Magnetically Assisted Capsule Endoscopy: A Viable Alternative to Conventional Flexible Endoscopy of the Stomach?

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07/09/2016

Acknowledgements

"Somewhere, something incredible is waiting to be known."- Carl Sagan

Thank you to my family for always supporting me. Thank you to Dr ME McAlindon for always encouraging me. And finally, thank you to Mike for never doubting me.

Abstract

INTRODUCTION: Oesophagogastroduodenoscopy is the investigation of choice to identify mucosal lesions of the upper gastrointestinal tract, but it is poorly tolerated by patients. A simple non-invasive technique to image the upper gastrointestinal tract, which could be made widely available, would be beneficial to patients. Capsule endoscopy is well tolerated by patients but the stomach has proved difficult to visualise accurately with capsule technology due to its' capacious nature and mucosal folds, which can obscure pathology. MiroCam Navi (Intromedic Ltd, Seoul, Korea) is a capsule endoscope containing a small amount of magnetic materialwhich has been made available with a handheld magnet which might allow a degree of control. This body of work aims to address whether this new technology could be a feasible alternative to conventional flexible endoscopy of the stomach.

METHODS: Four studies were conducted to test this research question. The first explores the feasibility of magnetically assisted capsule endoscopy of the stomach and operator learning curve in an ex vivo porcine model. This was followed by a randomised, blinded trial comparing magnetically assisted capsule endoscopy to conventional flexible endoscopy in ex vivo porcine stomach models. Subsequently a prospective, single centre randomised controlled trial in humans examined whether magnetically assisted capsule endoscopy could enhance conventional small bowel capsule endoscopy by reducing gastric transit time. Finally a blinded comparison of diagnostic yield of magnetically assisted capsule endoscopy compared to oesophagogastroduodenoscopy was performed in patients with recurrent or refractory iron deficiency anaemia.

RESULTS:In the first study all stomach tags were identified in 87.2% of examinations and a learning curve was demonstrated (mean examination times for the first 23 and second 23 procedures 10.28 and 6.26 minutes respectively ($p<0.001$). In the second study the difference in sensitivities between oesophagogastroduodenoscopy and conventional flexible endoscopy for detecting beads within an

ex vivo porcine stomach model was 1.11 (95% CI 0.06, 28.26) proving magnetically assisted capsule endoscopy to be non-inferior to flexible endoscopy. In the first human study, although there was no significant difference in gastric transit time or capsule endoscopy completion rate between the two groups (p=0.12 and p=0.39 respectively), the time to first pyloric image was significantly shorter in the intervention group (p=0.03) suggesting that magnetic control hastens capsular transit to the gastric antrum but cannot impact upon duodenal passage. In the last study, a total of 38 pathological findings were identified in this comparative study of magnetically assisted capsule endoscopy and conventional endoscopy. Of these, 16 were detected at both procedures, while flexible endoscopy identified 14 additional lesions not seen at magnetically assisted capsule endoscopy and magnetically assisted capsule endoscopy detected 8 abnormalities not seen by oesophagogastroduodenoscopy. No adverse events occurred in either of the human trials. Finally magnetically steerable capsule endoscopy induced less procedural pain, discomfort and distress than oesophagogastroduodenoscopy (p=0.0009, p=0.001 and p=0.006 respectively).

CONCLUSION: Magnetically assisted capsule endoscopy is safe, well tolerated and a viable alternative to conventional endoscopy. Further research to develop and improve this new procedure is recommended.

The majority of the work described in this thesis has been published in peer reviewed journals and/or at national or international conferences, *Appendix 1.*

Contents

List of Abbreviations

APS	Active pixel sensor
BMI	Body mass index
CCE	Colon capsule endoscopy
CE	Capsule endoscopy
CECR	Capsule endoscopy completion rate
CEST	Capsule endoscopy structured terminology
CI	Confidence interval
CIS	CMOS Image Sensor
CMOS	Complementary metal oxide sensor
CT	Computed tomography
DAE	Device assisted enteroscopy
DBE	Double balloon enterosocopy
DR3	Data Recorder 3
FDA	Food and Drug Administration
FICE	Fuji Intelligent Colour Enhancement
GI	Gastrointestinal
GOJ	Gastro-oesophageal junction

GORD	Gastro-oesophageal reflux disease
GTT	Gastric transit time
IBD	Inflammatory bowel disease
IDA	Iron deficiency anaemia
IR	Dr I Rahman
IQR	Interquartile range
JAG	Joint Advisory Group
KD	SR K Drew
MACE	Magnetically assisted capsule endoscopy
MEM	Dr ME McAlindon
MFH	Dr MF Hale
MK	Dr Matthew Kurien
MMC	Magnetically manoeuvrable capsule
MRE	Magnetic resonance enterography
MRI	Magnetic resonance imaging/imager
NSAIDS	Non-steroidal anti-inflammatory drugs
OGD	Oesophagogastroduodenoscopy
OGIB	Obscure gastrointestinal bleeding
OTT	Oesophageal transit time

PCC2	PillCam Colon 2
RAPID	Reporting and Processing of Images and Data
RHH	Royal Hallamshire Hospital
RS	Dr R Sidhu
SB	Small bowel
SBCE	Small bowel capsule endoscopy
SBTT	Small bowel transit time
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
STH	Sheffield Teaching Hospitals
UGI	Upper gastrointestinal
UK	United Kingdom

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Chapter 1 Introduction

1.1 Evolution of CE

The introduction of capsule endoscopy (CE) in 2000 proved a pivotal moment in the field of gastroenterology, providing a new non-invasive means of imaging the, previously difficult to access, small bowel (SB). A swallowable pill camera acquires images (subsequently converted to a video format on a computer) as peristalsis propagates it through the gastrointestinal (GI) tract. It is now established as the first-line investigation for diseases of the small bowel. Uptake of small bowel capsule endoscopy (SBCE) has been swift in the UK with 91% of gastroenterologists using CE in a survey in 2010 and more than 1.5 million procedures performed worldwide by 2014.(1, 2)*Figure 1* illustrates how demand for capsule endoscopy and device assisted enteroscopy in our region has altered since conception of the services.

The evolution of capsule technology can be traced back to a major milestone in electronics; the development of the transistor by American physicists William Shockley, Walter Brattain and John Bardeen in 1947. This semi-conductor device, used to amplify and switch electronic signals and power is considered one of the building blocks of modern electronics and has allowed miniaturisation of electronic items such as calculators, radios and computers. The inventors were awarded the Nobel prize in physics in 1956.(3)

Shortly after, flexible 'fibrescopes', consisting of a bundle of glass fibres capable of transmitting an image were presented by Harold Hopkins.(4, 5) Hopkins also worked on image improvement tools familiar to the modern endoscopist, such as white balancing and zoom lenses. After visiting Hopkins British laboratory in the mid-1950s, Basil Hirschowitz returned to the United States to focus on applying this new fibre-optic technology to endoscopy. Science became reality in 1957 when he

passed the first prototype down his own throat in 1957 and subsequently down that of a patient*(Figure 2)*. His work was published in the Lancet in 1961.(6)

Meanwhile Vladimir Zworykin, a Russian engineer and pioneer of television, had invented a 'radio-pill', which could be swallowed 'like any other medicinal capsule' and was capable of transmitting an FM radio signal as it passed through the human body permitting measurement of temperature.(7) Similar capsules capable of measuring pH and intestinal pressures were also developed during this period.(8, 9) The magnetic properties of Zworykin's capsule also meant it could be manipulated by magnetic forces outside the body, providing one of the first examples of the ideas underpinning this thesis.

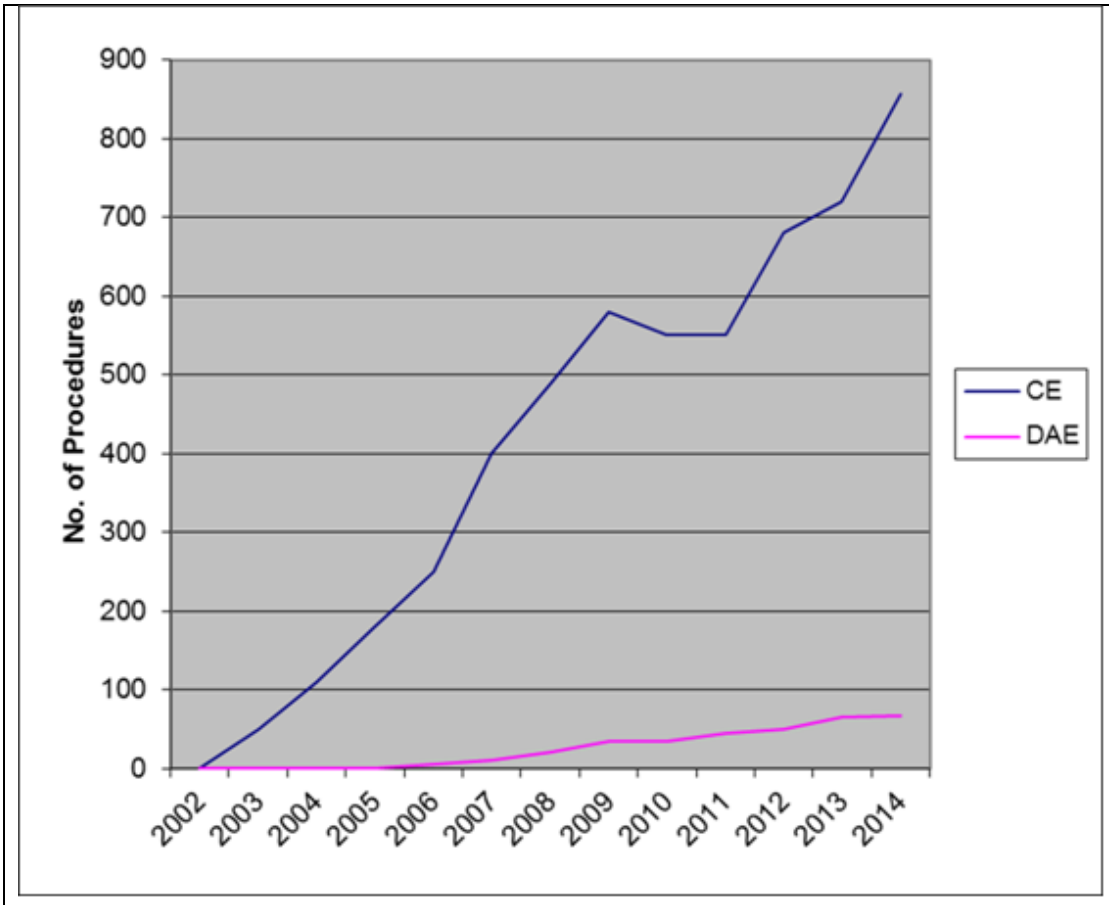


Figure 1: Graph of small bowel capsule endoscopy (CE) and device- assisted enteroscopy (DAE) procedures performed per year at Sheffield Teaching Hospitals NHS Foundation Trust,(10)

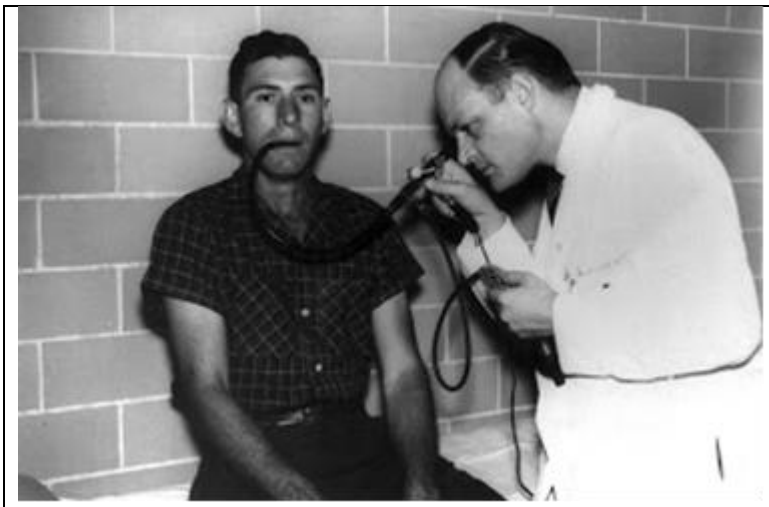


Figure 2: Basil Hirschowitz using one of the first fibre-optic endoscopes to examine the GI tract of a patient.(11) With permission.

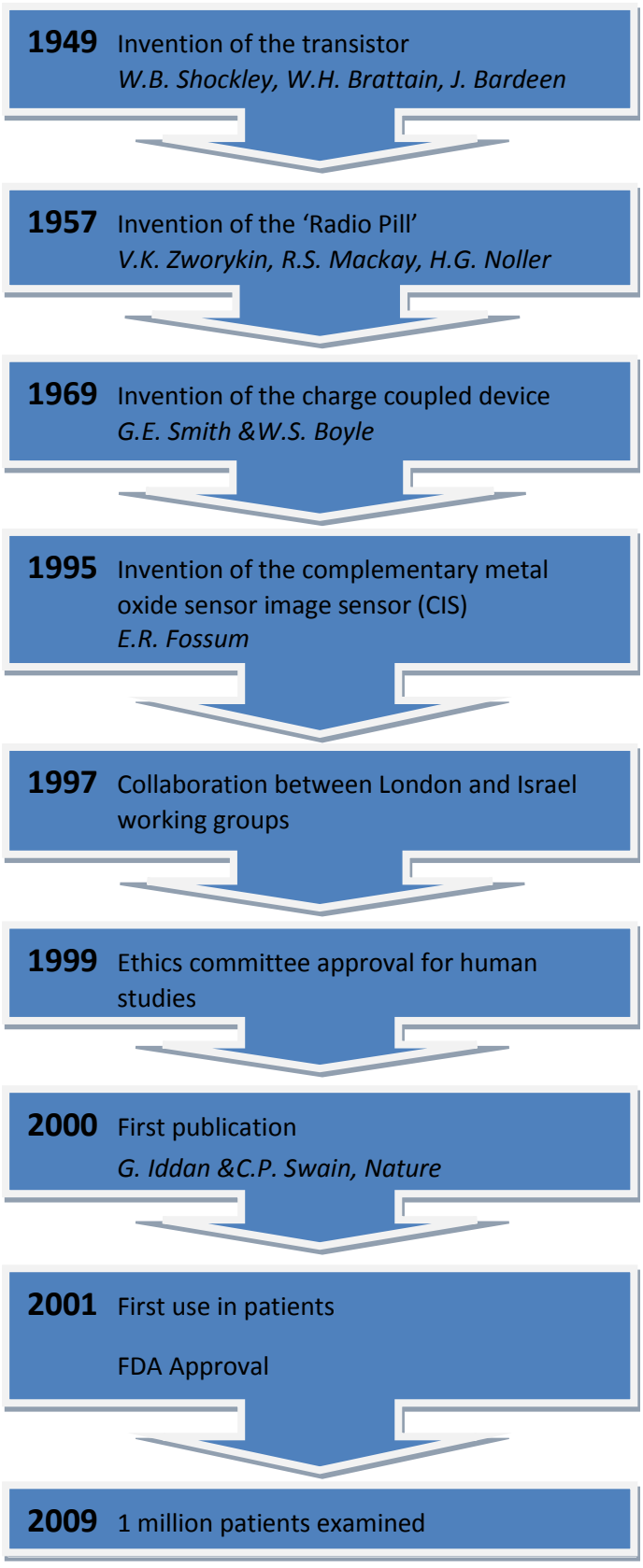
Several developments in digital imaging take us closer to the reality of video capsule endoscopy. The first of these was the invention of the charge coupled device in 1969 by Willard Boyle and George E Smith.(12) These devices enable light to be converted to electrical charge and subsequently a digital value and are widely used in a variety of medical and scientific situations where high quality images are required. Subsequently this technology was minutarised into the complementary metal oxide sensor (CMOS) active pixel sensor (APS) with intra-pixel charge transfer camera-on-a-chip technology or CMOS Image Sensor (CIS) by Edward Fossum in 1995.(13) The CIS is now widely utilised in a diverse array of settings including: mobile phone cameras, scientific and dental imaging, automotive safety systems and of course, video capsule endoscopy.

By 1997 two groups, one in London and one in Israel, were working independently to realise the potential of video capsule endoscopy. The first prototype model presented by the London group was a 'self-roving endoscope' small enough to be swallowed and with the capability to transmit images without the need for wires. Similarly to the 'radio capsules' from the 1960s, it was felt that magnetic forces could be used to enable capsular propulsion, in this case by a 'giant magnetoconstrictive alloy' in an externally applied magnetic field.(14) Subsequently the first live images of a pigs stomach using a wireless capsule, charge coupled device and microwave transmitter were presented in 1996.(15)

In 1997 Gavriel Iddan described a capsule with an innovative lens system using CMOS technology to keep the dimensions of the capsule within limits that would allow straight forward human ingestion.(16) The two groups began collaborating shortly after this, receiving ethical approval for the first human studies in 1999, which led to the seminal publication showing proof of concept in Nature in 2000.(17) A year later this new capsule technology was successfully used to investigate four patients with recurrent gastrointestinal bleeding at the Royal London Hospital.(18)This was followed by a pilot study comparing capsule endoscopy to push enteroscopy in patients with suspected gastrointestinal bleeding.(19) The yield of capsule endoscopy was double that of push enteroscopy and subsequently the capsule, manufactured by Given Imaging (Yoqneam, Israel), was

first approved for clinical use by the United States Food and Drug Administration.*Figure 3* illustrates a timeline of the evolution of capsule endoscopy.

Figure 3: Time Line of the Evolution of Capsule Endoscopy



1.2 Current Status of Capsule Endoscopy

1.2.1 Available capsule endoscopy systems

Much has changed since the early days of CE and there are now five companies manufacturing ingestible small bowel capsule endoscopes, 3 of which are United States Food and Drug Administration (FDA) approved. The majority are single use, disposable capsules that, once ingested, transmit images via radiofrequency to an external data recorder worn by the patient, thus preventing the need to retrieve the capsule.

PillCam Small Bowel

PillCam SB (Given Imaging, Yoqneam, Israel) was the first to received FDA approval and has been used in the majority of clinical trials of small bowel capsule endoscopy (SBCE), it is now into its third generation,'PillCam SB3'*(Figure 4)*. The system consists of a 20 x 11mm capsule, weight 4g; a sensing system comprising an array of sensor pads, a data recorder and battery pack; and a workstation (Reporting and Processing of Images and Data (RAPID)) which allows the images to be viewed as a continuous film. The capsule consists of a light source, lens, CMOS sensor, battery and a wireless transmitter. The capsule operates with an adaptive frame rate, capturing 2-6 images per second (>80 000 images in total) depending on the speed of transit of the capsule. The field of view is 156° with a magnification of 8:1.The data recorder in this system (DR3) contains a portable 'real-time' viewer, allowing direct viewing of 'live' images from the capsule. The current RAPID workstation includes several aids: a localisation system; a blood detector; a double and quadratic picture viewer; a quick view mode; inclusion of the Fuji Intelligent Colour Enhancement (FICE) system and an inflammation scoring calculator (Lewis score). Given Imaging also produce the commercially available oesophageal capsule endoscope (PillCam Eso) and colon capsule endoscopy, now into its second generation (PillCam Colon 2).

EndoCapsule

Introduced to Europe in 2005 and FDA approved in 2007, the EndoCapsule (Olympus, Tokyo, Japan) uses a high-resolution charge coupled device, rather than a CMOS to acquire images *(Figure 5)*. The 'Smart Recorder' combines a data recorder and image viewer, enabling playback and capture of live images as the examination is in progress. A 3-dimensional track function within the reporting software assists with localisation of the capsule when reporting to help guide further intervention, should this be necessary. An 'express-selected' mode allows quicker capsule reporting due to the elimination of similar consecutive frames, while the 'auto-speed-adjusted' function detects repetition in images and speeds up the frames-per-second accordingly. A small retrospective study suggested these tools reduced reporting times with no reduction in detection of clinically significant findings.(20) A number of randomised, comparative trials have shown the EndoCapsule to perform similarly to both PillCam SB and the MiroCam capsule (discussed below) in terms of diagnostic yields, with better image quality reported for the Endocapsule, compared to PillCam SB.(21-23)

MiroCam Capsule Endoscopy

Following its introduction in 2007, MiroCam (MC1000)was FDA approved in 2012. At 10.8 x 24.0 mm and 3.3g it is smaller than PillCam SB and has a field of view of 150° and a resolution power of 320x320 pixels. It's operation time of 11 hours is significantly longer than its competitors and this is achieved by utilising energy-conserving electric field propagation to transmit capsule images to the data recorder rather than radiofrequency.(24) A longer operating time was associated with improved capsule endoscopy completion rates (CECRs), while the power conservation strategies enabled higher quality images to be obtained and transmitted.(24, 25)MiroCam has been shown to have comparable diagnostic yields to both PillCam SB and EndoCapsule in a number of comparative studies.(23, 26-28) The upgraded version now available (MC1000-W) *(Figure 6)*has a field of view of 170°, a slight size increase to 10.8 x 24.5mm and reduced weight of 3.25g. The external data

recorder has wireless capabilities, enabling 'real-time' viewing of live capsule images using a compatible device (for instance an i-pad) without the need for a wired connection to the data recorder. MiroCam Navi is the sister capsule to the upgraded MC1000-W, mostly identical, except for the addition of magnetic inclusions within the capsule. An external magnet (MiroCam Navi controller) is available to allow some control of the capsule after ingestion by external manipulation of the controller. The MiroCam Navi system is utilised in the studies described throughout this thesis.

Omom Capsule Endoscopy

The OMOM small bowel capsule (Jinshan Science & Technology Group Ltd., Chongqing, China) was introduced in 2004 and features 'duplex data transmission'; essentially communication between the capsule and externaldata recorder which allows the frame rate, brightness and exposure of the capsule images to be modified. One of the major benefits of this interaction seems to be the improvement in CECRs.(29, 30) The system also provides a 'wireless universal serial bus monitoring' facility which enables the remote workstation to simultaneously monitor and adjust the capsule images and parameters in up to four patients.The capsule is 13 x 27.9mm and weighs <6g, it has a field of view of 140° and resolution of 0.1mm. The battery life is 6-8 hours, capturing images at a frame rate of 2 per second*(Figure 7)*.The OMOM capsule appears to perform at least as well as its competitors, with similar diagnostic yields reported in a large case-series, although no head to head comparative trials have been reported.(31) Complementary capsule products which can be used within this platform include an external capsule controller, a small bowel capsule with intrinsic memory which requires retrieval but prevents the need for the external data recorder, a colon capsule endoscope and a wireless capsular oesophageal pH monitoring system.

