal views, however this study was small (n=34) and uncontrolled [188]. The differences between the efficacy of a split or single dose therefore remain inconclusive until trial completion, but the current results support taking a dose of PEG in the morning of the procedure.

The results of this study have implications on patient experience of a combined upper GI and small bowel capsule endoscopy. A morning dose of PEG laxative improves distal small bowel views. However, the requirement for PEG laxative for a small bowel investigation in addition to upper GI MACE would be expected to negatively impact patient experience as patients better tolerated, and more were accepting of clear fluid only pre-procedure preparation. The majority (95%) of those randomised to a PEG

laxative group however were able to drink all or most of the preparation and there were no differences in tolerance between the single and split dose PEG preparations. Numerically more patients found the single dose acceptable than split dose, possibly because of its simplicity, but further power is required to conclude this on this finding.

It was not practical to control the volume of fluid consumed by those randomised to clear liquid (or additional liquid consumed by laxative groups) and so the differences in effects of equal volumes of liquid and active preparation cannot be determined. One previous study has suggested that preparation with 4 litres of clear liquids is not inferior to 2 or 4 litres of PEG suggesting that volume of water ingested before the procedure, and in transit with the capsule endoscope during examination, may therefore be more important than use of an active purgative [142]. The superior cleansing effect of PEG seen in the reviewer assessment may therefore be in fact due to a lack of clear fluids consumed by patients allocated to clear fluids only. If this is the case, it is likely that the additional litre of water consumed to distend the stomach prior to the upper GI MACE would augment small bowel mucosal views proximally, but its effect on distal portions is yet to be determined.

Although at the expense of patient tolerance, it would also be possible to use the solution of klean-prep as the fluid to distend the stomach as the opaque PEG precipitate sediments to a clear solution with time. One small study examined the effect of dosing 4 litres of klean-prep split three ways: the evening before, the morning of the procedure, and after swallowing the capsule [189]. They found that this preparation significantly improved distal segment views compared to clear fluids only. Further optimisation of the volume and the timing of PEG on the day of the procedure could help improve both distal segment views and patient experience by reducing the overall volume of liquid consumed prior to the examination.

The discrepancies in assessment of cleansing using computed and reviewer assessments remain a curiosity. There is a heterogeneity within the literature regarding bowel

cleansing trial endpoints. The most relevant endpoint is a difference in diagnostic yield, however this study is not powered to examine such differences in examination findings. Mucosal visibility is therefore an important surrogate for diagnostic yield, but this is difficult to measure consistently. The simplest measure of mucosal visibility is a dichotomised assessment of adequacy, but it is also the least objective. Individual elements which contribute to adequacy of examination, such as the degrees of fluid opacity (with bile and turbid fluid) and degrees of mucosal obscuration (with bubbles and chyme) have been previously scored and summated to quantify cleansing [190,191]. Brotz et al. (2009) have validated such a score which have been used in this and previous trials [141,142,187]. However, these assessments are still somewhat subjective with the original validation reporting moderate interobserver variation with a kappa of 0.47 [190], and in another study an even fairer concordance (k=0.38). [141] A reproducible objective measure of mucosal clarity, independent of the reviewers, is therefore highly desirable. The CAC score, originally described by van Weyenberg et al (2011) was validated against the QI reference described by Brotz and colleagues (2009) and van Weyenberg et al. have reported a strong correlation between the CAC and QI by two independent reviewers (r= 0.68 and 0.75 respectively). The present study reports a weaker, but moderate correlation (r= 0.56).

Hookey et al. (2017) found no difference in overall and CAC score by quartiles between PEG and clear fluids only, despite suggesting that by reviewer assessment (0-5: inadequate to excellent cleanliness) clear fluids resulted in better cleansing than PEG (mean difference 0.4 p=0.03). No assessment of individual quartiles by reviewers were performed in their study. In our study, we show a trend towards better QI overall (mean difference 0.3, p=0.05) and a significantly better QI in the fourth quartile (mean difference 0.7, p=0.006) with PEG laxative compared to clear fluids only, and in fact we also demonstrate a trend towards better CAC in the fourth quartile (mean difference 0.3, p=0.10) with PEG compared to clear fluids only. Taken together, both our and Hookey's (2017) studies might suggest that the CAC is insensitive compared to reviewer assessment in the determination of bowel cleanliness and if so, with the completion of trial the differences in CAC between clear fluids and PEG in the fourth quartile might become more obvious, although potentially not statistically significant.

7 THE ECONOMIC IMPACT OF MAGNET CONTROLLED CAPSULE ENDOSCOPY IN THE INVESTIGATION OF THE UPPER GI TRACT IN THE POST COVID-19 ERA

7.1 Abstract

Introduction: Since the outbreak of the Coronavirus disease 2019 (COVID-19) pandemic, restarting endoscopy services worldwide has been challenged by decreased capacity due to mounting infection prevention and control procedures. Advancements in endoscopy have led to the use of increasingly less invasive endoscopes, an ultrathin transnasal endoscope (TNE) and a magnet controlled capsule endoscope (MACE). We examine the economic viability of TNE and MACE in the post-COVID-19 period.

Methods: The cost of OGD, TNE and MACE were estimated using a combination of activity based 'bottom up' costing and a top down averaging of fixed costs. Baseline endoscopy capacity pre-pandemic was extrapolated from local endoscopy and decontamination datasets. Costs of TNE and MACE were compared against conventional OGD in scenarios where capsule endoscopes were priced differently, tissue biopsies were required and assuming post COVID-19 capacity is between 30 and 75% of pre-pandemic values.

Results: The baseline pre-pandemic capacity for OGDs was 8.5 procedures (95% CI 6.5 – 10.5) per endoscopy session. The baseline cost of OGD, TNE and MACE prior to the COVID-19 pandemic was £121.67, £90.10 and £329.40 per procedure. Post pandemic we estimate that costs for OGD and TNE will increase by between 0.30 to 1.12 and 0.27 to 1.03 times for respectively. At current prices of capsule endoscopes cost parity with OGD is unattainable, but if prices are discounted to £200, cost parity would be achieved at 38% capacity and at £100 per capsule (£117 per procedure overall), the costs of MACE would on par with OGD at baseline. If capsule endoscopes are discounted to £100, cost parity between MACE and OGD can be achieved at baseline capacity, 70% capacity and 30% capacity, if 16%, 28% and 56% of MACE cases proceeded to OGD for biopsies.

Conclusion: A reduction in endoscopy capacity results in an increase in the cost of conventional OGDs and TNE. At current prices of capsule endoscopes, MACE is too expensive for widespread adoption in diagnostic upper GI endoscopy, however reductions in prices may make it more competitive, especially where capacity for conventional endoscopy is limited.

7.2 Introduction

The demand for upper GI endoscopy has increased over the last decade and up to 2% of the population of the United Kingdom (UK) and 3% of Medicare beneficiaries in the United states (US) undergo oesophagogastroduodenoscopy (OGD) per annum. [192,193] On the 11th of March 2020 Coronavirus disease 2019 (COVID-19) was declared a global pandemic and in response to the local contagion peaks, all non-essential endoscopy services, including most OGDs around the world, have at some point been rapidly put on hold. In the deceleration phase of the pandemic, how best to mitigate the detrimental effects of the pandemic on the outcomes of GI diseases, while safely restarting endoscopy services is being considered. [160,194-196] The main risk in performing upper GI endoscopy with flexible endoscopes is that they are aerosol generating procedures (AGPs). [195,197] Infection prevention and control (IPC) procedures including screening, separation and isolation of patients and personal protective equipment (PPE) for staff are effective in reducing the risk of cross-contamination. [160] However, endoscopy services are now continually challenged by both decreased capacity due to these mounting IPC procedures on routine practice, which is estimated to limit capacity to between 30 to 75%, [196] as well as increased demand due to accrued patients on peri-pandemic waiting lists. There may therefore be a role for alternative less invasive diagnostic tests to supplement conventional endoscopy capacity.

Advancements in endoscopy technologies have led to the use of increasingly less invasive endoscopes. Transnasal endoscopy (TNE) with a much slimmer profile endoscopes are better tolerated than conventional OGD and routinely performed

unsedated. [21] Although still aerosol generating, [197] TNE produces less of an oropharyngeal reaction than conventional OGD and would be expected to be less aerosol generating. Less invasive than this, capsule endoscopes fitted with magnetic inclusions (Magnet controlled capsule endoscopy; MACE) can now be controlled with a handheld device or with robot computer assistance in a pool of swallowed water. They have shown potential in detecting gastric and oesophageal pathologies. [107,169] Patient tolerance of and acceptance of capsule endoscopy is excellent and with no intubation required MACE is considered an alternative non-aerosol generating upper GI endoscopic investigation. Nevertheless, no studies have yet compared the economic viability of upper GI capsule endoscopy with flexible endoscopy.

The aim of this study is to examine the costs involved in performing conventional OGD, TNE and robot controlled MACE and perform cost modelling to examine the economic impact of alternative upper GI endoscopy technologies in the post COVID-19 era.

