Hardware and Software Advances in Capsule Endoscopy

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Abstract

Capsule endoscopy was introduced in 2000 and has since become the investigative modality of choice for mucosal diseases of the small bowel. This innovative device, which comprises of imaging components encased within a pill-sized capsule, allows for non-invasive examination of the small bowel. The aim of this thesis is to evaluate advances in capsule endoscopy which have the potential to extend and improve the practice of this tool.

The first section of this thesis examines the impact of fatigue on the accuracy of small bowel capsule endoscopy interpretation. Capsule studies involve the presentation of many thousands of repetitive images, which are time-consuming to interpret. There is some evidence for the impact of fatigue in the detection of adenomas during colonoscopy. In comparison capsule interpretation is passive, has little visual variability, and may, therefore, have a greater potential to induce fatigue. Here we hope to establish if this does indeed occur and if so, whether it affects the quality of subsequent readings.

The second section investigates a potential solution to the numerous images presented. Omni-Mode is a novel rapid

reading algorithm which proposes to remove similar images in order to reduce the images presented. By limiting the images to only those displaying unique information, accurate diagnosis could be made in a fraction of the time. This software was evaluated in a multi-centre European trial, where the diagnostic accuracy and reading times achieved with Omni-Mode were compared to conventional reading.

The final section of this thesis explores the use of capsule endoscopy outside of the small bowel by means of a modification to the capsule hardware. The addition of magnetic material within the capsule allows in-vivo manoeuvrability under the control of an external magnet. Here we explore the use of a Magnetically Assisted Capsule Endoscope as an alternative to conventional endoscopy, providing a non-invasive method for examination of the upper gastrointestinal tract. In this study we have focussed on the detection of oesophageal pathology, which has the potential to be missed during the rapid oesophageal transit of a standard capsule endoscope.

Publications, awards and presentations arising from this thesis

Publications

1. Optimising the performance and interpretation of small bowel capsule endoscopy. Beg S, Parra-Blanco A, Ragunath K. Frontline Gastroenterol. 2018 Oct;9(4):300-308.

Awards

1. Awarded research funding at the BSG Dragon's Den conference 2015, for MACE project proposal
2. Poster of Distinction, UEG Week Barcelona 2017
3. Poster of Distinction, BSG Conference 2018

Research abstracts presented: Poster

1. How many capsule endoscopy cases can be read before accuracy is affected?
   Abstract of Distinction Digital Poster Session, BSG 2018

2. Omni-Mode reduces capsule endoscopy reading time, whilst maintaining accuracy, UEG Week Vienna 2018

Research abstracts presented: Oral

1. The accuracy and tolerability of Magnetically Assisted Capsule Endoscopy for the investigation of oesophageal pathology

   Oral presentation at Gastroduodenal and oesophageal free papers, BSG conference 2018

2. How many capsule endoscopy studies can be read in a given session before accuracy is affected?

   Poster Champ Session: Surgery, endoscopy and imaging' UEG Week Barcelona 2017

3. Optimising the performance and interpretation of small bowel capsule endoscopy

   4th National Capsule Symposium, Newcastle 2017

4. Optimising the performance and interpretation of small bowel capsule endoscopy, a review of the evidence.

   Olympus EndoCapsule course, Nottingham, 2018

Disclaimer

This thesis is the result of original work. These projects have been collaborative, with the details of the involvement of others is detailed in the acknowledgments and methodologies. No part of this thesis has been submitted for other degrees in any other universities but has been presented in conferences and meeting as detailed in the thesis.

Acknowledgements

As with all projects, there are many people who have contributed in order to make this work possible. I am grateful to the patients and medical professionals who have participated in the studies that form this thesis. These studies have resulted from the collaborations of different institutions across the UK as well as internationally and will hopefully be the foundation for future work to come.

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Abbreviations

ADR: Adenoma Detection Rate 50

BO: Barrett's Oesophagus.....143

BSG: British Society of Gastroenterology 47

CE: Capsule Endoscopy 19

CRF: Clinical Record Forms 91

DBE: Double Balloon Enteroscopy 20

DV: Dual View..... 45

ER: Experienced Reader 86

FICE: Flexible Spectral Colour Enhancement..... 62

fps: frames per second..... 22

FS: Fatigue Score 88

GI: Gastro Intestinal 19

IDA: Iron Deficiency Anaemia 29

MACE: Magnetically Assisted Capsule Endoscopy..... 67

NR: Novice Reader..... 86

OGD: Oesophago-Gastro-Duodenoscopy 145

OV: Oesophageal Varices.....143

PEG: polyethylene glycol 42

PVT: Psychomotor Vigilance Test 89

QV: Quad View..... 45

RS: Reference Standard 88

SBE: Single Balloon Enteroscopy 39

SBI: Suspected Blood Indicator 62

SV: Single View..... 45

Chapter 1: Introduction

Current practice in capsule endoscopy

1.1.1 The introduction of capsule endoscopy

The diagnosis Gastro-Intestinal (GI) disease through direct endoscopic visualisation has become the gold standard for the assessment of mucosal pathology. Since the introduction of the first rigid endoscope, there have been numerous developments that have resulted in the routine availability of high definition flexible endoscopic investigation of the upper and lower GI tract. Despite contributing to over 90% of the GI surface area, investigation of the small bowel has in contrast lagged behind. This has predominantly been due to challenging anatomy caused by its length, tortuous course and relatively mobility, making endoscopic negotiation difficult.

In 2000 a new technique to overcome these obstacles was made available with the introduction of Capsule Endoscopy (CE) This pill size camera can be simply swallowed, with images of the small bowel acquired as it passively passes through the GI tract. Images are transmitted to a receiving device, which is then transferred to a computer work station for interpretation. With this minimally invasive technique, the entire small bowel can be visualised in a single procedure.

CE came about from the work of two individuals working separately but simultaneously, Gavriel Iddan, an Israeli electrical engineer working on missile technology and Professor Paul Swain, a British gastroenterologist. The combination of these efforts was used to design the first capsule, aptly named the M2A (mouth to anus), manufactured by Given Imaging. This was first reported in a landmark Nature communication [1].

The introduction of CE coincided with the inception of Double Balloon Enteroscopy (DBE) in 2001 [2]. The use of an extended length endoscope with inflatable balloons makes it possible to negotiate the bowel and deliver therapy to lesions identified at CE.

Since its introduction, millions of CE examinations have been performed, with nearly 5000 scientific papers published concerning this technique. Hardware and software developments mean that CE has an improved specification. In fact capsule endoscopy is no longer limited to the small bowel, with commercially available models designed to examine the oesophagus and colon. Developments in capsule locomotion, biopsy acquisition, drug delivery and enhanced imaging mean that capsule endoscopy has the potential to become a pan-

endoscopic technique and may rival conventional endoscopy in the future [3].

1.1.2 Commercially available capsule endoscopes

At present there are five commercially available CE systems; PillCam (Given Imaging), EndoCapsule (Olympus), MiroCam (Intromedic), CapsoCam (CapsoVision) and OMOM (Chongqing Jinshan Science & Technology) [4]. Each of these share the same core components, which include; an imaging device, a lens, a light source and a battery, all of which are encased within a non-biodegradable toughened plastic casing. In all but one system (CapsoCam), images acquired from the capsule are transmitted wirelessly to a receiving device, before being uploaded and read at a workstation using proprietary software. Differences in the design and technical capabilities of these components lead to subtle differences in capsule specification, as summarised in

Table 1.

As first to the market, PillCam is the most widely used in clinical practice and studied in the literature. This system is now in its third generation (PillCam SB3), boasting improved image resolution and an adaptive frame rate, which increases from 2 frames per seconds (fps) to 6 fps when the capsule is sensed to be moving at a high velocity. The EndoCapsule

system followed shortly afterwards in 2004, offering a 3Dimensional tracking function to enable the localisation of detected lesions in order to guide the therapeutic approach where this is required. Triangulation between the capsule and the sensing pads enables CE location in the bowel to be estimated, although remains relatively inaccurate with errors of up to13.26cm^3 [5] While examination time may be used as a surrogate marker of position, variation in transit times and the non- linear passage of the capsule means that this is highly unreliable.

The MiroCam capsule uses electric field propagation, which exploits the patients' body as a conductor for data transmission. This reduces energy consumption compared to radio-frequency based systems, enabling a long battery life in spite of its smaller dimensions [6].

CapsoCam is able to offer a 360 degree 'panoramic' view, owing to four laterally placed cameras. This may have the potential to result in a greater diagnostic yield through an increased number of images, although this needs to be offset against longer reading times [7,8]. The images acquired are stored within the capsule and so a receiving device is not required. Retrieval of the capsule following expulsion from the

body is required, with a magnetic wand provided to aid recovery. This could be advantageous in certain settings, such as rural areas where patients are not able to attend hospital but could receive equipment through the post. However, this is clearly not suitable for all patients, with a proportion unable to retrieve the capsule within an observational study [9].

The OMOM capsule has been in use for many years and is well established in China and Asia, but has only been recently available in the USA and Europe. This capsule boasts duplex data communication, where the endoscopic view can be evaluated, allowing for real-time adjustments of parameters such as frame rate, brightness and exposure in order to optimise the quality of the examination.

There are few head to head trials comparing the clinical implications of using one capsule versus another. Where these exist, no significant differences have been demonstrated,

Table 2. Which capsule endoscopy system is used, is therefore determined by user preference, with cost and procurement undoubtedly influencing these decisions.

Table 1: Specifications of the commercially available capsule endoscopy systems

Model	Company	Dimension (mm)	Weight (grams)	Field of view (degrees)	Frames per second	Image sensor	Transmission	Battery life (hours)
PillCam (SB3)	Given Imaging	26x11	1.9	156	2-6	CMOS	Radio-frequency	11
MiroCam	Intromedic	24x11	3.25	170	3	CMOS	Electrical field propagation	12
Endocapsule (EC-10)	Olympus	26x11	3.3	160	2	CMOS	Radio-frequency	12
OMOM (2)	Jiangshan	28x13	4.5	140	2	CMOS	Radio-frequency	10
CapsoCam (SV2)	Capsovision	31x11	4	360 (laterally)	20	CMOS	Images stored	15

Table 2: Head to head trial comparing different capsule endoscopy systems

Study	Country	Systems compared	No of cases	Study Design	End points	Summary of results
Hartmann D et al (2007) [10]	Germany (single centre)	EndoCapsule vs PillCam	40	Sequential capsules (randomly assigned order)	Diagnostic yield and completion rate	• Higher diagnostic yield in EndoCapsule- not statically significant. • Higher completion in EndoCapsule system (100% vs 82.5%)
Cave DR et el (2008) [11]	USA (multi-centre)	EndoCapsule vs PillCam	51	Sequential capsules (randomly assigned order)	Diagnostic yield, completion rate and quality of view	• No significant difference in diagnostic yield • Subjective judgment in image quality favouring EndoCapsule
Kim HM et al (2010) [12]	Korea (single centre)	MiroCam vs PillCam	24	Sequential capsules (randomly assigned order)	Diagnostic yield and completion rate	• No significant difference in diagnostic yield • Higher completion in MiroCam system (83.3% vs 58.3%)
Pioche M (2011) [13]	France (Multi-centre)	MiroCam vs PillCam SB2	73	Sequential capsules (randomly assigned order)	Diagnostic yield, transit and capsule reading time.	• Statistically non-significant higher yield using MiroCam system • 95.2% vs 78.6% accuracy

Koulaouzidis et al (2012) [14]	UK (single centre)	MiroCam vs PillCam SB1/2	619	Retrospective analysis (209 MiroCam, 262 SB1, 148 SB2)	Identification of the Ampulla	• Ampulla was identified in 9.5% cases • No difference in ampulla detection or number of frames in which this was visualised
Hong SP et al (2012) [12]	Korea (Single centre)	MiroCam vs PillCam	141	Retrospective analysis (57 studies using MiroCam and 84 using PillCam)	Visualisation of the papillae	• Higher frequency of papillae detection using MiroCam (13.1% vs 29.8%)
Dolak W et al (2012) [15]	Austria (single centre)	MiroCam vs EndoCapsule	50	Sequential capsules (randomly assigned order)	Diagnostic yield and completion rate	• No significant difference in diagnostic yield • No significant difference in completion rate
Choi EH et al (2013) [16]	USA (multi-centre)	MiroCam vs PillCam	105	Sequential capsules (randomly assigned order)	Diagnostic yield and completion rate	• No significant difference in diagnostic yield • Higher completion in MiroCam system (93.3% vs 84.3%) •

Pioche M (2014) [7]	France (Multi-centre)	CapsoCam vs PillCam SB2	73	Sequential capsules (randomly assigned order)	Diagnostic yield	• Technical issues with the CapsoCam system in 11 patients and with PillCam in 2 patients. • No significant difference in diagnostic yield.

1.1.3 Indications for Capsule Endoscopy

Anaemia

The investigation of GI bleeding is the most common indication for small bowel CE, accounting for 50- 70% of studies performed [17]. Bleeding may be overt, with evidence of haematochezia or melena, or may be occult with clinical symptoms or biochemical evidence of iron deficiency anaemia (IDA).

Where overt bleeding occurs, the strategy for investigation will depend on the suspected location of the causative lesion. In a small proportion of cases, bleeding will originate from the small bowel and therefore cannot be diagnosed by gastroscopy or colonoscopy. The standard next line of investigation is CT angiography, however, a 'hot capsule,' performed whilst the patient is actively bleeding may be used to investigate the cause. The highest diagnostic yields are observed in those who undergo CE within 48 hours [18]. Earlier use of CE in those hospitalised with GI bleeding and a normal gastroscopy, may reduce the need for other investigations [19]. When bleeding is profuse, intraluminal blood may obscure the responsible lesion, with the additive information gained by CE being the confirmation of a small bowel source and an approximate location. It is worth remembering at present CE cannot deliver

therapy and so further intervention with enteroscopy, radiology or surgery may be required, thus limiting its impact in such scenarios. It is intuitive that the diagnostic yield of CE would be higher if there is active overt bleeding, and this is indeed supported by the literature. Other factors associated with a higher diagnostic yield include increased age, warfarin use and the requirement for blood transfusions [20–22]. When CE images appear normal and the source of bleeding is not identified, long term outcomes are good, with low rates of re-bleeding [22–24]

Occult or obscure GI bleeding is usually investigated with bidirectional endoscopy and a trial of iron replacement therapy in the first instance. Where the cause of IDA remains undiagnosed and is recurrent or persistent, investigation of the small bowel may be indicated. Ongoing IDA may still be attributable to upper GI or colonic lesions, missed at original endoscopy, with the most commonly missed lesions including Cameron ulcers, Dieulafoy's lesions and angioectasia [25]. The aetiology of small bowel pathology is influenced by age, with the commonest lesions in those under 40 years old including small bowel tumours, Dieulafoy's lesion and Meckel's diverticulum whilst those over 40 have predominantly angiodysplastic lesions, which account for 40% cases [26].

Inflammatory bowel disease

CE can be used to investigate mucosal features of non-stricturing Crohn's disease in those with suspected inflammatory bowel disease, or to assess extent or response to treatment in those with an established diagnosis. Given that 30-35% of patients will have solely small bowel Crohn's and a further 50% will have large bowel disease with small bowel involvement, this may aid diagnosis in those in whom colonoscopy is normal or has only subtle abnormalities.

The CE diagnosis of Crohn's disease can be subjective, with the diagnosis entertained when erosions and ulcers are seen. It can, however, be difficult to differentiate Crohn's disease from other ulcerating pathologies, such as NSAID use [27]. The Lewis score is a proposed diagnostic criterion, by which oedema, ulceration, nodularity and stricturing is assessed to assign a score which correlates with degree of disease activity. The Lewis score is linked with prognosis, with higher scores linked with steroid requirement and hospitalisation [28]. This score can be automatically calculated using the PillCam system software. Where interobserver agreement in attributing this score based on endoscopic features has been undertaken and interclass correlation coefficient of up to 0.96 has been demonstrated [29].

In a meta-analysis comparing the accuracy of CE in the diagnosis of Crohn's disease to that of alternate modalities, CE was found to have a diagnostic yield higher than that of barium studies (63% vs 23%), colonoscopy with intubation of the terminal ileum (61% vs 46%) and CT enterocolysis (69% vs 30%) [30]. MRE is considered to be the modality of choice for the assessment of small bowel IBD, however it is worth noting similar diagnostic yields between CE and MRE where 400 patients across 10 studies were evaluated. Additionally there is the suggestion that CE may be more sensitive where there is a proximal distribution of mucosal abnormalities[31,32]. Surprising, one study suggested that CE was considered to be preferable to MRE by patients, in spite of the requirement for pre-procedural fasting and bowel preparation [33] The risk of capsule retention limits the use of CE as a first-line diagnostic test and in practice is often performed following radiological examinations [17].

A capsule specifically designed assessment and surveillance of Crohn's disease has been introduced. This features a double head with a combined 336 degree angle of view and battery life which allows visualisation of both the small and large

bowel. The benefit of this approach has yet to be established in clinical practice.

Polyps and tumors

Small bowel tumours are relatively uncommon, usually presenting insidiously with vague symptoms. This diagnosis, however, accounts for 5-7% of those with anaemia and is the most common cause of those with anaemia below the age of 40 years. The detection and estimated prevalence of small bowel tumours have actually increased since the introduction of CE. The most common small bowel tumours, in the order of frequency include; adenocarcinoma, carcinoid, lymphoma, gastrointestinal stromal tumours. Reports on the accuracy of detecting tumours are however conflicting, with some series demonstrating tumours following negative CE. This is perhaps in part due to the speed at which the capsule passes any lesion, with transit the highest in the duodenum [34–36]. CE is now used routinely to assess small bowel polyps for those with known polyposis syndromes such as Peutz-Jeghers and Familial Adenomatous Polyposis.

1.1.4 Alternatives investigations of the small bowel

Imaging of the small bowel can be achieved by a variety of alternative modalities, with the choice determined by the diagnostic/ therapeutic intent. When compared, CE can be seen to offer the least invasive approach to achieving mucosal visualization, **Table 4.** There is good concordance between endoscopic methods and capsule, which means that this is often used as the initial investigation, in order to select those who require intervention. Capsule endoscopy allows the possibility of complete visualization of the small bowel, with a low risk profile, **Table 3**.

Table 3: Risk profile associated with capsule endoscopy

Complication	Risk	Comments
Capsule aspiration	• This describes the risk of aspirating the capsule into the trachea. • Published data suggest that this occurs in up to 0.1% of patients undergoing capsule endoscopy [37]. • There is a male preponderance and an association with increasing age and comorbidities [37]	• Capsule endoscopy should be either avoided in those at high risk of aspiration, or endoscopic placement of the capsule should be considered [38]. • Where the capsule is aspirated, this will usually resolve spontaneously with the patient coughing it up, however, bronchoscopy and retrieval with a Roth net may be required [39].
Capsule retention	• Capsule retention is defined as the failure to pass the capsule endoscope two weeks following ingestion • The risk of capsule retention in the small bowel for all comers is 2%. • The risk of retention rises to 3.6% (95% CI, 1.7%-8.6%) where IBD is suspected [40]. • Where there is established IBD the rate is higher still at 8.2 % (95% CI, 6.0%-11.0%) [40]	• Where the caecum is not visualised during capsule reading, an abdominal x-ray to confirm evacuation after 2 weeks is recommended [38]. • Cross-sectional imaging or successful passage of a patency capsule reduces the risk of retention. • Depending on the location and suspected cause, capsule retention can be managed expectantly or by endoscopic or surgical removal [41]. • The potential long term sequelae of small bowel obstruction or perforation are rare [40].

Interference with implantable devices	• A theoretical risk of CE is interference with pacemakers and implanted cardioverter defibrillators.	• Whilst there is no definitive study to refute this phenomenon and this remains a relative contraindication in manufacturer literature • Large studies including such patients have failed to demonstrate this is a significant clinical problem [42].

Table 4: Investigative modalities of the small bowel

Modality	Description	Advantages	Disadvantages
Barium Studies	• X-ray imaging of the small bowel is performed following the ingestion of contrast medium.	• Quick • Non-invasive • The outline of the luminal wall is defined and large lesions can be identified.	• Unable to assess subtle mucosal pathology • Histological samples cannot be obtained • Therapeutic intervention cannot be performed • Superseded by more advanced modalities.
Magnetic resonance imaging	• MRI imaging following administration of contrast medium	• Non-invasive • Able to assess structural changes in the small bowel. • Allows for assessment of transmural and extraluminal pathology.	• Histological samples cannot be obtained • Therapeutic intervention cannot be performed • The yield for the detection of vascular lesions is low.
Computed Tomography	• CT imaging following administration of contrast medium	• Non-invasive • Able to assess structural changes in the small bowel.	• Histological samples cannot be obtained • Therapeutic intervention cannot be

		• Allows for assessment of extraluminal pathology.	performed • Radiation associated with repeated scans
Sonde Enteroscopy	• A fibre optic bundle, with no manoeuvrability, is introduced into the duodenum from the nasal passage, with the aid of a standard orally introduced gastroscopy. • Once in the small bowel, the Sonde endoscope is propelled forward by small bowel peristalsis [43].	• Direct mucosal inspection possible	• This procedure can take up to 7 hours. • Precise control is not possible. • There is no therapeutic channel, leading to an inability to acquire biopsies or perform therapeutic procedures • Rarely used since the introduction of newer endoscopic modalities
Intraoperative endoscopy	• An enteroscope is introduced either orally or via a surgically formed enterotomy [44]. • The small bowel is manually pleated along the endoscope either at laparotomy or with	• Total examination of the small bowel can be achieved within a single procedure. • Direct mucosal inspection possible • histological specimens can be obtained	• This is impractical for routine examination • Time-consuming • Resource intensive • Invasive • Requires general anaesthesia

	the aid of laparoscopic adjuncts.		
Push Enteroscopy	• The endoscope is pushed along the length of the small bowel • Usually performed using a paediatric colonoscope, so the purchase of specialised equipment is not required • The examination is complete once it is no longer possible to overcome bowel looping.	• Direct mucosal inspection possible • Can be performed under sedation • Quick • Acquisition of histology and therapeutic procedures can be performed. • The diagnostic yield of PE has been shown to be 53%, resulting in a change in management in 45% of patients	• A complete examination of the entire length of the small bowel is not achievable, with the depth of insertion usually limited to the proximal jejunum. • This may be adequate in certain clinical scenarios, one series demonstrated that 36% of causative lesions identified at PE, were in fact within reach of a standard gastroscope.
Balloon Assisted Enteroscopy	• Double Balloon Enteroscopy (DBE) uses an extended length Fujinon endoscope, (working length of 2 meters) coupled with a latex over-tube with an expandable balloon on the	• Direct mucosal inspection possible • Therapeutic intervention is possible • Total examination of the small bowel is possible (although	• Two operators are required for this technique, with an operator required to manage the over tube and balloon inflation. • Training in this

	tip of the scope and at the tip of the over-tube [2]. • While advancing the scope and pulling back with appropriately manipulated balloons it is possible to pleat the small bowel along the scope as it advances forward. • Single balloon endoscopy (SBE) works on similar principles, an over-tube with a single balloon is loaded onto an extended length Olympus endoscope, the tip of the endoscope is used to hook the small bowel.	may require multiple procedures to achieve this) • This procedure is both invasive and uncomfortable and is therefore usually performed under general anaesthetic or deep sedation • Procedures can take up to 90 minutes • There is a small risk of pancreatitis.	technique is required.

Quality in capsule endoscopy

There been increasing recognition of the impact of quality in endoscopy, this has been borne out of data on the completion of colonoscopy, which showed the caecum was only reached in 76.9% of patients [45]. A greater focus on monitoring and training means that the average caecal intubation rate is now over 92% [46]. While colonoscopy has defined measurable parameters which can be related to patient outcomes, this is more difficult to establish in CE. Whilst there have been attempts to define quality parameters in clinical practice these serve mainly as guidance [38]. Factors which are generally considered important quality can be divided into patient and reader factors (**Table 5**).

Table 5: Factors influencing capsule endoscopy quality

Patient factors	**Reader factors**
Indication	Training
Bowel prep	Previous experience
Small bowel transit time	Viewing mode
Incomplete visualization	Reading speed

1.1.5 Bowel preparation

In common with conventional endoscopy, adequate mucosal views are required to make an accurate diagnosis. Complete cleansing of the small bowel is challenging due to the constant secretion of gastric, biliary and pancreatic fluids. This is further compounded by the passive nature of CE, which does not allow for the flushing or suctioning of bubbles and debris.