CapsoCam

A major disadvantage to conventional capsule endoscopy is the potential for missed lesions due to the limited field of view'single head' capsule model used by the majority of commercially available capsules. The CapsoCam (Capsovision, Saratoga, CA, USA) attempts to deal with this issue by using four panoramic side viewing cameras to give a 360° field of view*(Figure 8)*. Unlike the other capsules the CapsoCam SV-1 stores all images within the capsule itself, thus no external receiver is necessary, although the patient is required to collect the capsule on expulsion. This method has the advantage of much better power management which allows a high frequency of images (20 frames per second in the first 2 hours, dropping to 12 frames per second thereafter) and a battery life of fifteen hours. 'Smart motion sense technology' allows more efficient use of the battery;preventing the capsule from capturing frames when it is stationary, while increasing the frame rate when the capsule is in motion. For those more familiar with traditional methods of capsule endoscopy reporting however, the CapsoCam video output may represent a challenge, since the video shows the intestinal lumen opened out flat 'like a book', rather than the traditional forward luminal tunnel view of other capsule systems *(Figure 9)*. There is limited published data using CapsoCam, but where it is available the CapsoCam SV-1 appears to be a feasible and reliable method to image the small bowel and seems to be comparable to PillCam SB in terms of diagnostic yields.(32, 33)The duodenal papilla, identified in only 18-43% of conventional CE due to its' angular position, was visualised in 70% of examinations using CapsoCam SV1, suggesting this type of capsule may improve diagnostic yields by identifying pathology potentially missed by the traditional forward viewing capsules.(33-36)A summary of the differing capsules and their features is presented in *Table 1*.

	*Figure 4: The PillCam SB3 capsule and data recorder, showing the 'real-time' viewing panel. With permission.*
	*Figure 5: The EndoCapsule system; showing the ingestible capsule endoscope and the external data recorder with 'real-time' viewing screen. With permission.*
	*Figure 6: The MiroCam MC1000-W capsule, the external data recorder and an example of the viewing platform With permission.*
	*Figure 7: The OMOM capsule system, A: capsule workstation, B: capsule endoscope. With permission.*

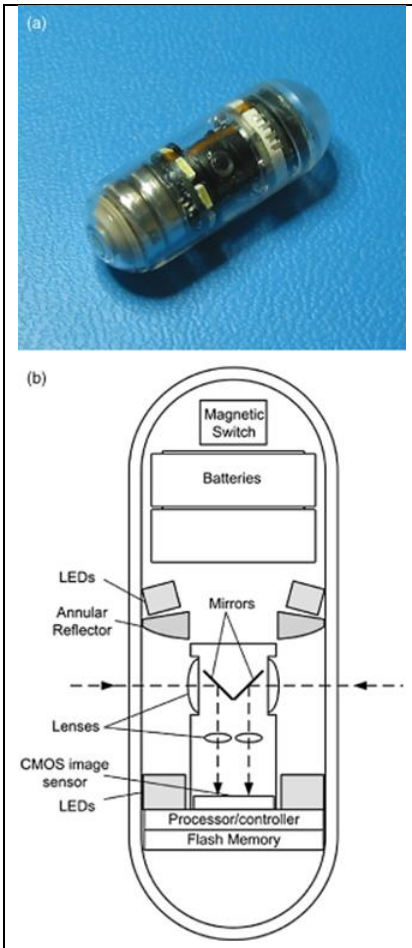


Figure 8: The CapsoCam system. (a) CapsoCam capsule, (b) technical representation. With permission.

Figure 9: Capsocam small bowel images show the tubular small bowel lumen opened out, 'like a book'.

Table 1: Comparison of the different capsule systems

Capsule system	**Size (mm)**	**Weight (g)**	**Field of view (°)**	**Image capture rate (frames/second)**	**Operating time (hours)**
PillCam SB3	26x11	4	156	2-6	8
EndoCapsule	26x11	3.3	160	2	12
MiroCam MC1000-W	24x11	3.25	170	3	12
OMOM	28x13	<6	140	2	6-8
CapsoCam	31x11	4	360	12-20	15

1.2.2 Current indications for small bowel capsule endoscopy

Obscure Gastrointestinal Bleeding

The commonest indication for SBCE is GI bleeding (obscure or overt). United Kingdom (UK) and European guidelines recommend SBCE as the first-line investigation, after non-diagnostic upper and lower GI endoscopic investigation, in patients with obscure gastrointestinal bleeding (OGIB).(37, 38) CE identifies pathology in 46-60%(39) of such patients and is more sensitive than small bowel computed tomography (CT), small bowel barium contrast radiology, magnetic resonance imaging, angiography and push enterosocopy.(40) Double balloon enteroscopy (DBE) has similar diagnostic yields to CE in this context (41) but is considerably more invasive, procedure times can be lengthy (1-2 hours), sedation or general anaesthesia is often required and completion rates are less compared to CE (62.5% compared to 90.6% respectively; $p<0.05$).(42) As such DBE remains the interventional counterpart to CE, allowing direct visualisation, biopsy or therapy to abnormal areas already identified and located by CE. A recent meta-analysis demonstrated that the yield at DBE is significantly higher (75%) after a positive CE compared to after a negative CE (28%).(43) Flat vascular lesions, angioectasia and inflammatory lesions are the most common findings *(Figure 10)*, while small bowel tumours account for 5-10% of patients presenting with OGIB.(44) Factors associated with a higher diagnostic yield from CE in patients with OGIB include low haemoglobin measurements/transfusion dependence, older age and closer proximity of CE to the bleeding episode.(45-47)

Crohn's Disease

CE can be used to assist with diagnosis of Crohn's disease or assessment of disease activity and extent in patients with known Crohn's disease. CE has superior diagnostic yields to small bowel barium studies, ileo-colonoscopy, push enteroscopy and CT enterography in both suspected and

established small bowel Crohn's disease.(48-50) CE appears to be better than magnetic resonance enterography (MRE) at identifying small bowel mucosal lesions, while MRE is more accurate at diagnosing mural, peri-mural and extra-enteric manifestations.(51, 52)European guidelines recommend SBCE as the next appropriate investigation in patients with suspected Crohn's disease, without obstructive symptoms, after negative ileocolonoscopy.(37)With capsule retention occurring in 5-13% of those with Crohn's disease(53), cross sectional imaging (for instance MRE) is seen as the investigation of choice for those with known Crohn's disease or suspected Crohn's disease with obstructive symptoms, since trans-mural involvement can be defined in cross section. Radiology may not exclude short strictures in all cases (54) and therefore to confirm functional patency of the GI tract, a dissolving capsule (the same size and shape as the capsule endoscope) containing a radiofrequency tag has been developed (PillCam Patency capsule, Given Imaging, Yoqneam, Israel). Absence of the radio frequency signal 30 hours post ingestion predicts safe GI transit of the capsule endoscope.(55, 56)

CE findings suggestive of Crohn's disease can be rather non-specific and include ulceration, erythema, mucosal oedema and strictures *(Figure 10)*. This presents a significant challenge to the interpreting physician since minor mucosal breaks may occur in 10-15% of normal individuals while mucosal erosions are present in two thirds of patients taking non-steroidal anti-inflammatory drugs (NSAIDS).(57) Characteristics of small bowel injury due to NSAIDS include multiple petechiae, loss of villi, erosions, and ulcers with round, irregular, and punched-out shapes, and thus can be difficult to distinguish from Crohn's disease endoscopically *(Figure 10)*.(58) However, concentric diaphragmatic strictures are considered pathognomonic of NSAID mucosal injury and can present with obstructive symptoms. Endoscopic balloon dilatation is an effective strategy for such strictures since the muscularis propria remains intact leading to a low perforation rate.(59, 60)

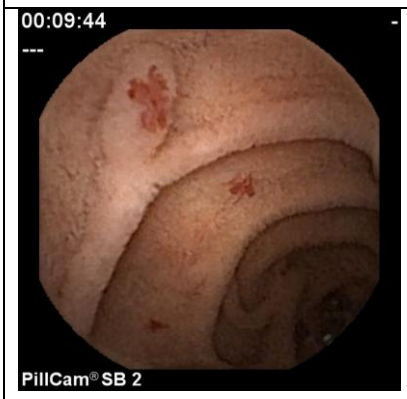
Coeliac Disease

Typical mucosal changes of coeliac disease such as scalloping, nodularity, loss of mucosal folds and mosaicism can be seen at CE *(Figure 10)* with a sensitivity of 89% and specificity of 95% as reported in a recent meta-analysis.(61) Although CE may be considered in coeliac antibody positive patients unwilling to undergo endoscopy, duodenal biopsy remains the gold-standard for the diagnosis of coeliac disease. However, a recent study found CE useful in equivocal cases of coeliac disease, particularly in patients with antibody negative villous atrophy in whom findings either confirmed the suspected diagnosis or provided evidence of an alternative diagnosis such as Crohn's disease.(62) CE may also be of benefit in those with known coeliac disease on a gluten free diet with on-going symptoms or alarm symptoms to exclude complications such as ulcerative jejunitis and small bowel lymphoma *(Figure 10)*.(63)(64)

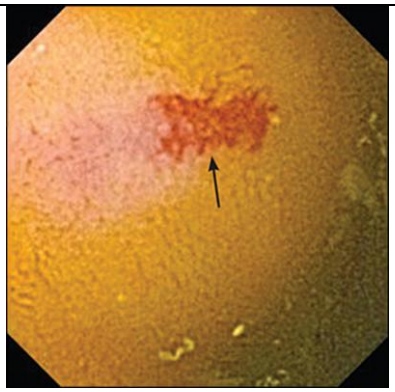
Small Bowel Tumours

Most small bowel tumours present with anaemia or obscure GI bleeding, but may present late with abdominal pain or weight loss.(65, 66) They include malignant or potentially malignant (gastrointestinal stromal tumours, adenocarcinoma, carcinoid, lymphoma), benign (haemangioma, hamartoma, adenoma, lipoma) and metastatic lesions (particularly from melanoma, lung, renal or breast primaries) *(Figure 10)*.CE is more accurate than small bowel barium radiology at detecting small bowel tumours and can also detect smaller lesions in comparison to magnetic resonance imaging.(53) CE can miss some lesions which are mainly sub-mucosal and thus if there is a high index of suspicion, cross-sectional imaging such as a contrast enhanced CT scan is recommended.(67, 68) CE and DBE are comparable for detecting small bowel tumours, while DBE has the advantage of biopsy plus therapeutic potential, such as stenting, balloon dilatation and localization prior to surgery.

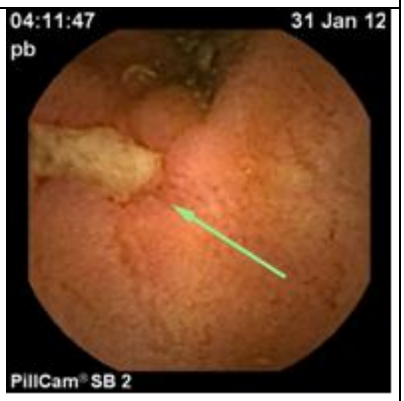
Figure 10: Pathological findings encountered during small bowel capsule endoscopy



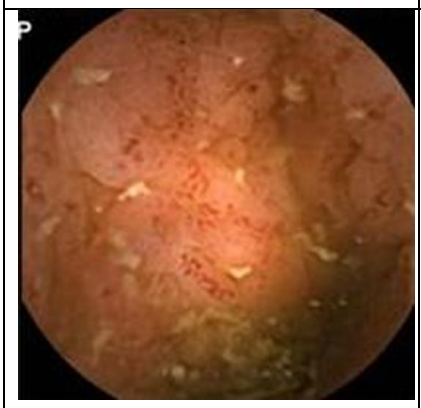
(a) Angioectasia



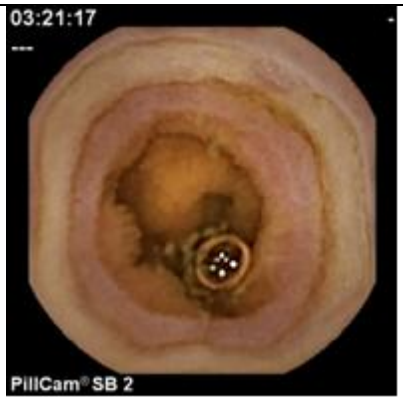
(b) Angioectasia



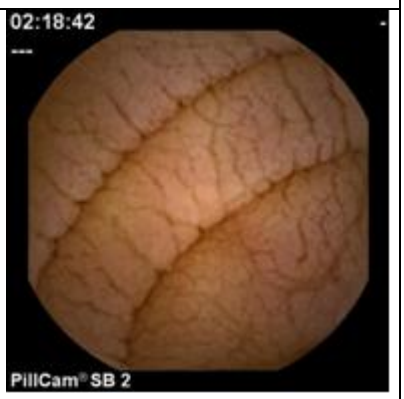
(c) Crohn's ulcer



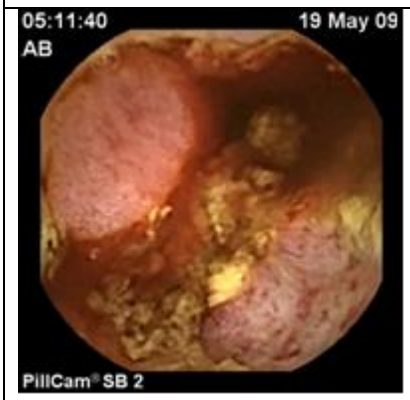
(d) Crohn's ulceration



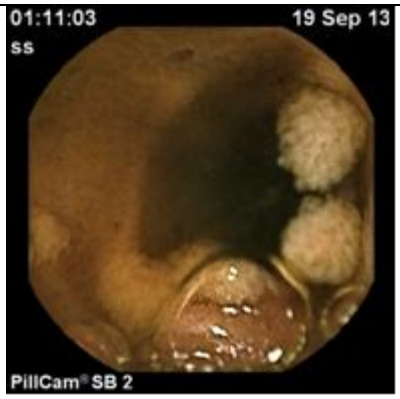
(e) NSAID ulceration



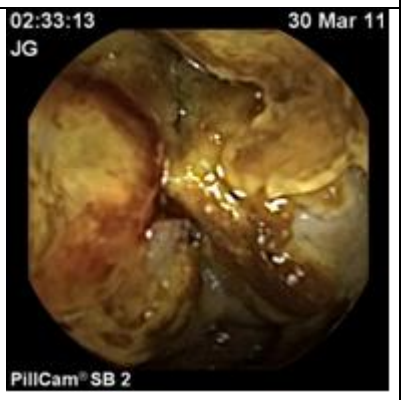
(f)Coeliac disease



(g)Enteropathy associated T-cell lymphoma



(h)Peutz-Jeghers polyps

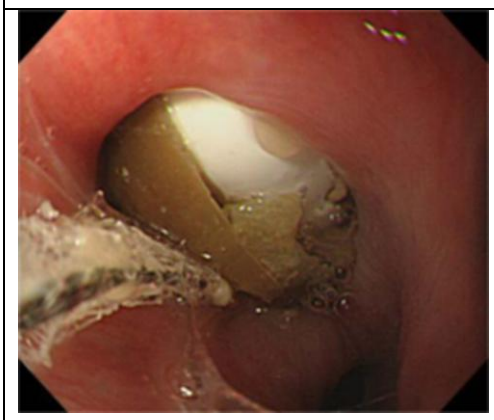


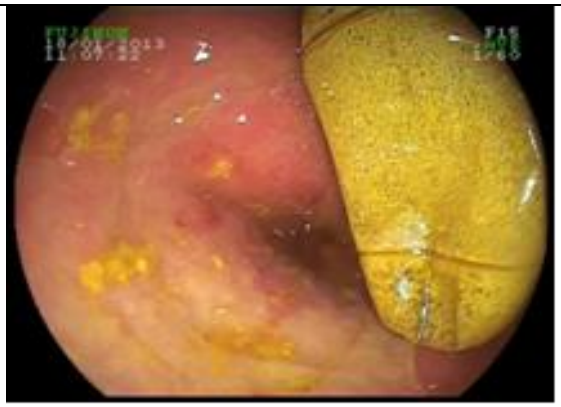
(i) Small bowel adenocarcinoma

1.2.3 Limitations of capsule endoscopy

Although CE is generally considered a safe and straightforward procedure, there are a few limitations. Capsule retention is reported in up to 2% of procedures and risk factors include prolonged use of non-steroidal anti-inflammatory drugs, previous abdomino-pelvic irradiation and Crohn's disease.(53, 69)The OMED-ECCO consensus guidelines recommend considering CT or MRE as first line modalities to evaluate the small bowel in patients with established Crohn's disease because they additionally demonstrate transmural and extramural complications.(70) However, confirming functional patency using a PillCam Patency device is also recommended in the event that CE is required because of unremarkable or non-diagnostic cross-sectional imaging. Small bowel radiology cannot be guaranteed to exclude short strictures (54) and thus a pre-procedure patency capsule should be considered in any high risk patient. This is a dissolving capsule (the same size and shape as the capsule endoscope) containing a radiofrequency tag*(Figure 11)*. Failure to detect the radio frequency signal using a handheld scanner 30 hours after ingestion suggests functional patency of the GI tract and predicts uncomplicated excretion of the capsule.(55, 71) The concern with capsule retention is that it may lead to intestinal obstruction or perforation. In fact, it seems capsule retention is mostly asymptomatic and rarely causes obstruction.(72, 73) In some cases one can follow an expectant approach, although future magnetic resonance examinations are contraindicated.(74) In most cases retrieval is eventually required and this can be done with medical, endoscopic or surgical methods.(75, 76)

Figure 11: Capsule retention and the Agile patency device





(a) Capsule endoscope retained at a benign stricture. The stricture has been reached by conventional endoscopy and dilatation is attempted.

(b) The Agile patency capsule is retained at a stricture. The stricture is reached by double balloon enteroscopy for histological sampling.

A potential risk of interference with permanent implantable cardiac devices such as pacemakers and defibrillators by the radiofrequency of the capsule and data recorder has been anticipated, although several studies of many different device models have failed to demonstrate this and therefore they should not be considered as contraindications.(77-79) However, not every model of every device has been tested and therefore it is prudent to risk-assess each patient individually. The development of a local policy in agreement with the resident cardiology department is a sensible approach to avoid confusion.

Bronchial aspiration is a rare complication, with only a small number of cases reported in the literature.(80-83) It occurs more commonly in older patients with no prior history of swallowing disorders and may be asymptomatic. Utilisation of a 'real-time' viewing device to determine the

position of the capsule can be re-assuring if doubt exists following ingestion. Expectoration can be achieved spontaneously by coughing, or retrieval may be necessary using a bronchoscope.(80, 84)

Capsule ingestion is contra-indicated in patients with known dysphagia. Similarly patients with altered upper GI anatomy (Billroth II, Nissen fundoplication, Zenkers diverticulum), known gastro-paresis or mechanical gastric outlet obstruction present technical challenges to the procedure. The AdvanCE capsule delivery device (US Endoscopy, Mentor, Ohio) is a cradle fitted to the end of a standard flexible endoscope which can be used to deploy the capsule into the small bowel under direct vision. In a small series it has shown to be safe and effective with minimal training required to operate the equipment.(85, 86) This approach could also be considered for any patient with the above contra-indications or if a previous CE examination failed or was incomplete due to a prolonged gastric transit time.

Delayed gastric emptying is a common contributing factor to incomplete small bowel examination.(87) The use of pre-procedural pro-kinetics such as metoclopramide, domperidone and erythromycin remains contentious. Two systematic reviews and meta-analyses have attempted to resolve this issue with varying outcomes. Koulaouzidis et al showed an improvement in CECR but not diagnostic yield following pre-procedural pro-kinetics (88), whereas Kotwal et al found no improvement in CECR.(89) Unselective use of pro-kinetics exposes all patients to the potential risks of these drugs, such as extra-pyramidal side-effects in the case of metoclopramide. Use of a real-time viewer to identify patients with prolonged gastric transit after capsule ingestion may allow more appropriate use of these drugs and has been shown to be useful in some smaller studies.(90-92)

Inpatient status seems to be associated with both prolonged gastric and small bowel transit times and is an independent risk factor for incomplete CE.(87, 93, 94) A combination of acute illness, co-morbidities, multiple medications and the sedentary nature of a hospital admission may all play a

part in reducing gut motility. However, delaying CE should be balanced against the fact that patients with suspected small bowel bleeding have higher diagnostic yields the shorter the time interval between the bleeding episode and CE.(46, 95) In such cases an inpatient procedure may allow early diagnosis and subsequent therapy to be planned without delay.

With each CE examination producing between 2-5 hours of small bowel video footage (96) and the potential for an abnormality to be visible in only a small number of frames (97), CE is undoubtedly a time consuming process requiring dedicated attention. Software additions aimed at streamlining the reporting process are available but data is limited and most can only be considered as supportive tools. However, there is good evidence to support the use of endoscopy nurse 'pre-readers' and this can be an effective strategy to facilitate timely reporting as demand increases.(98)

An effectual reporting process relies on the accurate detection and description of abnormalities and the ability to root such findings within the clinical context and translate this into appropriate management advice. The use of a capsule endoscopy structured terminology (CEST) has been suggested in order to improve inter-observer agreement in capsule endoscopy reporting.(99, 100) However, this can be time consuming and cumbersome to perform and moderate variation is still noted even amongst experts.(101)

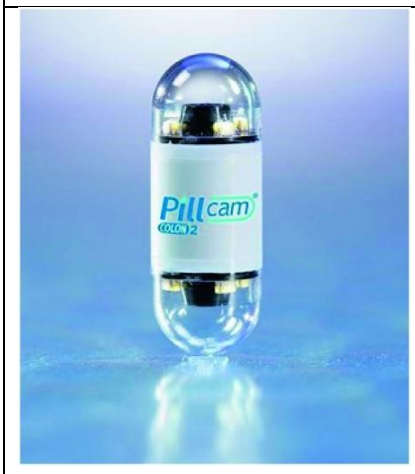
Finally capsule endoscopy is currently a diagnostic modality with no biopsy or therapeutic capability. This remains a significant limitation and may hinder the uptake of newer capsules to image other areas of the gastrointestinal tract. However, capsule technology is rapidly advancing and prototype 'biopsy' capsules have already been described in the published literature and will be discussed further in the sections below.