7.3 Methods

Process maps of diagnostic upper GI endoscopy pathways using flexible endoscopy and Magnet controlled capsule endoscopy (MACE; NaviCam, AnX Technologies Robotica Corp., Texas, USA) were developed in consultation of two research fellows, two consultant gastroenterologists and two endoscopy nurse specialists. Total costs of the three upper GI modalities were estimated using a combination of a) bottom up aggregation of costs associated with each procedure and b) top down averaging of fixed costs. The reason for this combination of approaches is because fixed costs for running an endoscopy session (such as equipment, maintenance and staff costs) are incurred irrespective of the number of procedures performed and therefore the unit cost of a procedure will depend on the volume of procedures performed per endoscopy session. In contrast costs including endoscopy consumables and costs of endoscope reprocessing

are incurred with each individual procedure. The costs described in the following sections are itemised in Appendix 6.

7.3.1 Fixed costs

The fixed costs for running an endoscopy session include endoscopy equipment, maintenance and staff costs. The equipment costs for setting up a new endoscopy room to perform 10 upper GI endoscopies per session was amortised over 10 years. For flexible endoscopy, we assume 10 endoscopes were required to perform two sessions per day. Similarly, 10 data recording belts were assumed to be required for MACE sessions. Wages for healthcare professional staff were calculated on a pro rata basis for each four-hour session based on published pay scales for UK NHS healthcare professionals. [198] In addition to the endoscopist, OGD sessions require a staff nurse and healthcare support worker in both the endoscopy room and endoscopy recovery. Sedation is not required for both TNE and MACE so in addition to the endoscopist, TNE sessions only require one staff nurse in the endoscopy room, and MACE sessions only one support worker in addition to the endoscopist.

7.3.2 Costs per procedure

The costs of individual procedures include endoscopy consumables, endoscope reprocessing and potential adverse events. Facilities for endoscope reprocessing were shared across different speciality groups and its costs were therefore calculated per single endoscope wash cycle. Equipment costs for reprocessing endoscopes were amortised over 10 years and divided over a total number of wash cycles. Two support workers are required for endoscope reprocessing and local audit data has shown each cycle requires 54 minutes of staff time. Data from the UK National endoscopy database (NED) suggest that 50% of OGDs are performed with conscious sedation (Personal communication; K. Siaw). Finally, we consider costs related to adverse events requiring

hospital admission based on the 2018/19 NHS schedule of reference costs. [199] Wang et al. (2018) have reported that the rate of outpatient OGD related infections is 1.08% and 64% require admission into hospital. [79] Therefore we assume that 0.69% of all OGDs have admissions into hospital for OGD related infections.

7.3.3 Scenario analyses: pre- and post COVID-19 and need for biopsies

Endoscopy capacity and costs were based on demand for OGD and endoscope reprocessing extrapolated from 10 years of local data (Royal Hallamshire Hospital, Sheffield, UK) between 2010 and 2020. At baseline, the most optimal pre COVID-19 pandemic capacity (100% capacity) was defined as the number of OGDs per session assuming all diagnostic OGDs over the 10-year period were performed in a single endoscopy room over two endoscopy sessions every five-day working weekday.

In scenario analyses, the cost of different endoscope technologies post-pandemic is estimated where capacity is assumed to be between 30 and 75% pre-pandemic, and where capsule endoscopes are priced differently. [196,200] Costs of alternative technologies (TNE and MACE) are examined against conventional OGD assuming that all three technologies have equivalent clinical effectiveness. One exception is that should patients undergoing MACE require tissue biopsies, they will require a subsequent flexible endoscopy. Therefore, further scenario analyses examining the cost of MACE with increasing probabilities of requiring biopsies and a second flexible endoscopy was compared against a straight to OGD or TNE strategy.

7.4 Results

Process maps of patient pathways during flexible endoscopy and MACE are illustrated in Figure 19.

7.4.1 Fixed costs per session

Endoscopy equipment amortised over 10 years' costs £47,991 for OGD, £50,119 for TNE or £10,680 for MACE per annum. Maintenance of flexible endoscope and MACE systems cost £19,812 and £2,500 per annum respectively. Therefore, the cost of endoscopy equipment and maintenance is more expensive for flexible endoscopy (OGD £130.40 and TNE £134.48) than MACE (£25.34) per endoscopy session (Table 15). An OGD session is supported by a registered nurse and a support worker in both the endoscopy room and endoscopy recovery area each and amounts to £196.97 per session. In contrast a TNE list is supported by a single nurse in the endoscopy room and a MACE list is supported by a single support worker preparing patients for MACE, amounting to £52.64 and £45.85 respectively. The endoscopist are either consultants (£173.61 per 4-hour session), non-consultant middle grade doctors (£104.51 per session), advanced nurse practitioners (£81.67 per session) or in the case of MACE, a trained support worker (£45.85 per session) which averages to £119.93 for flexible endoscopy and £101.41 for MACE for an endoscopist per session. Overall staffing of an OGD, TNE and MACE session amounts to £316.90, £172.54 and £147.25 per 4-hour session respectively.

7.4.2 Costs per procedure

An average of 18,000 endoscope reprocessing cycles occurred each year. Each endoscope takes 54 minutes of staff time on average to process which amounts to £9.20 per cycle and reprocessing consumables for each endoscope amounts to £20.70. With the cost of equipment amortised over 10 years and maintenance amounting to £154,344

and £135,436 per year respectively, each endoscope reprocessing cycle costs £46.00 per cycle (Table 15).

The consumable costs of endoscopy are significantly greater with MACE as the price of capsule endoscopes are £309.00 in comparison to the consumable costs of a sedated OGD at £10.48, unsedated OGD or TNE at £8.00 and tissue biopsies which costs an additional £6.12. The costs of airborne respiratory precautions (level 2 PPE) are £4.50 per individual which amounts to £13.50 for an OGD (three sets) and £9.00 (two sets) for a TNE. The rate of OGD related infections requiring admission into hospital are estimated to be 0.69% of all OGDs, costing £1,996 per admission, and an average of £13.84 per OGD. [79,199]

7.4.3 Scenario analyses

A total of 44,288 diagnostic outpatient OGD procedures were performed in the 10 years between 01/01/2010 and 31/12/2019. The baseline pre-pandemic capacity for OGDs was 8.5 procedures (95% CI 6.5 – 10.5) per endoscopy session. The baseline cost of a OGD, TNE and MACE prior to the COVID-19 pandemic was therefore £121.67, £90.10 and £329.40.

In the time during and after the COVID-19 pandemic, the cost of each OGD and TNE will depend on the number of procedures performed per endoscopy session (Figure 20). Assuming capacity of GI endoscopy services ranges between 30 to 70% of pre-pandemic values, [196] the cost of OGD and TNE will be between £257.89 to £157.71 and £183.31 to £114.56 respectively (Figure 20). MACE is non-invasive with no aerosol generation and therefore baseline capacity is assumed to be feasible. At the current price (£309) of capsule endoscopes, cost parity of MACE procedures with OGD and TNE occurs only when between one to two flexible endoscopies are performed per session or between 13-21% of baseline capacity is achieved. If the prices of capsule endoscopes are discounted to £200, cost parity would be achieved at 3.2 OGDs per

session or 38% capacity, and at 1.9 TNEs per session or 23% capacity. At £100 per capsule (£117 overall), MACE would be cheaper than OGD at baseline and on par with TNE when 5.3 procedures are performed per session or at 63% capacity, assuming no tissue biopsies are taken (Figure 20).

In scenario analysis assuming tissue biopsies need to be performed using OGD and TNE after MACE, the cost of biopsies depends on conventional endoscopy capacity and cost of flexible endoscopy (Figure 21). If capsule endoscopes are discounted to £100, cost parity between MACE and OGD can be achieved at baseline (pre-COVID-19, 100%) capacity, 70% capacity and 30% capacity, if 16%, 28% and 56% of MACE cases proceed to OGD for biopsies (Figure 21a). Cost parity between MACE and TNE can be achieved at 60% capacity and 30% capacity, if 9% and 39% of MACE cases proceed to TNE for biopsies (Figure 21b).

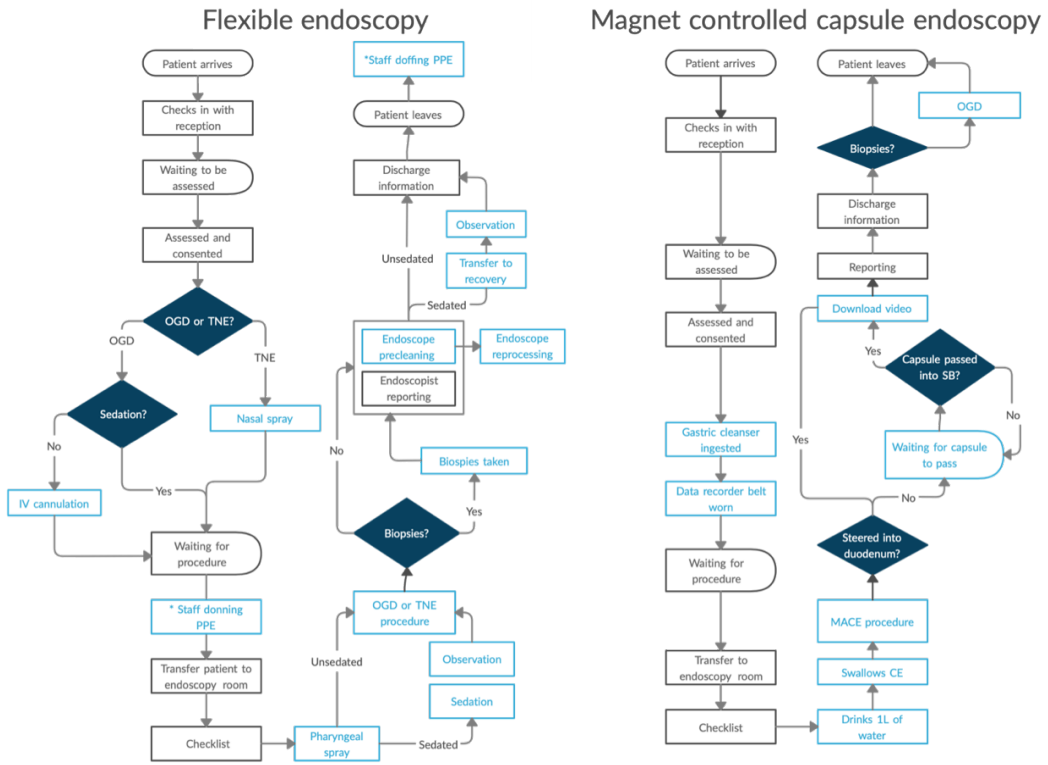


Figure 19: Process maps of flexible endoscopy (OGD and TNE) and magnet controlled capsule endoscopy (MACE)

Processes in blue highlight differences between endoscopic modalities and are accounted for in the study. *Costs of personal protective equipment (PPE) are accounted for in post COVID-19 cost analyses. SB small bowel, CE capsule endoscopy.