There are numerous studies examining the impact of purgatives on mucosal cleansing, with conflicting results. Several meta-analyses have pooled the results of these studies and suggest that the use of polyethylene glycol (PEG) is superior to a clear liquid diet alone [14,47,48]. A PEG preparation lends itself as an ideal candidate for intestinal lavage, as this is a transparent solution, the mucosa can be visualised through any residual fluid. Further, it has been proven to be more effective than available alternatives such as sodium phosphate regimes [48]. When the volume was evaluated, there was no benefit in terms of cleansing or diagnostic yield with the use of a 4 litre PEG regime over 2 litres, with the latter being more patient friendly [49,50].

One study examines the effect of the timing of bowel preparation, concluding that there was improved mucosal visibility when using a split-dose regime with the last litre of

PEG given 4 hours pre-procedure rather than 10 hours [51]. A pilot study aimed to overcome the common problem of poor distal views, by using a 'booster' consisting of a single sachet of Picolax administered one hour after the capsule is swallowed, following the consumption of clear fluids without purgatives during the previous day. Although a statistically significant difference in the number of lesions was not demonstrated when compared to a 2L PEG regime, distal views were improved, with the potential to offer a cheaper and more tolerable preparation regime [52].

In selected cases, it may be appropriate to forgo bowel preparation. Where patients are admitted with acute suspected small bowel bleeding it is known that a positive diagnosis is more likely to be made if this test is performed within a short period of the bleeding episode [20,53,54]. As the location of bleeding is the primary point of interest, rather than subtle mucosal pathology, the administration of preparation may result in a delay without a clear clinical benefit.

Antifoaming agents such as simethicone have been proposed as a premedication to disperse bubbles, commonly encountered in the duodenum. This has been trialed with good

effect, having been found to provide superior views of the proximal small bowel compared to a clear liquid diet alone [55]. Where antifoaming agents were combined with bowel preparation an improvement in visualisation was observed [55–57].

1.1.6 Complete small bowel visualisation

The battery life of the first generation of capsules was limited to 8 hours, leading to a proportion of studies where the caecum was not reached. In order to overcome this potential limitation the concept of increasing the transit speed through the gastrointestinal tract with pro-kinetics was introduced. This appears to have a positive effect on completion rates with no deleterious effect on diagnostic yield [58]. However, in the current era of capsules with minimum recording times of 12 hours, routine use of pro-kinetics is rarely required and is usually limited to cases where the capsule has failed to exit the stomach after one hour [9,59].

Conversely, caution must be exercised where the small bowel transit time is very short. This implies the rapid passage of the capsule through the bowel, which with a fixed image capture rate will inevitably mean that there will be incomplete

visualisation of the mucosa. Slower transit times are associated with higher diagnostic yields [60].

1.1.7 Reading settings

A CE study typically results in the acquisition of tens of thousands of images. A clinically significant lesion may be present on just a single frame and could, therefore, be missed. The likelihood of missing lesions can be influenced by the way in which the capsule studies are read. Within the various interpretation software programs there is an option to read one (Single View: SV) Two (Dual View: DV) or four frames (Quad View: QV) as either sequentially or overlapping images. Use of QV overlap mode means that any one image is viewed four times, as it is seen moving across the screen there is a longer exposure to the image compared to SV. The display of the images does, however, occupy the whole screen, requiring greater use of peripheral vision compared to a single central image. In addition the speed at which the images are presented, expressed as frames per second (fps) can be adjusted across a numerical scale.

A study evaluating a single 15 minute video clip containing 60 frames during which there was a pathological lesion was performed in 9 different viewing modes; SV at 10 fps, 15 fps

and 25 fps, DV at 10 fps, 15 fps and 25 fps, or QV at 10 fps, 15 fps and 25 fps. This confirmed that increased speed was associated with an increased chance of missing lesions. The optimal setting was found to be QV overlapping at 10 fps (detecting 51 of the 60 lesions), compared to the single image setting at 25fps which detected just 14 [61]. This is supported by a study examining the most commonly used reading combinations, which found SV at 25fps, had a mean diagnostic yield of 26%, and compared to 45% when reading SV at 15fps. When four images were displayed in the overlap view there was no reduction in accuracy compared to SV at 15fps, even when increasing the speed to QV 20 fps and even QV 30 fps [62].

It is difficult to determine the optimal display mode for CE, as there is an element of variability between readers. However, data to date suggest that slower frame rates and multiple sequential images offer the greatest chance of detecting lesions. In daily clinical practice, a range of speeds should be used. It is appreciated that the passage of a capsule through the duodenum and the proximal jejunum is faster than that through the ileum. It is this phenomenon that results in the ampulla, the only landmark within the small bowel, to be visualised during just 10% of CE examinations [63].

1.1.8 Training and accreditation

CE does not form a part of the mandatory endoscopy training for gastroenterologists in most countries. Those that read capsule are therefore self-selecting, with this skill self-taught by interested physicians in a situation where the need for CE services has arisen. Studies in assessing accuracy and competence in CE are hampered by the fact that there is known significant intra-observer variability, even between experts [64–66]. Further in clinical practice it is not always necessary to identify all lesions present in order to arrive at the same clinical conclusion.

In the UK, the British Society of Gastroenterology (BSG) does not mandate a minimum experience prior to undertaking capsule reading and at present there is no formal accreditation process as for other endoscopic procedures. International guidance suggests an experience of 10- 25 supervised cases should be performed prior to independent practice. These recommendations are largely inferred from secondary findings from studies on training in CE. A Korean study of 12 gastroenterology trainees specifically set out to determine the learning curve in CE. By reading one capsule per week, it was shown that it required 11 weeks to reach kappa coefficients of 0.80 between the trainees and an expert reader [67].

The Mayo Clinic has developed the only CE competence test (CapCT), consisting of three elements; a multiple choice quiz on topics pertaining to the use of CE, video clips and images of pathological findings and finally a formal review of a full capsule case, with interpretation of findings and formulation of a management plan. Scores from each component are summed, with a requirement to reach at least 82% of the total available score of 100 prior to independent practice. When this tool was trialed in a group of gastroenterology fellows, who had no prior teaching in capsule endoscopy but were experienced in flexible endoscopy, it was found that only those with prior experience of 21-35 cases read were able to reach a mean score of 85% after a 4-hour teaching intervention. Experienced readers had a mean score of 91% [68].

Training has been proven to be beneficial in the interpretation of CE examinations. An 8-hour hands-on training course delivered to 268 participants throughout four European countries has been evaluated. This demonstrated that 10 twenty-second videos with a range of findings were read more accurately following the training course. Where readers had previous CE experience the baseline score was higher compared to novices, however an improvement in detection and interpretation was still observed [69].

A background in conventional endoscopy appears to correlate with a better ability to interpret CE. When 10 gastroenterology trainees with experience in flexible endoscopy were compared with 5 medical students, it was seen that they were more likely to pick up pathology, and less likely to produce false positives [70]. This is corroborated by the findings of the European training study, which found prior experience in conventional endoscopy was a predictor of better baseline score, independent of the degree of prior capsule experience[69].

1.1.9 Selection of readers

There is increasing interest in employing nurses as physician extenders in the provision of endoscopy services. The relatively short learning curve and low risk profile make CE particularly appropriate for non-physician reading. Several studies have demonstrated that nurses are able to detect lesions accurately in a 'pre-reading' capacity [71–78].

One study estimated adopting this approach would enable a cost-saving of as much as $324 per case read [78]. Observational studies highlight some differences in the way in which nurses read, with a greater tendency to mark up more lesions of doubtful significance [71].

1.1.10 The impact of fatigue

Fatigue can be defined as a temporary state of reduced mental or physical performance capability. This can be precipitated by a variety of causes ranging from boredom, disrupted sleep to physical or mental exertion. At present there are no studies that have investigated fatigue in the context of CE. Given its repetitive nature, the potential to be physically strenuous and the requirement for visual attention, it is conceivable that fatigue is experienced during endoscopy. Examining this phenomenon is limited by the absence of measurable outcomes, common to all procedures.

Most studies of fatigue in endoscopy have focused on the Adenoma Detection Rate (ADR) in colonoscopy, as this outcome can be expressed numerically, has known demography and is linked to health outcomes.

Table **6** summarises the studies in colonoscopy that investigate the impact of fatigue. These predominantly consist of retrospective analyses examining ADR throughout the day, with the presumption that fatigue increases with time. The findings, on the whole, are inconsistent, perhaps because of confounding factors which cannot be accounted for in retrospective analyses **Table 6.**

The accurate interpretation of CE requires a high degree of concentration. Hundreds of thousands of similar images are viewed sequentially in a continuous video stream, within which abnormal images may be limited to just a few frames. Compared to conventional endoscopy, this is a passive process, with no additional stimulus provided by the patient or from colleague interaction and as such parallels radiology. Studies in radiology have demonstrated a reduced ability to detect pulmonary nodules on CT with fatigue, subtle fractures, as well as impacting upon objective measures such a visual accommodation, which reduces during a long day of reporting[79–81] It is unknown whether fatigue affects the accuracy of capsule endoscopy reporting, although the high intra-observer variability reported in reading studies suggests this is possible. This phenomenon is investigated in Chapter 2.

Table 6. A summary of the studies examining fatigue in colonoscopy

Study	Country	Number of procedures	Methodology	Key findings
Freedman JS et al (2011) [82]	USA Single centre	1486	Retrospective 12 months screening and surveillance	• PDR 47% • No significant difference throughout the day
Lee A et al (2011) [83]	USA Single centre	1,083	Retrospective 4 months Screening and surveillance	• Overall ADR 27.4% • Each elapsed hour in the day was associated with a 4.6% reduction in PDR
Gurudu SR et al (2011) [84]	USA Single centre	4,665	Retrospective 12 months screening and surveillance	• ADR was significantly lower in the PM, if scoping all day • No significant difference in ADR between afternoon and morning if scoping for a single session
Lurix E et al (2012) [85]	USA Single centre	3085	Retrospective 12 months screening and surveillance	• overall 31% ADR • no difference in ADR between am and pm sessions • No difference according to position

Teng TY et al (2016) [86]	Singapore Single centre	533	Retrospective 12 months All outpatient elective colonoscopy	• Overall ADR was 25 % • ADR was 29 % in the AM group compared to 21 % in the PM group • The withdrawal was significantly longer in the AM (12 min) compared with the PM (10 min)
Subramanian S et al (2015) [87]	UK Single centre	2574	Retrospective 12 months	• ADR monitored across a three-session day • No significant difference across a three-session day
Singh S et al (2016) [88]	USA Single centre	2305	Retrospective 58 months	• There was a non-significant trend towards a lower ADR for males in PM • ADR for females was lower in PM than in AM colonoscopies • Females had a prolonged intubation time and a longer procedure time.
Almadi MA et al (2015) [89]	Canada Single centre	430	Retrospective consecutive colonoscopies of 10 gastroenterologists and 2 surgeons	• The overall AD rate was 25.7%. • A threshold of 3 hours of endoscopy time performed before the index colonoscopy was associated with decreased ADR.

Lee CK et al (2015) [90]	Korea Multicentre	457	Prospective 10 months Ambulatory consecutive colonoscopies	• The overall ADR of the study population was 39.7% • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire performed used to test fatigue • The ADR was lower in fatigued endoscopists than non-fatigued endoscopists 25.0% vs. 42.6%
Borda F et al (2014) [91]	Spain Single centre	1,000	Retrospective Ambulatory consecutive colonoscopies	• Overall 30.5% ADR • No difference between am and pm in completion, ADR or PDR
Munson GW et al (2011) [92]	USA Single centre	3846	Retrospective 12 months Average-risk screening	• No reduction in PDR across a three-shift day • No change in mean withdrawal time • Shift 2 had the highest PDR (44.7%).
Lee A et al (2017) [83]	USA Multicentre	259,064	Retrospective 36 months screening and surveillance	• No relationship between ADR and morning vs afternoon endoscopy • No relationship between ADR and the number of procedure performed before or procedure difficulty.

1.1.11 Rapid reading algorithms

There has been an attempt to exploit advances in information technology to aid the interpretation of CE, by both enhancing the detection of lesions and by reducing the number of normal images reviewed. Given that the movement of a capsule through the bowel is non-linear, multiple duplicate images are captured. Removal of such images from the reading stream offers the possibility of dramatically reducing reading times. Several software algorithms have been developed to remove redundant images and only present clinically relevant frames. In clinical practice however the success of this approach has been mixed. Whilst reading time is undoubtedly reduced, some studies quote an unacceptably high lesion miss rate. This is likely to be due to the capsule software being unable to differentiate between subtle mucosal pathology and normal mucosa. The rapid presentation of non-sequential images may also be harder to for the viewer to visually process causing relevant images to be overlooked. It is worth mentioning that these studies determine success of their software by number of lesions detected, the so-called diagnostic yield. Whilst this allows an objective measurement in performance, it is not the most transparent endpoint. It is difficult to be certain of the

clinical impact of detected lesions and indeed there is not perfect concordance between finding detected on CE and DAE.

The PillCam RapidView software offers Quickview, this allows the proportion of images excluded to be determined by the reader. Several studies have demonstrated reasonable accuracy in the detection of major lesions [93–95], **Table 7**. When compared to alternate time-saving strategies this software enhancement proves to be less promising. Reading in SV or DV at 20fps was more accurate than the use of Quickview, although not as rapid [96]. Further, it has been demonstrated that viewing alternate frames, by adopting the four image sequential view and covering half the screen with a piece of paper led to a lower lesion miss rate compared to the use of Quickview. Implying that the selection of excluded frames was less accurate than random exclusion of half the images [97].

Similarly, the OMOM similar picture elimination software has three modes, with increasing proportions of removed images. While each mode reduced reading times, only Mode 1, with the least images excluded had a sensitivity greater than 85%, saving a mean reading time of 9 minutes [98].

The equivalent EndoCapsule software has been evaluated in a single study comprising of 70 CE cases. This utilised two modes Express Selected, where repeat images are removed and Auto Adjust, where the repeated images are maintained within the viewing stream but are viewed at an increased speed. One lesion out of the 40 known lesions was missed in either time-saving mode, leading to an accuracy of 97.5% [99]. This software has been recently superseded by Omni-mode, which claims to be able to reduce the images displayed by 65% through the 'intelligent' removal of repeated as well as overlapping images. To date this has been studied in a Japanese multicentre trial, which showed the software was able to correctly remove images whilst maintaining all the pre-identified major lesions in 40 selected cases [100]. The impact of this software in daily clinical practice is investigated in Chapter 3.

Table 7: A summary of the time-saving software in the interpretation of small bowel capsule endoscopy

Study	Country	System	Study Design	Summary of results
Saurin et al (2018) [101]	French (multicentre)	MiroCam Express View	• Prospective evaluation of 83 patients across ten centres, with gastrointestinal bleeding • Gold standard reading determined by consensus.	• Mean reading time reduced from 39.7 minutes to 19.7 minutes • Standard reading and a sensitivity of 93.3% for significant lesions, while Express View 82.2%
Hosoe et al (2016) [100]	Japan (Multi centre)	EndoCapsule: Omni-Mode	• 40 pre-selected cases (based on the presence of lesions) • Each case read twice in Omni-Mode and twice in Normal-Mode	• Reduction in average reading time from 75 minutes to 27 minutes. • 65% reduction in displayed images • Sensitivity of 87%
Xu Y et al (2014) [98]	China (single centre)	Omom: Similar Picture Elimination	• Retrospective study of 148 capsule studies. • Read in four modes Normal, Level I, Level II, Level III and Level IV • Each case read by four independent endoscopists	• Reading time reduction of 25.1-55.0% compared with Normal-Mode. • Normal: sensitivity of 93.8% • Mode I: sensitivity of 87.7%

				• Mode II: sensitivity of 77.8% • Mode III: sensitivity of 70%
Halling M et al (2014) [102]	Denmark (Single Centre)	Pill Cam: QuickView	• Analysis of 12 video clips with findings • 40 capsules of patients with suspected Crohn's disease	• Quickview missed 40% of ulcers seen in the normal viewing mode • This effect is pronounced for terminal ileal lesions
Subramanian et al (2012) [99]	UK (Single centre)	EndoCapsule: Express Selected/ Auto Adjust	• 70 capsule cases • Read in three mode, Normal (15 fps), Express selected + Overview, Adjusted mode + Overview • Each case read by two independent endoscopists	• Normal: sensitivity of 100%, taking an average of 45 mins • Express Selected: sensitivity of 97.5%, an average 19 mins • Auto-Adjust sensitivity of 97.5%, an average 34mins
Kyriakos et al (2012) [96]	Greece (Single Centre)	Pill Cam: QuickView	• 100 capsule studies pre-selected cases • Cases read in 5 different modes, Normal at 10 fps, Normal at 20 fps, Normal-Mode with two images at 20 fps, Automatic mode 10 fps, QuickView at 3 fps	• All time-saving modes were faster than reading in Normal-Mode at 10 fps • Best compromise between speed and accuracy is Normal-Mode at 20 fps, with either a single or dual image.

Saurin JC et al (2012) [95]	French (multicentre)	Pill Cam: QuickView	• 106 patients recruited across 12 centres • Quickview vs Normal-Mode reading	• 94% of significant lesions were identified • Mean reading time of 11.6 mins using QuickView
Koulaouzidis A et al (2012) [94]	UK (Single Centre)	Pill Cam: QuickView	• Retrospective review of 106 cases • Normal-Mode vs Quickview vs Quickview with BM	• Over 50% of ulcers missed in cases of suspect Crohn's using QuickView • 64% of potential/bleeding lesions were detected in the context of overt/occult bleeding
Shiotani A et al (2012) [103]	Japan (Single Centre)	Pill Cam: QuickView	• 100 capsule studies read in QuickView vs normal reading • One nurse, two trainees and one experienced reader	• Unacceptable miss rate • Miss rate was greatest in physicians with limited experience.
Hosoe N et al (2012) [104]	Japan (Single Centre)	Pill Cam: QuickView	• 45 capsule studies • Gold standard reading= two experienced readers • 3 trainees with no prior CE experience read in Normal-Mode, Automatic mode and QuickView.	• Reduced reading time in automatic and QuickView compared to Normal-Mode • 179 missed lesions when using QuickView

Westerhof et al (2009) [97]	Netherlands (Single centre)	Pill Cam: QuickView	• 200 cases included • First 100 read in Normal-Mode and then only alternate images • Second 100 read in Normal-Mode then with QuickView	• Normal-Mode average reading time of 17 mins • Miss rate of 4% when viewing alternate images. • Average reading time of 10 mins • Miss rate of 13% with QuickView. Average reading time of 4.4 mins

1.1.12 Lesion characterisation software

The use of advanced imaging has become commonplace in the identification and characterisation of lesions during endoscopic procedures. This concept has been replicated within the PillCam capsule endoscope with the adoption of Flexible Spectral Colour Enhancement (FICE). FICE is a post processing visual enhancement technology, which by using proprietary software algorithms converts white light images to a restricted range of wavelengths in order to enhance the mucosal surface pattern. Perhaps due to the lack of control and manoeuvrability afforded by flexible endoscopy, the results of CE FICE have been disappointing. Evaluation across studies showed there was no increase in the detection of lesions, although some settings demonstrated improved lesion delineation [105]. The evidence for Blue Mode Imaging is still emerging [106,107].

The Suspected Blood Indicator (SBI) is a tool available within the various capsule software programs. This highlights frames where an excess number of red pixels have been identified and may, therefore, represent a bleeding lesion, **Figure 1**. This function is activated by merely selecting the SBI mode within the reading software, these results in highlighted frames or regions along the scroll bar. In the context of

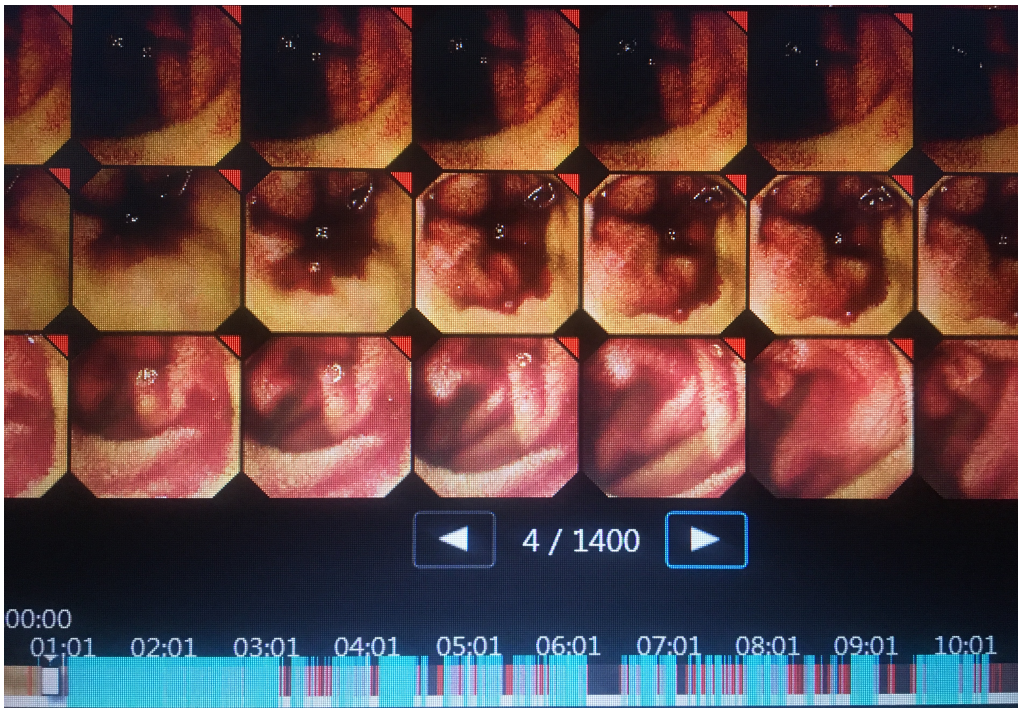
gastrointestinal bleeding, this should obviate the need for a complete review of the capsule case, allowing the reader to quickly identify lesions and their location. Studies in clinical practice have however been disappointing, with reported sensitivities as low as 20% [108–110].

A meta-analysis of 16 studies comprising of 2049 patients, confirmed a high sensitivity of 98.8% in the detection of actively bleeding lesions. This fell to a sensitivity of just 55.3% and a specificity of 57.8% in the detection of lesions with bleeding potential that were not actively bleeding during the examination [111]. It is noteworthy that the SBI has been trialled exclusively using the PillCam capsule software, its utility in the alternative systems is unknown.

One study attempted to understand the limitations of the SBI with the passage of a capsule through an experimental small bowel model. Red lesions were displayed on backgrounds of varying colours, commonly encountered in clinical practice [112]. This demonstrated a significantly improved likelihood of detecting lesions superimposed on a pale magenta or yellow background as compared to pale yellow or brown. As this is a factor that cannot be influenced by the operator it remains a major limitation of this approach.

The accuracy of the SBI function is insufficiently accurate to allow its use as a time-saving technique in clinical practice. Instead it could be considered as a useful adjunct to ensure no lesions have been missed following initial reading and interpretation.

Figure 1: Images highlighted by the Suspected Blood Indicator



1.1.13 Artificial Intelligence

Artificial intelligence (AI) refers to the ability of computer systems to mimic intelligence to perform tasks which are traditionally limited to humans. This is very much an evolving area with huge potential within medical field. Within endoscopy this approach is already showing promise, with AI detecting almost a third more adenomas during colonoscopy than visual diagnosis [113] Further, computer-aided diagnosis can be used to differentiate between hyperplastic and adenomatous polyps with an accuracy superior to that of endoscopy trainees [114]. In CE challenges to AI are posed by the uncontrolled movement of the capsule at varying velocities within the small bowel and well as the inability to overcome debris within the lumen. More significant is probably the decision as to what is considered to be an abnormality, given the known intraobserver variability in conventional reading. Using a dataset of 4206 capsule abnormalities, one group has been able to develop an algorithm that detects 99% of lesions in just over 5 minutes, compared with 74% using conventional reading [115] Further work is required to validate this in daily practice.