1.3 Colon Capsule Endoscopy

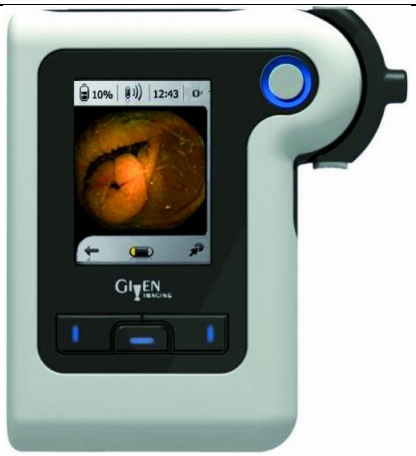
Direct examination of the colonic mucosa by colonoscopy is the accepted 'gold standard' for investigation of suspected diseases of the colon. Colonoscopy is an important tool in the ongoing re-assessment, surveillance and management of inflammatory bowel disease (IBD) and due to its high sensitivity for polyp detection; it plays a role in colorectal cancer screening and surveillance programmes. However effective as a diagnostic tool, colonoscopy remains hampered by poor patient acceptability and this is reflected in disappointing uptake in colorectal cancer screening programmes worldwide.(102)

Colon capsule endoscopy (CCE) was introduced in 2006 and allows direct colonic mucosal visualisation without the need for intubation, air insufflation or sedation.(103) Now in its second generation, PillCam Colon 2 (Given Imaging, Yoqneam, Israel) (PCC2) consists of a 11.6mm x 31.5 mm capsule with a camera at each end (angle of view 172°) giving a combined field of view of almost 360°*(Figure 12).* It has an adaptive frame rate (between 4-35 frames per second) allowing the number of images captured to be altered depending on the motion of the capsule. Interaction between PCC2 and the external data recorder (DR3) facilitates this function and also enables recognition of small bowel mucosa and the generation of prompts by DR3 to direct the patient to take booster doses of bowel preparation. A polyp size estimator is included in the reporting software.

Figure 12: Colon capsule endoscope system (a) colon capsule endoscope with bi-directional cameras (b) interactive data recorder (DR3). With permission.(104)



(a)



(b)

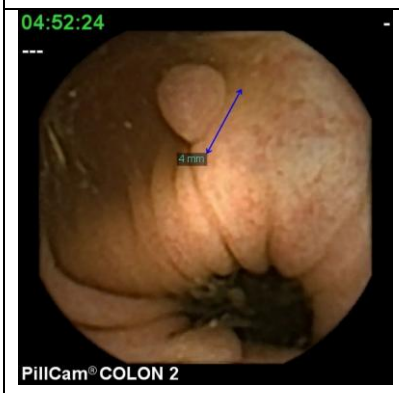
In several studies PCC2 has been proven to be safe, feasible and reliable in the detection of colonic polyps and tumours when compared to conventional colonoscopy.(105-107) In the largest study to date (689 patients) PCC2 was able to detect adenomas 6mm or larger with 88% sensitivity (95% confidence interval (CI) 82-93%) and 82% specificity (95% CI 80-83%) and adenomas 10mm or larger with 92% sensitivity (95% CI 82-97%) and 95% specificity (95% CI 94-95%).(107) CCE is included in the European Society of Gastrointestinal Endoscopy guidelines and has been recommended in average risk individuals (i.e. no alarm symptoms) who do not appear to be at increased risk of colorectal cancer.(108) CCE has also been demonstrated to be of value following incomplete colonoscopy by allowing visualisation of previously un-accessed colonic segments and detection of potentially missed pathology.(109, 110) A recent prospective comparative trial has shown PPC2 to have a superior diagnostic yield compared to CT colonography in this group.(111)

The use of CCE in patients with inflammatory bowel disease is less well defined, although small studies have shown promising results. CCE has been shown to detect active mucosal inflammation

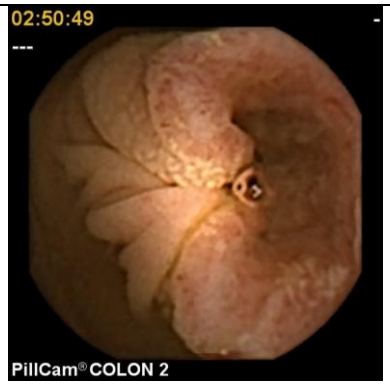
with a sensitivity of 89% and specificity of 75% compared to standard colonoscopy in a series of 100 patients with suspected or known ulcerative colitis.(112) Other studies have reported similar results but only in small numbers and mostly with PillCam Colon 1, the predecessor to PCC2.(113-117) Only two studies have evaluated the utility of CCE in the evaluation of Crohn's disease (total 18 patients), although both found CCE was safe and feasible.(118, 119)

The position of PPC2 compared to other imaging modalities for the colon remains to be established, but current data suggests it is safe and compares favourably to CT colonography and even to conventional colonoscopy when performed in "tandem" or "back to back" colonoscopy trials.(120, 121)With appropriate infrastructure and systems in place CCE has been shown to be feasible in the outpatient setting in some cases, providing less disruption to home and work life and a more patient-centred means of disease management.(122)*Figure 13* illustrates common pathologies detected by CCE.

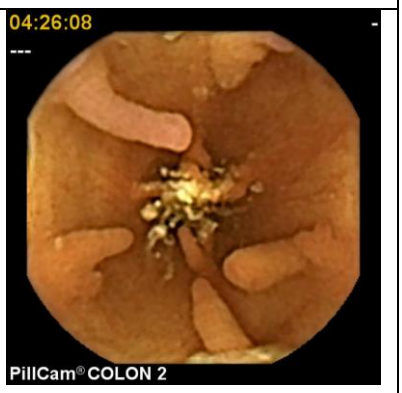
Figure 13: Pathological findings encountered during colon capsule endoscopy



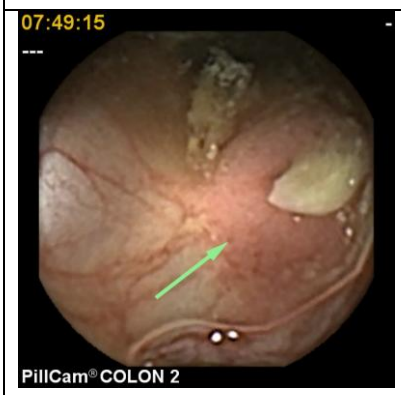
(a)Sessile polyp



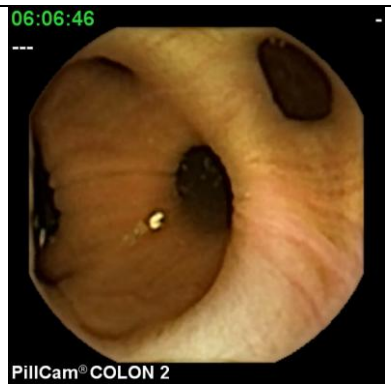
(b)Colon adenocarcinoma



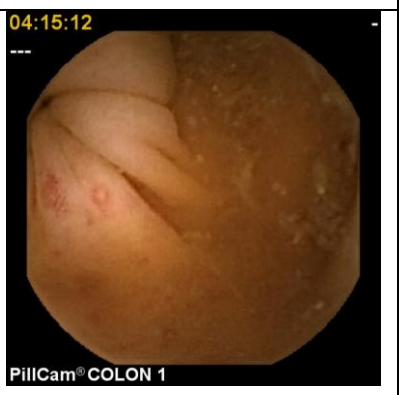
(c) *Colonic pseudopolyps*



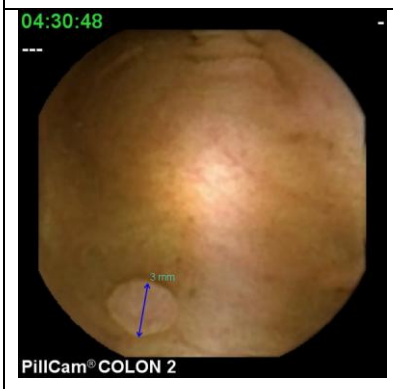
(d) Discrete Crohn's ulceration



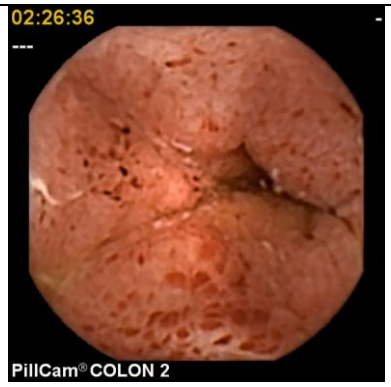
(e) Diverticulosis



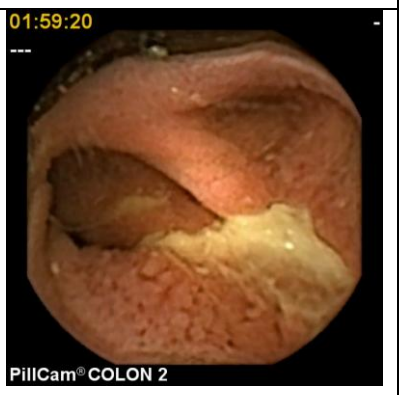
(f) NSAID Colopathy



(g) Diminutive polyp



(h) Crohn's colitis



(i) Anastomotic Crohn's disease

1.4 Oesophageal Capsule Endoscopy

Following the success of SBCE, the first capsule designed to image the oesophagus (PillCam Eso, Given Imaging, Yoqneam, Israel) was introduced in 2004, followed by its successor PillCam Eso 2 in 2008. Unlike the small bowel capsule it has a camera at both ends, acquiring simultaneous bidirectional images at a higher rate, 9 per head (i.e. total 18 frames per second) to overcome rapid transit through the oesophagus*(Figure 14)*. The battery life is much shorter, at 30 minutes, than conventional SBCE, but the capsule still passes through the whole gastrointestinal tract. The capsule is 11 x 26mm and has a field of view of 169° for each head. Three lenses and an automated adjustable light source enable high resolution images to be obtained.(123) The advantage of oesophageal CE over conventional oesophagogastroduodenoscopy (OGD) is that it avoids the need for intubation or sedation and thus it can be particularly useful for anxious patients or those who refuse endoscopy.

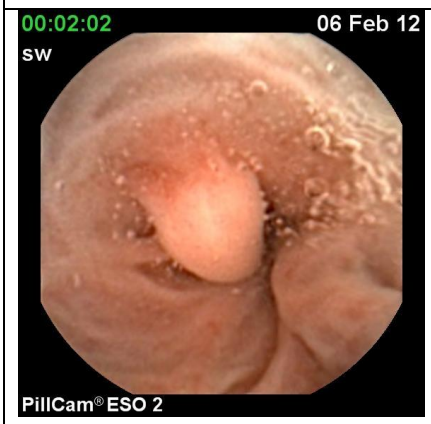
	*Figure 14: Oesophageal Capsule Endoscopy System. With permission.*

Normal solid oesophageal transit time is between 4-8 seconds (124) and therefore despite small bowel or colon capsule endoscopy ingestion being performed in an upright position normally, this clearly needed modification to allow oesophageal capsule examination. A 'simplified ingestion protocol' where the patient ingests the capsule while lying in the right lateral position is recommended to delay oesophageal transit of the capsule and maximise the number of oesophageal images obtained.(125) Sips of 15mls of water are allowed every 30 seconds, either through a syringe,

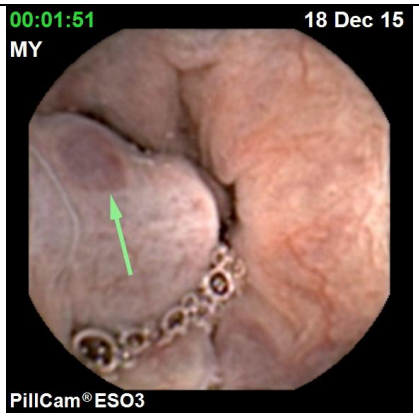
or via a straw, until the capsule enters the stomach. This protocol seems to delay oesophageal transit time and improve the visualisation rate of the gastro-oesophageal junction compared to the originally used protocol where the capsule was ingested supine with 20mls of water.(126)

Due to the inability to take biopsies or examine the stomach, PillCam Eso is only likely to be useful in certain specific clinical situations. Oesophageal conditions which require screening in high-risk populations and surveillance once identified would seem appropriate indications for oesophageal capsule endoscopy. Primary prophylactic treatment of oesophageal varices in cirrhotic patients with medium-large varices reduces the risk of bleeding and thus the importance of screening and surveillance of such patients using OGD is highlighted in clinical guidelines.(127) A recent meta-analysis of 619 patients showed the pooled sensitivity and specificity of PillCam Eso (compared to conventional OGD) in the detection of oesophageal varices to be 83% and 85% respectively.(128) OGD also remains the gold standard for surveillance of Barrett's oesophagus. In a meta-analysis in 2009 including 618 patients, the pooled sensitivity and specificity of PillCam Eso for the diagnosis of Barrett's oesophagus was 77% and 86% respectively.(129) Although, in both these circumstances the authors were led to conclude oesophageal capsule endoscopy could not be considered a replacement for OGD, it was found to be a safe test with a favourable tolerability profile and thus may be a useful alternative for the nervous patient refusing conventional endoscopy.(130) Examples of images obtained during oesophageal capsule endoscopy are illustrated in *Figure 15*.

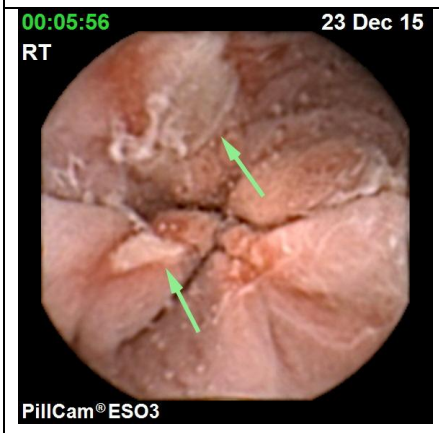
Figure 15: Pathologic findings encountered during oesophageal capsule endoscopy



(a) Oesophageal varix and regenerative nodule



(b) Oesophageal varix with red spot (arrow)



(c) Oesophagitis

1.5 The future of capsule endoscopy

Relentless technical progression has allowed considerable improvements to capsule endoscopes. Superior quality multi-element lenses and adaptive illumination allow a wider angle of view and enhanced picture clarity. Power management strategies have increased the duration and performance of capsule endoscopes and are imperative to facilitate other capsule technological advancements.

1.5.1 Software and Data Analysis

Accurate reporting of a CE examination is time consuming and requires focussed attention since abnormalities may be evident in only a small number of frames.(97) This has prompted attempts to produce software tools to enable a shorter capsule reading time while maintaining diagnostic accuracy. The Suspected Blood Indicator automatically highlights frames containing multiple red pixels as a marker of bleeding or vascular abnormalities. However, with a reported sensitivity of <60% in the presence of active bleeding it cannot be recommended as anything more than a supportive tool.(131, 132) Quick View allows time efficient capsule reading by selecting 2-80% of frames (as set by the reader), producing a condensed video for review. Results are promising with excellent lesion detection rates and significantly shorter reading times.(133, 134) Fujinon intelligent chromoendoscopy (FICE) enhances surface contrast in three specific wavelengths (red, green and blue) and appears to improve the definition and surface texture of small bowel lesions already detected with white light. Whether this actually influences detection rates or clinical outcomes still remains uncertain.(135, 136)

Three dimensional reconstruction of the GI tract seems to assist diagnosis at conventional endoscopy by enhancing mucosal textural features and abnormalities.(137-139) A version for small bowel CE using a software-enabled technique to convert a two dimensional CE image to a threedimensional representation has been trialled. It improved visualisation of a significant

proportion of vascular lesions but, surprisingly, was less beneficial for inflammatory and protruding lesions.(140) Automated tumour recognition software algorithms aiming to detect image frames containing specific textural features associated with cancerous tissue have also been successfully applied to pre-recorded capsule videos.(141, 142)

Miniaturizing such systems to enable activity during the process of capsule examination may open the field for biopsy of abnormal tissue or targeted therapeutics. Demosthenous et al developed a capsule that, rather than capturing images, scans the small bowel mucosa as it travels passively through, using infrared fluorescence endoscopy to identify early mucosal changes associated with small bowel cancer.(143)Such innovations are not isolated to small bowel CE; Ankri et al recently reported a new optical detection method specifically designed for colorectal cancer. The technique uses immune-conjugated gold nanorods to differentiate between normal and cancerous tissue and could be integrated into standard colon capsule endoscopy systems.(144) Further research is required to define the utility of these advances in clinical practice.

Of course, the use of capsules is not only limited to visualisation of the gastrointestinal tract. Capsules are available that can measure the pH of the lower oesophagus over the course of 48 hours, avoiding the need for invasive catheter pH monitoring.(145, 146) While capsules capable of transmitting information about small bowel pH, (147, 148) motility, (149-151)pressure (152, 153)and temperature(154, 155) are in various stages of development. Capsules with a combination of these functions could be applied to the diagnosis and differentiation of patients with motility disorders.

1.5.2 Biopsy

A capsule with biopsy capabilities would be a major advance for capsule technology, allowing histological sampling of abnormal tissue identified during capsule endoscopy without the need to resort to subsequent flexible endoscopy and biopsy. For capsule biopsy to become a reality two things are required; firstly accurate localisation of the capsule is necessary to ensure that the correct tissue is sampled, secondly the capsule needs to be capable of removing and retrieving the desired tissue in sufficient amounts for histological analysis. Ironically the Crosby capsule, the traditional means of obtaining a jejunal biopsy to confirm a diagnosis of coeliac disease (by a string-tethered capsule allowed to travel passively though the gut before a trigger enables a piece of tissue to be sliced off and retrieved through an aperture in the capsule) is now inspiring many of the emerging biopsy-capsule prototypes.(156)The Nano-based capsule-Endoscopy with Molecular imaging and Optical biopsy 'NEMO' project is a collaboration between academic and industry pioneers to produce a capsule with recognition, anchoring and bio-sensing capabilities to enable accurate pathology detection and diagnosis.(157, 158) Similarly the Versatile Endoscopic Capsule for gastrointestinal TumOr Recognition and therapy 'VECTOR' project, funded by the European Commission, is developing a mini-robot comprising sensors, controls, and a human-machine interface aiming to detect and intervene in early GI cancer.(159) Other capsules using 'micro-grippers' to fold and grab tissue samples or electromagnetic micro-actuation systems to extract a histological sample have also been described in prototype form.(160, 161)

1.5.3 Targeted Therapeutics

With the advent of real-time viewing and the potential of accurate capsule localisation the notion of targeted drug delivery also becomes feasible. Potentially, this could be applied to a number of clinical situations; localised application of steroid or immunomodulation for isolated Crohn's disease for instance, or targeted use of haemostatic spray to an actively bleeding lesion. One prototype can deliver an injection of 1ml of targeted medication while using a holding mechanism to resist movement by peristalsis*(Figure 16)*.(162) The prototype produced by Yim et al uses manipulation of an external magnetic field to offer two drug delivery modes, either a slow infusion or as a bolus, directly to the required area within the stomach.(163) Whereas, the iPill (Phillips Research, Eindhoven, The Netherlands) uses bowel transit time and pH sensors to gauge gut location before drug delivery and is being trialled in Crohn's disease and colorectal cancers. Beyond drug delivery to direct endoscopic therapy to intestinal bleeding lesions; the iRoboCap, aprototype capsule driven remotely via wireless internet commands, was able to apply endoscopic clips to simulated lesions during phantom model experiments.(164)

1.5.4 Air insufflation and lens washing

In conventional endoscopy air insufflation and lens washing are utilised to allow detailed mucosal visualisation of collapsed structures such as the colon and stomach and to remove luminal debris from obstructing the lens. Currently capsule endoscopy procedures try to overcome these issues by using ingested liquid preparations to distend and cleanse the colon, but this is not always successful. Research is underwayto further resolve these problems by producing capsules able to release a volume of gas or cleansing liquid to distend the bowel and mobilise luminal debris. Pasricha et al have produced a wireless colonic capsule which can insufflate carbon dioxide and was successfully used to obtain a complete colonic examination in in-vivo studies.(165) Alternative designs using gas-producing chemical reactions or 'controlled phase' transition of a stored liquid within the capsule to release a distention volume of gas have also been used in ex-vivo experiments*(Figure 17)*.(166, 167)The difficulty of integrating such systems within a miniature capsule was resolved by Ciuti et al, by producing a 'softly-tethered' capsule which could inject water and suction luminal contentseffectively in ex-vivo experiments.(168)The majority of the capsules described remain in prototype phase and although further progress is needed, the wealth of research currently occurring in this field suggests that more exciting developments are likely to be on the horizon.