Table 15: Costs of Oesophagogastroduodenoscopy (OGD), transnasal endoscopy (TNE) and Magnet controlled capsule endoscopy (MACE)

	OGD	TNE	MACE
a) Fixed cost (£) per endoscopy session			
Equipment	92.30	96.38	20.54
Maintenance	38.10	38.10	4.80
Staff	316.90	172.57	147.25
	447.30	307.05	172.60
b) Costs (£) per procedure			
i) Reprocessing one			
Equipment	8.57	8.57	-
Maintenance	7.52	7.52	-
Staff	9.20	9.20	-
Consumables	20.70	20.70	-
	46.00	46.00	-
ii) Endoscopy consumables			
Procedure	8.00	8.00	309.10
Sedation	2.48	-	-
Biopsy	6.12	6.12	*
PPE	13.50	9.00	-
	30.10	23.12	309.10
iii) Complications	13.84		
Total	£89.94	£69.12	£309.10

a) Fixed costs per 4 hour endoscopy session, b) costs per procedure for i) reprocessing the endoscope and ii) endoscopy consumables, and iii) costs of complications requiring inpatient admission. PPE Personal protective equiptment. *Biopsies after MACE depend on cost of OGD, see Figure 21.

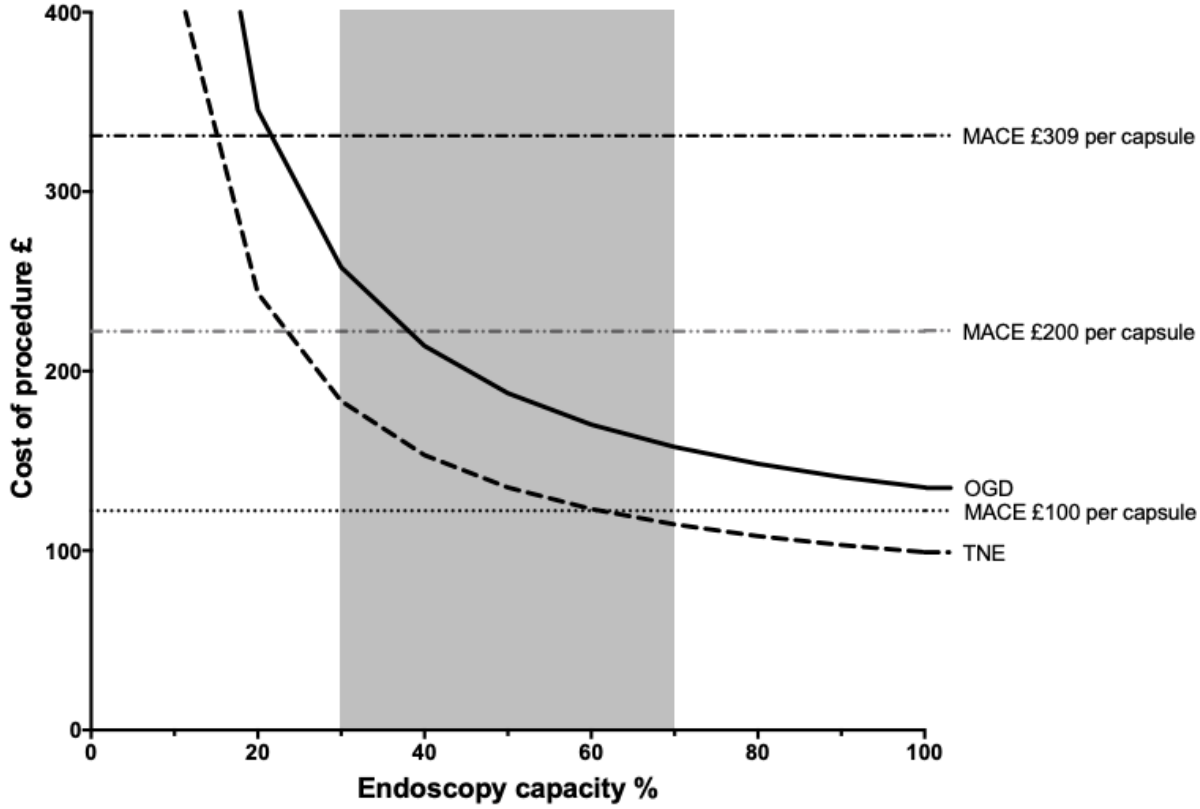


Figure 20: Cost of OGD and TNE vary with endoscopy capacity

Cost of flexible endoscopy (y axis) increases with reduction in endoscopy capacity (x axis). The current price of MACE capsules is £309. As MACE is a non-AGP, cost of procedure is dependant on price of capsule only. In two scenarios when prices of capsule endoscopes are discounted: at £200, cost parity between MACE and OGD can be achieved at 40% endoscopy capacity and when discounted to £100, cost parity between MACE and TNE can be achieved at 60% and cheaper than OGD at full capacity.

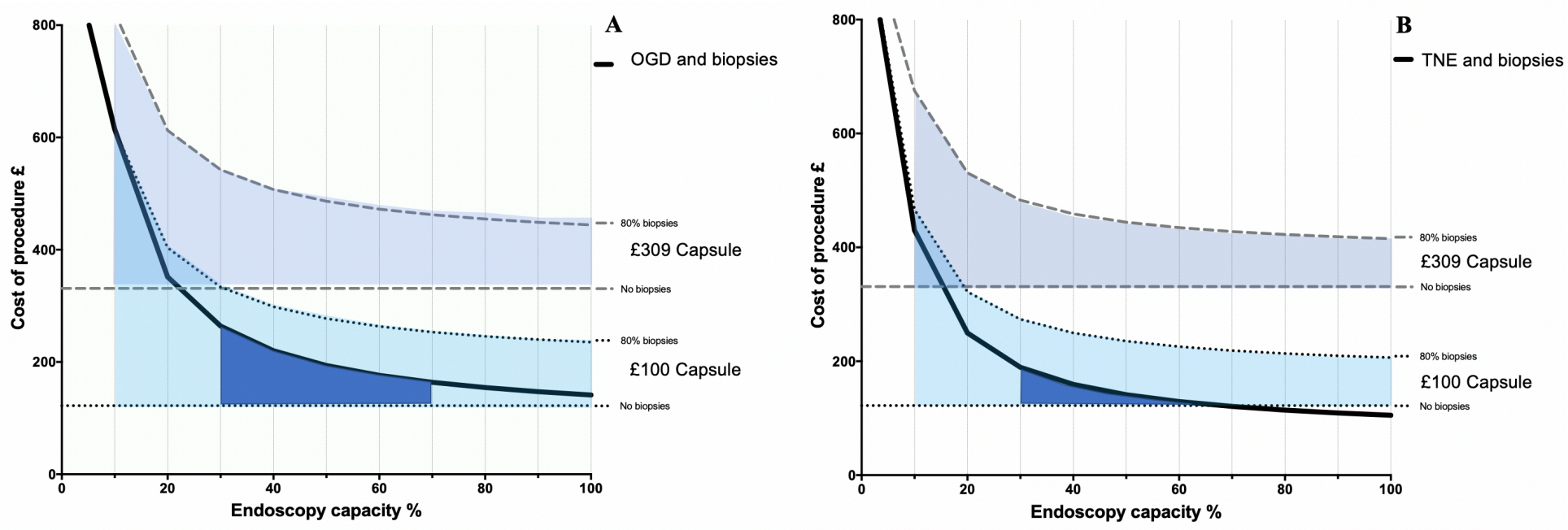


Figure 21: Cost parity analysis of OGD and TNE with MACE when tissue biopsies are required.

Two scenarios model the cost of MACE presently (£309 capsule) and discounted capsules (£100 capsule) when A) OGD and B) TNE are subsequently performed for tissue biopsies. Shaded areas show range of cost of MACE depending on percentage of cases proceeding to flexible endoscopy for tissue biopsies (from 0% - 80% requiring biopsies). The dark blue shaded areas depict where cost parity exists between a direct to OGD or TNE strategy, and a MACE followed by OGD or TNE for biopsies strategy assuming capsules are discounted to £100 and endoscopy capacity ranges from 30 – 70%.