Hardware advances in capsule endoscopy

In order to be able to achieve greater capabilities with CE, it is necessary to improve the hardware of the currently available models. There are multiple prototype capsules in development, with the primary areas of interest including increased visualisation, capsule manoeuvrability, the ability to acquire biopsies and the ability to deliver therapy.

1.1.14 Increased visualisation

The standard small bowel capsule endoscope uses a single lens, acquiring images in the forward view. CapsoCam (CapsoVision, USA) is a novel capsule which is able to offer a panoramic view, by means of four cameras placed to allow a 360-degree lateral view. The capsule measures 11 mm by 31 mm and has a battery life of 15 hours.

Where the CapsoCam has been compared to PillCam it was noted that a greater number of lesions were detected, there was however good concordance in results with both systems. As might be expected, the reading time of the CapsoCam was longer, owing to a greater number of images. In another study, positive identification of the ampulla, the sole landmark of the small bowel, was measured. It was found that within the 33 patients studied the ampulla was visualised in 70%,

which compares favourably to the reported rate of ampulla visualisation of 10-44% [7,8]. The prototype MicroBall is a further extension to this concept, with 6 cameras contained within a spherical capsule, studies as to its utility are awaited.

Where CE is performed outside of the small bowel, multiple lenses are required to capture a greater field of view as necessitated by the larger luminal diameter. The second-generation PillCam CCE-2 (Medtronic) is a double-ended capsule with each lens having a 172^{o} angle of vision. An adaptive frame rate which ranges from 4 fps whilst stationary to 35fps when moving, avoids excessive image acquisition [116].

Similarly the oesophageal capsule PillCam ESO3 (Medtronic) attempts to overcome the rapid passage through the oesophagus by using a double-headed capsule with an angle of vision of 174^{o} at each lens. The battery life is reduced to just 20 mins to allow the acquisition of images at a rate of 35 fps during the rapid transit through the oesophagus [117].

1.1.15 Manoeuvrability

One of the major limitations of CE is the lack of control and manoeuvrability. CE locomotion is solely attributable to GI

peristalsis and varies along the course of the GI tract. This constraint is most apparent with the stomach when attempting to use CE in the upper GI tract. The capacious stomach means that without the ability to direct the capsule, the majority of the mucosal surface would be missed. CE control is also a pre-requisite for future capsule which may be able to deliver the therapeutic intervention.

Whilst there are several prototypes for manoeuvrable CE, the most success has come from the use of magnets. By inserting magnetic material within a CE and using an external magnet, it is possible to manipulate movement. Research in this field has exploded, with the first Magnetically Assisted Capsule Endoscopy (MACE) performed as a self-experiment in 2010, with over 4000 procedures undertaken in the intervening years (**Table 8**). The greatest experience has originated from China, where due to its popularity a clinical consensus statement has been written top guide its use [118]. MACE systems can be divided into those that are manually controlled with a handheld magnet or those controlled by means of a robotically controlled external magnet.

Manual MACE systems

In 2010 the first MACE was developed by modifying a colon capsule by inserting a stack of magnetic discs beneath one of

the capsule domes of the 1st generation PillCam Colon [119]. Whilst there were no adjustments in the dimensions of the capsule, the addition of magnets caused a doubling in weight, from 3.5g to 7g. The capsule was controlled externally by a handheld paddle (10 cm x10cmx 3cm), specifically designed for this study. Forces of up to 256g/cm2 can be achieved between the magnets in the capsule and those in the paddle. Images are transmitted via sensors placed on the patients' torso, to an external receiver and can be viewed in real-time.

This model was the first self-trialled by the study author, proving that the concept was indeed feasible. Coexistent use of a gastroscope meant that capsule movement and response to the magnet could be directly assessed [119]. This prototype has assessed in a larger study of healthy volunteers, demonstrating that on average the capsule can be held at the GOJ for longer to its contemporary oesophageal capsule, the ESO2, (111-1514 seconds versus, 47-1474 seconds). The GOJ, however, was adequately visualised less often with the MACE (23% vs. 73%), perhaps attributable to the lower frame rate of the modified capsule compared to the oesophageal capsule [120]. Similarly, promising results were noted on gastric examination, with over 75% of the gastric mucosa visualised

in 7 of the 10 patients examined. This CE was an experimental model and is not commercially available.

Using similar principles, the Intromedic (Seoul, South Korea) have developed the MiroCam-Navi from the addition of magnetic material within their standard small bowel CE**.** As with the small bowel model, images are transmitted via electric field propagation rather than radiofrequency transmission. It is because of this that the capsule can remain small in size (10.5mm x 15.5mm) and lightweight (4.75g) despite the addition of magnets. Control is achieved by a handheld magnet. Images are sensed via a sensor belt and are transmitted via Wi-Fi to a computer **Figure 14**.

This system has been evaluated in 12 ex- vivo porcine models, where it was possible to manipulate the movement of the MACE in order to identify 6mm beads sewn onto the mucosal surface [121]. A total of 90 beads were placed, with the number of beads within an individual model variable, with 2 stomachs having no beads to avoid bias. The use of different coloured beads avoided the re-identification of previously identified beads. MACE was able to 88% of the beads, compared to 89% using conventional endoscopy. The most common location of missed beads in both modalities was in the gastric body. It is

noteworthy that in this and all studies using MACE systems that the MACE has a longer procedural time than OGD, which may influence findings given previous studies of conventional endoscopy which shows a relationship between mucosal inspection time and lesion detection [122].

A series performed in 26 healthy volunteers showed the combination of position change and strategic placement of the handheld magnet enabled visualisation of the major upper GI landmarks, although with inferior quality in the proximal stomach [123]. A nasogastric tube was inserted to help differentiate between the fundus and the antrum, which can be more easily, confused that when undergoing conventional endoscopy. Control of the capsule was defined as the ability to hold at the capsule for at least a minute at 5 predefined landmarks, this was achieved in 88% of instances. Optimal positioning within the stomach to achieve visualisation has been informed by previous CT modelling studies [124].

In a study of 49 patients with IDA who underwent MACE combined with small bowel CE in a single procedure, were more likely to have causative pathology identified than with conventional endoscopy [125]. This included the identification of focal gastric lesions such as angioectasia and polyps.

Whilst manoeuvrability has been demonstrated, this is in part dependent on location. The force exerted on the MACE is not sufficient to overcome GI forces, with an inability to translocate the capsule upwards within the oesophagus against the direction of peristalsis or into the pylorus in order to reduced gastric transit times [126].

Robotic MACE systems

In parallel with the introduction of handheld systems has been development of robotically controlled systems. A collaborative partnership between Olympus (Japan) and Siemens (Germany) resulted in an 11mmx 31mm capsule with dual cameras and a central magnetic component. Steering of the capsule is achieved by a large (1m x 2m) external magnet system, within which the patient lies **Figure 2**. Control of the magnet is electronic, with the operator using a control panel at a designated workstation. Images obtained from the capsule can be viewed in real-time alongside information as to the orientation of the capsule.

This MACE system was the first used in patients, in a feasibility study of 24 patients and 29 volunteers who had undergone an OGD prior. This demonstrated that it was possible to achieve

comparable views of the distal stomach, with the fundus a relative blind spot, seen adequately in just 73% of patients. Approximately half of the UGI lesions diagnosed in this study were identified by both modalities, and an additional six were seen at OGD only and interestingly and additional 10 by MACE only[127].

These findings were confirmed in a larger cohort of 61 patients [128]. When lesions diagnosed a MACE were compared to those noted at gastroscopy there was a 58% concordance, with an additional 31 lesions diagnosed at MACE only. It is noted that the majority of these lesions could be considered to minor and would not ultimately affect patient care. A potential confounder in these findings is the performance of OGD prior to the MACE, sometimes with the procurement of biopsies.

The largest study with this technology involved 189 symptomatic patients, who underwent MACE prior to OGD [129]. Pathological findings were divided into major (those requiring biopsy or therapy) and minor lesions, with MACE having a specificity and sensitivity for major lesions of 94 % and 62% respectively. The importance of position change was established, with a left lateral position offering the best views of the cardia, fundus and body, whilst the right lateral position

best visualised the antrum and pylorus. The mean examination time was 11 minutes, compared to the 6 minutes required to complete a gastroscopy.

Using a similar concept, Akon technologies have developed a 12mmx 28mm capsule has a viewing dome at one aspect and magnetic discs at the other. A C-arm magnet, with 5 degrees of freedom, is robotically controlled either under direct control using a joystick or using an automated programme. Real-time review of the images is via a remote workstation **Figure 2**.

A pilot study using the NaviCam Capsule (Akon Technologies) in 34 healthy volunteers demonstrated feasibility of this technique. A premedication of water and a carbon dioxide producing powder was used to achieve gastric distention. Improved views were attempted with additional powder given during the procedure. Patient movement was not employed. The antrum, body and incisura were seen in 100% of patients, with the cardia and fundus seen in 82.4 % and 85.3% respectively. A larger study of 68 patients demonstrated 78% concordance in lesion detection between MACE and OGD [130]. The forces exerted on the capsule appear to be more effective than those of a hand-held magnet, with the AKON system able

to translocate MACE across the pylorus and reduced pyloric transit time from 58.4 minutes to just 4.69 minutes [131].

This MACE system has also been trailed in a paediatric population, with a mean age of 12 years old. All 84 children were able to swallow the capsule and change positions, in order to allow for a complete gastric examination [132].

A prototype MACE has also been used in the colon, during which movement of the capsule could be manipulated an external magnet in 78.8% of patients [133]. Range of movement was confirmed by means of simultaneous colonoscopy. Whilst this study was not designed to determine lesion detection, the possibility of inspecting colonoscopy blind spots, such as behind folds, makes this technique attractive.

Figure 2: Robotic MACE systems

Top: Olympus Siemens system [127]
Bottom: Akon system [130]

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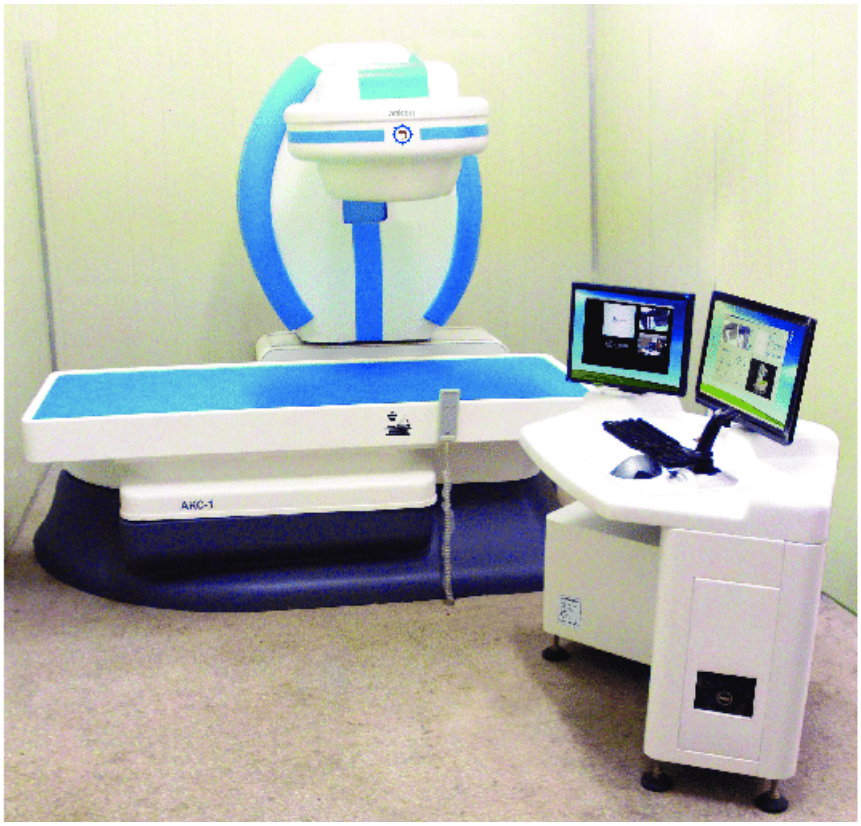


Table 8: A summary of in-human MACE studies

Authors	System	Number of Patients	Study design	Country	Findings
Swain et al (2010) [119]	Modified PillCam Colon	1	Pilot MACE with simultaneous OGD	Single (UK)	• First in human proof of concept study • Modified capsule endoscope could be controlled using an external magnet.
Keller et al (2011) [120]	Modified PillCam Colon	10	Case series Healthy volunteers MACE vs esophageal capsule	Single centre (Germany)	• Increased esophageal transit, when under magnetic control • Unable to translocate the capsule up and down the esophagus • No complications
Rey et al (2010) [127]	Olympus-Siemens	53	Case series OGD followed by MACE	Single centre (France)	• 29 healthy volunteers and 24 patient s • 30 lesions identified, of which 14 identified by both modalities • 6 lesions diagnosed by OGD only • 10 lesions diagnosed by MACE only

Rey et al (2012) [128]	Olympus-Siemens	61	Patient series MACE followed by OGD	Single centre (France)	• Two patients excluded as unable to swallow the capsule • A total of 108 lesions detected, of which 66 detected by both modalities • 14 lesions missed by MACE • 31 lesions missed by OGD
Liao et al (2012) [134]	Akon NaviCam	34	Case series Healthy volunteers	Single centre (China)	• Cardia and fundus identified as potential blind spots, with complete visualization in 82% • Mean examination time 43.8 mins
Qian et al (2016) [130]	Akon NaviCam	60	Case series Only patients with positive findings/ incomplete views underwent OGD.	Single centre (China)	• Average examination time of 42 minutes • Optimal positions for visualizing landmarks established • 13 patients also had and OGD • 100% agreement between MACE and OGD findings
Zhou et al (2015) [130]	Akon NaviCam	68	MACE followed by OGD	Single centre (China)	• Two patients excluded, as declined to undergo OGD • 91.2% agreement in gastric findings

Denzer et al (2015) [129]	Olympus-Siemens	189	Case series MACE followed by OGD	Single centre (France)	• Three patients were excluded from analysis due to oesophageal impaction of the capsule and one because of an inability to swallow the capsule. • Per patient accuracy in lesion detection of 90.5% and negative predictive value of 95.2%
Liao et al (2016) [130]	Akon NaviCam	350	MACE followed by OGD	Multicentre (China)	• MACE missed lesions seen at OGD in 10 patients • All missed lesions were focal (ulcers/polyps/SMT) • One episode of capsule retention, secondary to a duodenal peptic stricture
Rahman et al (2016) [123]	MiroCam Navi	26	Case series Healthy volunteers MACE followed by OGD	Single centre (South Korea)	• Examination time of 24 minutes • The capsule could be held for at least one minute at pre-defined stations in at least 88% of cases • Agreement in 8 of the 9 lesions diagnosed on OGD • No complications

Hale et al (2016) [126]	MiroCam Navi	120	RCT to determine steering across the pylorus 60 magnetic steering vs 60 passive	Single centre (UK)	• Mean BMI 27 • No difference in transit time between passive and magnetically assisted translocation into the small bowel • No complications
Ching et al (2018) [125]	MiroCam Navi	49	Prospective cohort MACE including small bowel, followed by OGD	Single centre (UK)	• Patients undergoing investigation for IDA • Pathology beyond the duodenum identified in 34.7% • MACE had higher diagnostic yield for lesions which may cause anaemia
Jiang et al (2018) [131]	Akon NaviCam	200	100 patients underwent MACE with steering into the duodenum, compared with a historic cohort	Single centre (China)	• Reduced the pyloric transit time with the aid of magnet control • It was possible to steer the capsule into the duodenum in 59% using magnetic control, compared to 17% passively.
Zhou et al (2018) [131]	Akon NaviCam	3182	Retrospective analysis. Only patients with positive findings	Multicentre (China)	• Asymptomatic patients undergoing gastric cancer screening • 62% patient were male • Mean age 44.8 years

			underwent OGD.		• 27 case of capsule retention, none of which required intervention • 7 patient advanced gastric cancer diagnosed by MACE
Qian et al (2018) [132]	Akon NaviCam	10	Self-controlled comparison	Single centre (China)	• 10 patients awaiting ESD for endoscopically diagnosed superficial gastric cancer • MACE identified 11 of the 12 gastric lesions • The missed lesion was located in the cardia • Able to correctly identify location and lesion size
Qian et al (2018) [135]	Akon NaviCam	84	Case series Paediatric population MACE including small bowel, followed by OGD	Single centre (China)	• Mean age of 12 years old • All children were able to swallow the capsule • 100% sensitivity in the detection of gastric lesions • The sensitivity of 96% compared to radiological imaging (52%) • No complications

1.1.16 Conclusions and aims of thesis

This literature review demonstrates the rapid development in CE technology since its introduction in 2000. Despite this CE is still predominantly performed for the investigation of small bowel disease and is hampered by the time-consuming review of multiple images.

Possible advances in the way in which CE is performed will be investigated in this thesis. This will include trying to determine whether the way in which CE is interpreted can be optimised through determining whether fatigue plays a role in routine reading. Here we aim to explore the number of CE videos that can be read before there is a reduction in accuracy of lesion detection.

New software that aims to reduce reading times will also be assessed to determine whether lesion detection is non-inferior to standard reading.

The use of MACE to diagnose oesophageal pathology will be explored by comparing the presence of Barrett's Oesophagus and varices on MACE and conventional OGD.

Research questions

Thesis strategy

Three projects were designed and performed in order to answer the questions posed by this thesis.

Study 1: Does accuracy in small bowel capsule endoscopy interpretation decline with fatigue?

Study 2: Can Omni-Mode reduce reading times whilst maintaining accuracy?

Study 3: Can Magnetically Assisted Capsule Endoscopy accurate diagnose oesophageal pathology?

Chapter2:. Does accuracy in small bowel capsule endoscopy interpretation decline with fatigue?

Abstract

2.1.1 Introduction

Capsule endoscopy interpretation requires the review of many thousands of images, with lesions limited to just a few frames. It is not known whether fatigue influences accuracy in capsule reporting. In this study, we aim to determine whether lesion detection declines according to the number of capsule videos read.

2.1.2 Methods

32 participants, 16 of which were novices and 16 experienced capsule readers took part in this prospective evaluation study. Six capsule studies, of equal duration and with a variety of lesions, were independently read by two expert readers to form a 'Reference Standard' reading. Participants read all six capsules in a randomly assigned order, within a single sitting. Baseline Psychomotor Vigilance Test and Fatigue Score were recorded prior to commencing. These measurements were repeated after every two capsule videos read. Changes in

lesion detection and measures of fatigue were assessed across the duration of the study.

2.1.3 Results

Mean agreement with the 'Reference Standard' reading was 48.3% (SD: 16.1), and 21.3% (SD: 15.1) for the experienced and novice readers respectively. Lesion detection declined significantly after reading a single capsule case among experienced readers ($p= 0.01$). By the 2nd case, there was no significant difference in accuracy between Experienced and Novice readers. Fatigue Scores increased with the number of cases read, however measures of fatigue did not correlate with reading accuracy.

2.1.4 Conclusion

This study demonstrates that reader accuracy declines after reading just one capsule study. This has potential implications for clinical practice, with the experienced readers in this group reporting their normal practice is on average of 3.5 capsule readings per clinical session. Subjective and objective measures of fatigue were not sufficient to predict the onset of the effects of fatigue.

Introduction

Fatigue, defined a temporary state of reduced mental or physical performance capability, is commonly experienced phenomenon in daily life. This has been linked to an increased risk or error in a variety of tasks, from simple exercises such as manufacturing or administrative mistakes, to vehicle accidents [136]. In high-risk industries, such as the aviation sector, fatigue is monitored with processes in place to mitigate its potential effect [137–141].

There is some evidence to suggest that this phenomenon affects performance in the medical field. Studies have demonstrated decreased accuracy in fracture detection amongst radiologists after a full day of reading, prescribing errors after prolonged working hours and needle stick injuries associated with long shifts [142–144]. In the field of endoscopy several retrospective studies suggest reduced adenoma detection rates associated with procedures performed during the afternoon, when compared to morning sessions [83,86,88,145,146].

The accurate interpretation of capsule endoscopy requires a high degree of concentration. Hundreds of thousands of similar images are viewed sequentially in a continuous video stream,

within which abnormal images may be limited to just a few frames. Compared to conventional endoscopy, this is a lengthy and passive process, with no additional stimulus provided by the patient or from colleague interaction. It is unknown whether fatigue affects the accuracy of lesion detection in CE interpretation and whether this influences the diagnostic ability of this investigative modality. The aim of this study is to determine whether CE lesion detection decreases with increasing videos read.

Aims

The primary aim of this study is to determine whether CE lesion detection decreases with increasing videos read.

Secondary end points include determining whether fatigue can be measured using objective tests such as the PVT, whether readers change practice in accordance with fatigue and whether there is a difference in the impact of fatigue based on reader experience.

Methods

2.1.5 Study design

This was a prospective evaluation study. Ethics approval was received from the Faculty of Medicine and Health Sciences Research Ethics committee, University of Nottingham (EV07102016 16074). Written informed consent was obtained from all participants. A baseline questionnaire to establish participant characteristics was undertaken. Participants were asked to read six consecutive CE cases, with measures of fatigue taken throughout the study period, see Figure 4.

2.1.6 Participant selection

Participants were invited based upon meeting the eligibility criteria of either the Novice Reader (NR) Or Experienced Reader (ER) Groups. NR were physicians or nurses who had either little or no prior experience in the interpretation of CE but had experience of performing or assisting in conventional endoscopy of at least 12 months. ER were practitioners trained in CE interpretation and accredited for independent practice in their own institution. Recruitment took place within the UK, with readers across nine NHS trusts including both community hospitals and referral centres.

2.1.7 Sample size calculation

A sample size of 16 participants was required to be able to detect a 6% reduction in accuracy from the first and last case read with 80% power, assuming a standard deviation of differences of 8%, using a paired t-test with a 5% two-sided significance level. So that we could explore the differences between ER and NR, two groups of 16 participants were recruited. This gave a total study population of 32, exceeding the number required to detect a 6% reduction in accuracy across the study population, with a 90% power. The choice of a 6% reduction was an arbitrary figure, given there is no clear consensus as to what is deemed an optimal accuracy in capsule reading. An assumption was made that the agreement of ERs with the RS would reach 80% and a drop below this level could be considered as significant.

2.1.8 Capsule case selection

CE cases were selected from a database of historical cases performed at Nottingham University Hospitals for clinical purposes. In order to ensure that each video was of similar complexity and therefore comparable, videos were chosen according to the number and type of lesions detected. Where necessary, these anonymised cases were trimmed to ensure that they were of the same length, each with a small bowel

transit time of 3 hours. In order to exclude bias caused by case complexity, reading order was randomised between participants with the aid of a randomisation table. As such each video was read in each reading order an equal number of times.

A Reference Standard (RS) Reading for each CE video was derived from the independent, non-consecutive, interpretation of two experienced capsule readers. Each video was read at a speed between 10-14 frames per second [61]. The time code at which any identified lesion was first and last visible was noted, in order to establish the range at which a participant could correctly record a time code. Each lesion was scored as to its clinical significance according to the P-classification [147]. Discrepancies between identified lesions were resolved by consensus. Additionally, two lesions that were identified by participants, but not seen by the reference readers were included to formulate the most stringent RS reading possible. In all, 92 individual lesions were identified across the six cases (range 6- 26) which included commonly encountered lesions such as angiodysplasia, ulcers, erosions, lymphangiectasia and a diverticulum. The design of this study meant that single distinctive lesions, such as tumours, could not be included as this would skew the analysis. This seems reasonable give

tumours are not commonplace. For the same reason normal studies with no abnormal findings could not be utilised.

2.1.9 Fatigue scores

In order to measure the subjective experience of fatigue, participants were asked to rate their experience on a ten-point visual analogue scale. The Fatigue Score (FS) ranged from 1-10, where 1 represented completely alert and 10 extreme fatigue. This was performed prior to commencing the study and the repeated after every two capsules read Figure 4.

2.1.10 Psychomotor Vigilance Test

In order to obtain an objective assessment of fatigue, an abbreviated 3-minute Psychomotor Vigilance Test (PVT) was utilised, **Figure 3**. A validated personal computer form of this test was used on a laptop (Lenovo ThinkPad), with a 13-inch screen and using a gaming mouse, as per developer recommendations [148]. Participants were asked to press the mouse button as quickly as possible in response to a visual stimulus. The software used was able to measure response time to an accuracy of 10 milliseconds. A 3-minute trial run was performed before the baseline PVT exercise, to allow for familiarisation with this software.