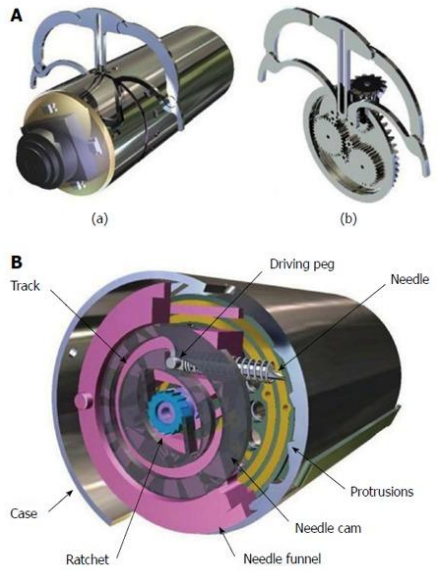
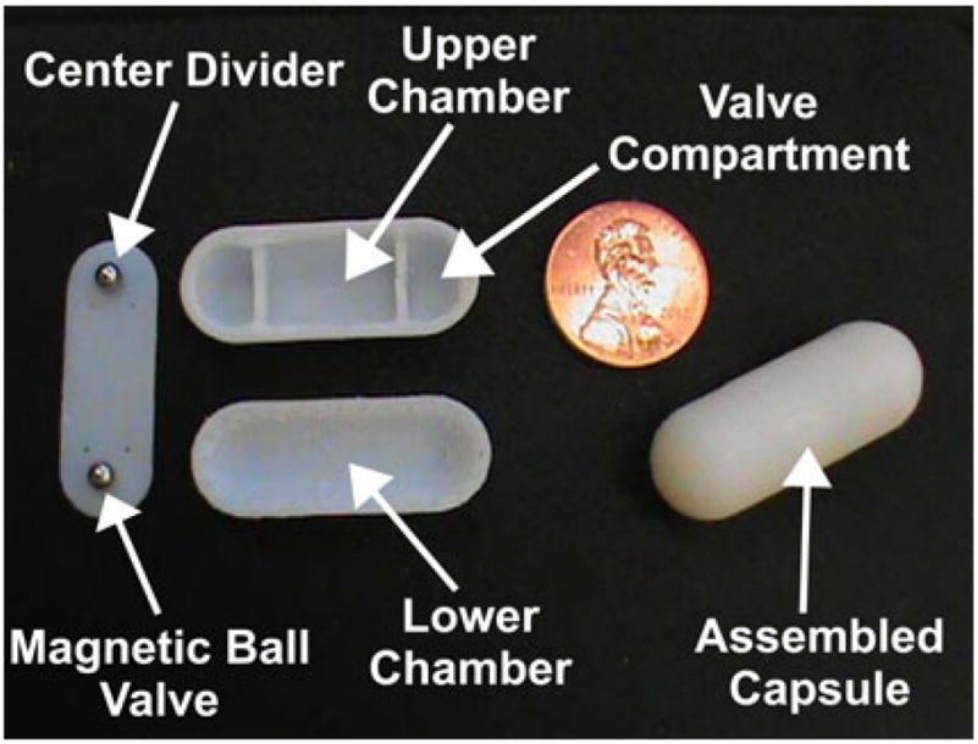


Figure 16: The mechanism devised by Woods et al to anchor the capsule in a desired position (A) so therapy can be applied (B). With permission.(162)

Figure 17: Capsule prototype and its components. The upper chamber is designed to hold the acid solution, while the lower chamber holds the powdered base. In the presence of an external magnetic field, the two magnetic ball valves move toward the top of the upper chamber, and the citric acid solution mixes with the potassium bicarbonate. The CO2 produced is vented through small perforated holes just under the midline of the capsule.©[2013]IEEE, (167)



1.5.5 Manoeuvrability

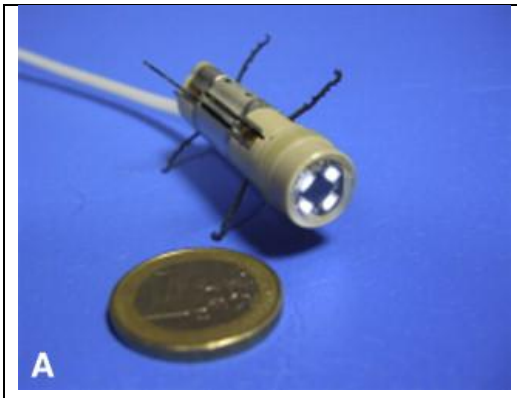
If the movement of a capsule could be controlled within the body after ingestion, this would represent a major turning point in the evolution of capsule technology. If the capsule motion through the gut was an active process, areas of interest could be inspected carefully, while interaction with the capsule could allow targeted biopsy and facilitate drug delivery. Furthermore, a steerable capsule could overcome the problems encountered examining the capacious stomach allowing accurate pan-enteric examination to become a reality. Motion control of capsules has been considered in a two different ways; the first using mechanisms within the capsule to achieve targeted movements and secondly, using external control mechanisms to mobilise the capsule. In this section I will consider these differing concepts and their application to capsule examination of the stomach.

Self-propelling capsules

Self-locomotion strategies using paddling, legs, fish-like movement and inchworm locomotion have all been described in the literature. Quirini et al produced a novel capsule device with 8 legs, 2 internal micro-electromagnetic motors and a gear system for actuating the legs. Their most recent study showed this prototype could travel 15 cm in 5 minutes, against peristalsis in an in vivo porcine colon, however the capsule did need to remain tethered to an external power supply in order to function*(Figure 18)*.(169)Shi et al modified this idea further by producing a capsule with spiral leg motion to reduce the potential for intestinal damage and a novel power system, 'WPT platform', which prevented the need for an attached external cable. This device was able to travel 23mm/minute through an ex vivo intestinal model while transmitting 30 image frames per second*(Figure 19)*.(170) Kim et al used the paddling motion employed to propel a canoe as the basis for their capsule endoscope, which could traverse the colon of an anaesthetised pig at a rate of 17cm/minute*(Figure 20)*.(171) Using an external electromagnetic field to control capsule movement

via an inchworm-type motion has also been used with success in ex-vivo models, while Woo et al utilised an electrical stimulus from within the capsule to prompt an intestinal muscular contraction, thus accentuating propulsion of the capsule through the intestinal lumen*(Figure 21)*.(172, 173)

Such designs have shown success in the tubular structures of the colon and small intestine, however the large volume of the gastric cavity requires a different approach. A number of investigators have considered using propeller-based capsules in a liquid distended stomach as a potential means of overcoming this issue. In the most recent study by De Falco et al, four propellers attached to an externally driven wireless capsule device were used successfully to examine the liquid distended stomachs of ex vivo models *(Figure 22)*.(174) Morita et al used an alternating-current magnetic field to cause vibration of a fin attached to a conventional small bowel capsule endoscope (PillCam SB). An operator used an external joystick to direct the capsule to examine the gastric cavity of a sedated dog, allowing the accurate identification of previously placed endoscopic clips *(Figure 23)*.(175) Other investigators have used the fields produced by magnetic resonance imagers as a basis for control of a capsule driven by a 'swimming' tail.(176) These developments represent an exciting field of emerging capsule technology, but they have yet to make the transition from experimental prototype to use in human subjects and thus there is some way to go before their clinical utility can be fully understood.



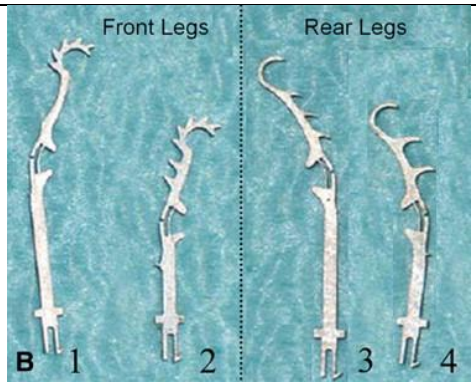
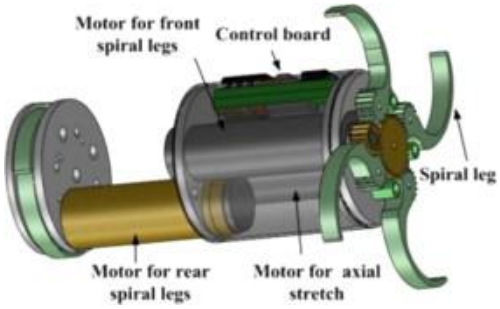


Figure 18: (A) The capsule prototype devised by Quirini et al uses gear actuated legs (B) to propel itself through tubular structures such as the colon. With permission.(169)



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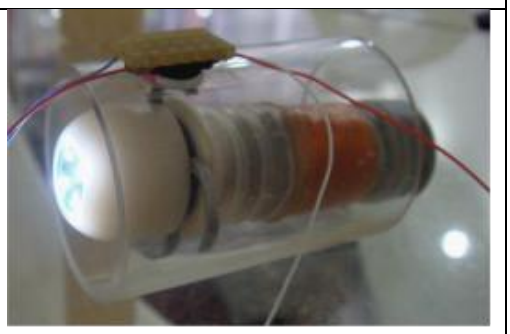
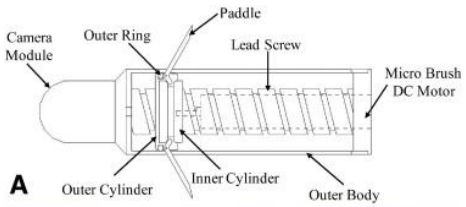


(b)

Figure 19: (a)The internal structure of the micro-intestinal robot devised by Shi et al. (b) Testing of the expanding force of the robot (within a tube). With permission.(170)



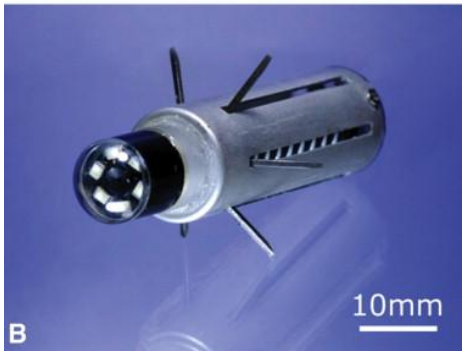
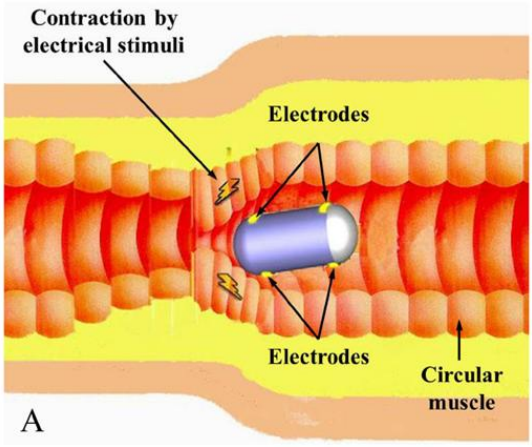
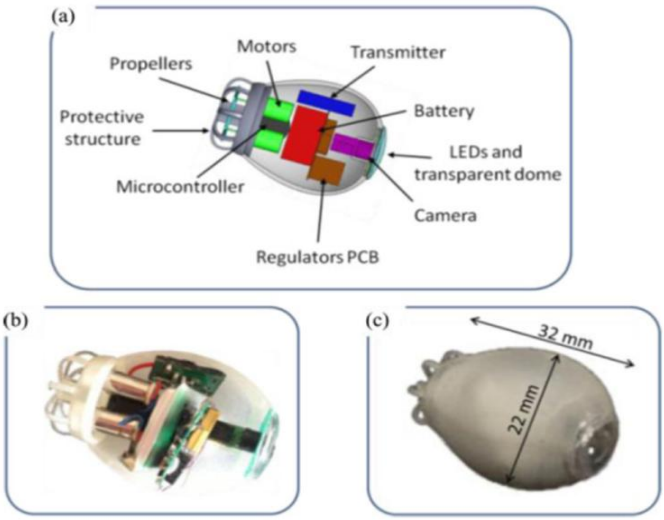
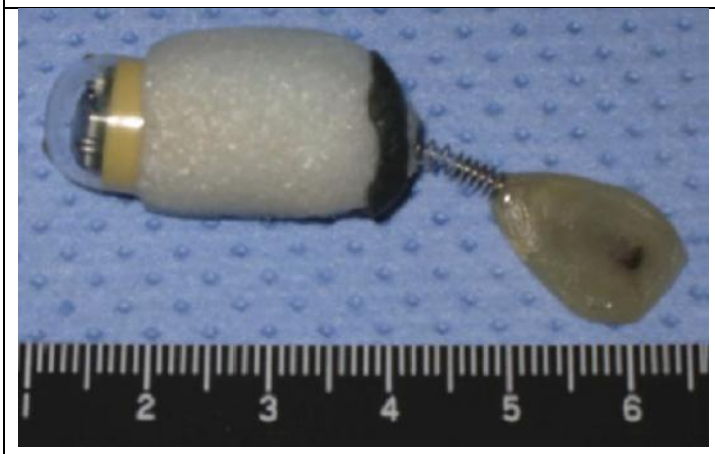


Figure 20: The paddling capsule endoscope devised by Kim et al. (A) Cross-section of the structure and major components of the capsule. (B) The final capsule prototype with legs fully expanded. With permission.(171)

	*Figure 21: The capsule devised by Woo et al uses an electrical stimulus to cause smooth muscle contraction of the intestinal lumen, thus propelling the capsule forwards. With permission.(172)*
	*Figure 22: The remote controlled capsule developed by De Falco et al can reach a speed of 1.5cm/second, driven by four propellers.©[2014] IEEE, (174)*
	*Figure 23: An applied alternating current magnetic field causes vibration of the fin attached to the capsule developed by Morita et al. With permission.(175)*

Remote manipulation using magnetic forces

Using the forces produced by a magnetic field to exert remote control over an ingested capsule endoscope seems to be the most promising area of developing mobile capsule technology since magnetic coupling is one of the few physical phenomena capable of transmitting a force through a physical barrier. This notion has been exploited for other uses within gastroenterology, including the positioning and localisation of naso-enteral feeding tubes (177, 178) and magnetic stent and foreign body removal.(179, 180)A number of prototype studies have demonstrated the feasibility of these conceptsfor capsule mobilisation in the stomach and colon using laboratory models, ex-vivo models and in-vivo porcine or canine subjects.(181-187)

Carpi et al described the first capsule to be controlled by an external magnetic field in 2006.(188) Subsequently they have developed a device which could be steered, using external magnetic control, throughout the entire gastrointestinal tract of a sedated pig. Tracking and localisation of the capsule was achieved using a robotic navigation system (Niobe, Sterotaxis, Inc, USA) already in clinical use for cardiovascular procedures.(189) A combination of robotic magnetic manipulation and air insufflation were utilised in the tethered capsule devised by Valdastri et al, to enable in vivo colonic inspection and the accurate detection and removal of implanted beads.(190) When this prototype was compared to colonoscopy for the detection of implanted pins in an ex-vivo models, there was no significant difference between the two modalities, although the duration of conventional colonoscopy was significantly shorter ($p=0.0001$).(191)

The ability to track and localise capsule movements is a helpful adjunct when developing capsule locomotive technology, allowing objective evidence of the movements of the capsule and mapping of the mucosa visualised. Similar technology has been used to successfully develop magnetic endoscopic imaging, a widely utilised colonoscopy training and practice tool. Compatible colonoscopes have built in tiny magnetic coils at regular intervals along the scope. The magnetic

fields in these wire coils induce an electric current in an external sensor coil which is then converted into a real-time 3-dimensional image, viewed on a monitor. Using endoscopic imaging led to a higher caecal intubation rate for inexperienced colonoscopists, compared to using on-demand fluoroscopy ($p=0.02$) in one study.(192) When compared to conventional colonoscopy, the duration of abdominal compression was shorter and fewer turn manoeuvres per patient were required in the magnetic endoscopic imaging group suggesting that the magnetic imager helped guide the endoscopist to perform a more efficient procedure.(193)A number of algorithms have been proposed to enable capsule endoscope tracking and localisation, although none have yet progressed beyond experimental design.(194-196)

1.5.6 Magnetic capsule examination of the human stomach

Given Imaging System

After a number of years of experimental designs and prototypes, magnetic guidance of a capsule endoscope to examine a human stomach was first described by Swain et al in 2010.(197) The team used a modified PillCam Colon capsule endoscope with one camera replaced by magnets. The capsule transmits images at 4 frames per second from a CMOS sensor. The external hand held magnet was made in two designs. The first used a magnet within a plastic box weighing 0.5Kg to give a maximum strength of 272g/cm^2. The second design used two rectangular magnets shaped into a paddle. Heavier at just under 3Kg, this design achieved a force of 256g/cm$^{2.}$ Like the conventional Given Imaging capsules, images were transmitted via radiofrequency to an external data recorder via sensors placed on the patients' torso. The first capsule began operating at a temperature of 60° when immersed in water, by use of a thermal switch. Subsequently this was modified to a radio-frequency switch.

The magnetically manoeuvrable capsule appeared to be easily manipulated in the oesophagus and stomach using a handheld external magnet.(197) A second study using the same apparatus found encouraging results with >75% of gastric mucosa visualised in 7 out of 10 patients undergoing the examination and no adverse events reported.(198) The portability of this system, which included a capsule endoscope, data recorder, 'real time' viewing monitor and hand held magnet is one of the major advantages of this technique when compared to conventional flexible endoscopy*(Figure 24)*. However, the technique relies on a trained operator employing fine motor skills to manipulate the capsule, based purely on the visual images fed back from the capsule and thus required a high level of skill and dexterity.

Olympus and Siemens system

Other groups have adopted a different approach, using an external magnetic field generated by, for instance a magnetic resonance imager, to control an ingested magnet-containing capsule. One such system, used by Rey et al, was developed by Olympus Medical Systems Corporation (Tokyo, Japan) in conjunction with Siemens Healthcare AG (Erlangen, Germany).(199)The system utilises a capsule with two charge-coupled device image sensors either side of centrally placed magnetic inclusions. Unfortunately the image resolution, depth of field and field of view of the capsule are not stated in the manufacturers information or by the authors, but these are said to be greater than the currently available Olympus EC type 1 capsule (145° field of view, 0-20mm depth of field) and the image capture rate is stated as 4 frames per second.

The patient lies within the magnetic guidance unit, which is similar in appearance to a computed tomography scanner, and produces dynamic magnetic fields and gradients with which to control the capsule. The system is capable of creating a magnetic field strength of 100 milliteslas (mT), but only field strengths of 3-10mT were utilised for the human studies.The images obtained from both capsule sensors are displayed on a monitor, together with the capsule orientation (devised using data from the guidance system) and suggested capsule manoeuvres, on a second screen. These manoeuvres are executed by an external operator using a joystick which leads to subtle alterations in the applied magnetic field, thus altering the position/orientation of the capsule*(Figure 25)*.The system also includes pre-programmed manoeuvres, such as jumping, which can be initiated by the operator.

Ingested water is used to provide gastric distention to improve mucosal visibility. Promising results were achieved in the first comparison with conventional upper GI endoscopy, with 58.3% of gastric lesions detected by both modalities, while 14 lesions were missed by magnetically guided CE and 31 lesions missed by OGD (that were seen by magnetically guided CE).(200)The subsequent study of 189 symptomatic patients found magnetically guided capsule only had a sensitivity of 61.9% (95% CI 38-82%), specificity 94.1% (95% CI 89.3-97.1%) and overall accuracy of 90.5% (95% CI 85.4-94.3%)

when compared to conventional upper GI endoscopy.(201) This led the authors to conclude that improvements would be necessary before this technique could be considered an alternative to flexible endoscopy of the stomach.

Ankon Technologies Co. Ltd. System

Liao et al describe a similar system to that used by Rey et al, but instead use a magnetic field generated by an external industry robot to manipulate the capsule*(Figure 26)*. This includes a capsule measuring 28 x 12mm with a CMOS image sensor at one end and magnetic material at the other. The field of view is 140°, with a resolution of 480x480 pixels, however, images are captured at a lower rate of 2 frames per second.The external magnet is contained within a robot in a C-arm configuration. The external magnet can generate a magnetic field of up to 200mT but much lower fields of 5-30mT were used in the studies reported below. Similar to the Olympus and Siemens system, two monitors provide capsule images and technical information such as magnetic field strengths. A joystick is used to adjust the applied magnetic field and manipulate the capsule, although pre-set manoeuvresare programmed into the system and can be utilised without the need to use the joystick.

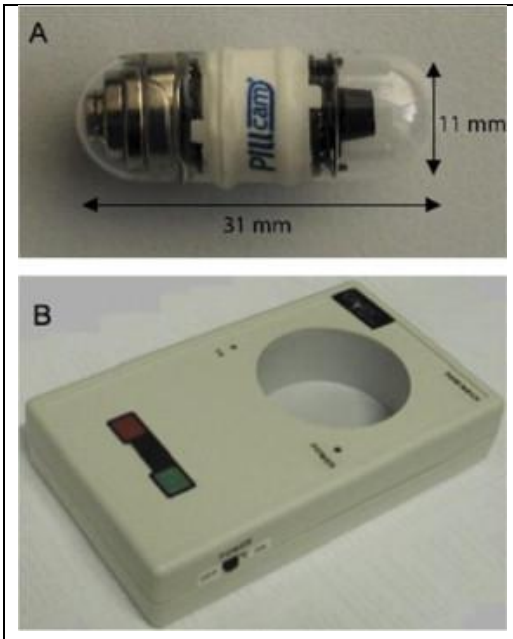
In their study of 34 healthy volunteers more than 75% of the gastric mucosa was visualised in 79.4% of the subjects and no adverse events were reported.(202) A comparison of this technique with conventional upper GI endoscopy in 68 patients showed an overall agreement of 91.2% with a kappa value of 0.765 ($p<0.001$).(203) The major drawback of both of these type of systems is that they require cumbersome, expensive equipment in order to function and thus, despite their non-invasiveness, the uptake of such techniques, outside the realms of specialist centres, is likely to be poor.

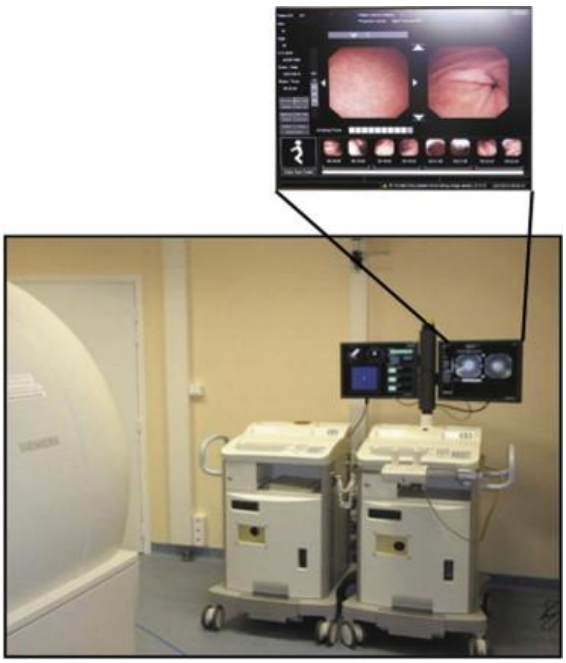
MiroCam Navi system

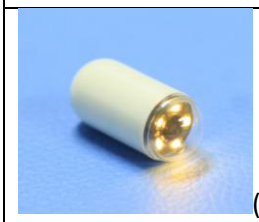
MiroCam Navi is a specially developed version of the MC1000-W capsule produced by Intromedic (Seoul, Korea). It has magnetic inserts and is available with an external magnet shaped much like a mallet. The MiroCam Navi system is utilised during this thesis and thus further technical specifications are described in the methods section, chapter 3. When I began this research there were no published studies using MiroCam Navi. A comparison of the differing magnetic capsule systems is presented in *Table 2.*

Table 2: Comparison of the different magnetic capsule endoscope systems

	Size (mm)	**Weight (g)**	**Field of view (°)**	**Depth of field (mm)**	**Image capture rate (frames/second)**	**Image resolution (pixels)**	**External magnet size (cm)**	**External magnet weight (Kg)**	**External magnet force**
Given Imaging system	31x11	7	156	0-30	4	N/A	10x10x3	3	256 g/cm
Olympus and Siemens system	31x11	N/A	N/A	N/A	4	N/A	100x200	Large static machine	100m/T (only 3-10m/T used in studies)
Ankon Technologies Ltd system	28x12	N/A	140	N/A	2	480x480	N/A	Large static machine	200m/T (only 5-30m/T used in studies)
MiroCam Navi	25.5x10.5	4.75	170	0-30	3	320x320	26x6.5x3.5	1.2	268 g/cm

	*Figure 24: (A) Given Imaging magnetic capsule (B) Hand held external magnet. With permission.(198)*
	*Figure 25: The Olympus and Siemens navigation system, control panel and capsule used by Rey et al. With permission.(199)*




(a)


(b)

Figure 26: Ankon TechnologiesCo. Ltd Navigation system used by Liao et al.(a) The ingestible capsule (b) the magnetic guidance unit. With permission.