7.5 Discussion

This study examines the economic viability of alternative upper GI endoscopic techniques in comparison to conventional OGD. The costs of increasing miniaturisation of non-invasive technologies like TNE and MACE may mean that compared to conventional OGD, these technologies might be cost-prohibitive. At baseline, prior to the COVID-19 pandemic, TNE was cheaper than conventional OGD predominantly because numerous more staff members were required to run a conventional OGD session to provide for airway support and recovery of sedated procedures. Capsule endoscopy obviates the need for both reprocessing of endoscopes and additional support staff in the endoscopy room and recovery, however despite this at the present prices of single-use capsule endoscopes, MACE is more expensive and not economically comparable to conventional OGD.

We examined the effect of a reduction in endoscopy capacity as a result of the global COVID-19 pandemic on the costs of flexible endoscopy. IPC policies to establish risk of infection (by screening patients prior to endoscopy with throat swabs and relevant exposure and symptoms history), followed by separation of patients flows and the use of PPE commensurate with their risk of infection all add to the logistical complexity of an endoscopy service and ultimately reduces capacity. [196] In endoscopy units where screening capacity is limited, or there are local outbreaks of COVID-19 cases or in patients with known or suspected COVID-19, heightened IPC policies are advised. These measures, including strict donning and doffing of PPE for staff and separation and isolation of patients by risk of contagion, can mean endoscopy capacity can be expected to be a low as a third. [200] Even where patients have a low risk of infection, estimates have suggested that only up to 75% of pre-pandemic endoscopy capacity could be achieved. [196] At these current estimates for post pandemic endoscopy capacity, we estimate that the cost of OGD will increase by 30% to 112% and TNE by 27% to 103%. Our study suggests that at current prices of capsule endoscopes, MACE is not

economically viable even where conventional endoscopy capacity is reduced to as low as 30%. However, where the price of capsule endoscopes is reduced by a third, there begins an opportunity consider MACE, and if prices are further reduced to a third of their current price, the cost of MACE and biopsies can be considered on par with conventional OGD.

Aerosols can harbour viable coronavirus for up to three hours [201] and actively replicating and transmissible viruses can be detected in airway secretions of, in particular, asymptomatic or mildly symptomatic individuals. [202] As such AGPs are an infection risk to inappropriately prepared patients and staff. Joystick-controlled MACE can be performed on a patient in a separate room with audio-visual links to endoscopist, control station and monitor, and furthermore the physical separation between the patient and the staff therefore eliminates the need for PPE. [203] Another, less obvious factor limiting the endoscopy capacity of aerosol generating endoscopies are the periods of time required for air recirculation in environments which can range from 20 minutes to an hour depending on adequacy of room ventilation. [204] MACE is not known to generate aerosols and so it is envisaged that MACE endoscopy capacity can be maintained compared to aerosol generating flexible endoscopies.

Studies which estimate costs of OGD by a 'bottom up' aggregation of component costs from Canada in 2019 [205] and Spain in 2014 [206] report a wide range in costs for an unsedated OGD (inflation adjusted cost of between £39 and £89).[f] These studies however do not report the costs and time required for high level disinfection during endoscope reprocessing. Crott et al. (2002) performed a micro costing analysis of OGDs which included endoscope reprocessing and report that in Canada, OGDs cost

[f] UK Inflation adjustments and exchange rates are calculated to July 2019 and sourced from https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator and http://www.xe.com respectively

between 103.09 and 130.11 Canadian $ or between £75.40 and £95.06 in 2019 after inflation. [207] They report the cost of reprocessing an endoscope to be $13.40 (£9.83 in 2019). A detailed micro costing of endoscope reprocessing from the United States however showed that reprocessing costs can in fact be more involved. [208] Reprocessing one endoscope took 76 minutes and between US $114 and 280 per endoscope to reprocess. The majority of this cost was between US$ 63 and $128 in endoscope repairs after failed leak testing. Locally in this study, such a cost is covered by maintenance contracts and therefore, excluding endoscope repairs, we report a cost of reprocessing (£46) within the range reported by Ofstead et al (in 2019: £39 – 117).

Several assumptions have been made which warrant discussion. We estimate the cost of performing upper GI endoscopy by examining the impact of diagnostic OGD, TNE or MACE only sessions. In reality many endoscopy lists are mixed with lower GI and or therapeutic or more complex procedures. Nevertheless, separating AGP from less aerosol generating procedures where possible would seem sensible in limiting risk of cross-contamination from infections. [195] Furthermore pre-pandemic, where theoretical demand and capacity allow, performing all diagnostic OGDs sequentially in one endoscopy room would be likely to yield significant cost savings and therefore felt to be a reasonable representation of full endoscopy capacity. The costs presented in this study do not represent a full economic costing but only costs which differ between endoscopic modalities. Costs not included in the analysis (including those related to COVID-19 screening and risk stratification, general hospital overheads, administration and histology) are therefore assumed to be similar between the different upper GI endoscopy procedures and not required for the purposes of a cost parity analysis. Nevertheless, there may be costs which we have not considered such as adverse events related to MACE and TNE, which we assume are negligible. Capsule retention in small bowel capsule endoscopy is estimated at 1% and although experience is limited in MACE, no cases of retention have been reported in 3182 upper GI MACE procedures. [124] Capsule aspiration is rare occurring in 0.1%. [93] Finally, epistaxis occurs after TNE in 2%, however the far majority of cases are self-limiting and do not need hospitalisation. [21] On the other hand, adverse events related to conventional OGD are more significant than previously thought. In a study of routine outpatient OGDs from

the USA, the rate of infections 30 days after OGD was 1.08% higher than of screening mammography, of which 64% of OGD related infections required hospital admission. [79] At this rate, locally this would have accounted for 31 admissions at an estimated cost of £61,000 per annum or £13.84 per OGD.

Finally, this is a cost minimisation study which assumes that MACE, OGD and TNE are clinically equivalent. Dysphagia is a contraindication for capsule endoscopy and therefore limit a group of patients undergoing MACE. In our study, 11% of patients had OGD for dysphagia increasing to 15% most recently in the year 2019. Otherwise, MACE has potential in detecting gastric and oesophageal pathologies compared to conventional OGD, [107,169] although larger studies, especially those examining a western population are warranted. This study suggests that the current prices of capsule endoscopes make MACE cost prohibitive, however in certain indications, MACE may offer added value to a patient's diagnostic pathway and therefore the cost effectiveness (as opposed to cost parity) of MACE should be examined in these circumstances. Patients undergoing handheld MACE for recurrent or refractory anaemia and upper GI bleeding have been shown to have a greater diagnostic yield than conventional OGD. [102,103] This may be in part because capsule endoscopes can further investigate the small bowel beyond D2 in the same examination, but also that MACE may be more able to detect certain lesions proximal to the D2 in reach of conventional OGD.

There is evidence that patients are unwilling to attend hospitals for fear of COVID-19 infection. [209] The optics of what was already an unpleasant procedure, has been further marred by the image of, and often imperceptible mumbles of, endoscopy staff dressed in PPE. The non-invasive and non-aerosol generating nature of MACE will therefore likely continue to be more preferable to patients than conventional OGD. Although MACE is currently more expensive than conventional OGD, the wider health economic cost effectiveness of MACE has not been considered. Most studies that examine the cost effectiveness of OGD in various settings utilise reimbursement costs which are often an inexact science, but are now increasingly used to reflect outcome and value-based reimbursement, as opposed to volume based reimbursement. [210] In the UK

National Health Service, an OGD without biopsies is reimbursed at £454 to the provider. [199] Assuming the actual full economic cost for MACE in this study does not exceed this reimbursement account, with unaccounted costs amounting to less than £125 (38%), a MACE costing £329 per procedure can still be reimbursed fully. The economic value therefore, of patient experience and potential benefits of a small bowel examination and lack of aerosol generation should be further examined.

8 DISCUSSION

This body of work aims to examine how capsule endoscopy can advance the quality of an upper gastrointestinal (GI) endoscopy. Capsule endoscopy is the gold standard endoscopic investigation of the small bowel [211] and a second line investigation of the colon in patients with an incomplete colonoscopy. [212] Capsule endoscopes designed to examine the upper GI tract are presently in limited use and has yet to be endorsed by societal guidance. However, with the recent Coronavirus disease 2019 (COVID-19) pandemic, there is push towards non-invasive endoscopic modalities such as capsule endoscopy.

8.1 How gold is the gold standard?

To advance capsule endoscopy in the investigation of the upper GI tract, we first examined the capabilities of the reference examination, conventional Oesophagogastroduodenoscopy (OGD) in Chapter 2. In a retrospective case control study of 627 oesophagogastric (OG) cancers we show that 48 cases (7.7%) have had previous OGDs up to 3 years prior to diagnosis, which have failed to identify the neoplastic lesion at its early stages. We further observe that missed upper GI cancer occurrence is associated with an increasing number of procedures during the endoscopy

session, but not the use of sedation, nor any metric related to the endoscopists procedural experience, background or types of and time of day of procedures.