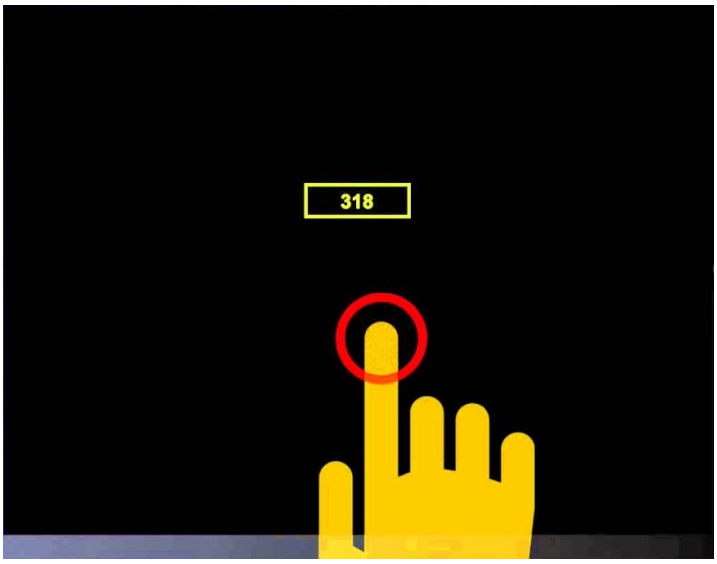


Figure 3: The appearance of screen during Psychomotor Vigilance Test

2.1.11 Capsule readings

All CEs were performed using the Olympus Endocapsule-10 system and were read using proprietary software displayed on a laptop with a 13-inch screen (Lenovo ThinkPad). A demonstration of the capsule interpretation software and operating features were given. Where the participant had no CE experience, a brief face to face tutorial in CE interpretation with the use of example images were delivered. All CE videos were viewed in the single image view mode, with the use of rapid reading software algorithms forbidden. Participants were given the freedom to choose speed range at which they viewed each CE case; this allowed a variation of 3 fps. There were five possible speed ranges: 7-10 fps, 11-14 fps, 15-

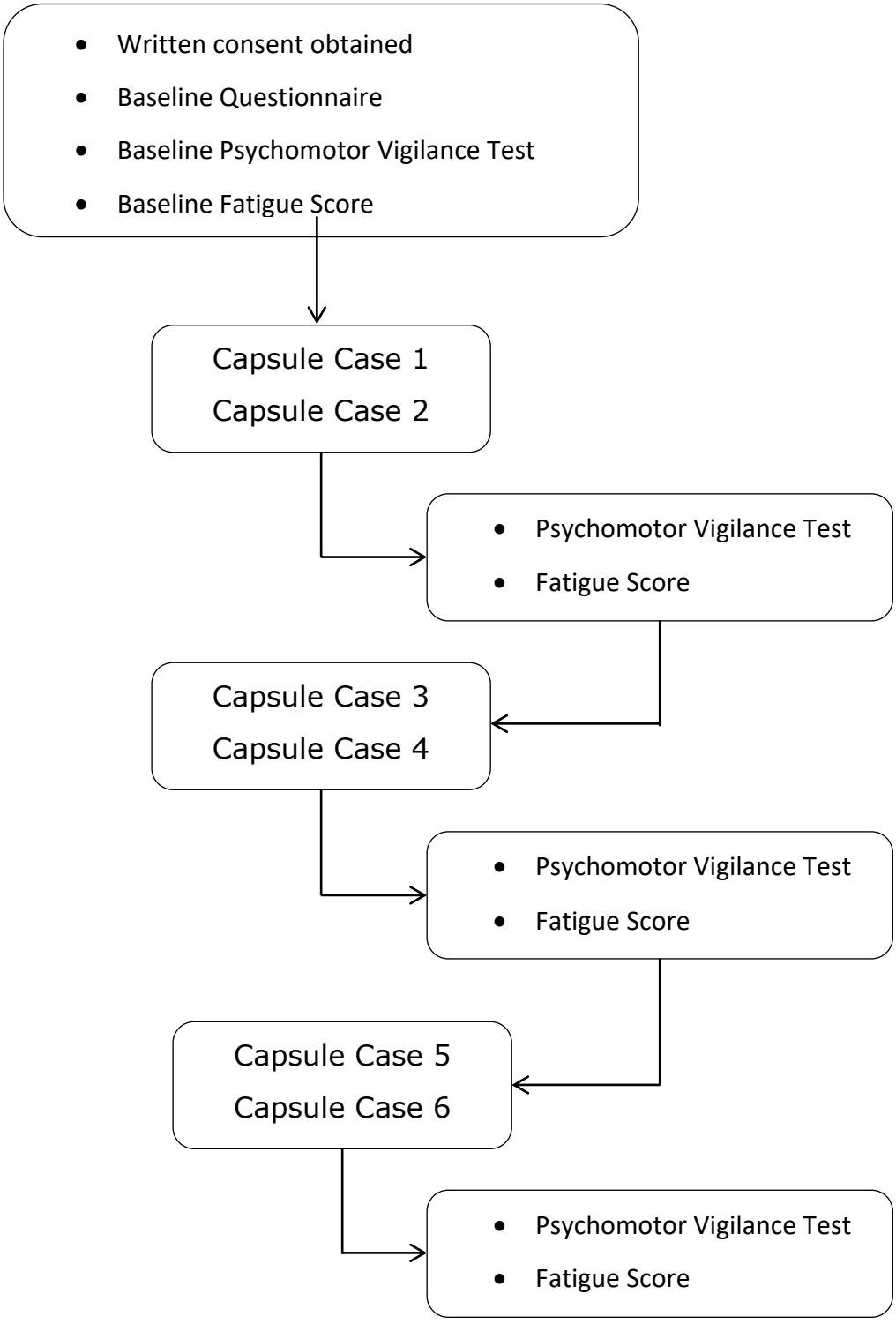
18fps, 19-22 fps, 23-26fps. The speed range could be changed in-between cases as per reader preference.

The study was performed as the first task of the day in order to mitigate against potential variability in fatigue caused by any preceding tasks and enable results to be comparable, although this may not be normal practice for all readers. The study was undertaken at a location chosen by the participant at their local institution so that no travel in excess of their normal daily routine was incurred. A quiet room was used in all cases, listening to music was not permitted and lighting was determined by participant preference. A prerequisite for participation was the ability to commit at least six hours without interruption or co-existing clinical commitments. However, no limit on the time taken to complete the study was imposed. Participants were supervised by the principal investigator, to allow for troubleshooting of any software problems as well as ensuring adherence to the protocol.

Clinical Record Forms (CRF) with the CE video findings were completed contemporaneously. The time taken to read each video was recorded to the nearest minute by the participant. The reading time was defined as the time taken to read the entirety of the study from the first pre-marked duodenal

image until the last pre-marked final image. This time included the time to mark up and review any detected lesions, but excluded the time taken to complete the CRF with the CE findings.

Figure 4: A schematic summarising the study protocol.



2.1.12 Outcome Measures

The primary outcome of this study was to establish CE reading accuracy changes with the progressive number of CE videos read. Secondary outcomes of this study included; the differences in lesion detection between ER and NR, the observed changes in reading practices across the duration of the study and the relationship between measures of fatigue and lesion detection.

2.1.13 Statistical analysis

Statistical analysis was performed using GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA. A p-value of less than 0.05 was considered statistically significant. Paired continuous data were compared using paired t-tests. Spearman's correlation was used to establish the relationship between non-normally distributed categorical and continuous data. Changes occurring across the study in relation to reading order were analysed using an ANOVA. A binomial logistic regression was used to identify the impact of lesion characteristics on detection. Kappa values between the two RS readings were calculated using Cohen's Kappa statistic.

Results

2.1.14 Baseline Characteristics

A total of 32 participants composed of 16 ER and 16 NR undertook this study to completion. The baseline characteristics of these cohorts are described in Table 9.

2.1.15 Lesion detection

The RS readers demonstrated a high level of inter-observer agreement with a Kappa value of 0.95 (CI: 0.95-0.96). When findings were compared to the RS reading, ER had a mean correct detection rate of 48.3% (SD: 16.1), whilst NR had a mean rate of 21.3% (SD: 15.1). When each CE video was analysed individually irrespective of reading order, the greatest proportion of correctly identified lesions was seen in case B (41%, 95%CI: 0.34-0.48) and the lowest in Case A (21% 95%CI: 0.15-0.27),

Table 9: Baseline characteristics of the study participants.

		Experienced Readers	**Novice Readers**
Gender distribution	Male	10	11
	Female	6	5
Job role	Consultant	11	3
	Trainee	3	12
	Nurse	2	1
Prior attendance on a training course	Yes	12	2
	No	4	16
Prior capsule experience (number of capsules read)	None	0	12
	0-9	0	4
	10-19	0	0
	20-49	3	0
	50-99	3	0
	100+	10	0
Previous endoscopy experience (years)	1- 3	1	1
	3 – 5	3	10
	5 +	12	5

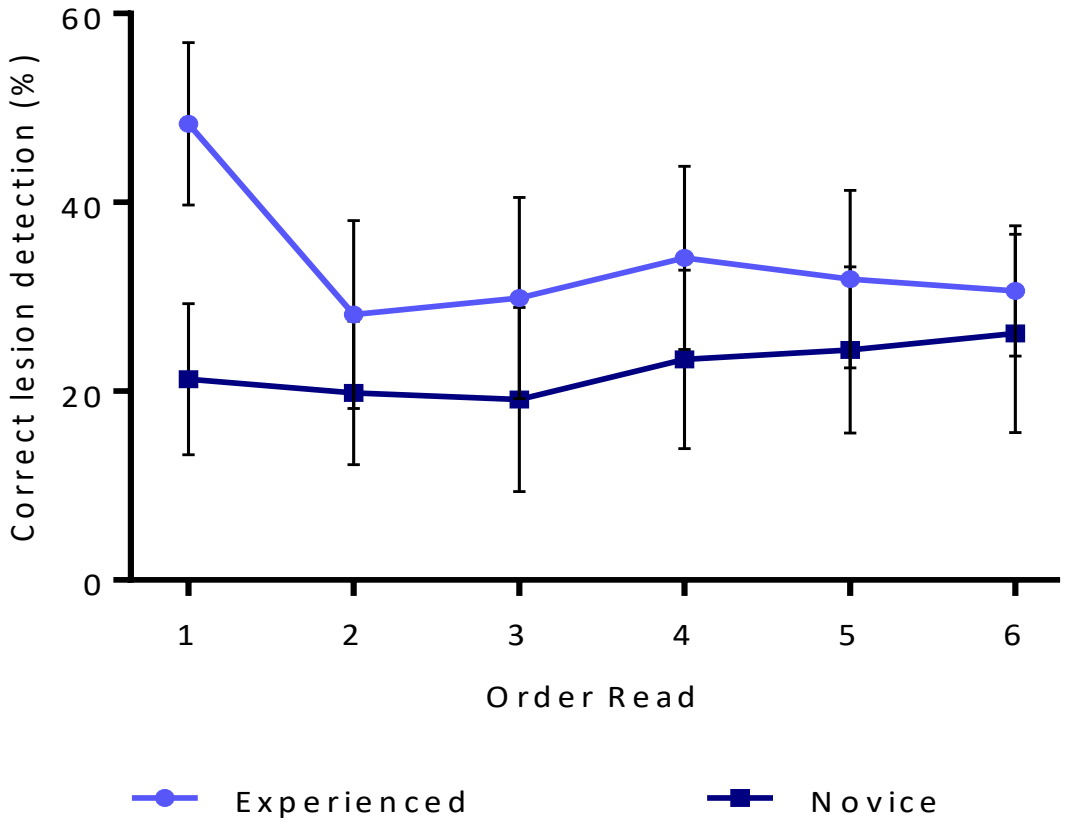
Table 10 Lesion characteristics of the capsule cases used in study.

Capsule Case	Lesions						Mean correct lesion detection % (95% CI)
	Angiodysplasia	Ulcer/ Erosion/ Petechiae	Polyp	Diverticulum	Lymphangiectasia/ Xanthoma	Total	
Case A	5	0	1	0	0	6	21 (0.15-0.27)
Case B	9	2	0	0	0	11	41 (0.34-0.48)
Case C	0	18	0	1	1	20	25 (0.19-0.31)
Case D	18	1	0	0	0	19	34 (0.28- 0.39)
Case E	0	8	0	0	2	10	26 (0.19-0.33)
Case F	0	26	0	0	0	26	22 (0.17-0.27)

2.1.16 The effect of reading order on lesion detection

Where the group was analysed as a whole there were no statistically significant differences in correct lesion detection in association with reading order. Where experience was considered, ER demonstrated a 20% decline in lesion detection between Case 1 and Case 2 (p= 0.01). This drop in lesion detection plateaued in subsequent cases read, with no significant difference found when comparing subsequent cases, **Figure 5.** In contrast, there was a non-significant trend towards improvement in lesion detection with case order amongst NR. Where lesion detection was compared between ER and NR, it was noted that ER detected significantly more lesions on reading Case 1 (p= <0.01). However, due to the decline in accuracy by ER, this difference was no longer observed by Case 2 (p= 0.17).

Figure 5: The proportion of correctly identified lesions according to reading order.



2.1.17 The effect of reading speed on lesion detection

The mean reading time to read a single capsule video was 32 minutes (SD: 10.8). There was no significant difference between the times taken to read individual videos. When analysed with respect to reading order a reduction in reading time was observed (p= 0.05). Reading times were on average 25% faster on reading Case 6 compared to Case 1, representing a mean reduction of 9 minutes and 36 seconds (range: 9 -11). This finding was supported by the observed trend to select faster reading speeds as the study progressed, **Figure 6** . Where correct lesion detection was analysed with respect to reading speed used a negative trend was noted in ER p=0.23, r-0.12 (CI: -0.32-0.08), which was statically significant amongst the NR, p= 0.02, r -0.24 (CI: -0.42- -0.03), **Figure 7.** Longer reading times were associated with greater accuracy in ER (p= 0.05, r: 0.19 (CI: -0.008-0.397) and NR (p= 0.02, r: 0.24 (CI: 0.038-0.423).

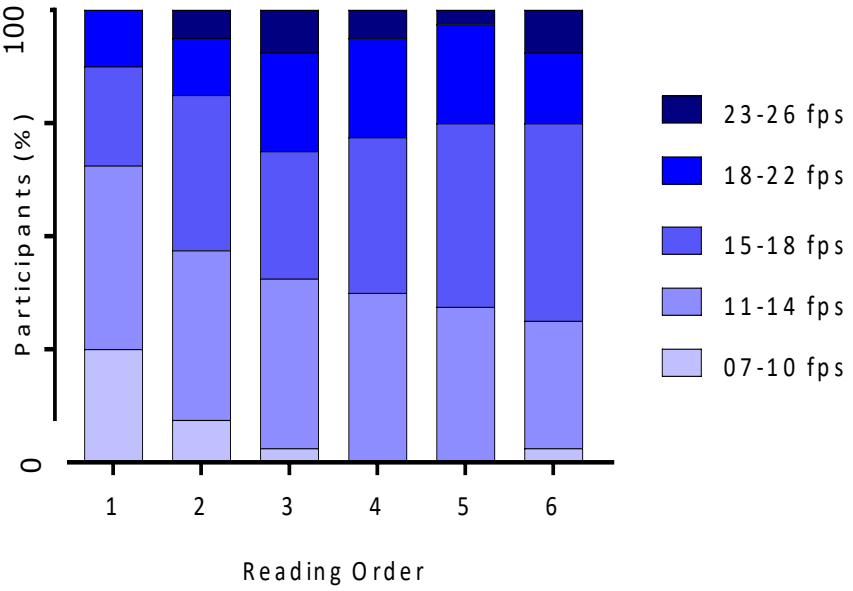


Figure 6: Changes in the choice of reading speed according to reading order

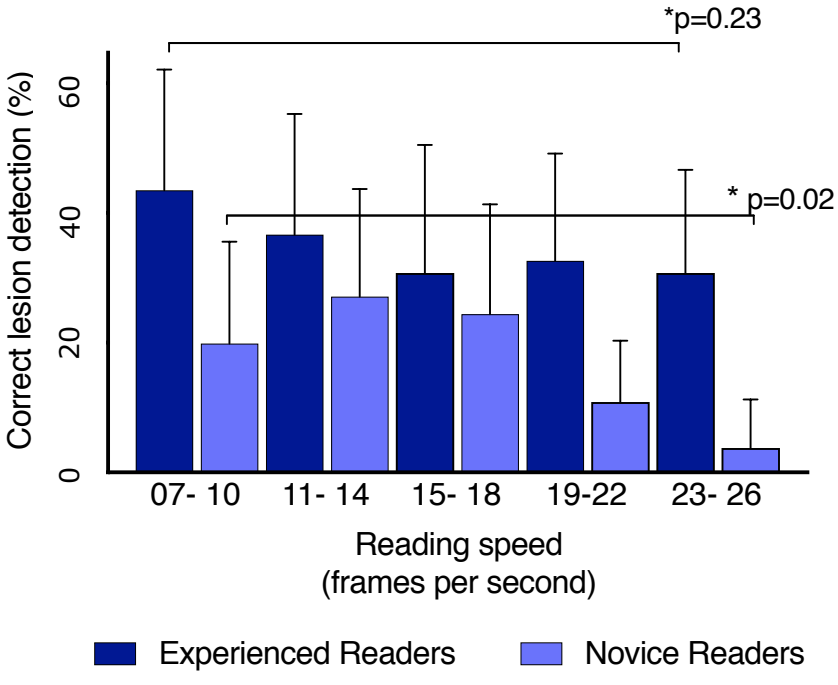


Figure 7: Correct lesion detection in relation to reading speed used.

2.1.18 The effect of lesion characteristics on lesion detection

The likelihood of detecting a lesion was assessed according to their characteristics, namely the nature of the lesion, its clinical relevance and how many frames it was visible for during the CE video. A logistic regression performed on a per lesion basis demonstrated that lesions which were more clinically significant were more likely to be detected and angiodysplasia were the easiest type of lesion to diagnose, **Table 11.**

Table 11: Binomial regression identifying factors which influence lesion detection

Variable		Odds Ratio	95% Confidence Interval	
P- Classification	P0	1	Reference category	
	P1	0.64	0.50	0.83
	P2	1.66	1.10	2.50
Lesion type	Lymphangiectasia/ Xanthoma	1	Reference category	
	Angiodysplasia	1.21	0.93	1.57
	Ulcer/ Erosion/ Petechiae	0.48	0.39	0.59
	Polyp	0.18	0.07	0.47
	Diverticulum	0.05	0.02	0.17
Number of frames on which lesion visible		1.003	1.002	1.004

2.1.19 Measures of fatigue

As the study progressed the subjective experience of fatigue increased across the Fatigue Score (p=0.01). There was also a non-significant trend towards increased mean PVT, **Table 12.** When both PVT and FS was analysed with respect to correct lesion detection there was no significant relationship, p= 0.47 (r -0.07) and p=0.12 (r -0.16) respectively **Figure 8** and **Figure 9.**

Table 12: Changes in measures of fatigue across the study

Measure of Fatigue	Baseline	Post 2nd capsule	Post 4th capsule	Post 6th capsule	P-Value
Mean average PVT msecs (SD)	263 (56.5)	252 (37.8)	260 (41.2)	263 (48.7)	**p>0.05**
Number of lapses	15	11	7	18	**p>0.05**
Mean Fatigue Score (SD)	2.7 (1.3)	3.3 (1.2)	3.6 (1.5)	4.3 (1.7)	**P=0.01**

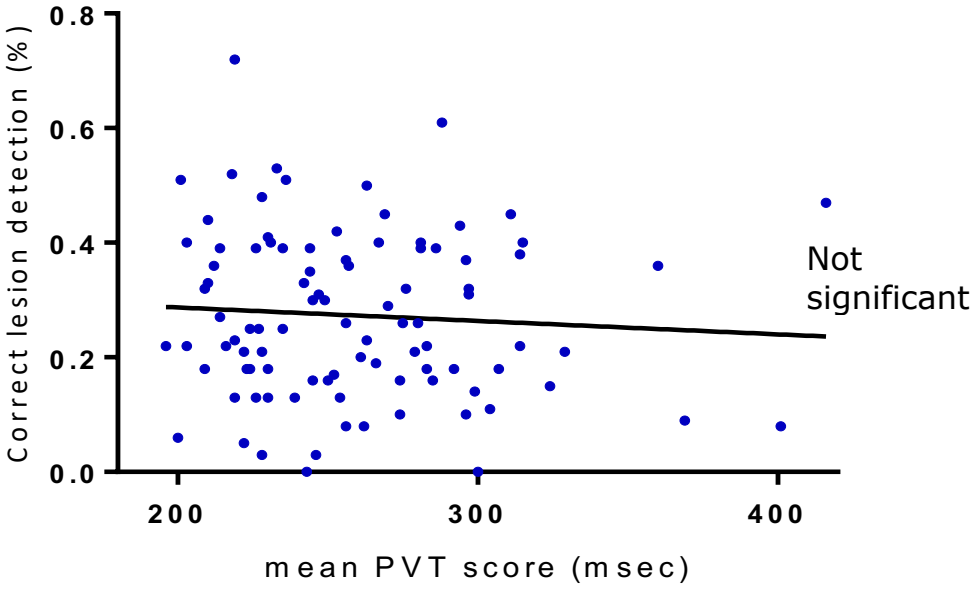


Figure 8: The relationship between mean PVT and correct lesion detection

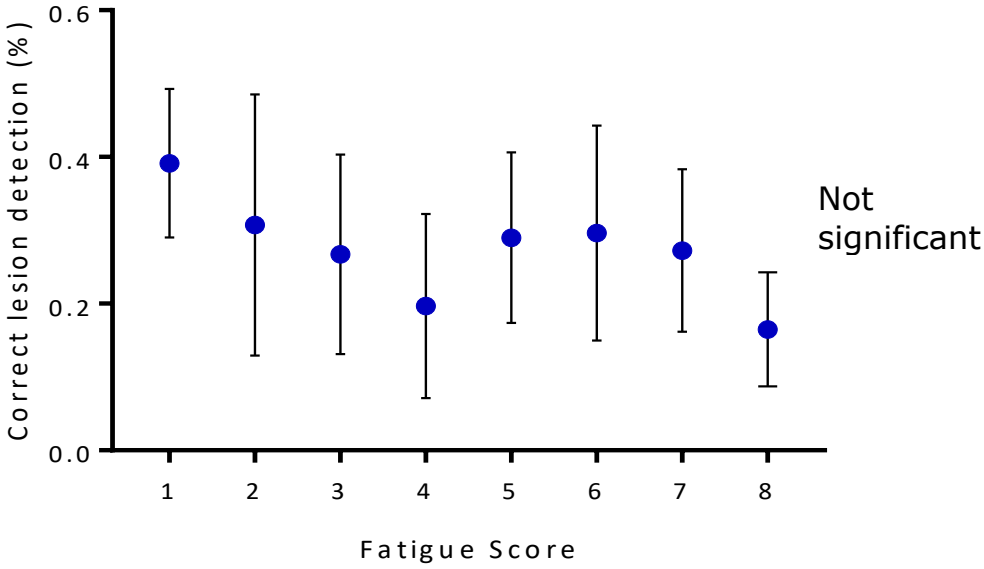


Figure 9: The relationship between mean Fatigue score and correct lesion detection

Discussion

2.1.20 Principle findings

This is the first study to prospectively examine the impact of fatigue in capsule endoscopy. This has demonstrated that with increasing cases read ER demonstrate a decline in lesion detection. The optimal number of capsules to read in a session appears to be just one. This phenomenon was not observed in NR, with no change observed. Several studies suggest that the learning curve for capsule endoscopy is between 15-25 cases, the observed improvement is likely to represent a learning effect attained during the study period [67,69]. By the end of the study, accuracy in lesion detection of the NR was not statistically significantly different to that of the ER.