1.5.7 Relevance of gastric capsule examination to current practice

Since the introduction of flexible endoscopes in 1957 there has been a rapid increase in the volume and complexity of services required as the diagnostic ability of endoscopy improves and therapeutic capability advances. Direct visualisation of the upper GI mucosal surface provides far more useful information than the two dimensional images produced by barium studies previously and thus flexible endoscopy has become the investigation of choice for diseases of the upper GI tract. Current indications for upper GI endoscopy are shown in *Table 3*.

Most upper GI endoscopies are performed without any complication or side-effects, but these do exist and form the basis for the consenting process (*Table 4*). Finally, many patients find the process of upper GI endoscopy anxiety provoking and in some cases this is preventative to performing the investigation.(204)

Currently 1% of the UK population per year will undergo flexible upper GI endoscopy (205) yet less than half of these reveal clinically significant pathology.(206, 207) Symptoms of dyspepsia and gastro-oesophageal reflux disease are common complaints with European prevalence estimated at up to 25.9% in a recent systematic review.(208) These conditions pose a significant burden to healthcare providers with up to 40% of sufferers consulting with a primary care physician (209) and the financial costs of managing the condition estimated at £500 million per year in the UK in 2002.(210) Healthcare professionals, in particular primary care physicians face difficult decisions in managing such patients. Guidelines do exist to assist with risk stratification of patients for endoscopy,(211) but rely mainly on the presence of alarm symptoms and unfortunately this approach can miss early upper GI cancers.(212, 213) On the other hand, open access to gastroscopy services has been available in parts of the UK for over 10 years but despite a significant increase in workload, reported to be up to 32% in one study, the early detection of upper GI cancers was not improved.(214)

Uncertainty remains over how best to manage patients with dyspepsia and in particular if/when to arrange endoscopy, with many physicians adopting a cautious approach of early endoscopy to avoid missing potentially serious pathology. Not only is this burdensome for endoscopy services, but also worrisome for patients who undergo the stress and anxiety of an invasive procedure despite the likelihood of a normal or insignificant result. Alternative investigative modalities able to directly image the upper GI mucosal surface, without the risks of intubation or sedation would be beneficial, particularly if they were more tolerable to patients. Availability of such services within the primary care community would provide improved accessibility and acceptability for patients with potential associated financial gains. Capsule endoscopy is an attractive option for examination of the stomach due to its favourable tolerability profile and relatively low complication rate. A simple, portable, inexpensive technique which could be easily utilised and widely implemented would be of most value and these considerations have formed the basis of this thesis.

Table 3: Indications for diagnostic upper GI endoscopy(215, 216)
GI haemorrhage
Dyspepsia
Abdominal pain
Vomiting
Dysphagia/Odynophagia
Iron deficiency anaemia
Weight loss
Diarrhoea
To obtain duodenal biopsies
Abnormal imaging i.e. barium meal or CT scan
Re-assessment of known pathology i.e. ulcer healing
Surveillance of known conditions i.e. Barrett's oesophagus, oesophageal varices
Screening for high risk conditions i.e. oesophageal varices, polyposis syndromes

Table 4: Complications related to upper gastrointestinal endoscopy		
Complication	Frequency	Reference
Overall	0.1-0.13%	(217, 218)
Death rate	0.05%	(219)
Morbidity	0.01-0.5%	(217, 220-222)
Sore throat	9.5%	(223)
Abdominal discomfort post-procedure	5.3%	(223)
Perforation	0.009 - 0.2%	(221, 223, 224)
Haemorrhage	0.15%	(217)
Cardiorespiratory complications secondary to sedation	0.5%	(225)

1.6 Summary of Overview

Gastroscopy is the conventional standard for examination if the upper GI tract but has drawbacks in terms of tolerability and risks of intubation. Capsule endoscopy is currently a focus of great technological interest due to its success as a diagnostic modality for the small bowel and favourable tolerability profile. The stomach has remained a challenge to capsule examination since a passive capsule is unable to view all areas of the gastric cavity. Capsules with magnetic steering capability are now available and present an opportunity to overcome this hurdle. Further research is required to determine the position of such devices in the modern upper GI investigational armoury.

Chapter 2 Aims

This body of work aims to address whether magnetically assisted capsule endoscopy(MACE) could be a feasible alternative to conventional flexible endoscopy for examination of the stomach. We will utilise the MiroCam Navi capsule system (Intromedic Ltd, Seoul, Korea), a simple, portable system which includes a handheld external magnet and a small bowel capsule endoscope containing magnetic inclusions.

NULL HYPOTHESIS: magnetically assisted capsule endoscopy is not a viable alternative to conventional flexible endoscopy for examination of the stomach.

These questions will be addressed by undertaking the following four studies:

Chapter 4: To examine feasibility of magnetically assisted capsule endoscopy of the stomach and operator learning curve in an ex vivo porcine model.

Chapter 5: To evaluate magnetically assisted capsule endoscopy compared to flexible endoscopy for visualising major gastric locations in an ex vivo porcine model: blinded randomised trial.

Chapter 6: To investigate feasibility in humans by examining whether magnetically assisted capsule endoscopy can enhance small bowel capsule endoscopy by hastening gastric transit: randomised trial.

Chapter 7: To assess magnetically assisted capsule endoscopy compared to flexible endoscopy for the identification of gastric pathology in humans; a pilot study.

When this project was initiated there were no publications describing the utility of MiroCam Navi for the examination of the stomach. Although this is a rapidly expanding area of research there remains a paucity of data regarding simple, portable techniques of gastric capsule examination. By evaluating

this technology we hope to provide insight into the viability of this technique and highlight areas where further research would be beneficial.

Chapter 3 Materials and Methods

3.1 Materials

Magnetically assisted capsule endoscope

The system we are trialling for this thesis is MiroCam Navi and it includes five main components: an ingestible capsule endoscope, a data recorder, a real-time viewer, an external hand-held magnet and a computer workstation for downloading and reviewing images*(Figure 27 & 28)*. The capsule endoscope is a small bowel capsule endoscope (10.5x25.5mm, 4.25g, field of view 170°) with the inclusion of a small amount of magnetic material. It contains a CMOS image sensor, a white light-emitting-diode as the illumination source and two silver oxide batteries as a power source. It has a resolution power of 320x320 pixels, depth of field 0-30mm and captures images at a rate of 3 frames per second. The MiroCam system differs from other small bowel capsule systems in that electric field propagation is used to transmit data from the capsule to the data recorder rather than radio-frequency. Radio-frequency communication technology has the drawback that it is significantly draining on the capsule battery life and thus MiroCam capsules provide a prolonged operating time of up to 12 hours. The images obtained by the capsule can be reviewed in real time by connecting a lap-top to the external data recorder or wirelessly using an iPad to connect to the Wi-Fi function of the external data recorder. Following the examination the recorded images are downloaded onto a workstation which produces a video for further review. The external magnet measures 26x6.5x3.5cm, weighs 1.2Kg and generates a magnetic force on the capsule of up to 268g/cm.

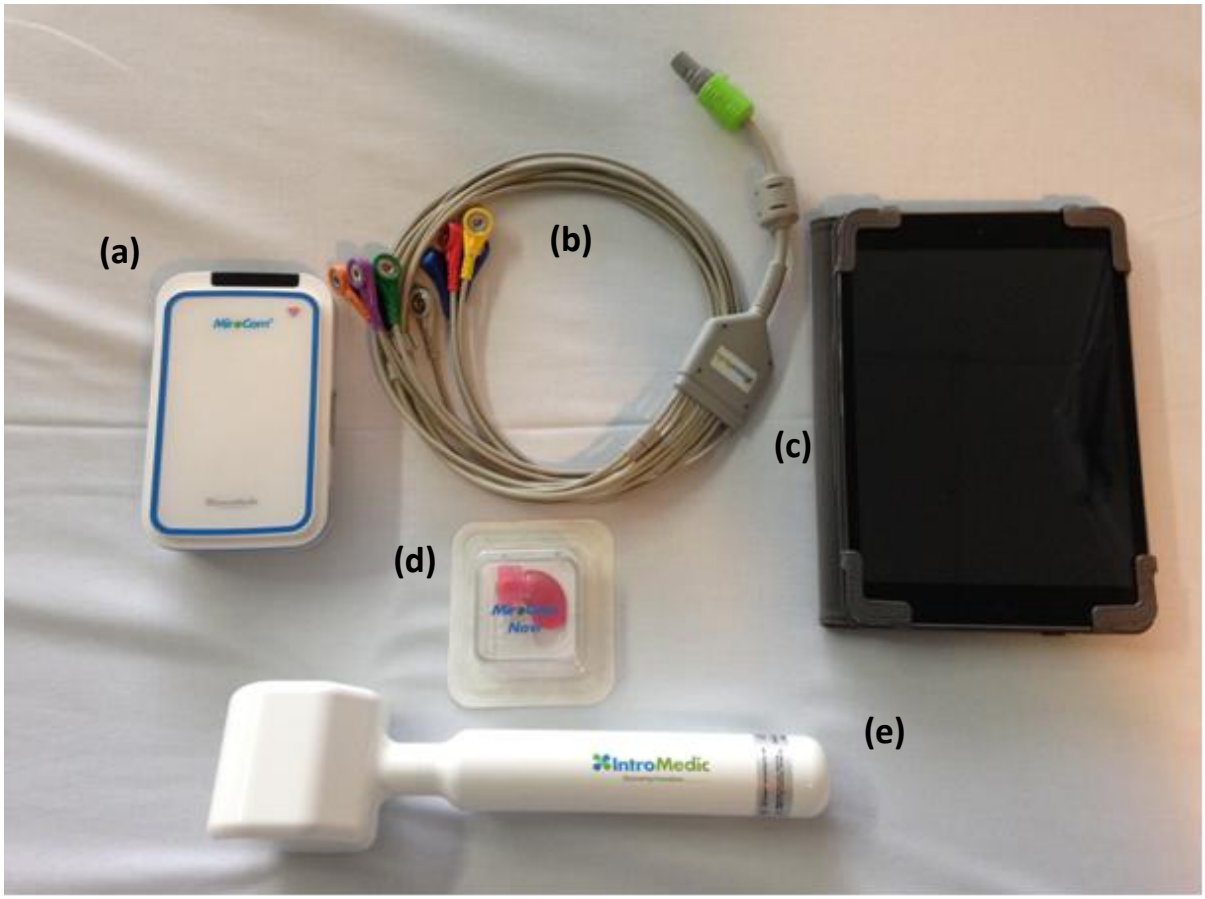


Figure 27: Components of the MiroCam Navi system (a) data recorder, (b) sensor leads, (c) i-pad real time viewer, (d) capsule endoscope, (e) hand held external magnet

Figure 28: MiroCam Navi capsule and schematic of using the external handheld magnet. With permission.

Ex vivo studies

Porcine stomachs have a similar anatomical size and shape to their human counterparts and thus are commonly used for endoscopy training purposes. Ex-vivo porcine stomach models in a standard mounting unit (Endo X TrainerTM, Medical Innovations International Inc, Rochester, Minnesota, USA) were used for these studies *(Figure 29)*. The stomach tissue was obtained from pigs aged 4-6 months and consisted of the oesophagus, stomach, first and second part of the duodenum. The tissue was purchased frozen and required defrosting and thorough irrigation with water in preparation for the study. A tube was inserted into the oesophagus to allow ease of passage of the flexible endoscope or capsule. The duodenum was closed using forceps. The stomach models were secured to the mount using plastic loops and netting. Opaque fabric was used to obscure the stomach models before examination commenced to ensure external visual localisation could not be used to assist the examination.

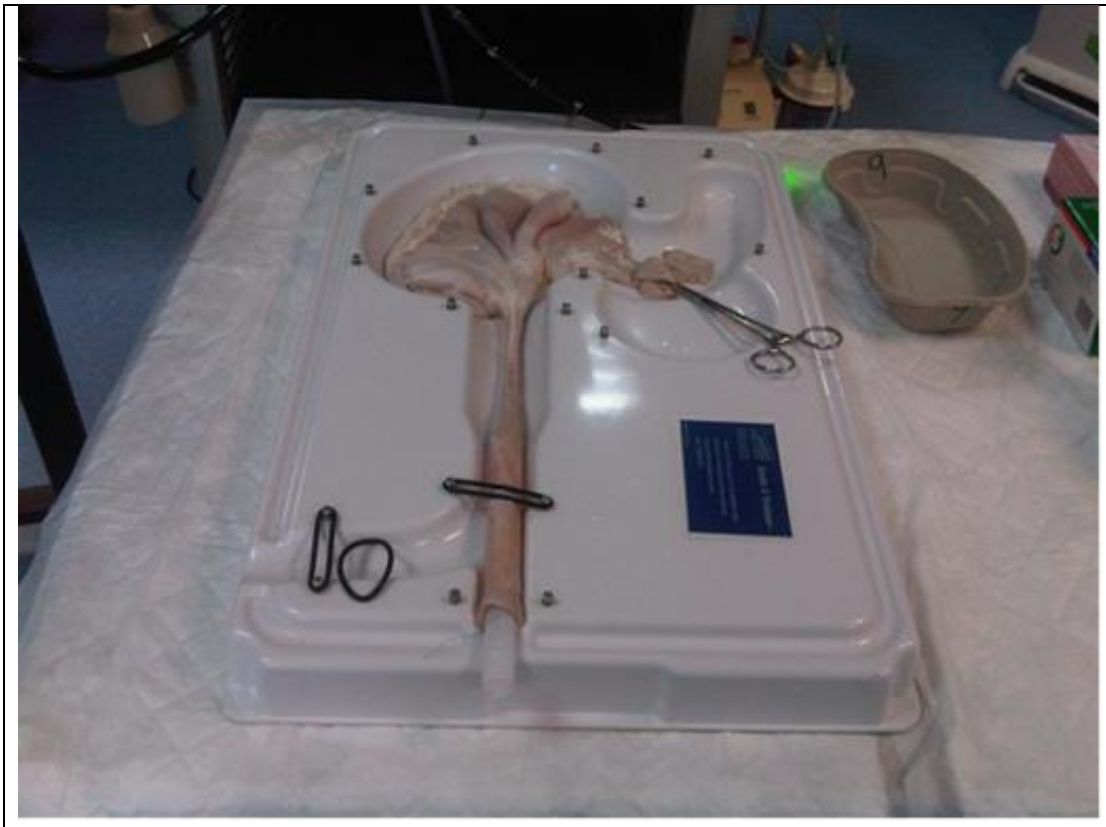


Figure 29: The Endo-X trainer used for mounting the ex-vivo porcine stomach tissue, shown here with a prepared stomach mounted and ready to use.

3.2 Patient recruitment

Further details for each study are available in the individual chapters.

Patients who required OGD and/or CE and were eligible to enter the studies were recruited from the Clinical Investigation Unit or medical outpatients at the Royal Hallamshire Hospital, part of Sheffield Teaching Hospitals NHS Foundation Trust. The Royal Hallamshire Hospital is an 860 bedded tertiary hospital, in the South Yorkshire region, serving a population of 2 million. This hospital is one of the pioneer centres for capsule endoscopy, providing a regional small bowel service for South Yorkshire since 2002 and currently performing >800 SBCE procedures per year.(10)

Both human studies described in this thesis have received approval from the regional research ethics committee and also by our local hospital trust clinical governance department.

Written informed consent was obtained for entry into a study (*Appendix 2 and 3*) and for each procedure (CE/OGD) within a study in every patient. Patients were given information leaflets (*Appendix 4 and 5*) and adequate time to consider their participation in the respective studies. The consent obtained was in accordance to the guidance produced by the Department of Health, General Medical Council and the British Society of Gastroenterology.(226, 227)

3.3 Statistical analysis

Methods and statistical analysis are individually outlined in each chapter. All calculations were performed using Statistical Package for the Social Sciences (SPSS) versions 19 to 21. All p values provided are 2 sided, with a value of <0.05 considered to be significant. Advice and support for statistical analysis was provided by staff at 'MASH-Maths and Statistical Help' through the University of Sheffield.

3.4 Methods

Technique of flexible endoscopy of the upper GI tract

Typical equipment found in a modern endoscopy suite include: a television monitor, video-processor, a light source, a pump for air insufflation, external suction and a water bottle for lens cleaning (*Figure 30*). Flexible upper GI endoscopy was performed using Olympus GIF-H260 endoscopes with a diameter of 8-11mm.

Patients are fasted for 6 hours prior to the procedure. The pharynx is anaesthetised using a lidocaine-based spray. The option of conscious sedation is available with a benzodiazepine such as midazolam (Hameln Pharmaceuticals, Gloucester, UK). This requires the insertion of an intravenous cannula and monitoring of the patient's pulse and oxygen saturations. Low flow nasal oxygen is administered during a sedated procedure.

A mouth guard is used to protect the patient's teeth and the endoscope. The endoscope is passed through the mouth guard to the back of the pharynx and the upper oesophageal sphincter. The oesophagus is intubated under direct vision and the endoscope is smoothly passed through the oesophagus and into the stomach. The pylorus is intubated to allowexamination of the first and second parts of the duodenum. The endoscope is then withdrawn slowly and retroflexed to allow thorough examination of the gastric cavity. Air insufflation is used to distend the stomach. Suction is available to remove any liquid, which may obscure views. Lens washing can be used to remove debris, which can prevent clear images.

Following the procedure the patient cannot take anything orally until 60 minutes after the initial pharyngeal anaesthesia to reduce the risk of aspiration. If sedation has been administered, the patient is taken to a recovery area to allow time to resume a normal conscious level, this can take up to 40 minutes.

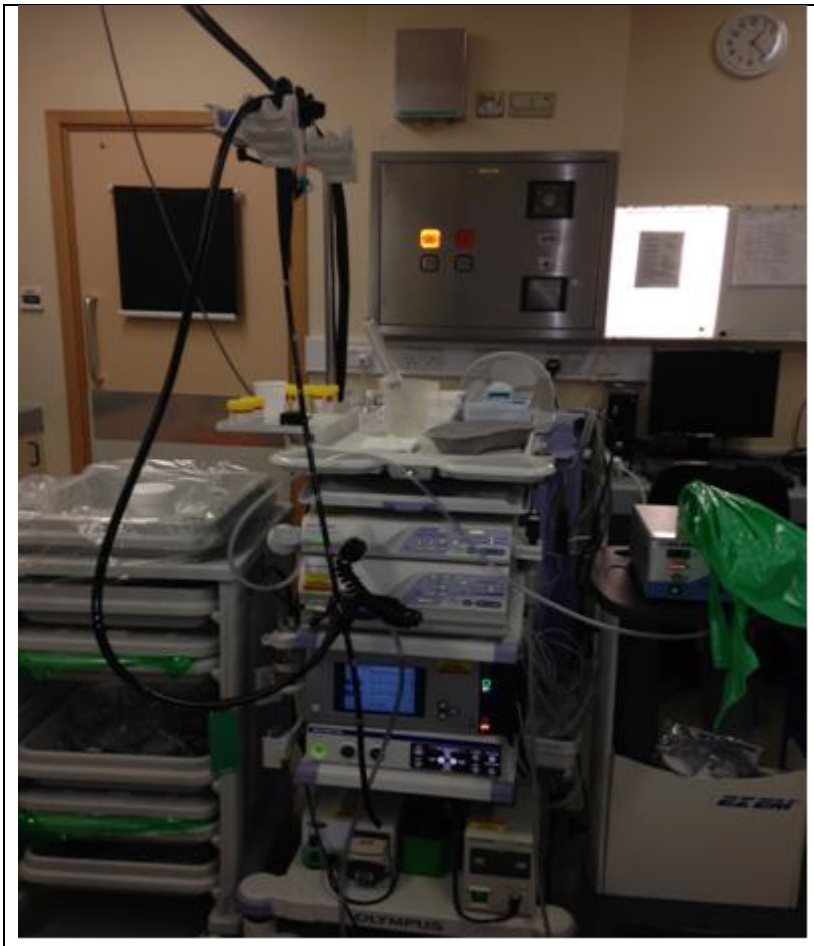


Figure 30: A typical flexible endoscopy stack.

Technique of magnetically assisted capsule endoscopy

Patients are fasted for 12 hours before the procedure. Prior to MACE the patient is required to drink 1000mls of water with 40mg of simethicone suspension. This is to aid gastric distention and to reduce the formation of bubbles, which can cause image distortion. Nine sensors are placed over the patients' abdomen and chest. These are connected to a data recorder which is synchronised with the individual capsule given to the patient. Water is provided freely for the patient to swallow the capsule with; usually 50-100mls is required. Once the capsule has been swallowed the handheld magnet is moved over the patient's abdomen using 'real-time' images viewed on a lap-top or iPad, to facilitate targeted movements of the capsule. Positional change is used to assist dragging

movements of the capsule from one area of the stomach to another. Following MACE the capsule is allowed to continue its' passive motion through the remainder of the GI tract.