Accepting that early lesions should have been visible at the index OGD is an extrapolation from our historical understanding of early gastric cancer biology, [22] the finding in Chapter 2 supports a body of literature suggesting that conventional OGD has its diagnostic limitations. [4,11,12] Successive endoscopic examinations may yield more pathology. In between 40 and 60% examined with push enteroscopy after conventional OGD for obscure GI bleeding have culprit pathologies proximal to D2 and therefore in reach of, and presumably missed by their initial OGD. [213,214] Similarly, when examined with small bowel CE, around 10% of patients have culprit upper GI pathology not originally reported on OGD. [167]

That OGD, the gold standard endoscopic investigation of the upper GI tract, is not a completely sensitive test is perhaps not surprising. A meta-analysis of studies where colonoscopies were done in tandem by different or the same colonoscopist show that the sensitivity of colonoscopy reduces with the size of adenoma, the overall miss rate of adenomas is 26% and significant and advanced adenomas are often missed in 9%. [215] Furthermore, studies comparing an alternative test, computed tomography (CT) colonoscopy, to optical colonoscopy show that between 12-17% of significant (>1cm) adenomas are detected on CT but not optical colonoscopy when compared to a composite diagnostic yield of both investigations, as opposed to assuming optical colonoscopy is the gold standard. [216,217]

Early stage OG malignancies are morphologically flat and more subtle than typical colonic adenomas which are commonly polypoid and more obvious. Accepting there are differences between the shape and adequacy in bowel preparation of a distended colon, oesophagus and stomach, the wealth of data from tandem studies of colonoscopy support the notion that subtle lesions like sessile serrated polyps and flat adenomas have high miss rates (27% and 34% respectively in a recent metanalysis). [215] Our finding that endoscopist procedural experience did not associate with missed cancer occurrence in the upper GI tract should therefore be interpreted cautiously. It is likely that ‘procedural

competence' irrespective of background and training is just the beginning of a journey, as Gotoda et al. aptly puts in a precis of gastric cancer screening techniques, *'(our) eyes can only see what the brain knows'* . [218]

In the efforts to increase the sensitivity of endoscopic examinations, perhaps the most significant, but yet intuitive finding, has been that pathology detection improves with increased examination time. [36,37,219] The finding that missed OG cancer occurrence is associated with an increasing number of procedures on endoscopy list perhaps suggest that an increasing workload affects endoscopists ability to perform a careful examination. With each additional procedure adds an additional turnover period, time which may reduce overall examination between patients. That increasing workload affects endoscopists may also be due to fatigue. It may be important to examine the effect of endoscopy session workloads on examination times to ensure endoscopists are given sufficient time to examine patients thoroughly. However, it is likely that as endoscopists gain knowledge and experience in detecting subtle lesions, examination times will consequently increase.

8.2 Effectiveness of capsule endoscopy in the upper GI tract

Upper GI Magnet controlled capsule endoscopy (MACE) requires minimal time between patients and with no need for conscious sedation could afford the endoscopist more time to examine the patient. In Chapter 3 we performed a self-controlled comparative trial of conventional OGD and MACE to examine patients experiences of both techniques. Patients tolerated MACE significantly better than conventional OGD with or without conscious sedation. Using two patient reported experience measures (PREM), the Universal patient centredness questionnaire (UPC-Q) and Endoscopy concern scale (ECS) scores, we show that patients are more accepting of MACE than OGD with or without sedation. Overall examination time was 8 times longer with MACE than OGD, although overall agreement in results between modalities was only 65%. In Chapter 4 we examined the use of an ultra-thin transnasal endoscope (TNE),

which is better tolerated and preferred by patients than conventional OGD. We showed in this unblinded study that both MACE and TNE are highly acceptable. However patient tolerance and acceptability marginally favoured MACE than TNE.

In both studies of conventional OGD and TNE we highlight that patient tolerance to MACE was superior to flexible endoscopy as the distresses of endoscope instrumentation (swallowing a capsule endoscope versus per oral or nasal intubation) were near absent with MACE, along with typical oro-pharyngeal distresses which accompany flexible endoscope intubation such as gagging, choking and vomiting. Consequent to these typical oro-pharyngeal reactions, both conventional OGD and TNE (both transnasal intubation and topical nasal spray application), have been shown to also be aerosol generating. [195,197] Robot controlled MACE can be performed on a patient at a distance, with audio-visual links to endoscopist, control station and monitor in a different room. [203] Therefore robot controlled MACE may have a further advantage in the future as the recent COVID-19 pandemic has put aerosol generating procedures (AGP) under considerable scrutiny [196].

One of the major limitations of capsule endoscopy is its inability to obtain tissue biopsies and although the preference for MACE was almost unanimous (bar one patient undergoing TNE), we hypothesised that the need for tissue biopsies and the requirement for another appointment for flexible endoscopy may mean that patients might prefer to have just a single examination with a flexible endoscope. However, somewhat surprisingly, we show that having experienced both examinations, in retrospect, patients would still have preferred to have MACE followed by conventional OGD or TNE in 83% and 64% respectively, even if biopsies were required in half of the cases. This goes to further support the superior tolerance and acceptance of MACE over conventional flexible endoscopy.

Our studies reported in Chapter 3 and 4 are in support of previous comparative studies between upper GI MACE and conventional OGD [101-105,107] and oesophageal capsule endoscopy and TNE [175] which suggest that capsule endoscopy is better tolerated and

accepted. There are clearly patients who benefit from sedation during conventional OGD and the current literature points towards greater patient satisfaction and willingness to repeat investigations with sedation. [55] Overall the acceptability of OGD is high when patients are sedated adequately, more so than when compared to colonoscopy for example. [65] However, consistent with comparisons of TNE and conventional OGD, [21] we show that patients would still prefer a more non-invasive option, and in this case even if there is a chance that a further invasive endoscopy is required for tissue biopsies. This may have implications in improving uptake of population based screening investigations which have been ongoing in China for gastric cancer. [124]

By using the UPC-Q we examine aspects which patients determine to be important during their endoscopy experience. Patients prioritised procedural tolerance in between 54 – 67% of procedures, the proportion of which decreased with increasingly less invasive modalities (i.e 67% OGD, 53% TNE and 53% MACE). Therefore, as procedural tolerance improves, it seems tolerance in itself becomes less important and other factors become more important. This has important implications in examining patient experience with capsule endoscopy. PREMs such as the ECS have been created to examine conventional flexible endoscopy, and not other endoscopic paradigms like capsule endoscopy. Although, the ECS was adapted for MACE in this study (for example by including swallowing the capsule and abdominal bloating from water ingestion), PREMs are mostly designed based on literature review, which are often clinician derived and uncommonly patient centric. [57] Therefore, the ECS may lack content validity in so far as patient experiences in capsule endoscopy are concerned and could explain why distresses to capsule endoscopy are distributed so tightly (IQRs mostly between 0 and 1) and skewed towards no distress. Semi-structured interviews of patients who have experienced capsule endoscopy better inform the context in which questions are asked in PREMs and thus assures content validity, however this was beyond the scope of this body of work. The Newcastle ENDOPREM is one such endeavour which aims to create a PREM to cover the breadth of endoscopic paradigms. [220]

The results of MACE and OGD agreed in two thirds of cases and where they did not, they missed pathology equally (5/30 lesions each) in our study. Although our comparative study of robot controlled MACE and OGD was not designed to examine the effectiveness of MACE in detecting pathology, our current experience suggests that further advancements in the capsule imaging technology could make it more capable in detecting oesophageal pathologies and further experience and training in the technique would make examinations more consistent, for example in improving transpyloric transit into the duodenum.

8.3 Improving on the clinical effectiveness of upper GI capsule endoscopy

Limited by its ability to take tissue biopsies, the ability of capsule endoscopy to routinely investigate the GI tract beyond the reach of the conventional flexible endoscope may be of some advantage. An 8 hour fast is the recommended pre-procedure preparation for MACE of the upper GI tract, [221] however the ideal preparation for the small bowel is still debatable. [182] In Chapter 6 we examine ways to optimise small bowel mucosal views, specifically examining the need for and timing of polyethylene glycol (PEG) laxative. In a randomised control trial of pre-procedure preparation for small bowel capsule endoscopy we randomised participants between a clear liquid diet group, of what would also normally be used for upper GI capsule endoscopy- fasting and clear fluids, and two groups of PEG laxatives given as a single dose of PEG laxative on the morning of the procedure, or a split dose (evening before and morning of) before the procedure. On reviewer assessment of bowel cleansing, we found that PEG laxative offered a cleaner distal quartile of the small bowel and initial results suggest that at least a 1 litre dose of PEG consumed during the morning of the procedure is beneficial. No conclusions can yet be reached about relative benefit of dosing interventions (single vs split dose) at present.

For the purposes of combining an upper GI and small bowel assessment in capsule endoscopy, further assessment of the timing of the morning dose of PEG prior

to the MACE should be examined. For example, if a single dose of 2 litres PEG is beneficial, would it be just as beneficial splitting a litre in the morning at 6am and a further litre just prior to the upper GI MACE, and what are the effects of a litre of clear liquid just prior to the MACE in comparison? As fluids are also required to distend the gastric lumen, understanding the effect of PEG or clear fluids just prior to upper GI MACE on mucosal views can inform ways to improve patient experience as the volume of liquid and frequency of pre-procedure doses of PEG reduce.