The concept of fatigability is supported by secondary outcome measures, which suggest a change in reading habit with increasing case number. Reading time reduced between an average of 9 minutes and 36 seconds between the first and last case read. This was reflected by a tendency to adopt faster reading rates as the study progressed. There was a negative correlation between the number of frames per second the video was viewed in and the likelihood of correctly identifying a lesion. This was most pronounced in NR, who were less capable of maintaining accuracy at the faster

speeds. This corroborates the findings of previous studies which suggest that the optimal way to read is at the slower speeds [61].

Lesions were more commonly identified if they were angiodysplastic and with increasing clinical significance. This may reflect the complex manner in which the eye is drawn to lesions, possibly determined by subtle unmeasured factors such as lesion contrast with background mucosal color, speed of capsule movement or patterns in lesion distribution [112].

The subjective experience of fatigue increased across the duration of the study. Given the nature of the study protocol, this is perhaps not an unexpected finding. The poor correlation with lesion detection implies self-rating fatigue alone cannot be relied upon to inform an individual whether the interpretation of further cases is advisable. This may in part be because there is an overlap in this scenario between fatigue and boredom with loss of concentration. It is known that fatigue is less recognised in the medical profession, with as many as 70% of consultant surgeons failing to recognise a link between fatigue and its potential impact on personal performance compared to 26% of pilots [149].

The PVT failed to show a statistically significant correlation with either CE case order or lesion detection within this study. It is postulated that this may be due to increased attention, due to what was effectively a change in task type. While CE interpretation is a passive process, the PVT was interactive, which may have served as a form of mental stimulation in itself. Further, the PVT test used in this study displayed a timer as the visual stimulus, which stopped counting once a reaction was elicited. Participants were therefore not entirely blinded as to the results of the PVT, this may have caused an unanticipated competitive drive where participants attempted to achieve the best possible score. Previous studies have demonstrated that PVT used in a similar context to this study demonstrated an improvement in the last score, which has been attributed to a 'spurt' in concentration secondary to the anticipation of the end of the exercise [150].

We selected the abbreviated version of the original 10-minute PVT for reasons of pragmatism. In previous studies, both 5 minute and 3-minute versions were found to be of lesser but reasonable sensitivity [151]. However, given that the observed changes were small the use of the abbreviated form may have in fact underestimated the impact of fatigue.

PVT may not be as accurate in measuring fatigue secondary to boredom and mental fatigue as in physical fatigue or in relation to sleep deprivation. Most of the existing studies using PVT have focused on the sleep-deprived state or prolonged working hours exceed those which were investigated. PVT may not be able to detect the subtle changes associated with the insidious onset of fatigue. Methods capable of measuring more subtle parameters, such as oculomotor changes, may have been more informative [143,152–154]. Whilst PVT is a useful tool in other scenarios, it fails to reach sufficient accuracy to be used as a tool to inform a capsule reader whether they have sufficient levels of concentration to undertake CE interpretation.

2.1.21 Study strengths and limitations

In order to test this hypothesis, it was necessary to construct a study which may not necessarily reflect daily clinical practice. We used the correct identification of lesions as a measurable outcome. In daily practice the eventual conclusion is derived from a combination of the CE findings and patient signs, symptoms and prior investigations. Where clinical findings are diffuse, such as widespread small bowel Crohn's disease, it is not necessary to identify each and every lesion in order to make an accurate diagnosis. However, in order to be

able to prove the point that lesion may be missed we instructed participants to identify all lesions present. Further, a proportion of CE performed with a valid clinical indication will be normal, it was not possible to include such videos as with no lesions to correctly identify the case would have been noncontributory to the data and lead to reduced study power.

Our baseline questionnaire demonstrated that the mean number of capsules read in a single session was 3.5. It could, therefore, be argued that reading six consecutive capsules is not a true to life scenario. As there are no previous studies to inform the onset of fatigue, we opted to use the maximal number of capsules that could be reasonably read during a standard 4-hour clinical session. Given lesion detection fell after reading a single capsule and 15/16 (94%) of readers who routinely read for service declared that they read more than one capsule in a single session, these findings appear to be relevant.

This study cannot not account for possible changes in behavior which may take place in clinical practice to ensure 'fatigue-proofing'. This phenomenon has been previously documented in pilots, who were found to informally incorporate strategies such as task rotation, task buffering and double checking, to

mitigate against error [155]. Possible strategies, which could not be employed by the participants within the confines of this study include prolonged breaks, alternating tasks or reading in a strategic order to account for clinical suspicion.

While some aspects of this study could be considered to be artificial, the methodology allowed us to obtain a cross-section of current practice. This included a mixture of specialist and community hospital physicians in a variety of locations across the country. The study was performed in a clinical environment which was either identical or very similar to that used in daily clinical practice. The majority of ER included in this study are considered to be national experts in the field, with clinical and research expertise in small bowel endoscopy. This study reinforces the fact that CE is associated with high intra-observer variability in spite of expertise.

2.1.22 Implications for clinical practice

This study demonstrates that fatigue with a consequent reduction in lesion detection occurs in capsule interpretation and is likely to be underestimated by readers. Awareness of this phenomenon will hopefully encourage greater recognition of fatigue prior to undertaking interpretation. Caution should be exercised if outsourcing capsule interpretation is

considered, as large numbers of cases are likely to be read within a single session. Further, where a capsule has been reported as normal, despite a high clinical suspicion there should be a low threshold for re-reviewing the case.

Potential future applications of these findings include being able to optimize the timing of capsule interpretation. Should a more sensitive marker of fatigue become apparent, it is conceivable that this could be used in order to determine whether concentration is sufficient.

Given that fatigue is likely to be caused by the monotony of repeat redundant images, software enhancements that reduce the number of frames that require viewing may allow for more videos to be read accurately within a single session. Further studies would be required to elucidate whether rapid reading software is able to offer advantages beyond the intended time-saving.

Additionally, the findings of this study may have implications in the research setting. In common with our research design, many studies concerning capsule endoscopy involve the detection of individual lesions within a video, rather than a holistic assessment as is common in clinical practice. Thus far

fatigue has not been considered as a potential confounder with the ability to influence lesion detection. Our findings would suggest that the number of cases interpreted in a single session should be recorded and potentially accounted for in subsequent analyses.

Conclusions

This study demonstrates that the proportion of correctly identified lesions significantly declines following a single capsule interpretation. Whilst this phenomenon may not be clinically relevant in all cases, this needs to be considered when reading cases that are high risk or where a capsule has been reported as normal despite high clinical suspicion. These findings could be used to inform workday planning in order to optimize the value of this investigative modality.

Chapter3:. Can Omni-Mode reduce reading times whilst maintaining accuracy?

3.1.1 Abstract

3.1.2 Introduction

A typical capsule endoscopy case generates tens of thousands of images, with abnormalities often confined to a just few frames. Omni-Mode is novel EndoCapsule (Olympus) software algorithm, which proposes to intelligently remove duplicate images whilst maintaining accuracy in lesion detection.

3.1.3 Methods

This prospective multicentre study took place across 9 European centres. Consecutive, unselected capsule endoscopy cases were read in conventionally in Normal-Mode, with every captured frame reviewed. Cases were subsequently anonymised and randomly allocated to another centre where these were read using Omni-Mode. Detected lesions and reading time were recorded, with findings compared between both viewing modes. The clinical significance of lesions was described according to the P-classification (P0, P1, and P2). Where a discrepancy in lesion detection in either mode was found, expert blinded review at a consensus meeting was undertaken.

3.1.4 Results

The patient population undergoing capsule endoscopy had a mean age of 49.5 years (range 18- 91), with the investigation of anaemia or gastro-intestinal bleeding accounting for 71.8% of cases. The average small bowel transit time was 4 hours and 26 min. The mean reading time in Normal mode was 42.5 mins. The use of Omni-Mode was significantly faster ($P<0.0001$), with an average time saving of 24.6 min (95%CI: 22.8- 26.9).

A total of 2172 lesions were identified, which were classified according to the P-Classification as P0 (1234), P1 (656) and P2 (237). Lesions were identified using both reading modes in 40% (n=936). 1186 lesions were identified by either Normal or Omni-Mode alone. Normal-Mode interpretation was associated with 647 lesions being missed, giving an accuracy of 0.70. Omni-Mode interpretations lead to 539 lesions being missed, with an accuracy of 0.75. There was no significant difference in clinical conclusions made between either reading modes.

3.1.5 Conclusions

This study shows that capsule endoscopy reading times can be reduced by an average of 40%, without any reduction in clinical accuracy.

Introduction

A typical small bowel Capsule Endoscopy (CE) case is composed of tens of thousands of images and typically takes between 30 -60 minutes to interpret [10,11]. This compares poorly to other diagnostic endoscopic procedures such as gastroscopy and colonoscopy, which require significantly less physician time with mean procedure times of less than 7 and 24 minutes respectively [122,156]. Many of the displayed images are duplicates owing to the uncontrolled, non-linear movement of the capsule across the length of the small bowel. The review of these images is non-contributory to the final report but account for significant time expenditure.

Several software algorithms have been proposed to remove redundant images from the viewing stream in order to reduce reading times. These have been evaluated in several studies, all of which confirm reductions in reading time, but with variable reports on the accuracy in lesion detection. There is some evidence that the selectivity of these software enhancements may compare less favourably than more crude time-saving strategies, such as reviewing only alternate images or adopting faster reading speeds with multiple images viewed [96,97].

EndoCapsule (Olympus) has introduced a novel rapid reading algorithm, which proposes to intelligently reduce a large number of repeat images **Figure 10.** A retrospective Japanese multicentre study has demonstrated a 64% reduction in reading times associated with 0.93 sensitivity in the detection of major lesions in pre-selected cases [100]. This software has yet to be tested in routine clinical practice. The primary aim of this study is to demonstrate non-inferiority of Omni-mode in lesion detection, compared to conventional, Normal-mode reading. The P classification was used to determine the clinical significance of any missed or detected lesions. Secondary outcomes included changes in reading time and differences in study conclusion.

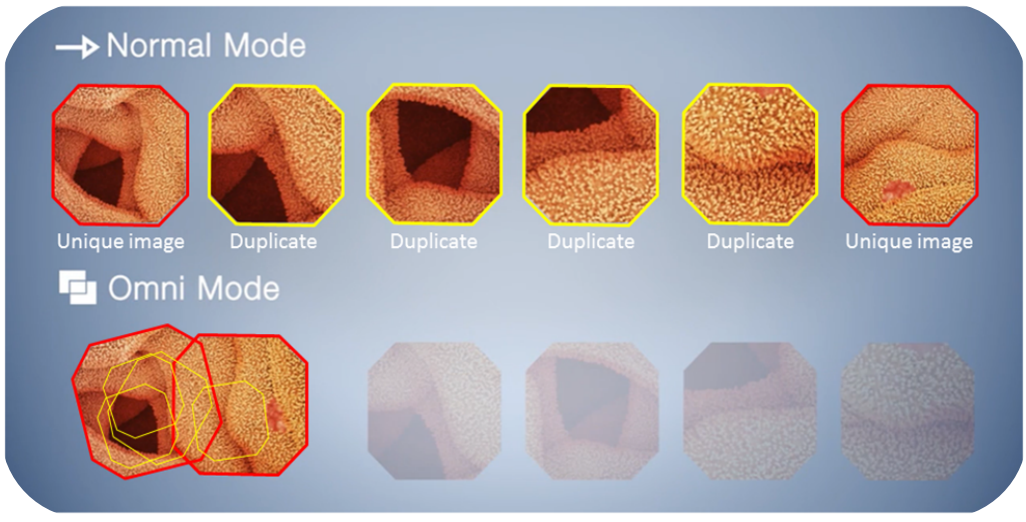


Figure 10: Schematic of the Omni-Mode concept
Courtesy of Olympus Europa

Aims

The primary aim of this study was to demonstrate non-inferiority of accuracy using the Omni-Mode software as compared to conventional Normal-Mode reading.

Secondary outcomes included changes in reading time and whether there were changes in study conclusion occurred as a consequence of changes in accuracy.

Methods

3.1.6 Study Design

This was a prospective multi-centre study, performed across nine hospitals within Europe and Russia, with coordination of the study at the lead centre, Nottingham University Hospital. Approval to conduct this study was sought prospectively from the Research and Innovation department at Nottingham University Hospitals (15GA010), with local approvals obtained by the participating centres. As there was no active patient participation, consent was not required for inclusion of anonymised cases.

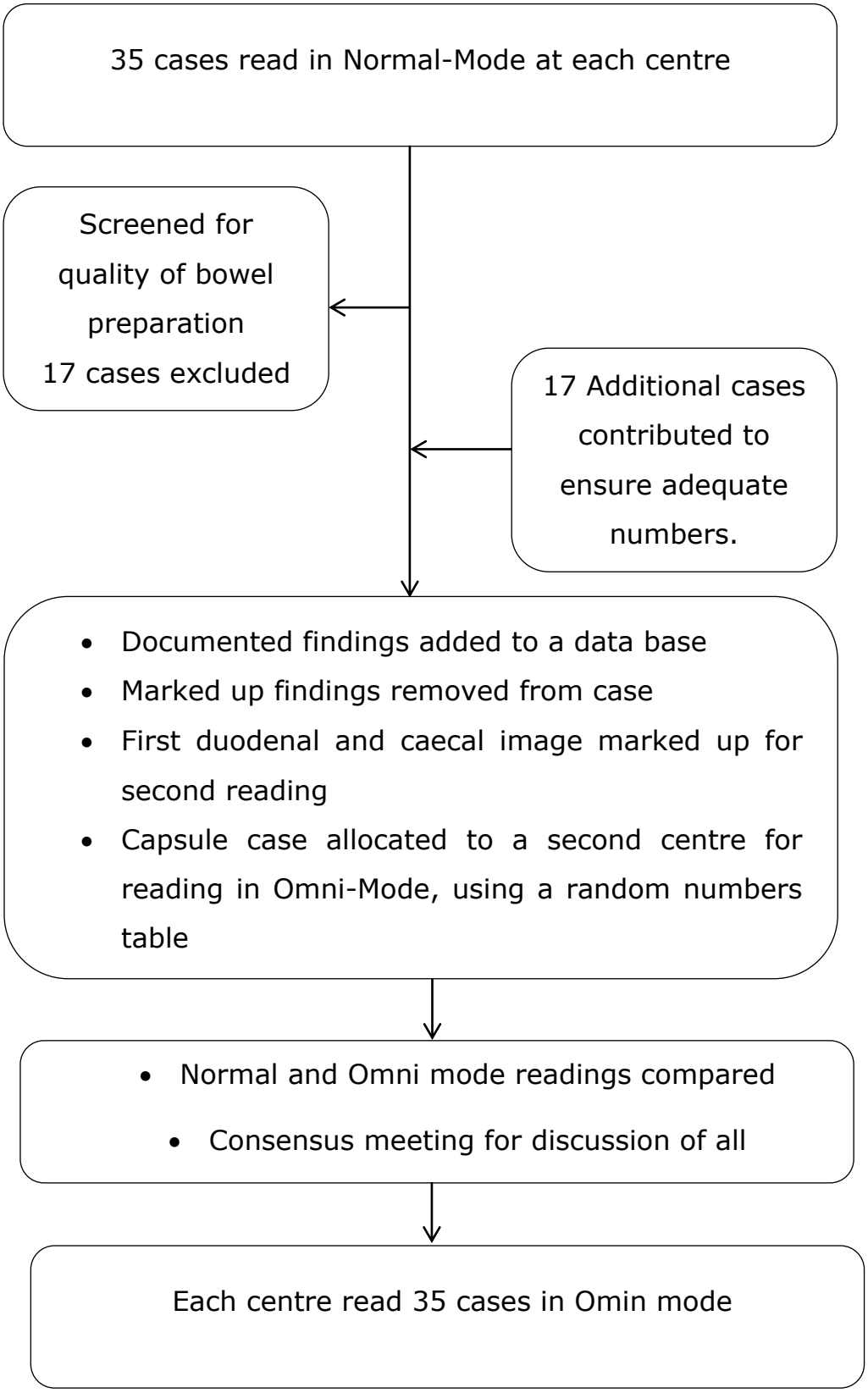
This study was designed to reflect routine clinical practice; a pragmatic design was therefore adopted. Consecutive unselected CE cases performed in adults for clinical purposes were contributed. All cases were performed using the Olympus EndoCapsule-10 system and interpreted using the associated proprietary software. The cases were read in the local centres prospectively as part of routine clinical practice. Each centre contributed 35 valid cases read conventionally, Normal-Mode, these were then randomised at the coordinating centre and sent out to be read in Omni-Mode at another centre. Each centre received 35 cases to be read in Omni-mode. The findings from the Normal-mode reading and Omni-mode were

compared in terms of reading time, lesion detection and clinical conclusion **Figure 11.**

3.1.7 Participating Centres

- Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom
- Maria Sklodowska-Curie Institute–Oncology Center, Warsaw, Poland
- Hospital Clinic de Barcelona, Barcelona, Spain
- Moscow University Hospital, Moscow, Russia
- University Hospital Rikshospitalet, Oslo, Norway
- University Hospital Heidelberg, Heppenheim, Germany
- Institut Arnault Tzanck, St Laurent du Var, France
- Edouard Herriot Hospital, Lyon, France
- Azienda Ospedaliero Universitaria, Maggiore della Carità, Novara, Italy

Figure 11: A schematic of the Omni study protocol



3.1.8 Sample size calculation

From previous studies, we know that conventional endoscopy capsule reading is able to detect clinically significant findings in 57% of patients who have a clinical indication for CE. Assuming the clinically significant findings detected using the Omni-Mode of less 57% with a non-inferiority limit of 7%, then a sample size of 309 patients would give 80% power to conduct a one-sample non-inferiority test to compare the diagnostic yield obtained from Omni-Mode to those obtained in Normal-Mode with $\alpha=0.05$. We know that conventional reading mode takes on average 45 minutes to read with a standard deviation (SD) of 15 minutes. Assuming that with Omni-Mode there will be 30% reduction in reading time then a sample size of 26 patients would give more than 95% power to detect that difference using a paired t-test with correlation of 0.1 and $\alpha=0.05$.

3.1.9 Inclusion Criteria

Complete CE video performed for clinical purposes, satisfying the below inclusion criteria were eligible for inclusion into this study.

- Adequate bowel preparation (as detailed below)
- Complete small bowel examination, with the caecum positively identified

3.1.10 Assessment of bowel preparation

The bowel preparation regimes employed locally were not altered for the purpose of this study. In order to ensure equity in the image quality of the cases contributed, each CE was assessed at the coordinating centre by reviewing a segment of the CE video at each quartile [49,157]. Preparation was classified as Excellent, Good, Fair or Poor. Where quality was judged to be poor the case was excluded, and a replacement case was contributed by the same centre Figure 11.

3.1.11 Standardisation of reading

This was a pragmatically designed study; as such readers were given the freedom to use their usual reading practices when interpreting the CE videos. This included the image display, which describes the number of simultaneous images viewed on the screen (one, two or four), as well as viewing speed. Readers were asked to remain within a range of speeds allowing a variation of four frames per second as it is known that both display mode and speed influences lesion detection [51,61]. Reading settings used were recorded on the CRF.

3.1.12 Reading time

The small bowel reading time was classified as the duration of time taken to read the case from the first duodenal image to

the first caecal image, including the time taken to identify and review any potential lesions, but excluding the time taken to complete the CRF. The time taken to read the case was recorded to the nearest minute.

3.1.13 Lesion classification

In order to ensure homogeneity amongst readers, all identified lesions were recorded and categorised by lesion type. In order to express the clinical significance of an identified lesion, a modified version of the P-Classification was used, this score ranges from P0- P2, where P0 lesions are of low relevance, P1 unknown relevance and P2 high relevance **Figure 12.** The score was determined by the initial physician interpreting the CE case during the Normal-Mode reading.

3.1.14 Per patient analysis

In order to determine whether changes in reading mode influenced patient care, readers were asked to make a free text conclusion based on the entire CE reading. This was categorized to be; Normal examination, Non-significant findings or significant findings, where a case was considered to be significant if there were findings that were either diagnostic or sufficient to initiate further investigations or therapy.

3.1.15 Randomization

All CE cases were sent to the coordinating centre, Nottingham University, for randomization to another centre to be read in Omni-Mode. As each centre serves as a regional center for CE, with access to device assisted enteroscopy, we did not expect any significant variation in the case-mix across hospitals. A random number table was constructed to ensure that no CE case could be randomized back to the contributing center and so that cases were distributed equally amongst institutions for the second reading. The CE cases were allocated a case number, from which it was not possible to ascertain from which center it originated.

3.1.16 Omni-Mode Readings

Thirty-five cases were sent to each centre to be read in Omni-Mode. These were accompanied by specific CRFs which contained the case details to provide clinical context, including age, gender, indication and previous investigations, as specified by the contributing centre. The first duodenal and caecal image, as determined by the Normal-Mode reader were marked within the case and on the CRF to ensure the same period of small bowel passage was evaluated. As with the Normal-Mode readings, readers had the freedom to select the number of images selected and the speed at which these were

displayed. Small bowel reading time was recorded to the nearest minute.

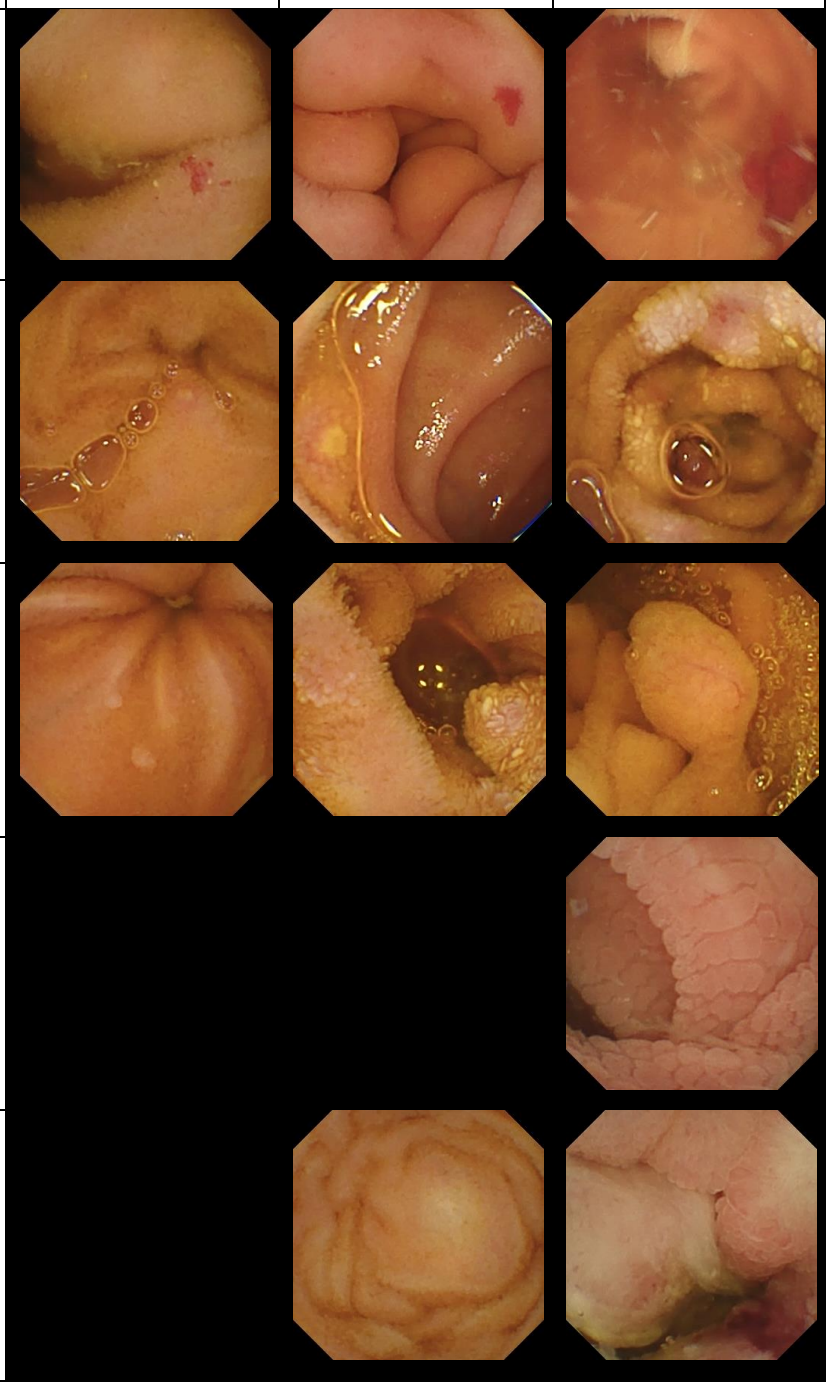
3.1.17 Consensus meeting

Lesions identified during Normal-mode and Omni-mode readings were compared. Where time codes and lesion code matched between readings they were considered to be detected in both modalities. Where discrepancies were noted, the lesion was reviewed to determine whether this was lesion was identified but at a slightly different point in time, whether this was a repeat image of an identified lesion or whether this was a true discrepancy. All discrepancies were discussed in a consensus meeting composed of representatives from the study group. Lesions were reviewed in order to determine if these were false positives or correctly identified lesions. The members of the consensus meeting were not given information as to whether the lesion was identified in Normal or Omni-Mode, in order to avoid bias.