If the patient is also undergoing SBCE the patient is allowed to drink after two hours and eat after four hours. The patient is allowed to be ambulant and leave the hospital during the subsequent recording period. The equipment is removed after eight hours. On completion of the procedure (eight hours after or when the recorder has stopped flashing), the data from the recorder is downloaded onto a computer workstation which allows approximately 50 000 images to be viewed as a continuous video. Images are obtained from the oesophagus, stomach, small bowel and part of the colon. The capsule is usually passed into the toilet within a further 72 hours, and can be flushed away. The capsule is for single use and is disposable.(228)

Measuring patient comfort and tolerability

One of the major advantages of CE over intubational endoscopy is that it is generally thought to be well tolerated by patients. Ultimately, improving the patient experience is one of the main forces driving advances in capsule technologies. If MACE was found to achieve similar diagnostic yields to conventional upper GI endoscopy then a major factor in introducing MACE as an investigative modality would be its' acceptability profile. It is therefore paramount that this is evaluated as part of this body of work.

Tolerability can be assessed using general measures such as; willingness to repeat the procedure, overall satisfaction and acceptance of the procedure. More specific factors include: pain, distress, anxiety, discomfort and symptoms which may be experienced during the procedure such as nausea or bloating. A combination of these variables seems the best way to measure a patients' tolerance of a procedure. Such an approach has been used in a number of published studies attempting to analyse patient experience during endoscopy.(229-231) Visual analogue scales, numeric rating scales and Likert scales provide a convenient means of documenting variables which can be measured on a

scale, such as pain. Common statistical methods can be applied to interpret visual analogue and numeric rating scale results but patients can have difficulty understanding how to complete such scores. Likert scales are more straightforward to complete but produce data which cannot be interpreted using standard statistical methods.

For the purposes of this thesis we developed a questionnaire *(Appendix 6)* to assess a patient's comfort during the procedures undertaken as part of the studies contributing to this body of work. The aim was to provide an objective analysis of patient comfort during MACE which could then be used to form comparisons between that and other procedures, for instance MACE and OGD in Chapter 7.

Using the Irvine(232) and Elphick(233)studies as a basis, the questionnaire uses visual analogue and numeric rating scales to enable participants to document their anxiety, discomfort and distress. The questionnaire will form part of the study protocol for Chapter 6 and 7. It will be given to participants before each procedure and collected after. The principal investigator or another member of the study team will be available to assist with any difficulties patients may experience completing the questionnaire.

3.5 Collaborations

The research described in this thesis was conducted in a collaborative manner. I am extremely grateful to the clinicians, nurses, health care assistants and administrative support staff who contributed. Chapter 4: Dr Stuart Riley and Ian Battey. Chapter 5: Dr Imdadur Rahman, Dr Praful Patel, SR Kaye Drew, Dr Reena Sidhu, Dr Stuart Riley and Ian Battey. Chapter 6: Dr Reena Sidhu, SR Kaye Drew, SR Anna Hawley and the nursing staff on the Clinical Investigation Unit at the Royal Hallamshire Hospital. Chapter 7: Dr Reena Sidhu, SR Kaye Drew, SR Anna Hawley, Dr Matthew Kurien, Dr Imran Aziz and Caroline Hirst. Finally this would not have been possible without the unflinching support, mentorship and supervision of Dr Mark McAlindon.

Chapter 4

Gastroscopy without a gastroscope! Feasibility in a porcine model using a magnetic capsule

4.1 Abstract

Introduction: Capsule endoscopy is a non-invasive tool used primarily to image the small and large bowel. Although a large volume organ, examination of the stomach might be enabled by magnetic control allowing manoeuvrability and positional change.

Methods: A pig stomach model was used in a feasibility study of magnetically steerable capsule endoscopy. Eight different coloured beads were sewn into each major location of the stomach (cardia, fundus, greater and lesser curve, anterior and posterior wall, antrum and D1). The stomach was distended with 1000mls of water. Endoscopy was performed according to a set protocol using a handheld magnet, MiroCam Navi (Intromedic Ltd), positional changes (supine, 30° right lateral, head down, 30° left lateral) and a "real time" viewer. The order and time each tag was identified was recorded alongside the total procedure time.

Results: All stomach tags were identified in 87.2% (41/46) of examinations. Missed tags included antrum (3/6), cardia (2/6) and posterior wall (1/6); none were missed in the latter 25 procedures. Mean examination times for the first 23, second 23 and all procedures were 10.28, 6.26 ($p<0.001$) and 8.27 (range 3.25-16.32) minutes and all were completed by 4 minutes after 39 procedures. The order in which tags were identified in the mid-body of the stomach (greater, anterior and posterior) was variable and interchangeable. If this area was considered as one site, the order of tag identification would be: cardia (1), fundus (2), mid body (3), lesser curve (4), antrum (5) and D1 (6) in 76.6% of examinations. No difficulties were observed with the current procedure protocol and therefore no modifications recommended.

Conclusion: Examination of the upper gastrointestinal tract is feasible using a magnet and positional change as demonstrated in this porcine model. A learning curve was evident and this model might be used for training in the future. Further investigation using porcine models and in humans is necessary to fully realise the scope of this exciting novel technology.

4.2 Introduction

There is little evidence that gastroscopy affects patient outcomes,(234) but it is uncomfortable and incurs the risk of intubation and sedation. Capsule endoscopy is a non-invasive tool used primarily to image the small bowel. The capacious stomach has proved challenging to capsule endoscopy since the passive motion of a standard capsule is unable to visualise all areas of the gastric cavity. Although a large volume organ, examination of the stomach by capsule endoscopy might be enabled by a capsule with steering capabilities.

At the time of designing and commencing this study there was published data available on the use of two capsules steered using external magnetic control. The first, pioneered by Keller et al used a simple handheld system and saw promising results in initial human studies (198), however unfortunately these have not been replicated subsequently. Following this, Rey et al presented data using a capsule steered with an applied external magnetic field produced by a device similar to a magnetic resonance imager.(199) The high cost and lack of portability of such a system preclude its use in routine clinical practice.

MiroCam Navi is a simple system, comprising five components, which is currently in clinical use as a small bowel capsule endoscope. When this study began there were no publications investigating the steering capabilities of the handheld magnet or the use of MiroCam Navi to image the gastric cavity. Without any published or local knowledge or experience using this equipment we elected to proceed with a series of ex vivo porcine studies to assess feasibility. The benefits of this approach are multiple: no ethical approval is required and thus studies could begin immediately, strategies of procedure and preparation could be resolved without putting a patient at inconvenience and finally multiple replicate experiments can be performed allowing the investigators to become familiar with the technique and any associated pitfalls. The advantage of cadaveric tissue over a mechanical

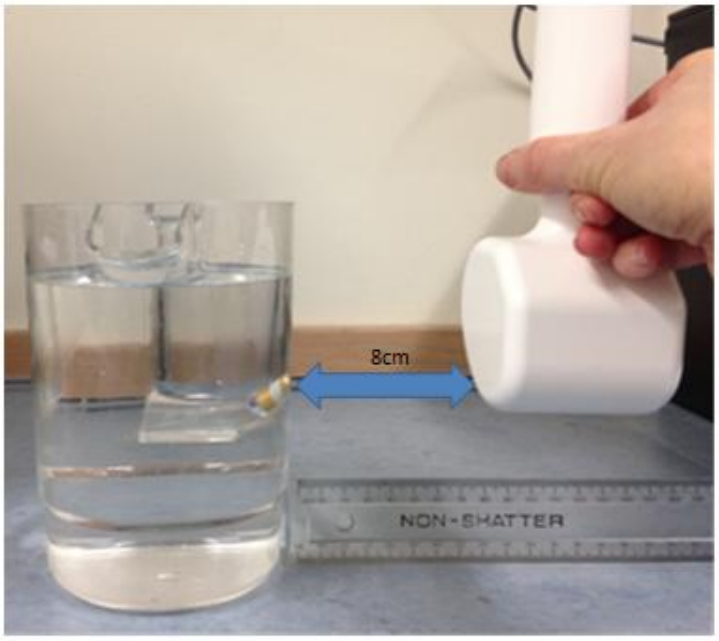
model is the higher degree of fidelity; it behaves much more like that of a human. The use of live animals is limited by expense, the need for expensive infrastructure and ethical concerns.

Ex-vivo tissue has been used extensively in endoscopy simulator-based training systems,(235) particularly in composite simulators such as the Erlangen active simulator for interventional endoscopy 'EASIE' (ECE-Training GmbH, Erlangen, Germany).(236, 237) The main drawback to such models is the time required to thaw the deep-frozen tissue, prepare and present it onto the mounting unit. Of course care must be taken when interpreting results from ex vivo studies since they may not always directly extrapolate to the intact living organ. Ex vivo models were used successfully in the original trials of capsule endoscopy for examination of the small bowel.(238)

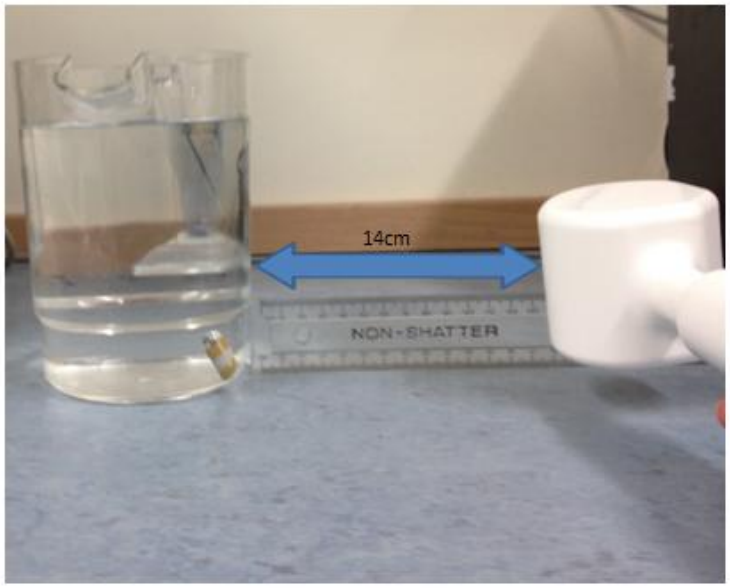
In this initial feasibility study we used an ex vivo porcine stomach model prepared with different coloured beads in major locations of the stomach. Following development of a protocol for examination I repeatedly examined this model aiming to identify all the beads in the shortest possible time.

The MACE gastric examination protocol was developed during practice with the capsule and external magnet in a variety of situations. Simple experiments using a jug of water were utilised to determine the optimal operating distance between the capsule and the external magnet and to demonstrate the effects on the capsule of distinct manoeuvres by the external magnet *(Figure 31)*.The capsule could be made to hover against the wall of the jug, midway up, but this required a shorter operating distance compared to when the capsule was resting at the bottom of the jug. Once in these positions the capsule could be tilted(left, right, up and down) and also flipped by 180° to face the opposite direction by making tilting and rotational movements of the external magnet *(Figure 31 and 32)*. Smooth tracing movements of the suspended capsule were much more difficult to achieve since very fine alterations in the operational distance could cause loss of the force between the two

magnets and subsequent dropping of the capsule out of its suspended field. Although one might imagine the external magnet to be manipulated in a smooth panning way much like an ultrasound probe, this was technically extremely difficult to maintain. Capsule steering was much more successful if approached by holding the capsule in a fixed suspended position and then employing the tilting and rotational movements described to visualise the surrounding area before moving on to another fixed position. For similar reasons, making targeted movements of the capsule over larger distances were best achieved by altering the orientation of the receptacle the capsule was contained in, rather than trying to drag the capsule using the external magnet.

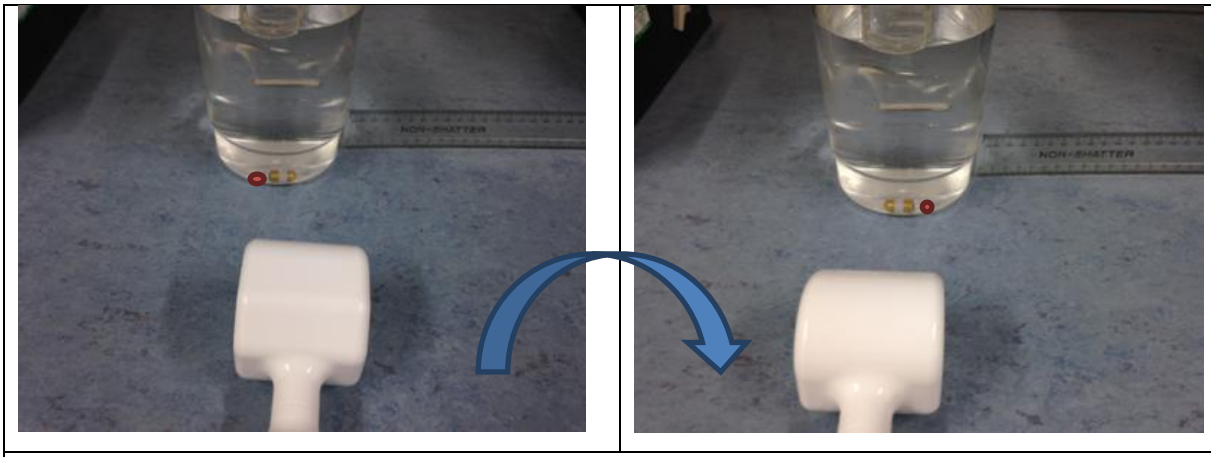


(a)

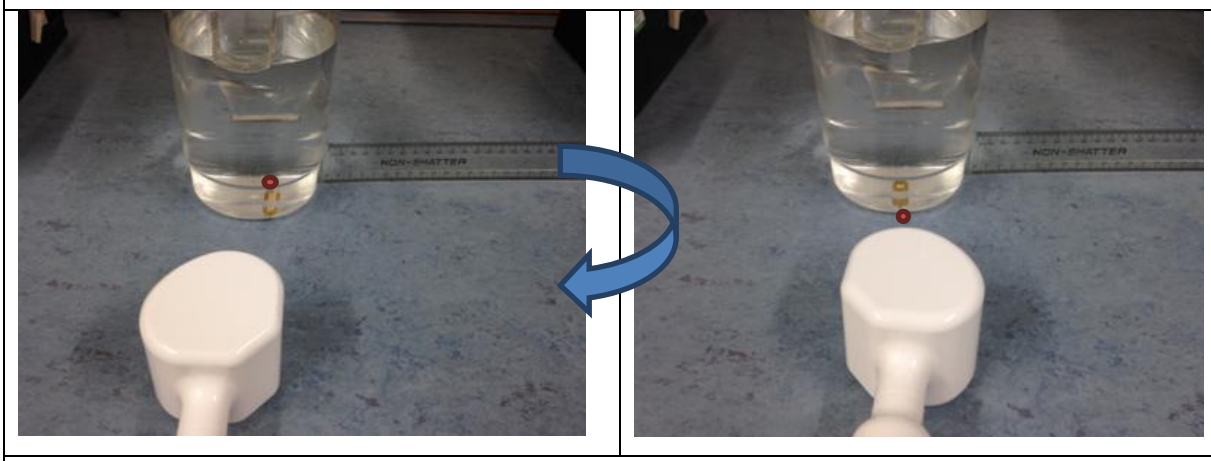


(b)

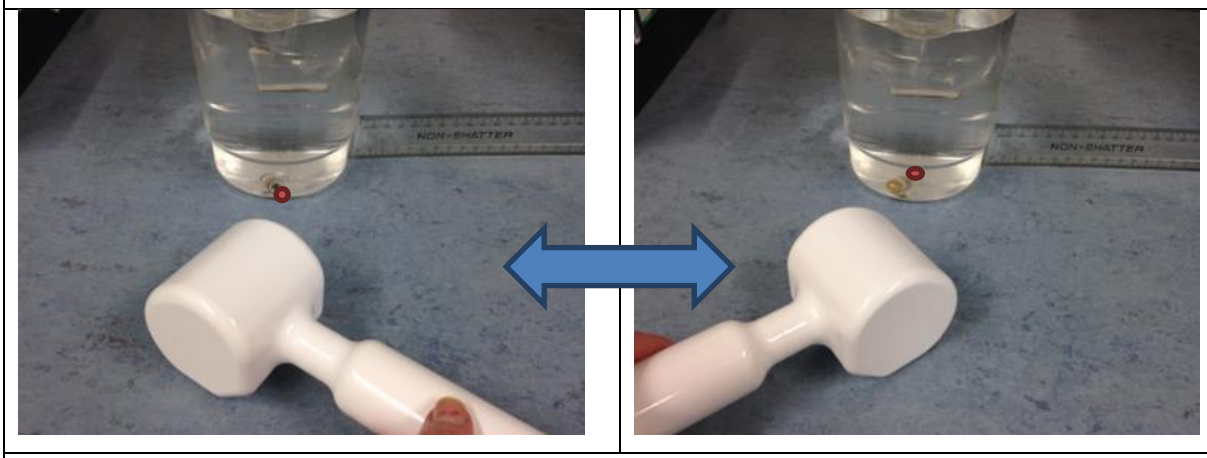
Figure 31: Preliminary studies using MiroCam Navi: (a) operating distance when suspended, (b) operating distance when resting



(a) Turning the controller from the starting position by a full 180° flips the capsule by 180° to face in the opposite direction.



(b) Turning the controller by 90° tilts the capsule to face up, turning a full 180° from this point tilts the capsule to face down.



(c) With the capsule resting flat, tilting the controller from side to side tilts the capsule

Figure 32: Potential directions of movement of the MiroCam Navi capsule using the external hand held magnet. Red dot represents the camera end of the capsule.

4.3 Methods

Device Description - See Chapter 3.

Aims

- to determine an adequate protocol for MACE
- to determine the number of procedures required to gain competency in this model
- to determine average procedure duration

Setting up the stomach model & performing MACE

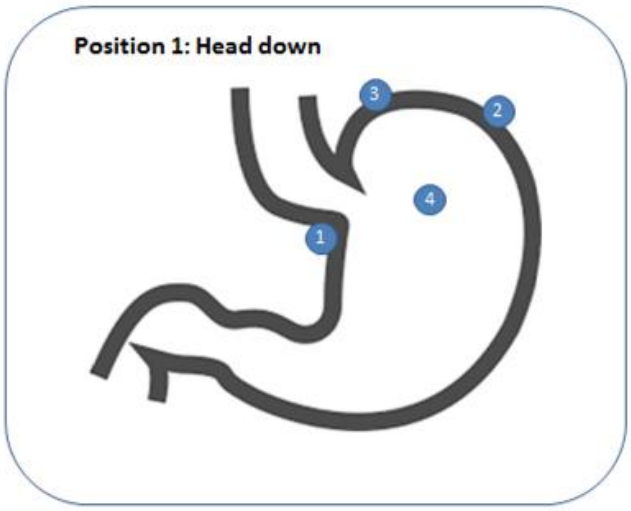
Further details are presented in Chapter 3.This study was conducted over a 72 hour period. Round plastic beads (diameter 6mm, colour; red, white, orange, pale blue, green, yellow, pink, purple, total number of inserted beads=8) (*Figure 33)* were attached to different anatomical locations of the stomach (cardia, fundus, greater and lesser curve, anterior and posterior wall, antrum and first part of the duodenum) via a gastrotomy made along the upper greater curvature *(Figure 34)*.

The stomach models were distended using 1000mls of water, syringed into the stomach using a tube within the porcine oesophagus. The duodenal exit was clamped using forceps, to prevent escape of the distention volume. After insertion of the capsule the tube was removed from the oesophagus and it was closed using forceps to prevent loss of the distension volume. Examination was conducted according to a set protocol of positional change of the stomach model ('head down', 30° left lateral, 30° right lateral) and external magnetic steering manoeuvres at specific locations to ensure consistency*(Figure 35)*. For ease of memory and to ensure a thorough examination, a four point approach in each position was employed to try and ensure each area of the stomach was sufficiently visualised. For this model the mounting system was tilted using blocks so the oesophageal 'head end' was tilted down, the blocks were then moved to allow tilting of the mount to the left and right. The order and time each tag was identified was recorded alongside the total procedure time. The

model was examined repeatedly until no beads were missed and procedure duration had reached a plateau.

Figure 33: Image of beads used during this study

Figure 34: A small gastrotomy was made along the greater curvature of the stomach to allow access to place the beads in situ.



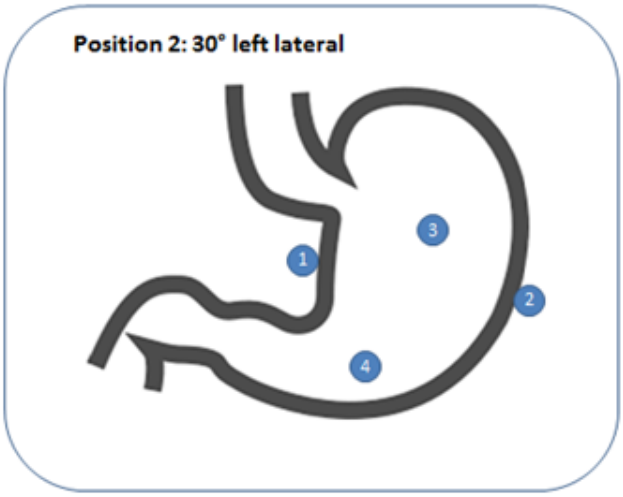
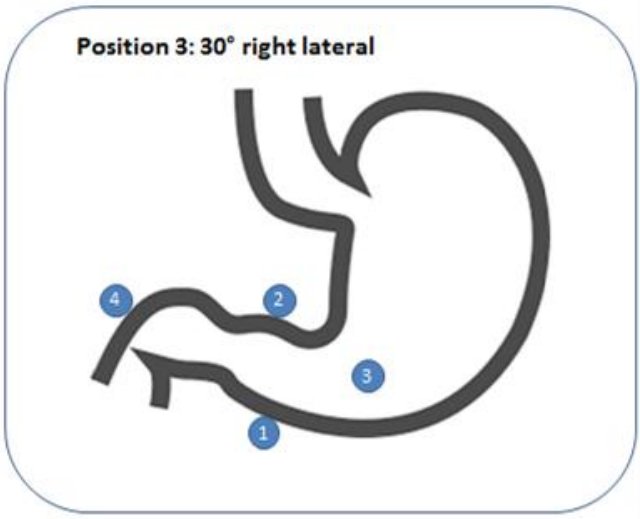


Figure 35: Schematic representation of the external locations used by the handheld magnet to examine the gastric cavity in each position. The external magnet was held in each location, then tilted from pole to pole and rotated in a circular motion to provide views across the gastric cavity from the fixed point to the mucosa on the opposite gastric wall. Tilting the capsule to the extreme, caused it to lie flat along the mucosa at the fixed point, thus giving a close up view of the mucosa surrounding each fixed point.