The utility of an upper GI MACE with a small bowel examinations should be considered. In patients with refractory and recurrent anaemia, a repeat upper GI investigation with MACE along with a small bowel examination have been suggested to be beneficial. [102] Only 20-30% of patients with iron deficiency anaemia have a normal OGD and colonoscopy, prompting a small bowel investigation. However two thirds of those refractory to iron after normal intubational endoscopies have small bowel pathology, [134] suggesting that at least 10% of anaemic patients would benefit from having a small bowel investigation in addition to an OGD and colonoscopy in the first instance. Pathology in the small bowel is considered to account for only 5% of all gastrointestinal causes of anaemia in historical fluoroscopic studies. [132] The endoscopic prevalence of lesions which cause occult small bowel bleeding amongst patients with initial presentations of anaemia are unknown and subject to an ongoing clinical trial.

8.4 Cost implications of upper GI capsule endoscopy

Having demonstrated how capsule endoscopy can offer a better patient experience than flexible endoscopic examination, and how MACE could be used to deliver greater clinical effectiveness by optimising bowel preparation for both investigations of the upper GI tract and small bowel, we acknowledge that the cost of novel technologies can often limit their advancement in clinical practice. In Chapter 6 we examine the economic impact of alternative technologies like MACE and compare them to flexible endoscopy. We perform a cost minimisation analysis between MACE, TNE and OGD.

This study concludes that the cost of MACE with present prices of capsule endoscopes is too dear to deliver an efficient service; that is, we found the cost of MACE to be at par with OGD and TNE only if between one to two flexible endoscopes were performed per four-hour endoscopy session. Scenarios where reductions in endoscopy capacity occurred in line with evolving post - COVID-19 pandemic recovery guidance suggest that the reduction in endoscopy capacity by 30 – 70% could increase the cost of performing OGD and TNE by between 30 and 112%. If prices of capsule endoscopes were to fall to a third, there would be potential to perform MACE with further conventional OGD and biopsies in between 28 to 56% of cases and still achieve cost parity between MACE and OGD.

8.5 Upper GI capsule endoscopy: a look to the future

The overall uptake of MACE will then depend on a number of factors. The clinicians and patients acceptance of MACE will largely be driven by accuracy of the device in the future. There are a number of technological advancements which would be required to improve the diagnostic accuracy of upper GI capsule endoscopy in this era of virtual chromoendoscopy and near focus imaging. Analogous to the initial difficulties with early generation transnasal endoscopes, capsule endoscopes would need to leverage novel imaging technology to improve resolution of images and provide greater mucosal detail. By comparison to transnasal endoscopy, the difficulties facing capsule endoscopy will be greater. Untethered to the physical ‘boxes’ of an endoscope stack, the capsule endoscope would need to be able to generate sufficient light to provide enough detail to a more sensitive image sensor, both supplied by a smaller but more efficient battery.

Finally, the cost of the device would be also an important factor. When capsule endoscopes are able to output images with a significantly greater image resolution there will be an opportunity to leverage artificial intelligence. Neural networks can now recognise anatomy of the upper GI tract during conventional flexible endoscopy and

feedback 'blind spots', informing an endoscopist in real time what areas have not yet been fully examined.[222] The Ankon Navicam MACE is presently able to automatically pilot the capsule in a preprogramed manner, but without feedback from inputs (i.e live endoscopy). In the future when capsule endoscopy image resolution allows neural networks to recognise capsule images of the upper GI tract, a truly 'smart' automated MACE examination can then be envisaged. This may help to develop workflow efficiencies which could offset the cost of capsule endoscopes.

One challenge for advancing capsule endoscopy in the upper GI tract remains finding a clinical pathway where MACE or other upper GI capsule endoscopy technologies can be clinically effective. The most common indication for upper GI endoscopy is dyspepsia, but as significant pathology is uncommonly found [146] and in fact other strategies such as a helicobacter test and treat strategy have been found more cost effective than straight to endoscopy strategies, [223] it is unlikely non-invasive MACE will make a measurable difference in the investigation of dyspepsia, especially considering current costs. In Western countries, one such area may be in the screening and surveillance of Barrett's oesophagus, however advancements in technology will require better control and improvements in image resolution of the capsule endoscope, to mirror that of transnasal endoscopy for example. Another area may be in the investigation of anaemia, where an upper GI and small bowel investigation could be both non-invasive and have the added value of an enteroscopy compared to conventional OGD alone. The additional value of such an approach would likely depend on both the prevalence of, and significance of, detecting flat vascular angioectasias not previously detected in historical radiological studies of small bowel pathology causing anaemia. [132] Nevertheless, the most significant causes of anaemia are still found in the colon in up to a third, [131] and with a quarter having pathology in both the upper and lower GI tract, [129] the most aspirational investigation would be a completely panenteric capsule endoscopy investigation. Battery technology and software would need to advance significantly to allow for a wide variation in panenteric transit time. However, in the management of Crohn's disease, such advanced capsule endoscopes which examine both small and large bowel disease have so far been shown

to be feasible, effective and more recently shown to be cost effective compared to conventional small bowel magnetic resonance imaging and ileocolonoscopy. [224,225]

8.6 Concluding remark

Capsule endoscopy remains a promising alternative upper GI endoscopic modality. We show in this body of work that it is a non-invasive examination that is accepted and preferred by patients over flexible endoscopy. It has a superior tolerance profile which may lend itself as being a non-aerosol generating diagnostic alternative during viral pandemics. Although conventional flexible endoscopy can be poorly tolerated it is necessary for tissue biopsies. Patients are however more inclined towards a capsule endoscopy prior to more invasive flexible endoscopy to acquire tissue only if required. However, this approach is presently too expensive with current cost of capsule endoscopes and further value based cost effectiveness studies of upper GI capsule endoscopy technologies are warranted.

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10 APPENDICES

APPENDIX 1: MACE CHECKLIST AND CLINICAL RESEARCH FORM

Checklist and pro forma for MACE	
Patient's name…….. Unit number……Date……	
Pre-MACE	Completed/Notes
1. The patient has been received and orientated to the MACE environment. The patient has been given an explanation of the investigation and understands what is involved.	
2. The patient has signed a consent form.	
3. The equipment has been checked and is ready for use. The vest is charged	
4. The patient has had only clear fluid a day before the MACE	Last ate time ……..
5. The patient has drank 80mg simethicone in 100mls of water	Time……
6. The patient has had their observations recorded. BP…….. Pulse…….. Temperature…….. Height…… Weight…… BMI…… Waist (cm)…… Hips (cm)……..	
MACE	
7. The vest is connected to the patient	
8. The 'real-time' viewer has been activated and the data recorder turned on, usb attached to console.	
9. The patient has been given 500 to 1000mls of water. Time recorded	Time…… to ……
11. The capsule is activated by light, view on console, wait 2 minutes and ensure voltage >2900mAH	
12. Patient ID on capsule view	
13. The patient is given the capsule to swallow (while in a right lateral position)	SIP? Y/N Time……
14. Magnetic steering with Ankon system	Time…….. to ……
Post-MACE	
15. Does the patient want SB investigated?	Y/N

MACE

Views	Clarity __/3	Distension __/3
Oes		
GOJ	Time to D1	Steered?
C		Ampulla? Y/N
F		
GC		
LC		
AB		
PB		
A		
P		
D1		
D2		

Findings:

APPENDIX 2: PATIENT QUESTIONNAIRE BEFORE AND AFTER MACE, CONVENTIONAL OGD AND TNE

Items on these questionnaires are adapted in part or adopted in whole from the Universal Patient Centeredness Questionnaire, [68] the Endoscopy Concerns Scale, [65] and the Hospital Anxiety and Depression score[164] and remain the intellectual property of the respective owners.

STH 19595 Questionnaire.

Section 1: Before capsule endoscopy

Participant Identifier

Your experiences with the pill camera test - in the areas that are most important to you

You will be having a pill camera test soon. We would like you to think of 3 things that are most important to you when you have the pill camera test. You can decide which things to include but they should be areas where changes can be made.

Importance and experiences

Please start by writing down the three things that are most important to you when you have your pill camera test:

Please write your *first* area here:

_____

Please write your *second* area here:

_____

Please write your *third* area here:

_____

Prioritise area

You have written down the things of importance to you when you have your pill camera test. We would now like you to rate how important each of these things were for you.

You have a total of 6 points. Divide these 6 points between the things above based on how important they are to you. The sum must be 6. If you have only written down two things then divide the 6 points between the two things.

I give the *first* area: ☐ points

I give the *second* area: ☐ points

I give the *third* area: ☐ points

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STH 19595 Questionnaire.

Section 1: Before capsule endoscopy (continued)

This part of the questionnaire helps doctors to understand how you are feeling currently. Read every sentence. Circle the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important.

I feel tense or 'wound up':			**I feel as if I am slowed down:**	
Most of the time	3		Nearly all the time	3
A lot of the time	2		Very often	2
From time to time (occasionally)	1		Sometimes	1
Not at all	0		Not at all	0
I still enjoy the things I used to enjoy:			**I get a sort of frightening feeling like "butterflies" in the stomach:**	
Definitely as much	0		Not at all	0
Not quite as much	1		Occasionally	1
Only a little	2		Quite often	2
Hardly at all	3		Very often	3
I get a sort of frightening feeling as if something awful is about to happen:			**I have lost interest in my appearance:**	
Very definitely and quite badly	3		Definitely	3
Yes, but not too badly	2		I don't take as much care as I should	2
A little, but it doesn't worry me	1		I may not take quite as much care	1
Not at all	0		I take just as much care	0
I can laugh and see the funny side of things:			**I feel restless as I have been on the move:**	
As much as I always could	0		Very much indeed	3
Not quite so much now	1		Quite a lot	2
Definitely not so much now	2		Not very much	1
Not at all	3		Not at all	0
Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**	
A great deal of the time	3		As much as I ever did	0
A lot of the time	2		Rather less than I use to	1
From time to time, but not often	1		Definitely less than I use to	2
Only occasionally	0		Hardly at all	3
I feel cheerful:			**I get sudden feelings of panic:**	
Not at all	3		Very often indeed	3
Not often	2		Quite often	2
Sometimes	1		Not very often	1
Most of the time	0		Not at all	0
I can sit at ease and feel relaxed:			**I can enjoy a good book or radio/TV program:**	
Definitely	0		Often	0
Usually	1		Sometimes	1
Not often	2		Not often	2
Not at all	3		Very seldom	3

STH 19595 Questionnaire.