3.1.18 Statistical analysis

Statistical analysis was performed using GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA. A p-value of less than 0.05% was considered statistically significant. Changes in reading time between reading modes were calculated using paired t-tests. Differences in proportions were determined using Chi-squared tests.

Figure 12: lesion severity classification (Modified from the P- Classification)

Descriptor	Classification		
	P0	P1	P2
Vascular lesions			
Inflammatory lesions			
Polypoid lesions			
Villous Atrophy			
Tumour			

Normal Variants
Diverticulum
Xanthoma
Intraluminal blood
Foreign body

Results

3.1.19 Baseline characteristics

This study included 315 cases, with equal contribution across the nine participating centres, **Table 13.**

Table 13: Baseline characteristics of included capsule cases.

Characteristic		Value/ Mean	Range/ %
Gender Distribution	Male	141	44.8 %
	Female	174	55.2 %
Age (years)		49.5	18-91
Indication	IDA	169	53.7 %
	Overt GI bleeding	57	18.1 %
	Evaluation of Crohn's	23	7.3 %
	Polyposis syndromes	21	6.7 %
	Diarrhoea	13	4.1 %
	Pain	17	5.4 %
	Abnormal imaging	5	1.6 %
	Other	10	3.2 %
Bowel Preparation Grade *	Excellent	117	37.1 %
	Good	137	43.5 %
	Fair	58	18.4 %
	Poor	3	0.9 %
Capsule Transit Time (HH:MM:SS)	Oesophageal transit	0:03:19	0:00:00 - 4:56:39
	Gastric transit	0:42:12	0:00:11 - 5:33:23
	Small bowel transit	4:26:23	0:23:42 - 13:36:26

*17 CE videos excluded due to poor preparation

3.1.20 Time saving

The use of Omni-Mode resulted in a mean time saving of 24.6 min (95%CI: 22.8- 26.9), p<0.0001, resulting in a mean reading time of 17minutes (**Figure 13**).

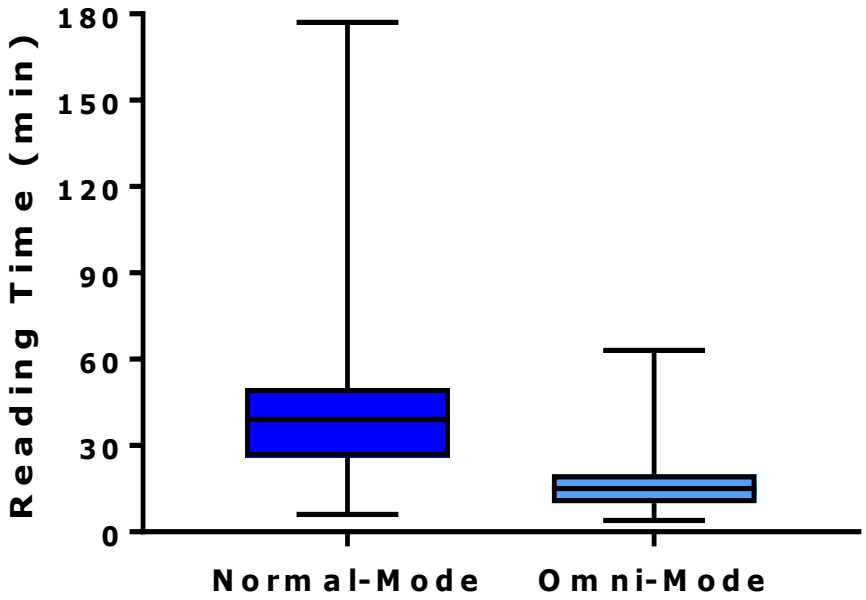


Figure 13: Changes in small bowel reading time according to reading mode used

3.1.21 Per lesion analysis

A total of 3735 lesions were identified across the 315 cases in either reading mode. Of these 1012 (27.1%) were determined to be repeat images of already identified lesions, leaving 2723 unique lesions. Following consensus review 594 (21.8%) lesions were excluded from analysis as they were considered to be false positives. Where the excluded lesions were analysed, 393 (20.9%) of a total of 1873 lesions detected in Normal-Mode were excluded, while 201 (11.2%) of the lesions detected in 1789 Omni-Mode were excluded. Despite the blinded review of lesions at the consensus meeting, a greater proportion of lesions were excluded from the Normal-Mode readings, with a difference of 9.7% (95% CI: 7.3- 12.1), p<000.1.

A total of 2127 lesions were included in the 'gold standard' interpretation following consensus review, with a mean of 6.8 lesions per CE case, lesion characteristics are described in

Table 15. Agreement between both modes was observed amongst 936 (44.0%) lesions. 647 (30.4%) lesions were seen in Omni-Mode only, while 539 (25.3%) were seen in Normal-Mode only, **Table 14.** This resulted in an overall accuracy of 0.70 (95%CI 0.68-0.72) for Normal-Mode and 0.75 (95%CI 0.73-0.77) Omni-Mode. There was a 5% greater chance of detecting lesions whilst using Omni-Mode (95%CI: 2.3-7.7), p=0.0002.

A sub-group analysis of the most significant lesions, classified as P2, revealed a total of 237 (11.1%) of such lesions. Normal-Mode missed 40 of these lesions, while Omni- Mode missed 27, resulting in an accuracy for the detection of major lesions of 0.83 (95%CI: 0.73-0.88) and 0.89 (95%CI: 0.85-0.93) respectively, with a difference between the two modes of 6% (95%CI: -0.3-12.3), p=0.060.

Table 14: Characteristics of missed lesions in either reading mode compared with consensus review

		Missed in Normal-Mode	Missed in Omni-Mode
Lesion type	Vascular lesions	179	140
	Inflammatory lesions	157	142
	Polypoid lesions	38	75
	Villous Atrophy	0	0
	Tumour	1	2
	Blood	20	5
	Foreign body	13	12
	Normal variants	239	163
P- Classification	P0	446	364
	P1	161	148
	P2	40	27
Total		**647**	**539**

Table 15: Lesion characteristics of all included lesions following consensus review

		P- Classification			Total	Proportion (%)
		P0	P1	P2		
Lesion Type	Vascular lesions	239	334	96	669	**31.5**
	Inflammatory lesions	229	216	71	516	**24.3**
	Polypoid lesions	129	58	24	211	**9.9**
	Villous Atrophy	2	0	1	3	**0.1**
	Tumour	4	9	3	16	**0.8**
	Foreign body	35	10	0	45	**2.1**
	Blood	3	29	42	74	**3.5**
	Normal variants	593	0	0	593	**27.9**
	Total	1234	656	237	**2127**	
	Proportion (%)	**58.0**	**30.1**	**11.1**		

3.1.22 Per– patient analysis

It is known that the identification of all lesions present is not necessarily required in order to derive an accurate case conclusion. CE conclusions were compared between reading modes as summarised in **Table 16.**

Table 16: Change in case conclusions between Normal and Omni-Mode

	Normal-Mode	Omni-Mode	Significance
Normal	62	71	p= 0.37
Non-significant lesions	107	104	p= 0.81
Significant lesions	146	140	p=0.63

3.1.23 Software analysis

When the viewing stream was examined to establish whether an identified lesion was removed, it was found that this occurred rarely. A total of 14 lesions were missed, none of which were major, giving rise an accuracy of 99.4% (95%CI: 0.98-0.99) for the software itself.

Discussion

3.1.24 Principle findings

This study has demonstrated that the use of Omni-Mode compares favourably with conventional reading, with a sensitivity of 0.89 for the detection of clinically significant lesions and no significant change in study conclusions. The use of Omni-Mode was associated with a 40% reduction in reading time, with a typical case taking 17 minutes to interpret.

3.1.25 Implications for clinical practice

It is perhaps not surprising that with the omission of images that there is a reduction in reading times. Existing rapid reading algorithms describe time saving in the region of 25-64% [93–95,98–102]. The use of Omni-Mode sits within the faster of this range. There are many positive implications of this time saving, with the potential to allow for rapid reading in urgent clinical settings, the reduction of in physician time expenditure, as well as mitigating against the acquisition of increasing numbers of images associated with advances in CE technology [7].

More significant is the accuracy of any software enhancement. It is known that increasing frame rate, the number of images viewed or excluding alternate images results in reduced

reading times with accuracies comparable with some existing software algorithms [96,97]. To date rapid reading software algorithms describe accuracies that range from 60-97%, with variations according to both the software used and the clinical scenario this is tested in [93–95,98–102]. Here we have demonstrated accuracies that compare favourably with conventional reading in an unselected population.

When considering accuracy it is important to bear in mind that while CE has become the first line investigative modality of the small bowel, it cannot truly be considered the gold standard test. Discrepancies are found when CE and direct mucosal inspection are compared [158,159]. In part, this is due to the fact that the correlation between lesion characteristics and clinical outcomes is not clear, especially for minor lesions [160]. Therefore which lesions are identified and whether they are considered to be significant will vary between readers. It is known that there is significant inter-observer variability in CE interpretation [64]. When testing new software enhancements it is not clear what is considered to be an acceptable accuracy, given the variability in conventional reading. While Omni-Mode readers failed to detect all lesions present, the accuracy observed is within the range of normal variability, which is

confirmed by the lower accuracy observed in the Normal-Mode readers.

Where lesions were missed during Omni-Mode readings, the viewing stream was reviewed at the 10fps, in order to determine whether the lesion was in fact excluded. This demonstrated a high level of accuracy of the software algorithm itself. This suggests that other factors such as reading speed and images displayed are more likely to be influential in reading inaccuracies than the use of Omni-Mode.

3.1.26 Strengths and Limitations

In view of the known inter-observer variability in CE interpretation and the multicenter nature of this study, expert consensus was used to evaluate reading discrepancies and to formulate a gold standard. Whilst this is not usual in clinical practice, this mitigates against conflicting results produced by false positive/ negatives, as well as allowing evaluation of the accuracy of Normal-Mode readings. This compares to other similar studies, which in the most use conventional reading by an expert in a study setting as the gold standard.

This is one of a few studies in this field to test software in daily practice, with cases read prospectively and using the readers

normal display preferences. This methodology may underestimate the time saving and accuracy afforded by the use of Omni-Mode, as cases were not necessarily read in the same viewing speed in each mode. Additionally, cases were not pre-selected and included lesions that are known to be easier to detect, such as angidysplasia. It is hoped that this design means that these results are more likely to be reproducible in daily clinical practice.

Conclusions

This study demonstrates that Omni-Mode can be used to significantly reduce reading times. As with all rapid reading algorithms, there is a chance of missing lesions and as such caution must be exercised when interpreting high risk cases. However using a realistic study model Omni-Mode was proven to be as accurate in lesion detection as conventional reading.

Chapter4:. Can Magnetically Assisted Capsule Endoscopy accurate diagnose oesophageal pathology

Abstract

4.1.1 Background

Magnetically Assisted Capsule Endoscopy (MACE) potentially offers a comfortable, patient friendly and community-based alternative to gastroscopy (OGD). This pilot study aims to explore whether this approach can be used to accurately diagnose oesophageal pathology.

4.1.2 Methods

The MiroCam-Navi capsule system was used to examine the upper gastrointestinal tract in patients due to undergo a clinically indicated OGD. A total of 50 participants were enrolled, of which 34 had known pathology, 17 Barrett's Oesophagus (BO), 17 Oesophageal Varices (OV), with 16 controls. Patients underwent the MACE procedure, with the operator blinded to the indication and any previous endoscopic diagnoses. The subsequent OGD was performed by an endoscopist blinded to the MACE findings. Diagnostic yield, comfort and patient preference between the two modalities were compared.

4.1.3 Results

Participants had a mean age of 61 years old and a M: F ratio of 2.1:1, with a mean BMI of 29.5 and an average chest measurement of 105.3cms. 47 patients undertook both procedures, 3 patients were unable to swallow the capsule. With the use of the magnet, it was possible to hold the capsule within the oesophagus for a mean duration of 190 secs and up to a maximum of 634secs. A correct real-time MACE diagnosis was made in 11/15 patients with OV (sensitivity 73.3% (44.9-92.2%) and specificity 100% (89.1- 100%)) and 15/16 patients with BO (sensitivity 93.8% (69.8- 99.8%) and a specificity of 100% (88.8- 100%)). MACE was considered more comfortable than conventional endoscopy ($p<0.0001$) with a mean score of 9.2 with MACE compared to 6.7 with OGD, when assessed on a 10-point scale. No MACE or OGD related complications occurred.

4.1.4 Conclusion

This pilot study demonstrates that MACE is both safe and well tolerated by patients. Accuracy for the diagnosis of BO was high and may therefore have a role in screening for this condition.

Introduction

Oesophago-Gastro-Duodenoscopy (OGD) has become the 'Gold Standard' investigation of the upper GI tract, allowing for the direct mucosal inspection and where required therapeutic intervention. This is not without drawbacks, endoscopy is often regarded poorly amongst patients, with this test perceived as both invasive and uncomfortable [161,162]. This diagnostic modality is resource intensive, requiring the use of a staffed and equipped endoscopy unit, as well as recovery facilities to enable the use of sedation. Growing demand and increasing strain on endoscopy departments mean that the development of a technique which takes procedures outside of the endoscopy department is an attractive proposition [163].

Capsule endoscopy offers a comfortable and minimally invasive alternative to conventional endoscopy [164,165]. The use of this technology beyond the small bowel is emerging [166]. Examination of the upper GI tract has thus far been limited by the rapid transit through the esophagus and the passive, undirected passage through the capacious stomach. With the use of a magnet within the dome of the capsule and an external magnet to manipulate movement, it is possible to

overcome some of these obstacles to enable complete examination of the upper GI tract.

The MiroCam Navi MACE system (Intromedic, South Korea) consists of a magnetic capsule which is steered using a 26cm x 3.5cm external hand-held magnet, allowing for portability. To date, experimental studies have demonstrated non-inferiority compared to OGD in identifying markers within an ex-vivo porcine stomach as well as demonstrating good visualisation of the major upper GI landmarks within healthy volunteers [121,123].

Aims

The primary aim of this study id to determine the accuracy of MACE in the diagnosis of oesophageal pathology.

Secondary outcomes include the feasibility of this test, patient tolerance, comfort and safety.

Methods

4.1.5 Study design

This was a prospective single blinded diagnostic cohort study, performed at Nottingham University Hospital, following approval from the local Research and Innovation department (Ref: 16GA006). All procedures were performed between July 2016 and September 2017. Approval to conduct this study was obtained from the East Midlands Research Ethics Committee (Ref: 16/EM/0089) and prospectively registered on clinicaltrails.gov (Ref: NCT02852161).

4.1.6 Sample size calculation

To date studies concerning the use of MACE have focused on proof of concept, with no information on diagnostic accuracy for pathology in the upper GI tract. Accurate power calculations are therefore not possible at this time. This study has been designed as a feasibility study, which will then inform power calculations for future trials.

For an observed sensitivity of 100%, a minimum of 17 patients were required in order to be able to obtain confidence intervals that exclude a sensitivity below 80%. We therefore aimed to recruit 17 patients undergoing OGD for Barrett's Oesophagus surveillance (BO), 17 for Oesophageal Varices

surveillance (OV) and to ensure a realistic diagnostic assessment, 16 controls without known oesophageal pathology that were scheduled to undergo a clinically indicated OGD.

4.1.7 Patient selection

Patients who were scheduled to undergo an OGD as part of the surveillance of known BO or OV were invited to participate in this study as cases. Those undergoing a clinically indicated OGD for the investigation of upper GI symptoms were invited to participate as controls. Patients who satisfied the eligibility criteria were approached by the study coordinator, with the MACE operator blinded to the indication for the endoscopy or any previous results. Patients who were pregnant, who had an implanted electronic or magnetic device, were unable or unwilling to swallow the capsule or those with known dysphagia or obstructive bowel pathology were excluded from participation. Written informed consent was obtained from all participants.

4.1.8 Interventions

Both diagnostic tests were undertaken on the same day, by two independent operators blinded to the findings of the other modality. The MACE procedure was performed first, to avoid

any artefact caused by scope trauma or biopsy acquisition during the OGD, Figure 15.

4.1.9 MACE

The MACE procedures were performed by a single endoscopist, with experience in both the MACE procedure as well as conventional upper GI endoscopy. As per standard pre-endoscopy preparation, patients underwent a 6-hour fast. Upon attendance for their procedure participants were instructed to consume approximately 1 litre of a solution consisting of water with six drops of simethicone (Infacol, Teva UK Ltd). Sensing pads were placed across the chest to enable the transmission of images from the capsule. Once lying supine at a 10-degree angle, the patient was instructed to place the capsule in the mouth, and then to swallow the tablet alongside water sipped through a straw. No sedation was administered to any patients. The hand-held magnet was held above the sternum in order to catch the capsule within the oesophagus. Real-time images were viewed using a tablet equipped with proprietary MiroCam software **Figure 14**. Patient movement and placement of the handheld magnet was used to manipulate the capsule in order to ensure a complete examination of the oesophagus and stomach. Once adequate images had been obtained or the maximum examination time

of 20 minutes had been reached, the capsule was released in the region of the pylorus and allowed to pass into the small bowel. Any abnormalities detected during the real-time examination were documented on a CRF contemporaneously. The quality of views obtained at each of the major landmarks was assessed by the operator using a 5-point scale (where 0 denotes the landmark was not visualised and 4 denotes complete views obtained). A period of at least one hour was given between undergoing the MACE and OGD, in order to allow the intra-gastric volume of water to reach its resting volume of 35mls [167].



Figure 14: The components of the MiroCam Navi MACE system

A: Computer

Real-time and saved images of the MACE procedure can be viewed using a tablet or laptop with proprietary MiroCam interpretation software.

B: Sensing system

The sensing system consists of 9 sensing pads that are placed at pre-designated points across the torso. Images are transmitted from the sensing box to a computer using Wi-Fi, allowing real-time assessment.

C: Hand held Magnet

26 cm x 3.5 cm hand held magnet.

D: Magnetically Steerable Capsule

11x 24mm capsule, with a weight of 4.2g. Images are obtained at a rate of 3 frames per second at a resolution of 320 x 320. The capsule has a field of view of 170 degrees and depth of field of 30mm.

4.1.10 OGD

OGDs were performed by experienced endoscopists, certified for independent practice. The procedures were performed using standard techniques, with no biopsies or interventions specifically performed as part of this study. Patients had the option of pharyngeal anaesthesia or intravenous sedation, with the requirement for post procedure recovery determined by this choice. Findings were ascertained by the performing endoscopist at the time of the procedure and documented on a CRF. The quality of views obtained at each of the major landmarks was assessed by the operator.

4.1.11 Questionnaires

A series of questionnaires were completed throughout the course of this intervention. These were carried out prior to any intervention, following the MACE procedure, following the OGD and finally two weeks following participation. Patients were provided with a prepaid addressed envelope in order to return the two-week questionnaire. Where questionnaires were not returned, the study coordinator contacted the patient by phone as a reminder within three weeks. The questionnaires included a visual analogue scale to assess overall procedure tolerability (0-10 scale, where 10 denotes the best possible

experience), with separate scores recorded for specific symptoms, including gagging, choking or pain incurred.

4.1.12 Monitoring for complications

In order to ascertain whether there were any MACE related complications, we sought permission from patients to call them two weeks post procedure. At the point the study coordinator answered any questions or queries they might have. If the capsule had not been seen to pass, we offered an abdominal x-ray to exclude capsule retention.

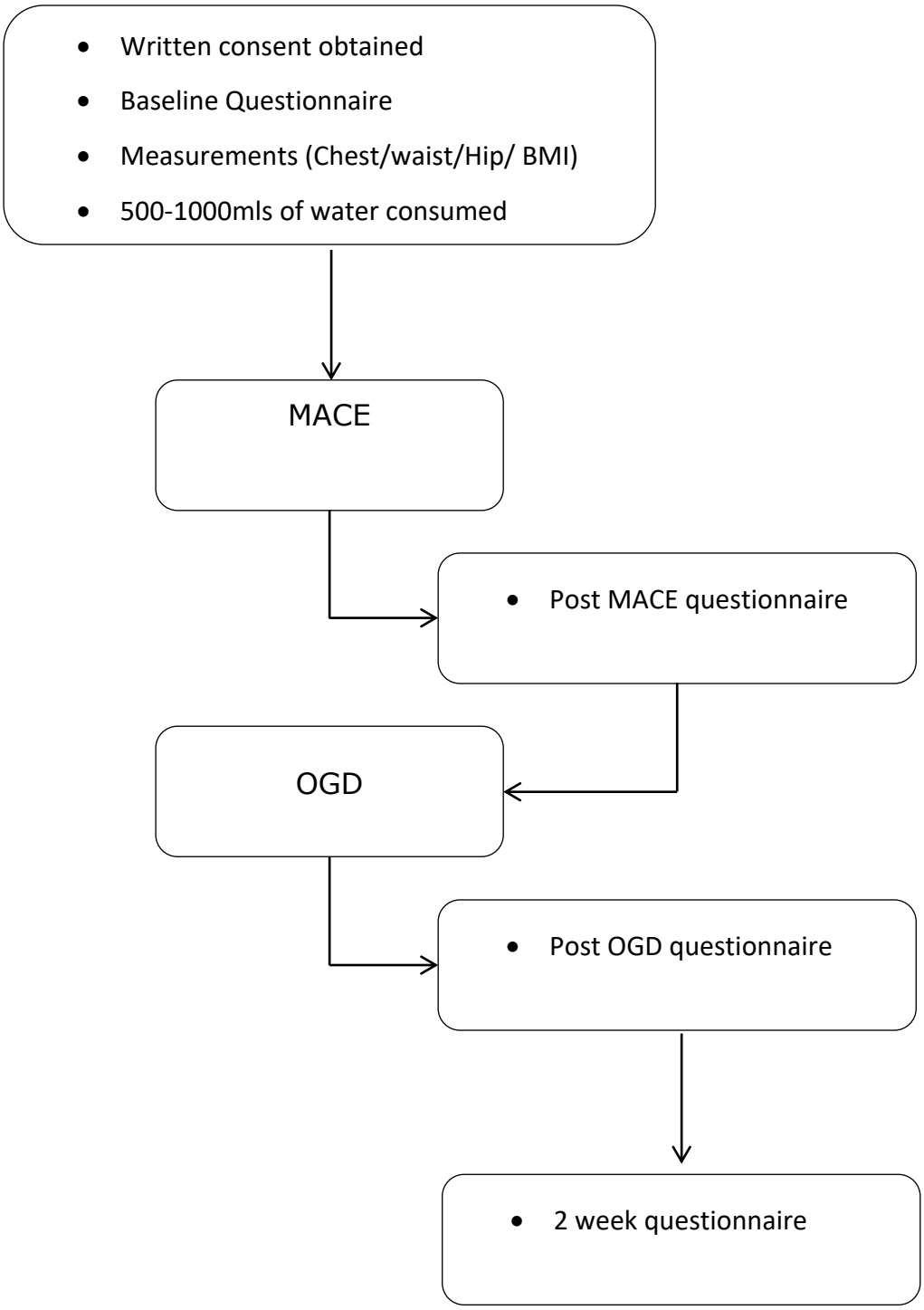
4.1.13 Image review and inter-observer agreement

Recordings of both the MACE and OGD procedures were taken with patient permission. Anonymised endoscopic images were reviewed without clinical information by five endoscopists, to establish whether diagnoses could be accurately determined post procedure. Video clips were edited to include the oesophageal images only, with any interventions or enhanced imaging techniques (such as the use of Narrow Band Imaging) performed during the OGD edited out to render the images comparable with those obtained during the MACE procedure.