 Position 3: 30° right lateral 4 2 3 1	

4.4 Results

All stomach beads were identified in 87.2% (41/47) of examinations. During the 6 examinations where beads were missed, these were missed in the antrum 50% (3/6), cardia 33% (2/6) and posterior wall 17% (1/6). No beads were missed in the latter 25 procedures.

The order in which beads were identified in the mid-body of the stomach (greater curve, anterior wall and posterior wall) was variable and interchangeable. If this area was considered as one site, the order of tag identification would be: cardia (1), fundus (2), mid body (3), lesser curve (4), antrum (5) and D1 (6) in 76.6% of examinations.

Graphical representation of procedure duration as procedure experience increased is presented in *Figure 36*. Mean examination times for the first 23, second 23 and all procedures were 10.28, 6.26 ($p<0.001$) and 8.27 (3.25-16.32) minutes. All procedures were completed by 4 minutes after 39 examinations, suggesting a plateau had been reached. No difficulties were observed with the current procedure protocol and therefore no modifications recommended.

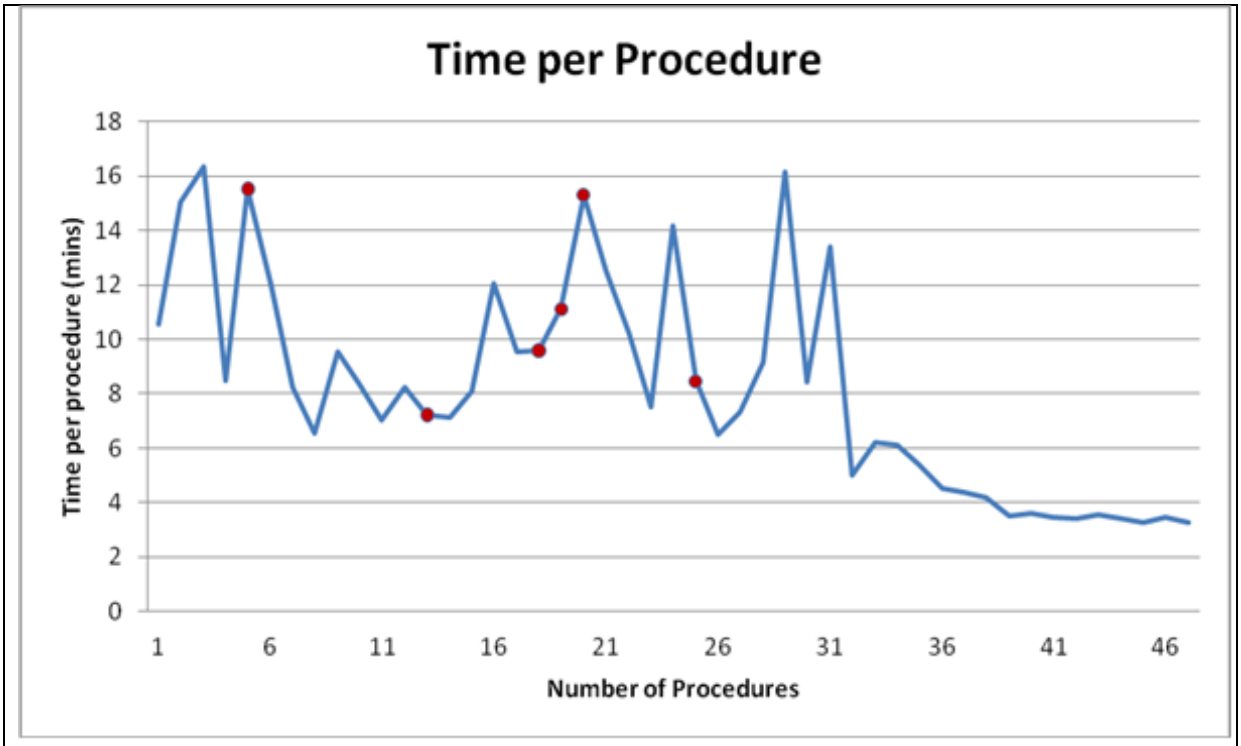


Figure 36: Procedure duration changes as the number of procedures performed increases. The red dots represent incomplete examinations (i.e. not all tags were identified)

4.5 Discussion

Examination of the gastric cavity is feasible using a magnet and positional change as demonstrated in this porcine model. Mucosal images obtained during the study were generally of excellent clarity although gastric mucous and debris could obscure the views at times. In subsequent studies using this model, thorough irrigation of the porcine tissue may prevent this problem. Bubbles at the air-fluid interface caused image distortion in a minority of examinations. Further work using porcine models and in humans should establish whether this is a continuing problem which requires addressing.

1000mls of water instilled prior to each procedure gave adequate distention and most large rugal folds were flattened to prevent beads becoming hidden. Positional change of the model assisted the distention of areas which would remain collapsed in the fasted state, such as the fundus. The gastric volume of an average adult human is 45-75mls in the fasted state and can expand to 1000mls or more after a meal.(239) It can also vary greatly depending on body habitus and eating routines. Since good results were obtained using 1000mls in this study it would be recommended to continue using this volume, however modifications may be necessary in studies in human populations.

Movements of tilting and rotating were particularly successful using the external handheld magnet. As expected, smooth dragging movements to alter the location of the capsule in the stomach were more challenging. Positional change of the model seemed to be particularly useful here, since with each movement the dependent area became distended and the capsule followed the flow of water and could then be tilted and rotated to provide adequate mucosal images. MACE examination was most effectively performed by using the systematic approach described in the methodology, however the gastric cavity is not a fixed, solid organ and thus modifications to the examination protocol are likely to be necessary based on the differing anatomy and visibility encountered during each individual procedure.Similarly, since the external outline of the stomach could not actually be

visualised during the study (to try and replicate the situation when examining humans), the previously described examination routine could only be used as a guide and prompt to adopt a systematic examination approach, rather than as a rigid protocol.

A learning curve was evident during this study, with >40 examinations providing a cut off for when competency is achieved. One of the major hurdles when learning to use this technique is maintaining the correct distance between the handheld magnet and the capsule. Too close and the capsule impacts against the gastric wall, 'tenting' the stomach wall up and preventing accurate movements; too far away and loss of control of the capsule is observed. The skill of maintaining adequate distance and making minute modifications in order to control and manoeuvre the capsule is difficult to acquire and requires repeated practice. As such this model might be used for training in the future since it provides a simple way to achieve this.

This is the first study to our knowledge confirming the feasibility of using MiroCam Navi to visualise the mucosal surface of the gastric cavity. The data suggests that a learning curve is apparent and more than 40 examinations confers proficiency in this model. The protocol for examination was effective and allowed satisfactory views of the gastric mucosal surface throughout the examination. Although this study is limited by only a single operator performing gastric MACE, the results are useful to guide further ex vivo studies using this technology and also provide a starting point for the consideration of examination protocols in human subjects.

Chapter 5

Magnetically assisted capsule endoscopy is equivalent to flexible endoscopy in the detection of markers in an excised porcine stomach model: results of a randomised trial

5.1 Abstract

Introduction: Capsule endoscopy is well tolerated but control of movement is likely to be needed to enable it to visualise the whole gastric surface. Technological developments have produced an external magnet to allow manipulation of the capsule within the gastric cavity.

AIMS: To compare magnetically assisted capsule endoscopyto flexible endoscopy for the detection of beads in a porcine stomach.

METHODS: Beads were sewn onto the mucosal surface of 12 ex-vivo porcine stomachs. Each model was examined by flexible endoscopy and magnetically assisted capsule endoscopy by two blinded investigators. Magnetically assisted capsule endoscopy was performed according to a protocol using positional change and magnetic steering. Outcome measures: number of beads identified, duration of procedure and location of beads identified.

RESULTS: Flexible endoscopy identified 88% (79/90) beads, magnetically assisted capsule endoscopy 89% (80/90). The difference in sensitivities is 1.11 with a 95% confidence interval (0.06, 28.26) and thus magnetically assisted capsule endoscopy is non-inferior to flexible endoscopy. Mean examination times for flexible endoscopy and magnetically assisted capsule endoscopy were 3.34 minutes and 9.90 minutes respectively.

CONCLUSIONS: In this study no difference could be shown between MACE and flexible endoscopy in thedetection of beads in a porcine stomach model.

5.2 Introduction

Oesophagogastroduodenoscopy is the 'gold-standard' for diagnosis of upper gastrointestinal tract pathology, but it is poorly tolerated and this can affect compliance with investigation, screening and surveillance.(240-242) A large proportion of flexible OGDs are normal or reveal insignificant pathology and despite efforts to devise 'appropriateness' scoring systems, correlation of symptoms with endoscopic findings is poor.(243) A simple non-invasive technique to image the upper gastrointestinal tract which could be made widely available would be beneficial to patients.

Capsule endoscopy is well tolerated by patients but gastric capsule examination remains a challenge since a passive capsule cannot visualise the entire mucosal surface of the capacious stomach in its collapsed (uninflated) state. Preliminary studies suggest that this may be possible using a handheld magnet to move a capsule around a fluid filled stomach: Keller et al. estimated visualisation of 75-90% of the gastric mucosa in 10 human subjects.(198) Early data using large magnetic guidance systems or robotically controlled magnetic devices are promising in terms of diagnostic yield (202), but such systems may be cumbersome and costly which is likely to limit widespread accessibility.

We performed a randomised trial comparing a new technique of MACE with conventional flexible endoscopy for identifying markers in porcine stomach models.

5.3 Methods

Device description (further details in Chapter 3)

MiroCam Navi (MC1000-WM) (Intromedic, Seoul, Korea) is a small bowel capsule endoscope (11x24mm, 4.2g, field of view 170°) including a small amount of magnetic material. It captures images at 3 frames per second and transmits these via electric field propagation to a data recorder connected via sensors on the patient's skin. An external magnet paddle can be used to manipulate the capsule within the gastrointestinal tract using real time images viewed on a lap-top. (*Figure 27*)

Aims and study design

To compare gastric mucosal visualisation by MACE and conventional flexible endoscopy in a porcine stomach model.

Performing the study

Ex-vivo porcine stomachs in a standard mount (Endo X TrainerTM, Medical Innovations International Inc, Rochester, Minnesota, USA) were used *(Figure 29)*. The tissue was obtained from pigs aged 4-6 months and consisted of the oesophagus, stomach, first and second part of the duodenum. A tube was inserted into the oesophagus to allow ease of passage of the flexible endoscope or capsule. The duodenum was closed using forceps. Opaque fabric was used to obscure the stomach models to ensure external visual localisation could not be used to assist the examination.

Round plastic beads (diameter 6mm, colour; red, white, orange, blue, green) were sewn into each stomach via a gastrotomy along the upper greater curvature. Twelve stomachs were prepared in pairs as follows: 2x0 beads (gastrotomy also performed so it was not externally apparent which models did not contain any beads), 2x1 bead, 2x2 beads, 2x3 beads, 2x4 beads, 2x5 beads, total 30 beads. Each stomach was coded by an independent observer.

Flexible endoscopy was performed in the usual way using Olympus Q240X endoscopes, by two practitioners (MFH and IR). MACE was performed with a handheld magnet suspended over the stomach at a height varying between 5-15cm, depending on the strength of magnetic attraction desired, and rotated to approximate one or other magnetic pole in order to effect tilting and rotation of the capsule*(Figure 37)*.

Figure 37: Operator IR performing MACE. The ex vivo porcine stomach tissue is obscured under opaque fabric. The operator is using a rotational movement of the external handheld magnet in a fixed position to give panning views of the gastric cavity, observed on the lap-top computer in real time.

In a previous feasibility study we have shown that 40 MACE procedures in this porcine system confers competence(244) and thus both investigators have trained to this level. The stomach models were distended using 1000mls of water. Examination was conducted according to a protocol of positional change ('head down', 30° left lateral, 30° right lateral) and systematic magnetic steering (*Figure 35)*. Blocks were used to tilt the mount to the required level. Both individuals were blinded to the number and location of beads in the prepared stomachs.

The study was conducted in three rounds at the Procedural Skills Unit, Sheffield Teaching Hospitals NHS Foundation Trust, United Kingdom. During each round the twelve stomach models were examined in random order using random.org. MFH and IR were randomised to performing either flexible endoscopy or MACE on each model and remained blinded to the results of the alternative test. Number and location of beads identified was documented alongside procedure duration.

Statistics

Statistics advice was provided by the Statistical Services Unit, University of Sheffield, UK. The primary outcome was the percentage of beads identified (sensitivity). This was performed as a non-inferiority study, expected sensitivity of 90% for both (0 estimated difference), difference of interest 10 percentage points (i.e. 80% is significantly worse). Therefore the new method would be considered to be non-inferior if the lower limit of the 95% confidence interval for the difference in sensitivities (MACE-flexible endoscopy) does not cross the non-inferiority bound of -10. A sample size of 85 beads was needed to achieve 81% statistical power. Specificity was expected to be 100% by both methods. A total of 90 beads were used (30 beads in 12 stomachs and 3 rounds performed). Location was defined as fundus, body or antrum. Data was analysed using SPSS. Procedure duration was compared using a paired t-test.

5.4 Results

Flexible endoscopy correctly identified 88% (79/90) beads, MACE 89% (80/90) beads. The difference in sensitivities is 1.11 with a 95% Confidence interval (0.06, 28.26) and thus MACE is non-inferior to flexible endoscopy in this setting (calculated using Miettinen & Nuriminen 1985 method).(245) MACE overestimated the number of beads on a single occasion. (*Table 4*)

Mean examination times in each round successively and overall were 3.46, 3.11, 3.13 and 3.34 minutes for flexible endoscopy and 10.11, 10.27, 9.27 and 9.90 minutes for MACE. Thus MACE procedure duration was significantly longer ($p<0.0001$).

Both procedures missed beads in the body of the stomach more frequently than other areas (6 beads each). Flexible endoscopy missed more fundal beads than MACE (5 beads versus 2). MACE missed more beads in the antrum than flexible endoscopy (2 versus 0).

Table 5: Beads identified by each technique (MACE and flexible endoscopy), across the three rounds conducted

		Flexible Endoscopy	**MACE**
Round 1	Correct Number of Beads Identified	26	24
	Missed Beads	4	6
	Location of missed beads	Fundus 1 Body 3 Antrum 0	Fundus 1 Body 4 Antrum 1
Round 2	Correct number of beads identified	25	29
	Missed beads	5	1
	Location of missed beads	Fundus 2 Body 3 Antrum 0	Fundus 0 Body 1 Antrum 0
Round 3	Correct number of beads identified	28	27
	Missed beads	2	3
	Location of missed beads	Fundus 2 Body 0 Antrum 0	Fundus 1 Body 1 Antrum 1 *Single bead overestimated in the body of the stomach.

Abbreviations: MACE=magnetically assisted capsule endoscopy

5.5 Discussion

In this study no difference could be shown between MACE and conventional upper GI endoscopy for the detection of beads in a porcine stomach model. The handheld magnet allowed excellent manoeuvrability of the capsule endoscope within the stomach and overall mucosal visualisation was very clear. Positional change allowed fluid distension of challenging areas, such as the fundus, and mobilisation of debris.

Important functions of conventional OGD which are not available to MACE are luminal inflation, washing of, and suction from, the mucosal surface. Gastric distension by instillation of 1000mls water appeared to allow adequate visualisation of the mucosa and in addition, the flow of water with positional change moved the capsule over larger distances whereas the magnet was used for finer manipulation. Some images were unclear or distorted due to debris on the mucosal surface or bubbles at the air-fluid interface. This could be addressed using positional change to create a flow of water to wash the mucosal surface, although clearly this was not as controlled as direct instillation of water through an endoscope channel. Visibility at OGD may be improved by prior ingestion of the surfactant simethicone and the mucolytic agents N-acetylcysteine and Pronase.(246, 247) Studies in MACE should be considered, since such agents could be easily ingested with the water used to distend the stomach.

An obvious and major difference between the ex-vivo porcine model and the human stomach is the absence of peristalsis in the former. Although only accounting for incomplete examinations in 3% of cases, Rey et al. describe difficulties encountered in MACE due to gastric contractions.(200) The impact of gastric motility could further be studied using the sedated domestic pig, as described in studies of robot controlled MACE.(248) However, there is evidence that hyoscine and topical peppermint oil can reduce contractility at endoscopy (249), so perhaps human studies to optimise gastric preparation for MACE would be the most appropriate next step.

The force between two magnets depends on the strength and orientation of both magnets and the distance and direction of the magnets relative to each other. The magnetic strength of the capsule and handheld magnet is fixed. The distance (from the capsule) and direction of the handheld magnet is changeable in order to influence the direction of the capsule. The magnetic permeability of human tissue is marginally less than that of air but this is not thought to be significant in the context of the small field strengths we are utilising here. Thus the distance between the capsule and hand-held magnet is the most important factor influencing control. If the magnet was held too close to the stomach, the capsule would jump to the anterior wall of the stomach requiring manual separation. Thus there were two ways in which to control fine movement. Altering the distance between the external handheld magnet and the capsule changed the depth of the capsule in the water, or its position in the longitudinal gastric axis. Rotational movements of the handheld magnet effected tilting and rotational movements of the capsule and scanning of the mucosal surface. Propelling the capsule endoscope from one area of the stomach to the other was more challenging and positional change was particularly helpful in this respect.

The external magnet weighs 1.2Kg and we found that the manoeuvring arm would become fatigued during a procedure so that two hands were needed to avoid large deviations. In human subjects the external magnet could be rested on the patient's abdomen when necessary, to prevent fatigue and provide a natural adjustable platform from which to effect fine and controlled adjustments in distance between magnets and rotation. The abdominal wall may, of course also be a limiting factor since truncal obesity will hamper the ability to approximate the handheld magnet to the capsule and magnets of greater strength may be needed for larger patients.

Surprisingly conventional flexible endoscopy missed a significant proportion of beads. Investigator skill is unlikely to be a factor since both investigators are experienced endoscopy practitioners having performed >1000 independent procedures each using similar endoscopic equipment. Anatomy may play a role since the porcine gastric fundus is more conical in shape than its human

counterpart. This was more pronounced in some of the models and led to difficulty adequately visualising this area by retroflexion. This may account for some of the beads missed by flexible endoscopic examination. Beads placed in the body caused confusion for both techniques. Errors occurred when the same bead seen twice was recorded as two separate beads and when a second bead identified in the gastric body was assumed to be the first bead already seen. This problem affected both techniques and therefore seems to reflect a more general issue of human fallibility when performing investigative procedures. However, mean examination time for flexible endoscopy was only 3.34 minutes, significantly faster than the recently recommended 8 minutes, which could have also played a role. (250)Of course, missed pathology occurs in conventional endoscopy: 10-20% miss rates for colonic polyps are documented in back to back studies of colonoscopy (120), while clinically significant pathology in the upper GI tract can be identified in 10-37% of repeat procedures for obscure gastrointestinal bleeding.(251-253) Moreover, flexible endoscopy also missed more pathology than MACE using the Olympus/Siemens magnetic device.(200)

MACE took considerably longer to perform than flexible endoscopy. Our pilot data demonstrating the learning curve of MACE showed reduced procedure time with increasing experience until the examiner had performed 40 studies.(244) The slower examination times may still reflect a relative lack of experience in what is a novel technique when compared to OGD. Furthermore, time taken to change position of the model is additional to the examination time and not necessary when performing OGD. Nonetheless, we and others (200) have found this model a useful learning tool prior to performing MACE in human subjects, although should it be widely adopted in the future, the technique lends itself well to computer simulation training.

Capsule endoscopy is an attractive option for investigation of the stomach due to its favourable tolerability profile and low complication rate. It may particularly benefit patients needing regular surveillance of conditions such as oesophageal varices or for population based gastric cancer screening programmes. This system comprises uncomplicated equipment with a straightforward

procedure and thus could be implemented easily in any gastroenterology department if similar success is demonstrated in human studies. The next important step in this process would be to demonstrate feasibility in human subjects using this technique and establish the nature of the learning curve and optimum patient preparation protocol.

Chapter 6

Does magnetically assisted capsule endoscopy improve small bowel capsule endoscopy completion rate? A randomised controlled trial

6.1 Abstract

INTRODUCTION: Delayed gastric emptying is a significant factor in incomplete small bowel capsule examinations. Gastric transit could be hastened by external magnetic control of the capsule. We studied the feasibility of this approach to improve capsule endoscopy completion rates.

METHOD: Prospective, single centre, randomised controlled trial involving 122 patients attending for small bowel capsule endoscopy using MiroCam Navi. Patients were randomised to either the control group (mobilisation for 30 minutes after capsule ingestion, followed by intramuscular metoclopramide 10mg if the capsule failed to enter the small bowel) or the intervention group (1000mls of water prior to capsule ingestion, followed by positional change and magnetic steering). Outcome measures: capsule endoscopy completion rate, gastric clarity and distention, relationship of body habitus to capsule endoscopy completion rate and patient comfort scores.

RESULTS: 122 patients were recruited (61 each to the control and intervention groups: mean age 49 years (range 21-85), 61 females). There was no significant difference in capsule endoscopy completion rate between the two groups ($p=0.39$). Time to first pyloric image was significantly shorter in the intervention group ($p=0.03$) but there was no difference in gastric transit times ($p=0.12$), suggesting that magnetic control hastens capsular transit to the gastric antrum but cannot impact upon duodenal passage. Gastric clarity and distention were significantly better in the intervention group ($p<0.0001$ and $p<0.0001$ respectively).

CONCLUSION: Magnetic steering of a small bowel capsule is unable to overcome pyloric contractions to enhance gastric emptying and improve capsule endoscope completion rate. Excellent mucosal visualisation within the gastric cavity suggests this technique could be harnessed for capsule examination of the stomach.

6.2 Introduction

Capsule endoscopy is a first line investigative modality for the small bowel of which it obtains circumferential and often detailed mucosal views of the narrow lumen during transit.(39, 48, 61, 254) It is non-invasive, does not require sedation and is much preferred by patients to intubational endoscopy.(232) Intuitively, however, it seems likely that the volume of the stomach, its collapsed state when fasted and unusual configuration will hinder the ability of capsule endoscopy to reliably identify pathology proximal to the small bowel.