Section 1: Before capsule endoscopy (continued)

Expectations:										
In regards to your upcoming pill camera test, how much, if any, have you been distressed by concerns about:										
	Not at all									Extremely
Telling friends/colleagues the nature of my upcoming test	1	2	3	4	5	6	7	8	9	10
Fasting prior to the test	1	2	3	4	5	6	7	8	9	10
Gagging during the test	1	2	3	4	5	6	7	8	9	10
Sensations of choking during the test	1	2	3	4	5	6	7	8	9	10
Sensation of bloating during the test	1	2	3	4	5	6	7	8	9	10
Vomiting during the test	1	2	3	4	5	6	7	8	9	10
Doctor seeing my food in the stomach during the test	1	2	3	4	5	6	7	8	9	10
Expressing emotions during the test	1	2	3	4	5	6	7	8	9	10
Having to swallow the pill camera	1	2	3	4	5	6	7	8	9	10
Potentially needing an injection of medication	1	2	3	4	5	6	7	8	9	10
Discomfort during the procedure	1	2	3	4	5	6	7	8	9	10
Discomfort after the procedure	1	2	3	4	5	6	7	8	9	10
Pain during the procedure	1	2	3	4	5	6	7	8	9	10
Pain after the procedure	1	2	3	4	5	6	7	8	9	10

Current feeling:										
Please rate how anxious you are at present and how much discomfort and pain, if any, you are in before the test:										
	Not at all									Extremely
Anxiety	1	2	3	4	5	6	7	8	9	10
Discomfort	1	2	3	4	5	6	7	8	9	10
Pain	1	2	3	4	5	6	7	8	9	10

STH 19595 Questionnaire.

Section 2: After capsule endoscopy

Your experiences with the pill camera test - in the areas that are most important for you

You have just had a pill camera test. We would like you to list 3 things that were most important to you while you were having the pill camera test, and then to rate them. You can decide which things to include but they should be areas where changes can be made.

Importance and experiences

Please start by writing down the three things that were most important to you when you were having your pill camera test (on the left), and rate your experience by ticking one box for each thing (on the right)

Please write your *first* area here:	What was your experience with the pill camera in this area?				
	Poor	Fairly Good	Good	Very Good	Excellent
_____	☐	☐	☐	☐	☐

Please write your *second* area here:	What was your experience the pill camera in this area?				
	Poor	Fairly Good	Good	Very Good	Excellent
_____	☐	☐	☐	☐	☐

Please write your *third* area here:	What was your experience the pill camera in this area?				
	Poor	Fairly Good	Good	Very Good	Excellent
_____	☐	☐	☐	☐	☐

Prioritise area

You have written down the things of importance to you when you had your pill camera test. We would now like you to rate how important each of these things were for you.

You have a total of 6 points. Divide these 6 points between the things above based on how important they were to you. The sum must be 6. If you have only written down two things then divide the 6 points between the two things.

I give the *first* area: ☐ points I give the *third* area: ☐ points

I give the *second* area: ☐ points

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STH 19595 Questionnaire.

Section 2: After capsule endoscopy (continued)

Experience:										
In regards to the pill camera test you just had, how much distress, if any, did you experience from:										
	Not at all									Extremely
Gagging during the test	1	2	3	4	5	6	7	8	9	10
Sensations of choking during the test	1	2	3	4	5	6	7	8	9	10
Sensation of bloating during the test	1	2	3	4	5	6	7	8	9	10
Vomiting during the test	1	2	3	4	5	6	7	8	9	10
Doctor seeing my food in the stomach during the test	1	2	3	4	5	6	7	8	9	10
Expressing emotions during the test	1	2	3	4	5	6	7	8	9	10
Having to swallow the pill camera	1	2	3	4	5	6	7	8	9	10
Potentially needing an injection of medication	1	2	3	4	5	6	7	8	9	10
Discomfort during the procedure	1	2	3	4	5	6	7	8	9	10
Discomfort after the procedure	1	2	3	4	5	6	7	8	9	10
Pain during the procedure	1	2	3	4	5	6	7	8	9	10
Pain after the procedure	1	2	3	4	5	6	7	8	9	10

Patient

Comfort of procedure overall……

- **None**: no discomfort – resting comfortably throughout
- **Minimal:** one or two episodes of mild discomfort, well tolerated
- **Mild**: more than two episodes of discomfort, adequately tolerated
- **Moderate**: significant discomfort, experienced several times during the procedure
- **Severe**: extreme discomfort, experienced frequently during the procedure

Would you:

1. Undergo same test again given the same medical circumstances? Y N
2. Advise a friend to undergo the same test with the same medical circumstances? Y N
3. Have the same test again in 1to 2 years if well and without any symptoms but if medical advice was that it's a useful test to screen for cancer? Y N

STH 19595 Questionnaire.

Section 3: Before oral or transnasal OGD

Your experiences with OGD (the flexible tube camera) - in the areas that are most important for you

You will be having a OGD soon. We would like you to think of 3 things that are most important to you when you have the gastroscopy, and then to rate them. You can decide which things to include but they should be areas where changes can be made.

Importance and experiences

Please start by writing down the three things that are most important to you when you have your gastroscopy:

Please write your *first* area here:

_____

Please write your *second* area here:

_____

Please write your *third* area here:

_____

Prioritise area

You have written down the things of importance to you when you have your gastroscopy. We would now like you to rate how important each of these things were for you.

You have a total of 6 points. Divide these 6 points between the things above based on how important they are to you. The sum must be 6. If you have only written down two things then divide the 6 points between the two things.

I give the *first* area: ☐ points

I give the *second* area: ☐ points

I give the *third* area: ☐ points

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STH 19595 Questionnaire.

Section 3: Before oral or transnasal OGD

Expectations:										
In regards to your endoscopy test, how much, if any, have you been distressed by concerns about:										
	Not at all									Extremely
Telling friends/colleagues the nature of my upcoming test	1	2	3	4	5	6	7	8	9	10
Fasting prior to the test	1	2	3	4	5	6	7	8	9	10
Gagging during the test	1	2	3	4	5	6	7	8	9	10
Sensations of choking during the test	1	2	3	4	5	6	7	8	9	10
Sensation of bloating during the test	1	2	3	4	5	6	7	8	9	10
Vomiting during the test	1	2	3	4	5	6	7	8	9	10
Doctor seeing my food in the stomach during the test	1	2	3	4	5	6	7	8	9	10
Expressing emotions during the test	1	2	3	4	5	6	7	8	9	10
Insertion of the scope into my nose or mouth	1	2	3	4	5	6	7	8	9	10
Insertion of intravenous line into my hand	1	2	3	4	5	6	7	8	9	10
Discomfort prior to the test	1	2	3	4	5	6	7	8	9	10
Discomfort during the procedure	1	2	3	4	5	6	7	8	9	10
Discomfort after the procedure	1	2	3	4	5	6	7	8	9	10
Pain prior to the test	1	2	3	4	5	6	7	8	9	10
Pain during the procedure	1	2	3	4	5	6	7	8	9	10
Pain after the procedure	1	2	3	4	5	6	7	8	9	10

Current feeling:										
Please rate how anxious you are at present and how much discomfort and pain, if any, you are in before the test:										
	Not at all									Extremely
Anxiety	1	2	3	4	5	6	7	8	9	10
Discomfort	1	2	3	4	5	6	7	8	9	10
Pain	1	2	3	4	5	6	7	8	9	10

STH 19595 Questionnaire.

Section 4: After oral or transnasal OGD

Your experiences with the OGD (the flexible tube camera) - in the areas that are most important for you

You have just had an OGD. We would like you to list 3 things that were most important to you while you were having the gastroscopy, and then to rate them. You can decide which things to include but they should be areas where changes can be made.

Importance and experiences

Please start by writing down the three things that were most important to you when you were having your OGD (on the left), and rate your experience by ticking one box for each thing (on the right)

Please write you *first* area here:	What was your experience with the OGD in this area?				
	Poor	Fairly Good	Good	Very Good	Excellent
_____	☐	☐	☐	☐	☐

Please write you *second* area here:	What was your experience the OGD in this area?				
	Poor	Fairly Good	Good	Very Good	Excellent
_____	☐	☐	☐	☐	☐

Please write you *third* area here:	What was your experience the OGD in this area?				
	Poor	Fairly Good	Good	Very Good	Excellent
_____	☐	☐	☐	☐	☐

Prioritise area

You have written down the things of importance to you when you had your OGD. We would now like you to rate how important each of these things were for you.

You have a total of 6 points. Divide these 6 points between the things above based on how important they were to you. The sum must be 6. If you have only written down two things then divide the 6 points between the two things.