4.1.14 Statistical Analysis

Statistical analysis was performed using GraphPad Prism, Version 7. A p-value of less than 0.05 was considered statistically significant. Normally distributed data were compared using paired t-tests, while non-normally distributed data were compared using Wilcoxon signed rank test. A multilinear regression model as used to identify factors which may influence oesophageal transit time. Sensitivity and specificity of diagnoses made by MACE were calculated based on OGD diagnosis being the gold standard. The intra-observer agreement in the recorded OGD and MACE images was determined using kappa statics.

Figure 15: A flow diagram summarising the MACE study protocol



Results

4.1.15 Baseline characteristics

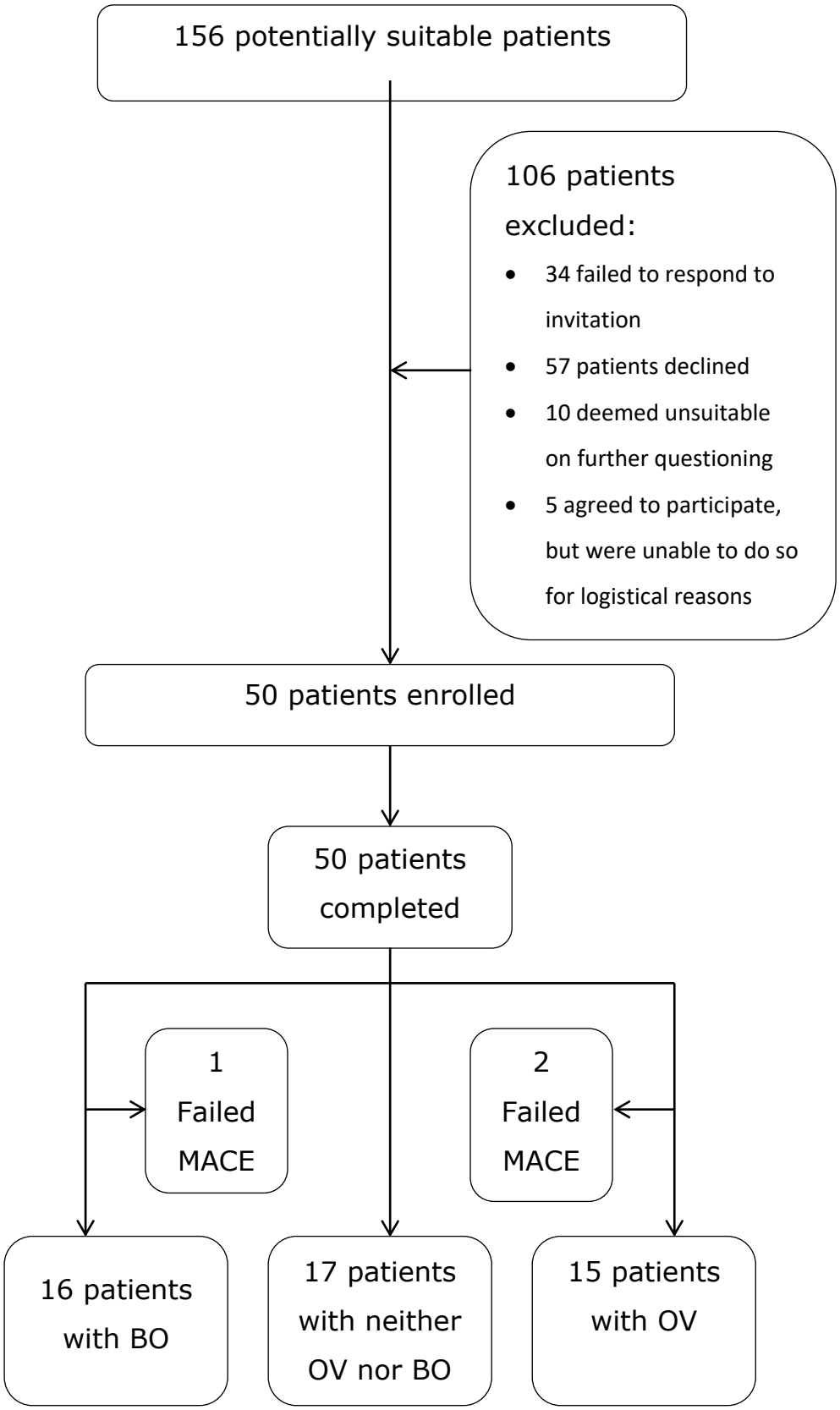
50 patients were recruited into the study, of which 47 (94%) completed the MACE procedure and 50 (100%) completed the OGD. As per the recruitment criteria, these were composed of patients with endoscopically diagnosed BO (17), OV (17) and patients with neither BO nor OV (16). The recruitment process and baseline characteristics of the study cohort are summarised below **Table 17** and **Figure 16**

Table 17: The baseline characteristics of study participants

Characteristic		**Number/ mean (range)**
Gender distribution	Male	34
	Female	16
Age (years)		60.5 (39-83)
Body Mass Index		29.5
Dimensions (cms)	Chest	104 (86-127)
	Waist	105 (63- 133)
	Hip	103 (92- 141)
Indication for procedure	Variceal surveillance	17
	Variceal screening	1
	Barrett's surveillance	18*
	Gastro-Intestinal bleeding	3
	Dyspepsia / pain	7
	UGI surveillance	4
Number of previous of OGDs (for any indication)		2.5 (0 - 12)

*One patient who was recruited in the Barrett's group did not have Barrett's on OGD and was therefore moved to the control group.

Figure 16: A flow diagram summarising study recruitment



4.1.16 Feasibility

All 50 patients were able to undertake the OGD. It is however of noted that 45% opted to have sedation, with a median dose of 3mg of midazolam and 50mcg of pethidine administered. Of the 50 patients recruited, three patients were unable to undertake the MACE procedure. In all cases this was due to being unable to swallow the capsule whilst supine, despite having no known swallowing disorders. All three managed to tolerate their OGD with the use of sedation. There were no post procedural complications using either technique, and no patients retained the capsule at two weeks.

4.1.17 Tolerance and patient preference

The MACE procedure rated more favourably than OGD for all comfort related domains. The mean VAS associated with MACE was 9.4, compared to 6.6 with OGD ($P<0.0001$). This trend persisted even when the use of sedation prior to OGD was taken in to account, **Table 18**. Further, MACE was considered more comfortable for each of the specific symptoms recorded, gagging, choking and discomfort. Participants who completed the two-week questionnaire (37 of 47 participants) preferred to undergo the MACE procedure, should they require a further procedure (73% vs 0%). This corroborates previous studies, where capsule visualisation has been used as an alternative

where patients have declined flexible endoscopy [165]. From this study design, it is not possible to ascertain whether improved comfort would result in greater take up rates.

Table 18: Comfort and tolerability of procedures

		MACE	OGD	P-Value
Specific symptoms	Gagging/ retching	0 (IQR 0-5.5)	6 (IQR 4- 9)	**0.0001**
	Choking	0 (IQR 0-0)	4 (IQR 0.5 -9)	**0.0002**
	Discomfort	0 (IQR 0-0)	5 (IQR 3-8.5)	**<0.0001**
Visual Analogue Scale	All patients (n=47)	9.4 (SD+/-1.3)	6.6 (SD+/- 2.6)	**<0.0001**
	Sedated cohort (n=31)	9.6 (SD+/- 0.8)	6.5 (SD+/- 0.5)	**<0.0001**
	Unsedated Cohort (n=16)	9.1 (SD+/- 1.8)	6.8 (SD+/- 2.5)	**0.0182**
Preference	Preferred procedure at 2 weeks	27/37	0/37	

4.1.18 Capsule manipulation within the oesophagus

Of the 47 patients who successfully swallowed the capsule, the oesophagus was visualised in all cases. Control of the capsule was variable, with a mean oesophageal transit time of 190secs, (range: 5secs- 634secs). It was not possible to identify any operator or patient factors which influenced oesophageal transit time. There was a non-significant trend towards increased transit time in association with increased operator experience as the study progressed, R=0.13 (CI -0.17- 0.41) p=0.39, **Figure 17.**

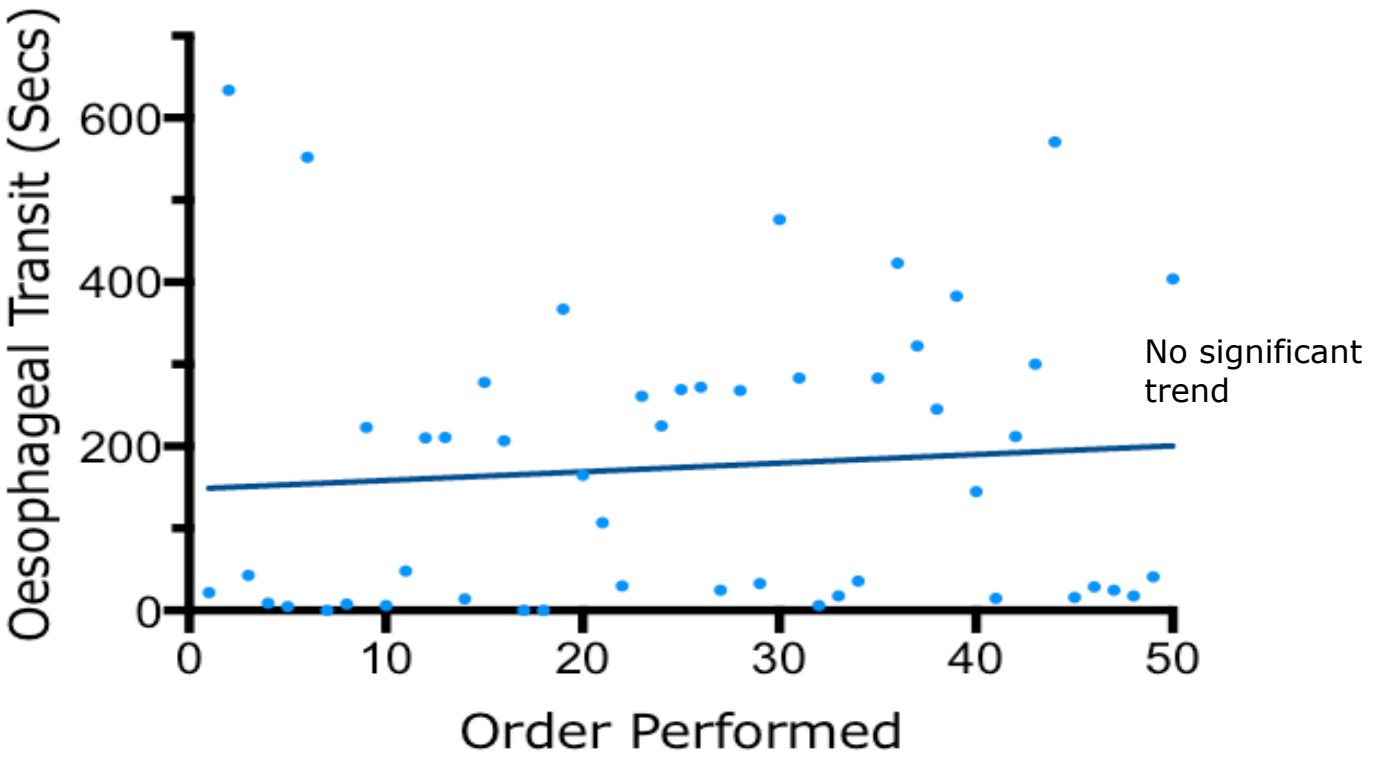


Figure 17: The learning curve for holding capsule in oesophagus

4.1.19 Capsule manipulation within the stomach

Complete visualisation of the stomach was attempted through a combination of position changes and use of the hand-held magnet. As demonstrated in previous studies, the fundus remains a potential blind spot during the MACE procedure, with OGD quality of views significantly superior, **Table 19**. This study was not powered to calculate the ability to detect gastric pathology; however 2 lesions seen on OGD were not seen on MACE, whilst 1 lesion was missed by OGD.

Table 19: The quality of endoscopic view at the major landmarks

		MACE	OGD	P-Value
Visualisation Median score/ Inter Quartile Range (IQR)	Oesophagus /GOJ	4 (IQR 4- 4)	4 (IQR 4- 4)	0.0005
	z- line	4 (IQR 4- 4)	4 (IQR 4- 4)	0.0176
	Fundus	3 (IQR 2- 4)	4 (IQR 4- 4)	<0.0001
	Body	4 (IQR 3- 4)	4 (IQR 4- 4)	0.0012
	Antrum	4 (IQR 3- 4)	4 (IQR 4- 4)	0.0002

4.1.20 Capsule manipulation into the duodenum

The magnet could not be used to transfer the capsule from the stomach into the duodenum. When the MACE examination was complete, the capsule was placed within close proximity of the pylorus, but it was not possible to overcome pyloric contractions in order to traverse the pylorus. For logistical reasons the equipment had to be removed early in 4 cases and so the capsule was not observed to transit into the duodenum. Of the 43 cases where the duodenum was entered, a gastric transit time of 35 mins (range: 2 mins- 2 hours 17 mins) was observed. This is consistent with a previous study, where it was concluded that the MiroCam Navi MACE system could not be used to reduce the gastric transit time, reporting an average passage of 35.5 minutes [126]. Active small bowel bleeding was diagnosed on capsule following the MACE in one patient, which was beyond the reach of the OGD.

4.1.21 Accuracy in the detection of oesophageal pathology

With the use of MACE, it was possible to make a correct real-time diagnosis in 15 of the 16 cases of Barrett's oesophagus, with no false positives **Table 20.** Where oesophageal varices were present, MACE was possible to diagnose these in 11 out of the 15 cases, with no false positives. This study was not powered to compare the length of the Barrett's segment or grade of varices between modalities. Oesophageal pathology other than Barrett's or Varices, was seen in 3 cases. This included one inlet patch and oesophagitis. All these lesions were seen in both imaging modalities, example images can be seen in **Figure 18** and **Figure 19.**

4.1.22 Intra-observer variability

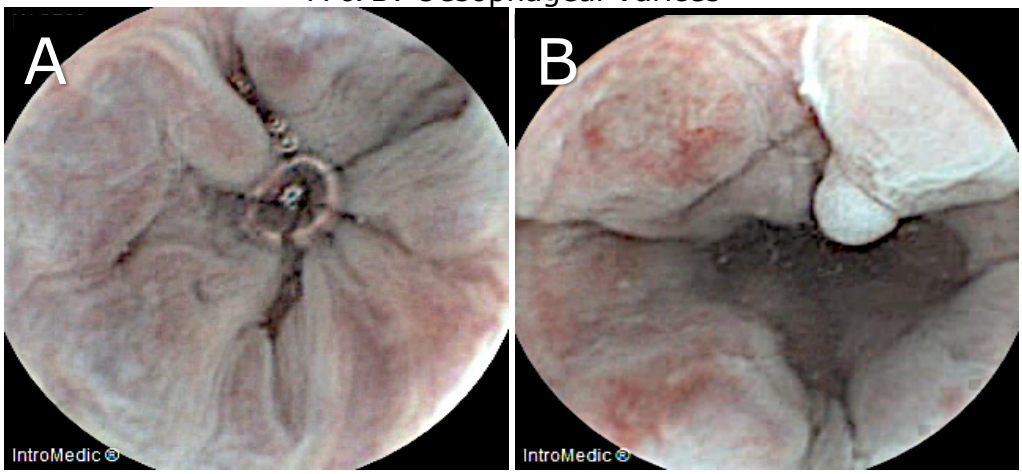
We attempted to offset potential operator bias by the post procedural review of the videos of both the OGD and MACE. These were reviewed by 5 endoscopists, all of whom are certified to be independent in UGI endoscopy but had no specific training in the interpretation of upper GI capsule endoscopy. Here we found that kappa values ranged from 0.44- 0.60 for agreement with the real-time MACE diagnosis and 0.69- 0.83 with OGD.

Table 20: Accuracy in the detection of oesophageal pathology

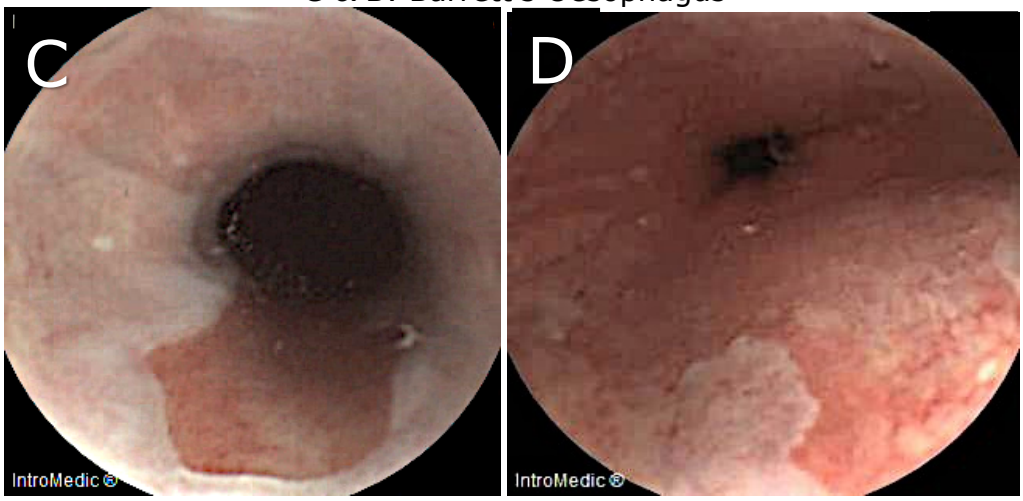
	Sensitivity	**specificity**	**Negative predictive value**
Detection of Barrett's	93.8% (69.8- 99.8%)	100% (88.8- 100%)	96.9% (82.3-99.5%)
Detection of Varices	86.7% (59.5- 98.3%)	100% (89.1- 100%)	95.7% (85.5-99.5%)
Detection of oesophageal pathology	90.3% (74.3- 97.7%)	100% (79.4- 100%)	84.2% (64.5-93.9%)

Figure 18: Example pictures of oesophageal pathology detected on MACE

A & B: Oesophageal Varices



C & B: Barrett's Oesophagus



E: Oesophagitis above a Barrett's segment F: Cervical Inlet Patch

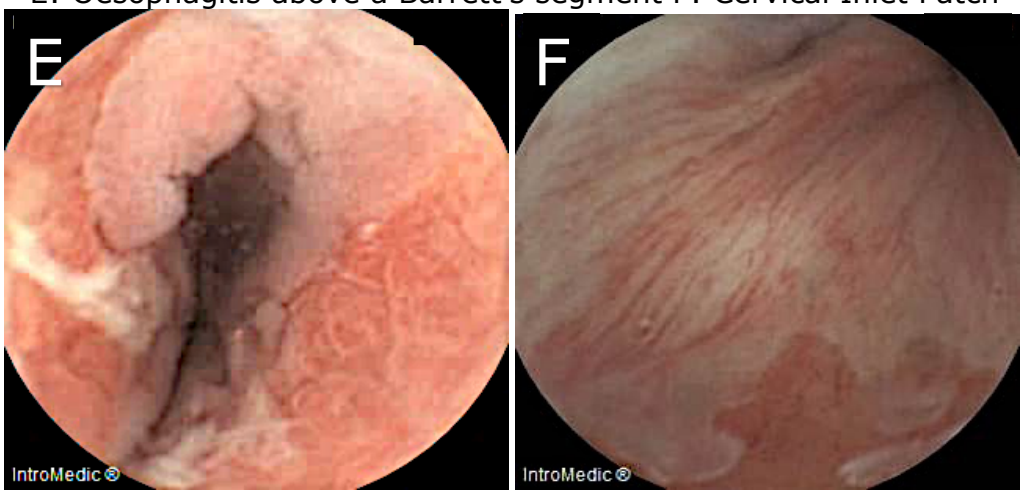
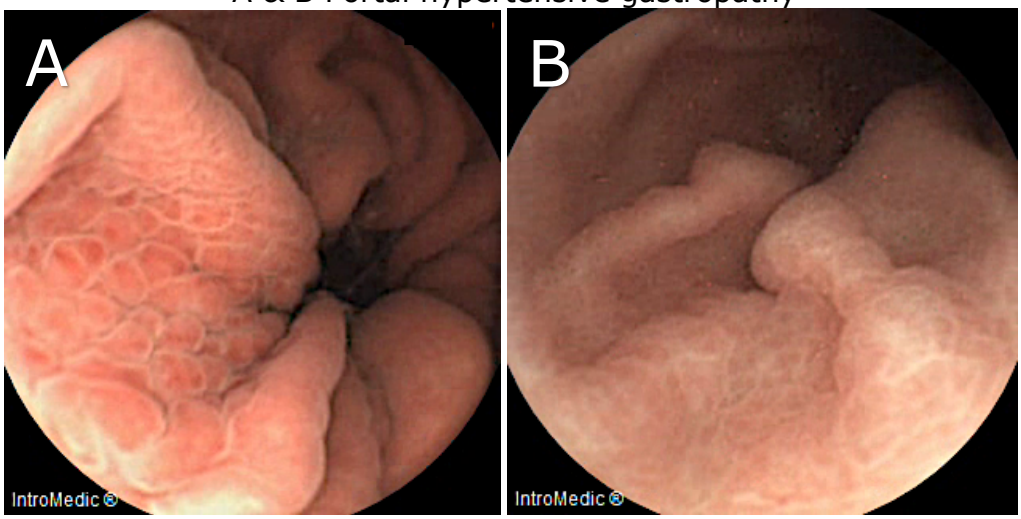
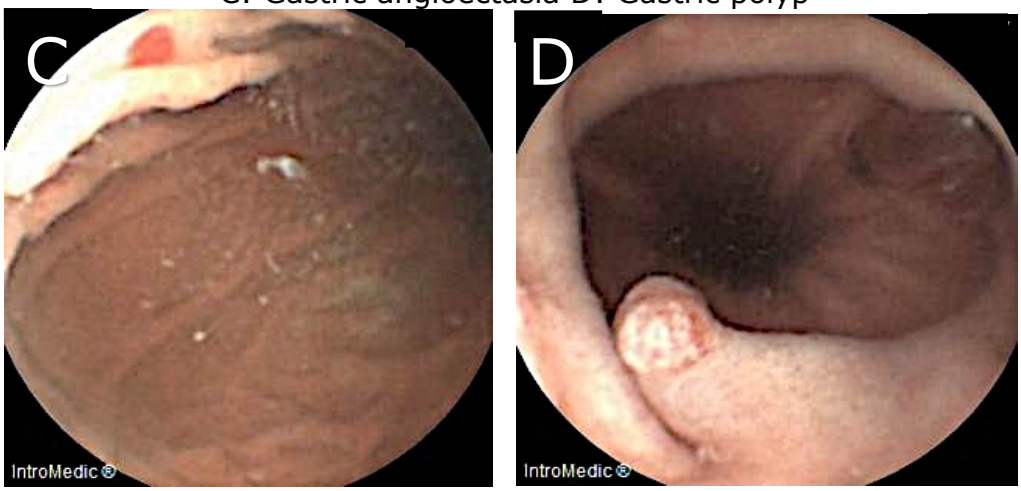


Figure 19: Example pictures of non-oesophageal pathology detected on MACE

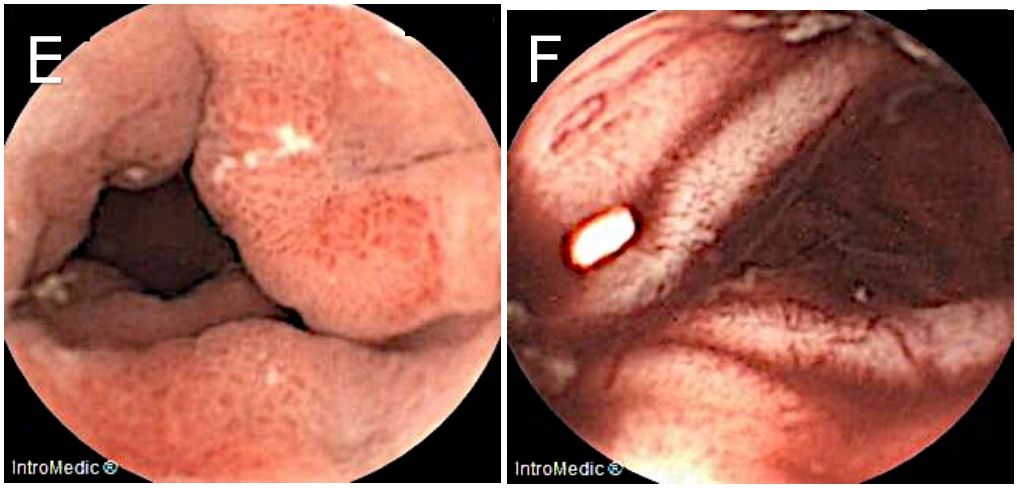
A & B Portal hypertensive gastropathy



C: Gastric angioectasia D: Gastric polyp



E: Duodenitis F: Active small bowel bleed



Discussion

4.1.23 Principle findings

The results from this study suggest that MACE is both technically feasible and safe. Accuracy in the diagnosis of oesophageal pathology as compared with OGD was reasonable. Patients reported high levels of comfort, preferring this investigative modality over OGD. No procedural related complications were encountered.

There was a difference in the technical success of -6% (94% with MACE versus 100% with OGD). This initial experience compares with published data suggesting a technical success of oesophageal intubation of 99% with OGD (with the use sedation if required) [168], 96- 99% with unsedated trans-nasal endoscopy [169,170], 93.9% using the cytosponge [171] and 98% and with a dedicated oesophageal capsule [172].

Once swallowed, it was possible to control the capsule within the oesophagus, as demonstrated by the oesophageal transit time. We arbitrarily took a transit time of over 60 seconds as a marker of successful magnetic capture of the capsule, which was achieved in 27 (57%) of the participants. However this is probably a conservative estimate of manoeuvrability, with a previous study of a non-magnetic oesophageal specific capsule

demonstrating an average oesophageal transit time of 14 secs (95% CI 4 to 86secs) when ingested in a supine position, or just 3 secs (95%CI: 3- 8secs) when the patients were standing at the time of ingestion [172]. Despite rapid transit, the GOJ was visualised a 100% and the z-line in 91.5%. It is possible that this could be improved further with modifications in capsule design, with the oesophageal capsule offered by PillCam-ESO3 taking 30 images per second. Were this modification to be applied, this could result in additional 5130 oesophageal images acquired per patient in our study cohort.

In this pilot study, we were able to demonstrate a reasonable accuracy for the detection of oesophageal pathology, although at present insufficient at present to replace conventional endoscopy. Our data compare to previous studies using either a string-capsule or the dedicated oesophageal capsule, which report accuracy in the diagnosis of OV of 86% (range: 77%-96%) [173–176]. We demonstrated better sensitivity for the presence of Barrett's, which has a pooled sensitivity of 86% [177]

4.1.24 Implications for clinical practice

There is increasing interest in developing minimally invasive, community-based techniques for investigation of the upper GI tract. MACE meets this brief, with the additional potential of providing pan-endoscopy within a single procedure. The current cost of capsule equipment has thus far been prohibitive for routine use. However this may be offset with the potential of performing this procedure with the aid of non-medical endoscopists or physician extenders and within the community setting without the requirement for sedation [178]. Whilst capsule endoscopy does not allow for the acquisition of histological samples, it is known that the majority of OGDs are diagnostic with no requirement for biopsies or intervention for many indications, with as many as 78% of those undergoing endoscopy for dyspepsia demonstrating no mucosal abnormalities [179]. With a high negative predictive value upper GI capsule could be regarded as a scouting technique, in order to detect those with major pathology or with pre-malignant change, who warrant more detailed assessment with advanced imaging or the acquisition of histology.

This technology exists within an environment that includes alternatives such as trans-nasal endoscopy and oesophageal capsule, as well as non-endoscopic techniques such as the

cytosponge. Limitations of the ESO capsule include its short battery life, which limits imaging to the oesophagus and stomach. The Cytosponge allows for the acquisition of cytological specimens to evaluate specific oesophageal pathology, but no endoscopic images and with evaluation limited to the oesophagus [171,180]. Unsedated nasal endoscopy is perhaps the most comparable modality being performed in the community, with no sedation and high levels of patient acceptability. Further on in its development, there has been an improvement in the quality of images obtained and high levels of diagnostic accuracy demonstrated. Specific benefits of MACE would be in those who have a condition which would benefit from pan endoscopy, such as those being investigated for iron deficiency anaemia or in those who decline flexible endoscopy.

Unanswered questions include whether the results of the MACE procedure would be as promising in an unselected population with a wider variety of pathology, in particular focal lesions.

4.1.25 Study strengths and limitations

This study was conducted within a single centre, with all MACE procedures performed by a single operator. While this ensures consistency in technique and environment, it does question the reproducibility of these results outside of this setting.

The endoscopic diagnosis made from the MACE procedures were made in real-time. The operator was not blinded to the appearances of the patient. Given that a proportion of the participants had underlying liver disease it could be argued that the phenotype of these patients may influence the operator of the pre-test suspicion of oesophageal varices. This potential bias is thought to be of minimal influence, given that the control cohort included patients with suspected OV and BO, which were correctly diagnosed as normal at both OGD and MACE.

Unanswered questions include whether the results of the MACE procedure would be as promising in an unselected population with a wider variety of pathology, in particular focal lesions. Further studies would be required to assess whether MACE is able to accurately diagnosis Barrett's segment length or Varices grade. Future work to advance this field would include an evaluation of this technique in a community setting and

performed by non -physicians, as well as an economic analysis of this approach as compared to OGD.

Conclusions

The findings from this pilot study demonstrate that the MACE procedure is safe and well tolerated by patients. Acceptable accuracy was demonstrated for the diagnosis of oesophageal pathology but require validation through larger studies. There is scope to optimize the available technology to improve upon these results further.

Chapter5:. Conclusions and future directions

In this thesis, we have reviewed the current and expanding role of capsule endoscopy in clinical practice. This technology is ideally suited to visualisation of the small bowel. However as discussed, at present there is little in the way of monitoring and standardisation of practice. There is ongoing work to introduce structured learning with accreditation prior to practice in the UK.

In the first study, we examined the potential impact of fatigue in capsule endoscopy interpretation. Here we have demonstrated that fatigue appears to have an effect on lesion detection after reading a single capsule video. This may have an impact in daily practice, as clinicians reported that they routine read more than three cases in a session. It is difficult to know if this directly translates to changes in management in real life. We have not been able to identify a reliable technique for measuring fatigue and concentration, which in the future could be a useful tool in work planning. This phenomenon may be applicable to other areas of gastroenterology and further work into this area may be helpful in optimising quality and standards, in the similar way in which high risk industries change working conditions in order to reduce risk and harm.

Future avenues for research include the evaluation techniques for measuring fatigue for the various endoscopic procedures performed and trying to change work habits in order to avoid the deleterious impact of this phenomenon.

We have evaluated the use of Omni Mode in reducing capsule reading times. This area remains interesting, as offers the potential to reduce the cost of this procedure through time-saving. We have demonstrated faster reading times and non-inferiority in accuracy of lesion detection. There remain questions as to what is an acceptable level of accuracy is and whether such algorithms can be adjusted to save even more time with reasonable sensitivities. It is likely that this field will evolve in the years to come with the introduction of artificial intelligence. Computer algorithms that aid polyp detection and characterisation are already being trialled in colonoscopy. Capsule would appear to be the ideal scenario to adopt artificial intelligence, which in the future may negate the need for human reading at all. Future work will invariably involve the development and evaluation of software to provide and automated report.

The last section of this thesis examines the use of a MACE system for upper GI endoscopy. Since the advent of capsule

endoscopy there has been the expectation that developments would increase capabilities of this tool, with the potential to revolutionise gastroenterology by replacing diagnostic flexible endoscopy altogether. The magnetic capsule is probably the closest we have come in terms of being able to achieve controlled upper GI endoscopy. While a lot of further work is required to develop this technology, manoeuvrability forms the basis of any real attempt to utilise capsule outside of the small bowel. Our study reports accuracies that are not yet sufficient to replace endoscopy, but it is conceivable that with adjustment to capsule properties, such as frames rate and depth of view, that these could be overcome. Future work in this area will need to involve changes to capsule to allow better control and visualisation in the upper gastrointestinal tract. A cost-benefit analysis of using capsule in an outpatient setting as an alternative to gastroscopy would be useful in guiding as to the usefulness of developing such technology.

Capsule endoscopy is here to remain in the field of gastroenterology, it is likely with improving the specification and increased automation, capsules are likely to play a greater role in our future practice.

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Chapter7:. Appendices

Appendix A: Fatigue study, participant information sheet

Appendix B: Fatigue study consent form

Appendix C: Baseline questionnaire for participants of the capsule fatigue study

Appendix D: FRISBEE CRF

Appendix E: FRISBEE VAS score

Appendix F: Omni study clinical record form

Appendix G: MACE study MACE clinical record form

Appendix H: MACE study, OGD clinical record form

Appendix I: MACE study, baseline questionnaire

Appendix J: MACE study post MACE questionnaire

Appendix K: MACE study post OGD questionnaire

Appendix L: MACE study, Two week questionnaire

Appendix M: MACE study, Patient Information Sheet

Appendix N: MACE study, Consent form

FRISBEE: PARTICIPANT INFORMATION SHEET

Fatigue in the Reading and Interpretation of Small Bowel capsulE Endoscopy?

Invitation:

You are being invited to take part in a research study. Before you decide we would like to explain why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?
Small bowel capsule endoscopy (SBCE) allows for mucosal inspection of the small bowel with relative ease. A sequence of several thousand images is produced, taking between 30 – 90 minutes to read and interpret. Pathology may be subtle and may only be present on isolated images. Concentration is therefore a prerequisite to accurate SBCE reading.

The model for SBCE services varies in different types of hospital. In tertiary referral centres where enteroscopy is available, SBCE may contribute significantly to work load. In contrast in smaller community hospitals the need for this service may be more intermittent. This leads to challenges in the provision to services, with on one hand readers being required to read a large volume of studies in a defined period of time, to readers reading a few studies but having no designated slot and having to fit this around pre-existing commitments. Both these scenarios create the possibility of readers having to interpret SBCE cases, whilst their concentration is suboptimal.

Fatigability has been demonstrated in various clinical scenarios. Whilst anecdotally this also experienced during SBCE, this phenomenon is yet to be demonstrated in the scientific literature. In this study we hope to determine whether accuracy in capsule endoscopy interpretation is associated with fatigue. If this is the case we hope to establish the number of cases that can be read before accuracy is significantly affected.

Why have I been chosen?
You have been chosen because you are either an established capsule endoscopy reader or a novice with prior endoscopy experience.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What will happen if I take part?
If you agree, you will be invited to select a convenient day where you have no other clinical responsibilities and have sufficient time in order to complete this study. In institutions where the Olympus capsule endoscopy reading software is not available, equipment to allow the interpretation of the cases will be arranged.

You will be asked to read a total of six capsule endoscopy cases. Each of these will have a study number and you will be given instructions of which order in which to read these. You will need to complete a questionnaire prior to starting as well as after every two capsule cases. Although there will be breaks in between cases, these will be limited in time. We would therefore suggest that you have no scheduled clinical commitments for the duration of your participation.

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

CONSENT FORM
(Draft Version 1 / Final version 1.0: date July 2016)

Title of Study: FRISBEE study

REC ref:

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1 dated July 2016 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I agree that the information gathered during this study can be stored by the University of Nottingham at the Biomedical Research Unit, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. ☐
I understand am free to opt out of this and still be eligible to participate in this study ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

1

FRISBEE Study Consent form
Final Version 1.0,19 July 2016

Fatigue in the Reading and Interpretation of Small Bowel capsulE Endoscopy (FRISBEE study) Baseline questionnaire

Name

What is your background?

- Nurse endoscopist
- Nurse capsule reader
- Gastroenterology trainee
- Gastroenterology consultant

How many years of endoscopy experience do you have?

- No previous experience
- Less than one year
- Between 1- 5 years
- More than 5 years

Have you ever had formal training in capsule endoscopy interpretation (course/supervision during training)?

- Yes
- No

What is your previous capsule endoscopy experience?

- No previous experience
- 0 – 10 cases
- 10-20 cases
- 20-50 cases
- 50- 100 cases
- 100 + cases

Is the interpretation of capsule endoscopy part of your current job role?

- Yes
- No

If yes, what is the maximum number of capsule studies that you would read in one clinical session?

- 1
- 2
- 3
- 4
- 5
- 6
- 6+

FRISBEE: Clinical Record Form

BRU ID ☐☐ - ☐☐☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

Details of Capsule Study

Number assigned to capsule study: ☐☐☐☐

Name of contributing hospital:

Name of capsule reader:

Reading Mode: ☐ 6 - 10 fps ☐ 10 - 14 fps ☐ 14 - 18 fps ☐ 18 - 22 fps ☐ 22 - 26 fps

Total reading time: ☐☐:☐☐:☐☐ **(excluding interruptions)**

		P- Classification	Time Code
Lesion 1		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 2		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 3		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 4		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 5		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 6		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 7		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 8		☐0 ☐1 ☐2	☐☐:☐☐:☐☐



BRU ID ☐☐ - ☐☐☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

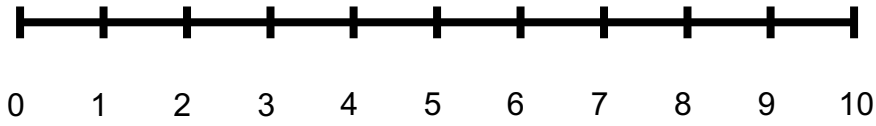
		P- Classification	Time Code
Lesion 9		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 10		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 11		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 12		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 13		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 14		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 15		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 16		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 17		☐0 ☐1 ☐2	☐☐:☐☐:☐☐
Lesion 18		☐0 ☐1 ☐2	☐☐:☐☐:☐☐

Conclusion of study and recommendations made

Page 2 - FRISBEE: Clinical Record Form

Visual Analogue Score (VAS)

Please rate your experience of fatigue, from 0 where you feel fatigued and unable to concentrate to 10 where you are fully alert.



Fatigued Alert

MACE STUDY: MACE CRF

BRU ID ☐☐ - ☐☐☐☐ Date of Procedure ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐ Endoscopist ☐☐☐

Patient measurements

Height (cm) ☐☐☐ Weight (kg) ☐☐☐

Waist (cm) ☐☐☐ Hip (cm) ☐☐☐ Chest (cm) ☐☐☐

Volume of water drunk pre procedure ☐☐☐

Volume of water drunk during the procedure ☐☐☐

Procedure time (mins:secs) ☐☐:☐☐

Landmarks:

			Clarity of view (1: no view, 4: perfect visualisation)
Z-line viewed	☐ Yes	☐ No	if yes: ☐ 1 ☐ 2 ☐ 3 ☐ 4
GOJ viewed	☐ Yes	☐ No	if yes: ☐ 1 ☐ 2 ☐ 3 ☐ 4
Hiatus Hernia	☐ Yes	☐ No	if yes size: ☐☐
Fundus	☐ Yes	☐ No	if yes: ☐ 1 ☐ 2 ☐ 3 ☐ 4
Body	☐ Yes	☐ No	if yes: ☐ 1 ☐ 2 ☐ 3 ☐ 4
Antrum	☐ Yes	☐ No	if yes: ☐ 1 ☐ 2 ☐ 3 ☐ 4
Barrett's	☐ Yes	☐ No	
Estimate of Prague Classification	☐ C	☐ M	
Oesophageal varices	☐ Yes	☐ No	No. of columns ☐☐☐☐ Varices grade ☐☐☐
Gastric varices	☐ Yes	☐ No	Varices grade ☐☐☐

Comments/Diagnosis/Findings

Adverse events scales from 0 - 10 (patient reported - doctor or nurse to ask)

Gagging/retching (0-10): ☐☐ Choking (0-10): ☐☐ Discomfort (0-10) ☐☐

Images protocol:

1- Normal Oesophagus/Barrett's/Varices overviews	☐ Yes	☐ No
2- Landmarks: Z-line/GOJ/Diaphragm/J-manoeuvre	☐ Yes	☐ No
3- Stomach	☐ Yes	☐ No
Video all procedure	☐ Yes	☐ No

Name of person performing procedure ☐☐☐☐☐☐☐☐ Signature ☐☐☐☐☐☐☐☐

Date ☐☐ - ☐☐ - ☐☐☐☐

MACE STUDY STANDARD ENDOSCOPY CRF

BRU ID ☐☐ – ☐☐☐☐ Date of Procedure ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

Endoscopist ☐☐☐ Assisted ☐ Yes ☐ No No. of attempts ☐☐

Sedation ☐ Yes ☐ No If yes: Midazolam dose ☐☐☐

Pethidine dose ☐☐☐

Procedure time (mins:secs) from insertion to withdrawal: ☐☐ : ☐☐

Landmarks: Clarity of view (1: no view, 4: perfect visualisation)

Z-line viewed	☐ Yes	☐ No	if yes:	☐ 1	☐ 2	☐ 3	☐ 4
GOJ viewed	☐ Yes	☐ No	if yes:	☐ 1	☐ 2	☐ 3	☐ 4
Hiatus Hernia	☐ Yes	☐ No	if yes size:	☐☐			
Fundus	☐ Yes	☐ No	if yes:	☐ 1	☐ 2	☐ 3	☐ 4
Body	☐ Yes	☐ No	if yes:	☐ 1	☐ 2	☐ 3	☐ 4
Antrum	☐ Yes	☐ No	if yes:	☐ 1	☐ 2	☐ 3	☐ 4
Barrett's	☐ Yes	☐ No					
Estimate of Prague Classification	☐ C	☐ M					
Oesophageal varices	☐ Yes	☐ No	No. of columns ☐☐☐☐		Varices grade ☐☐☐		
Gastric varices	☐ Yes	☐ No			Varices grade ☐☐☐		
J-manoeuvre with GOJ visualisation	☐ Yes	☐ No	if yes:	☐ 1	☐ 2	☐ 3	☐ 4
D2 intubation	☐ Yes	☐ No					

Comments/Diagnosis/Findings



Adverse events scales from 0 - 10 (patient reported - doctor or nurse to ask)

Gagging/retching (0-10): ☐☐ Choking (0-10): ☐☐ Discomfort (0-10) ☐☐

Images protocol:

1- Normal Oesophagus/Barrett's overviews	☐ Yes	☐ No
2- Landmarks: Z-line/GOJ/Diaphragm/J-manoeuvre	☐ Yes	☐ No
3- Stomach/pylorus/D2	☐ Yes	☐ No
Video all procedure	☐ Yes	☐ No

Name of person performing procedure Signature

Date ☐☐ – ☐☐ – ☐☐☐☐

Magnet Assisted Capsule Endoscopy (MACE) Study
Baseline Questionnaire

BRU ID ☐☐ - ☐☐☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

Short Form Spielberger State-Trait Anxiety Inventory (STAI-6)

Please read the 6 statements below and then tick the most appropriate box for each statement to indicate how you feel right now, at this moment:

A.1 - I feel Calm	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.2 - I am tense	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.3 - I feel upset	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.4 - I am relaxed	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.5 - I feel content	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.6 - I am worried	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much



Magnet Assisted Capsule Endoscopy (MACE) Study
Post Standard Gastroscopy Questionnaires

BRU ID ☐☐ - ☐☐☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

Short Form Spielberger State-Trait Anxiety Inventory (STAI-6)

Please read the 6 statements below and then tick the most appropriate box for each statement to indicate how you feel right now, at this moment:

A.1 - I feel Calm	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.2 - I am tense	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.3 - I feel upset	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.4 - I am relaxed	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.5 - I feel content	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.6 - I am worried	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much

Visual Analogue Score (VAS)

Please rate the experience of having the oral camera test (through the mouth) on the scale below by selecting a number from 0 (worst experience) to 10 (best experience):



0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10



Worst experience

Best experience



Magnet Assisted Capsule Endoscopy (MACE) Study
Post MACE Questionnaires

BRU ID ☐☐ - ☐☐☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

Short Form Spielberger State-Trait Anxiety Inventory (STAI-6)

Please read the 6 statements below and then tick the most appropriate box for each statement to indicate how you feel right now, at this moment:

A.1 - I feel Calm	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.2 - I am tense	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.3 - I feel upset	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.4 - I am relaxed	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.5 - I feel content	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.6 - I am worried	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much

Visual Analogue Score (VAS)

Please rate the experience of having the oral camera test (through the mouth) on the scale below by selecting a number from 0 (worst experience) to 10 (best experience):



0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐



Worst experience

Best experience

Magnet Assisted Capsule Endoscopy (MACE) Study
Two week Questionnaires

BRU ID ☐☐ - ☐☐☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐

Participant ID: ☐☐☐☐☐☐

Short Form Spielberger State-Trait Anxiety Inventory (STAI-6)

Please read the 6 statements below and then tick the **most appropriate box for each statement** to indicate how you feel right now, at this moment:

A.1 - I feel Calm	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.2 - I am tense	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.3 - I feel upset	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.4 - I am relaxed	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.5 - I feel content	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much
A.6 - I am worried	☐ Not at all	☐ Somewhat	☐ Moderately	☐ Very Much

MACE STUDY: PATIENT INFORMATION SHEET

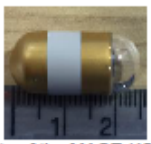
Study title: An observational study to evaluate a magnet assisted capsule endoscope in imaging the oesophagus: The MACE study.

Invitation:

You are being invited to take part in a research study. Before you decide we would like to explain why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

A standard camera test (gastroscopy) is relatively expensive as this is performed in hospital and whilst complications are uncommon these may occur; therefore this test is not suitable for use in every patient. There has been a lot of research to look for alternatives that are easier to perform and more comfortable for the patient. Magnet assisted capsule endoscopy (MACE) is one such alternative. This is a small camera, within a pill sized casing, which is simply swallowed. A hand held magnet is used externally, held at the chest, to help manoeuvre the capsule to enable clear views of the lining of the oesophagus. The purpose of this study is to see whether the magnetic assisted capsule endoscopy is as good as the standard camera test. We are asking 3 groups of patients to take part in this study: 1- Patients known to have Barrett's Oesophagus, 2- Patients who are known to have chronic liver disease (scarring of the liver) and 3- Patients with heartburn/indigestion/acid reflux symptoms or anaemia.



Life size photo of the MACE (10.8x 25.5mm)

There are certain conditions like Barrett's Oesophagus (where the normal cell lining of the gullet becomes similar to that of the stomach or small intestine) and Oesophageal Varices (swollen veins in the gullet) that can happen in patients who do not have any symptoms. Barrett's Oesophagus can occasionally lead to cancer of the gullet. Similarly, Oesophageal Varices can cause serious bleeding in the gullet. If these conditions are diagnosed and treated early then patients can avoid these complications.

If the results show that the magnetic capsule endoscopy is useful and more comfortable for patients, then this will mean that it can be used to diagnose many patients who may have these two conditions and treat them early. This can reduce the chance of complications and improve the quality of life and survival for these patients.

You will not need any sedation for this test, or have to undergo any other preparation, other than adhering to the instructions for your gastroscopy. You will undergo the magnetic capsule first. This involves swallowing the capsule, whilst wearing some sensing pads across the chest and abdomen. After the test the capsule will pass through the small and large bowel, before being passed naturally when going to the toilet. Passage of the capsule may take several days, you do not need to retrieve the capsule, although we do ask you to look after passing stool to see if the capsule has passed. After this you will have the standard gastroscopy, which can be performed using throat spray or sedation depending on your preference. We would like you to complete some questionnaires both on the day and two weeks after, so we can determine how comfortable these tests were.

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

CONSENT FORM
(Final version 2.0: date Apr 2016)

Title of Study: MACE study

REC ref:

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1 dated November 2015 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw from this study then information may still be used in the project analysis, unless I indicate I would like this to be removed. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4.I understand and agree that an anonymised recording of the MACE and endoscopy procedure will be taken for to assess the quality of these procedures. ☐

5. Optional: I agree that the information gathered about me can be stored by the University of Nottingham at the Biomedical Research Unit, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway. I understand am free to opt out of this and still be eligible to participate in this study (if this is the case please leave box empty) ☐

7. I agree to my GP being informed of my participation in this study. ☐

8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes[1]

[1] MACE Study Consent form
Final Version 2.0, April 2016