I give the *first* area: ☐ points

I give the *second* area: ☐ points

I give the *third* area: ☐ points

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STH 19595 Questionnaire.

Section 4: After oral or transnasal OGD (continued)

Experience:										
In regards to the gastroscopy you just had, how much distress, if any, did you experience from:										
	Not at all									Extremely
Gagging during the test	1	2	3	4	5	6	7	8	9	10
Sensations of choking during the test	1	2	3	4	5	6	7	8	9	10
Sensation of bloating during the test	1	2	3	4	5	6	7	8	9	10
Vomiting during the test	1	2	3	4	5	6	7	8	9	10
Doctor seeing my food in the stomach during the test	1	2	3	4	5	6	7	8	9	10
Expressing emotions during the test	1	2	3	4	5	6	7	8	9	10
Insertion of the scope into my nose or mouth	1	2	3	4	5	6	7	8	9	10
Insertion of intravenous line into my hand	1	2	3	4	5	6	7	8	9	10
Discomfort during the procedure	1	2	3	4	5	6	7	8	9	10
Discomfort after the procedure	1	2	3	4	5	6	7	8	9	10
Pain during the procedure	1	2	3	4	5	6	7	8	9	10
Pain after the procedure	1	2	3	4	5	6	7	8	9	10

Patient

Comfort of procedure overall……

- **None**: no discomfort – resting comfortably throughout
- **Minimal:** one or two episodes of mild discomfort, well tolerated
- **Mild**: more than two episodes of discomfort, adequately tolerated
- **Moderate**: significant discomfort, experienced several times during the procedure
- **Severe**: extreme discomfort, experienced frequently during the procedure

Section 4: Post-OGD

Would you:

1. Undergo same test again given the same medical circumstances? Y N
2. Advise a friend to undergo the same test with the same medical circumstances? Y N
3. Have the same test again in 1to 2 years if well and without any symptoms but if medical advice was that it's a useful test to screen for cancer? Y N

STH 19595 Questionnaire.

Section 5: After both capsule endoscopy and OGD.

1. If you needed investigation for symptoms again, would you prefer to have the capsule endoscopy (CE) or tube camera (OGD) to examine your upper GI tract?
   Circle one [CE / OGD]

2. If after a capsule endoscopy, you were told you needed to have biopsies taken you would require a tube camera (OGD) to obtain the biopsies.

   a. If after CE the chance was of requiring a further OGD was **1 in 20** would you prefer to have the CE or OGD initially? Circle one [CE / OGD]

   b. If after CE the chance was of requiring a further OGD was **1 in 10** would you prefer to have the CE or OGD initially? Circle one [CE / OGD]

   c. If after CE the chance was of requiring a further OGD was **1 in 5** would you prefer to have the CE or OGD initially? Circle one [CE / OGD]

   d. If after CE the chance was of requiring a further OGD was **1 in 4** would you prefer to have the CE or OGD initially? Circle one [CE / OGD]

   e. If after CE the chance was of requiring a further OGD was **1 in 2** would you prefer to have the CE or OGD initially? Circle one [CE / OGD]

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APPENDIX 3: BLINDED REVIEWER ASSESSMENT OF BOWEL CLEANSING

This is an example template of the pseudoanonymised cases (columns) and the quantitative index (QI), qualitative evaluation (QE) and overall adequacy of assessment (OAA) used by the blinded reviewer. This method of assessment has been adopted in whole from Brotz et al. (2009)[190] and remain the intellectual property of the respective owners.

	0c4d1w33	0DUhNQ33	0GfJPA33	0O0qww33	13EemQ33
Quartile 1					
% of mucosa visualised					
Fluid and Debris					
Bubbles					
Bile/chyme staining					
Brightness					
QE					
OAA					
Quartile 2					
% of mucosa visualised					
Fluid and Debris					
Bubbles					
Bile/Chyme					
Brightness					
QE					
OAA					
Quartile 3					
% of mucosa visualised					
Fluid and Debris					
Bubbles					
Bile/Chyme					
Brightness					
QE					
OAA					
Quartile 4					
% of mucosa visualised					
Fluid and Debris					
Bubbles					
Bile/Chyme					
Brightness					
QE					
OAA					

APPENDIX 4: PARTICIPANT CLINICAL RESEARCH FORM FOR BOWEL CLEANSING STUDY

Does split-dose preparation produce better cleansing and diagnostic yield than no preparation at all in small bowel capsule endoscopy?

Patient details:

Name

Address

Date of birth

Trial number

Randomised to:

Single dose PEG……. Split dose PEG ……. Fast only ……

Date of procedure ……

Indication for procedure

a. Suspected small bowel bleeding
b. Suspected (but not known) Crohn's disease
c. Assess established Crohn's disease
d. Assess coeliac disease
e. Polyposis syndromes
f. Abdominal pain
g. Abnormal radiology
h. Other: what? ……

Co-morbidity (please list all):

Medications: please list names (not doses):

Patient Name……

Capsule Endoscopy

Time of first oesophageal image ……..

Time of first gastric image ……

Time of first duodenal image …… Gastric transit time = …….. mins

Time of first caecal image …… Small bowel transit time = …… mins

Diagnosis / diagnoses (defined as a clinically significant lesion)

Computed assessment of cleansing score = ……

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STH20061
Participant questionnaire, v1, 07/08/2017

APPENDIX 5: PARTICIPANT PRE-PROCEDURE QUESTIONNAIRE ON TOLERANCE AND ACCEPTANCE OF BOWEL PREPARATION

Participant Trial Number……

Does split-dose preparation produce better cleansing and diagnostic yield than no preparation at all in small bowel capsule endoscopy? Participant Tolerance Questionnaire

1. If you were given a laxative drink before your test, were you able to drink:
   (you do not need to answer this question if you only fasted and had no laxatives)

   a. All of it
   b. Most of it
   c. Some of it
   d. None of it

2. Would you say that **overall,** the preparation for the test, whether it be laxatives, or not (i.e. just a period of fasting), was:

   a. Perfectly tolerable
   b. Mildly intolerable
   c. Moderately intolerable
   d. Severely intolerable
   e. Unable to tolerate it at all

3. Please tick the relevant box for each of the following, according to whether or not they were present at all, or if they were mild, moderate, severe or completely intolerable:

	None	Mild	Moderate	Severe	Completely intolerable
Bloating					
Dizzy					
Nausea					
Vomiting					
Abdominal pain					
Poor sleep					
Bad taste					

Would you be willing to repeat the VCE test with the preparation you used? Yes☐ No☐

Thank you!

APPENDIX 6: ITEMS COSTED IN ECONOMIC IMPACT STUDY

List of equipment [required per room], maintenance costs and consumables used (required per procedure). * Items of personal protective equipment

Endoscopy room

Olympus GIF HQ 290 or GIF- XP 290N [10]
Olympus EVIS Lucera Elite video system [1]
CO2 cylinder holder, cables and accessories [1]
CO2 insufflator [1]
Endogator EGP-100 [1]
A set of air channel connectors, tubes, blocker and leak test connectors [1]
Various IT equipment
Observations machine [1]
Portable airway suction unit [1]
Patient trolley [1]
Plastic trays and lids [10]
Maintenance contracts [per scope and per stack]

Reprocessing unit

Multichamber Washer disinfector [8]
Drying cabinet [4]
Vapour phase Hydrogen peroxiade sterilisers [1]
Trolley washer [1]
Reverse osmosis unit and connectors [1]
Vacuum packer [1]
Maintenance contracts

- Sterilising and quality management systems
- Trolley washer
- Washer disinfector
- Reverse osmosis unit
- Drying cabinets
- IT equipment
- Parts and additional callouts (once a month)

Endoscopy consumables

Galipot (1)
Gloves (2 pairs)
Mouth guard (1)
Xylocaine and spray catheter (1)
Phenylephrine and lidocaine nasal spray (1, TNE only)
Nonenzymatic pre clean (1)
Blood pressure cuff (disposable per session)
Endogator water jet connector (per session)
CO2 tubing (per session)
Biopsy valve (1)
Biopsy forceps
Sample pot, formalin solution and transport bag

Reprocessing consumables

Hats (two / cycle)
Gloves (3 pairs/ cycle)
Gown (3 pairs / cycle)
Pre-cleaning pod (one / cycle)
Leak test filter (one / 10 cycles)
Detergent for leak tester (one/ 750 cycles)
Sink detergent (one /400 cycles)
Brushes (one / cycle)
Red and green plastic bags (two / cycle)
Vacuum pack (one / cycle)
Washer: water, electricity, disinfectant and detergent (per cycle)

MACE room

Ankon NaviCam system and capsule locator [1]
Data recorders [15]
Maintenance contract

Sedation

Blue IV cannula (1)
Disposable tourniquet (1)
5ml Luer slip syringe (1)
Drawing up filtered needle (1)
10ml Luer slip syringe (1)
Clinell alcohol wipe (1)
Kidney dish (1)
Cotton ball (1)
Nasal cannula and O2 tube 2m (1)
Midazolam 2mg/2ml (1)
10ml saline (1)

MACE consumables

AKT-1 Capsule endoscope (1)
Simethicone 80mg/ml

50ml syringe (1)
Yankauer suction and tube (1)
Stack suction tube and liner (2 per session)
Water (sterile; 3L per session)
Simethicone 80mg/ml
Disposable face shield *
Hair cap*
Waterproof gown*
Face mask respirator (FFP) 3*