However, we have shown that MACE detects beads sewn into all areas of an ex-vivo water-containing porcine stomach as reliably as conventional OGD, implying that a degree of control may allow a complete examination.(255) Preliminary human studies using magnets to control capsule movement in fluid filled stomachs also suggest diagnostic yields which compare favourably with OGD.(200, 201)Marelli et al., however, identified gastric pathology using a capsule with a higher frame acquisition rate and imaging devices at either end (PillCam Eso, Given Imaging, Yoqneam, Israel) without using magnets or other methods of control and with much smaller ingestion volumes.(256)This is consistent with studies of anaemic patients having capsule endoscopy primarily to image the small bowel (but providing some gastric images during transit) identifying pathology in the oesophagus, stomach and duodenum, missed by OGD, in up to 10% of cases.(257, 258) These data raise the question as to whether or not the degree of control is sufficient to add significantly to the diagnostic potential of this developing technology.

Transit of the capsule through the pylorus is easily recognised and identification of the first duodenal image to mark the beginning of the small bowel is standard practice during capsule endoscopy reporting. By using this landmark, studies suggest that delayed gastric emptying is a major factor in incomplete small bowel capsule endoscopy examinations which are thought to occur in up to 30% of small bowel capsule endoscopy procedures.(53, 259) The use of pro-kinetics to stimulate gastric

peristalsis has been shown to be effective in reducing gastric transit time and improving capsule endoscopy completion rate (CECR).(92, 260) These medications carry a risk of adverse reactions, parenteral administration is uncomfortable and a simple mechanical method which allows sufficient control to steer the capsule into the small bowel may be a desirable alternative.

Understandably there has been an assumption in most trials that volume distension of the stomach using swallowed water will allow visualisation of a greater surface area, act as a mucosal cleansing agent and provide a suitable medium in which a magnetically controlled capsule can move. Whether it is distension, mucosal cleansing, purging or a combination of these actions, preparation clearly improves mucosal visibility and improves diagnostic yields in small bowel capsule endoscopy.(88, 89, 261, 262) Control of capsule movement in a stomach prepared to optimise distension and visibility may pave the way for non-invasive gastric MACE.

In this study we have compared MACE with a standard protocol to determine if control using a magnet can be demonstrated by the achievement of a readily definable and in terms of small bowel examination, clinically useful endpoint: small bowel CECR. We have compared two different preparation regimens in terms of clarity of gastric mucosal images and distension to determine if higher volume fluid ingestion improves the quality of gastric visualisation.

6.3 Methods

Patients

Patients referred to our institution for small bowel capsule endoscopy between February 2014 and February 2015 were invited to participate. Patients who were younger than 20 years, pregnant, unable to speak or understand English or with permanent pacemakers, intra-cardiac devices or any other magnetically or electrically controlled devices were excluded. Patient age, sex, height, weight, waist-hip ratio and body mass index (BMI) were recorded. Small bowel capsule endoscopy was performed after a 12 hour fast and ingestion of 2 litres of polyethylene glycol during the evening prior to the morning examination.

Procedures were performed using MiroCam Navi (Intromedic, Seoul, Korea), a small bowel capsule endoscope containing magnetic inserts (dimensions 24 x 11mm, weight 4.2g, field of view 170°, depth of view 30mm, operation time 12 hours) (*Figure 27*). Images acquired from one end are captured at a rate of 3 frames per second and transmitted to a data recorder via electric field propagation. These images can be viewed in real-time via a wireless connection to an iPad (Apple Inc., Cupertino, CA) and subsequently after downloading onto a computer workstation. Each participant completed a numeric rating scale questionnaire based on that used by Irvine et al (263) documenting their comfort before and during their procedure, plus a statement as to whether they would be willing to undergo a repeat procedure*Appendix 6*.

Study design

Prospective, randomised controlled trial, approved by the local institution and regional ethical review board (NRES Committee Yorkshire & The Humber 14/YH/1010, Clinical trials number: NCT02282852). Patients were randomised using a computer-generated random number sequence to enter one of two protocols:

1. Control protocol

The standard small bowel capsule endoscopy protocol at our institution was used. The capsule was ingested using 200mls of water with 5 drops of simethicone. Patients then mobilised around the department for 30 minutes. The position of the capsule was established using a real-time viewer. If the capsule failed to enter the duodenum, metoclopramide (10mg intramuscularly) was administered, followed by further mobilisation. If the capsule remained in the stomach after a further 30 minutes an intravenous dose of erythromycin (250mg in 100ml normal saline) was given.

2. Intervention protocol

A gastric distention volume of 1000mls of water containing 5 drops of simethicone was ingested by the patient immediately prior to capsule ingestion. The patient swallowed the capsule with water ad libitum in the sitting position and subsequently adopted the supine position to allow examination to commence. MACE was performed by a single operator (MFH) using a handheld magnet (Navi Controller, Intromedic Ltd). Holding the magnet over the abdominal wall, the capsule could be rotated along its longitudinal axis to obtain close up images of the gastric mucosa or the lumen by altering the polarity of the magnet with pronation and supination of the wrist. Movement of the magnet in a longitudinal or transverse direction across the abdominal wall were used to achieve subtle movements of the capsule within the dependent pool of water. Larger movements of water were used to wash the capsule from one area to another by positional change of the patient from supine to the right lateral position, occasionally using the left lateral position if orientation of the capsule within the stomach was proving difficult*(Figure 38)*.

Once enough imaging had been acquired to allow orientation within the stomach, the manoeuvres described were used to try and drag the capsule into the antrum and orientate it towards the pylorus. Thereafter, a variety of approaches were used to assist trans-pyloric passage, most commonly involving the patient leaning towards the right lateral position and the magnet held over

the right lateral chest wall or posteriorly as far as the vertebral column. If the capsule failed to pass through the pylorus using magnetic control, within the allotted time limit of 30 minutes, the patient transferred to the relevant section of the control protocol.

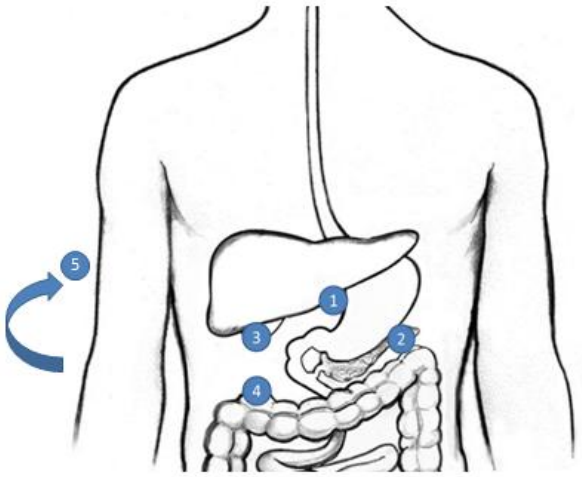


Figure 38: The handheld magnet was manipulated at each approximate location (1-4) successively, starting in a supine position. Location 1 and 2 were used to realise the location of the capsule within the gastric cavity. Location 3, 4 and 5 were used to assist trans-pyloric passage of the capsule.

Analysis

Based on the available literature and our local data, assuming a CECR of 70% using our standard (control) protocol, 60 patients were required per group to be able to detect a 20% improvement in small bowel CECR with a 5% 2 sided significance level, 80% power. Quantitative data are summarised with parametric statistics, the mean and standard deviation or with non-parametric statistics, the median and interquartile range. The unpaired t-test was used to compare age between the two study groups and the χ^2 test was used to compare sex and indication for small bowel capsule endoscopy between study groups. First pyloric view and gastric transit time were not normally distributed and thus the Mann Whitney test was used to compare the differences in these variables between the two groups. Gastric distention and mucosal visualisation (as measured on a 1-4 scale) between the two groups was also compared using a Mann Whitney test, although we must highlight

there are some limitations of using this test when there are only 4 possible outcomes to compare. Small bowel transit time between the two groups was compared using an unpaired t-test. Linear regression was used to assess the correlation between BMI or waist-hip ratio and gastric transit time. An unpaired t-test was used to assess the correlation between BMI or waist-hip ratio and CECR. The diagnostic yield, CECR and patient willingness to undergo a repeat procedure were measured as a simple 'yes' or 'no' and thus were examined using Fisher's exact test.

The small bowel capsule endoscopy videos were read and reported in the conventional manner, which included annotation of the anatomical landmarks (first gastric, duodenal and caecal images), by one of two experienced capsule endoscopists (KD, MEM). One individual (MEM) studied all gastric imaging, assigned a score (adapted from that used by Eliakim et al. 1: excellent; 2: good; 3: fair; 4: poor)(105) for both clarity of the gastric mucosa images and distension of the gastric lumen and additionally marked the first image seen during the examination of the pylorus. All reviews were done in random order and blinded to the protocol assigned.

Outcome measures

The primary outcome measure for the effect of magnetic control on trans-pyloric transit of the capsule was CECR. Secondary outcome measures were; gastric mucosal clarity, gastric distension, relationship of body habitus to CECR and patient comfort scores.

6.4 Results

A total of 122 patients were prospectively recruited to the study between February 2014 and February 2015. The capsule was retained in the stomach for the duration of the procedure in two patients and thus only demographic data and CECR were analysed (*Figure 39*). 11 patients did not return their comfort questionnaires and thus were excluded from the patient tolerance analysis. No significant adverse events were recorded.

Demographic data and indications for small bowel capsule endoscopy

Demographic data and CECR from 122 patients and full data from 120 patients were submitted for final analysis (34 men, mean (SD) age 49.6 ± 17.8 years, range 20-85 years). There was no significant difference in age (p=0.86), sex (p=0.55), indication for small bowel capsule endoscopy (p=0.58), BMI (p=0.37) or waist-hip ratio (p=0.53) between the two groups (*Table 5*). All but 1 patient (in the intervention group) were ambulatory outpatients at the time of the procedure.

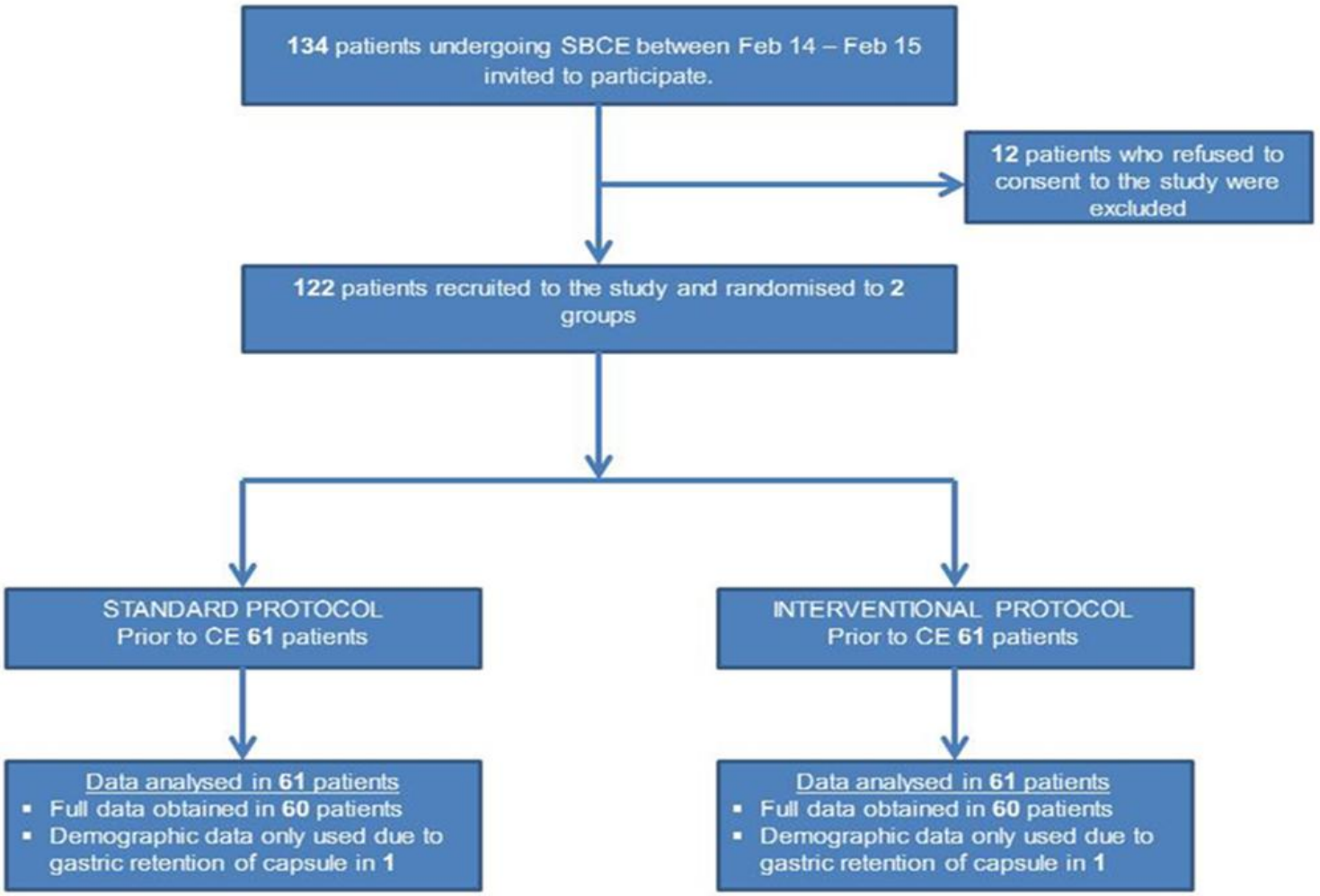


Figure 39: Study flow chart

Table 6: Demographical data and indication for procedure for each group

	GROUP	
	CONTROL	INTERVENTION
Number	61	61
Mean (SD) age, years	49.5 ± 18.1	49.5 ± 17.8
Sex		
Men	15	19
Women	45	42
Indication for CE (number (%))		
OGIB or IDA	11 (18)	14 (23)
Abdominal pain and/or diarrhoea	31 (52)	26 (43)
Known Crohn's disease	6 (10)	13 (21)
Coeliac disease	9 (15)	7 (11)
Polyposis syndromes	1 (2)	0 (0)
Other	2 (3)	1 (2)
Mean BMI (SD)	29 ±9.5	27 ±5.4
Mean Waist-Hip Ratio (SD)	0.89 ±0.15	0.90 ±0.08

Abbreviations: SD=standard deviation CE=capsule endoscopy, OGIB=obscure gastrointestinal bleeding, IDA=iron deficiency anaemia, BMI=body mass index

Transit times, CECRs and adverse events

The overall CECR for all study patients was 87.6%, with a median gastric transit time of 35.5 minutes (12.5-65.0) and mean small bowel transit time of 276.8 (±132) minutes. No significant difference in oesophageal transit time, CECR or small bowel transit time was noted between the two groups (p=0.54, p=0.39 and p=0.42 respectively). However, the pylorus was visualised in a significantly shorter time in the intervention group (p=0.03), but this did not impact on pyloric transit since there was no significant difference in overall gastric transit time between the two groups (p=0.12) (*Table 6*). Gastric mucosal clarity and distention were graded significantly better in the intervention group based on the 1-4 scale used (p<0.0001 and p<0.0001 respectively), these data are further illustrated in *Table 7*.

Sub-analysing the intervention group, in 23 (37.7%) procedures the capsule was able to be manipulated into the duodenum under magnetic control within the 30 minute time frame. There was no significant association between BMI and CECR (p=0.51) or waist-hip ratio and CECR (p=0.94). Similarly, there was no significant association between BMI and gastric transit time, assessed using linear regression, (R^2=0.002) or waist-hip ratio and gastric transit time (R^2=5.987). There were no known cases of capsule retention or serious adverse events in any of the study participants.

Magnetic steering and gastric visibility

After ingestion the capsule was commonly propelled to a dependent area along the greater curvature. Manipulation of the external magnet at the level of the xiphisternum with the patient in the supine position could affect tilting and rotational movements of the capsule in order to determine the location of the capsule and the direction of the gastric antrum (*Figure 40*). Right lateral movement of the magnetic controller could direct the capsule to the gastric antrum in some cases, whereas a change to the right lateral position was required in other participants. Once the pylorus was visualised, further movements with the external magnet over the epigastrium, right

upper quadrant and back (depending on body habitus) could bring the pylorus directly in view. Manipulation of the capsule depended on a complex assessment of the participant's body habitus, degree of gastric distention and likely surface anatomy of the stomach in varying positions, together with fine movements of the external magnet and interpretation of images received to the iPad viewer.

Patient tolerance

Patients completed a numeric rating scale questionnaire before the procedure documenting their current and anticipated procedural pain and discomfort on a 1-10 scale (0=no pain/discomfort, 10=worst pain/discomfort ever). After the procedure they were required to document their actual pain, discomfort and distress during the procedure on the same 1-10 scale. Finally each participant was asked whether they would consider undergoing a repeat procedure. There were no significant differences in procedural pain, discomfort or distress between the two groups (*Table 8*). 98% of participants in each group were willing to undergo a repeat procedure if necessary.

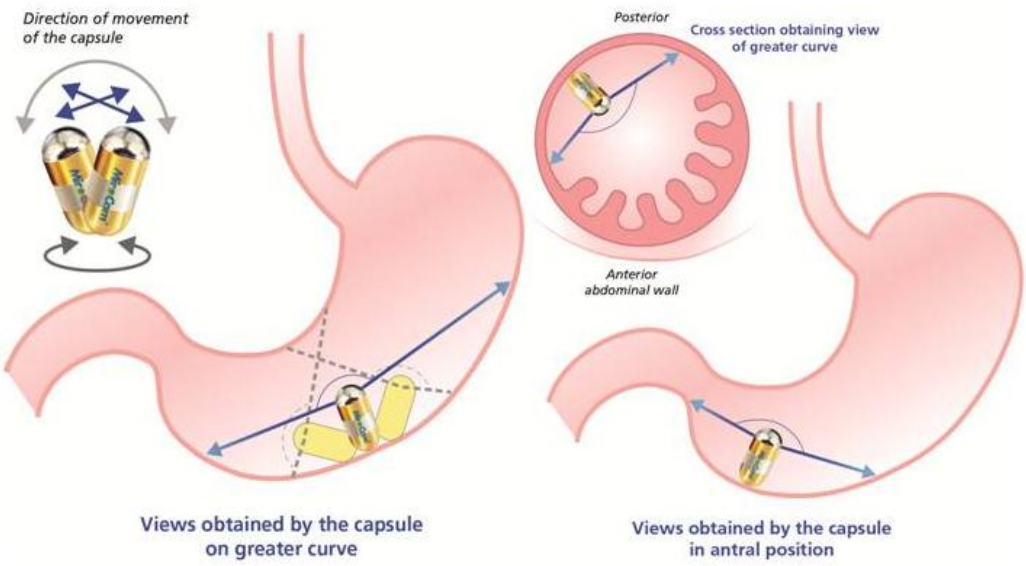


Figure 40: Schematic diagram of potential MACE manoeuvres

Table 7: Comparison of transit times for each group

	GROUP		
	CONTROL	**INTERVENTION**	P value
Median OTT (IQR) (sec)	19 (10-34)	19 (13-25)	0.54
Median first pyloric image (IQR) (min)	8 (3-25)	5 (3-10)	0.03
Median GTT (IQR) (min)	23 (13-66)	55 (13-64)	0.12
Mean SBTT (SD) (min)	327 (±127)	317 (±128)	0.42
CECR (%)	87	89	0.39
Gastric mucosal clarity (1-4 scale)	3 (2-3)	1 (1-2)	<0.0001
Gastric distention (1-4 scale)	3 (3-4)	2 (1-3)	<0.0001
Diagnostic yield (%)	31	36	0.70

Abbreviations: OTT=oesophageal transit time, IQR=interquartile range, sec=seconds, min=minutes, GTT=gastric transit time, SBTT=small bowel transit time, CECR=capsule endoscopy completion rate

Table 8: Comparison of gastric mucosal clarity and distension for each group

		Number of patients	
		Control Group	**Intervention Group**
Gastric Mucosal Clarity Score (1-4)	1	14	33
	2	16	23
	3	20	3
	4	11	2
Gastric Distension Score (1-4)	1	6	28
	2	6	15
	3	33	15
	4	16	3

Key: Gastric mucosal clarity and distention measured on 1-4 scale (1: excellent; 2: good; 3: fair; 4: poor)

Table 9: Comparison of patient comfort scores by group

	Group		
	Control	**Intervention**	**P value**
Pre-procedural discomfort Median (IQR)	1 (1-3)	1 (0-3)	0.90
Pre-procedural pain Median (IQR)	0 (0-2.8)	0 (0-3)	0.98
Expected discomfort Median (IQR)	2 (0-4)	2 (0-3.8)	0.98
Expected pain Median (IQR)	2 (0-4)	1 (0-3)	0.42
Procedural pain Median (IQR)	0 (-)	0 (-)	0.58
Procedural discomfort Median (IQR)	0 (0-1)	0 (-)	0.43
Procedural distress Median (IQR)	0 (-)	0 (-)	0.54
Repeat procedure (%)*	98	98	

Abbreviations: IQR=interquartile range

*Willingness to undergo a repeat procedure

6.5 Discussion

Magnetic control does not appear to be clinically useful in improving CECR as a tool to assist in small bowel capsule endoscopy and this was not affected by body habitus. However, the more rapid identification of the pylorus suggests that a magnet can exert a degree of control which allows the endoscopist to orientate themselves in the stomach and which is likely to be clinically useful for gastric capsule endoscopy. Gastric preparation with a litre of ingested water containing simethicone offers better gastric mucosal clarity and distension than a 200ml volume. It follows that a clean, adequately distended stomach is an important aspect of successful MACE, allowing the operator to identify gastric landmarks more easily and thus manipulate the capsule more effectively to achieve the required end. Importantly, MACE is a procedure which induces no measurable pain, discomfort or distress to patients. Further studies of control and preparation are needed to understand the potential of MACE as a non-invasive upper gastrointestinal diagnostic tool.

After ingestion, the capsule commonly dropped to the dependent part of the distal gastric body and could be manipulated to view both the antro-pyloric region and upper gastric body simultaneously. As with the study of Rey et al. using the Siemens electromagnetic guidance system, the pylorus was readily identified and whilst progress could be made toward it, it could not be done sufficiently quickly to avoid posterior displacement by powerful antro-pyloric contractions.(200) Efforts to do so were further hampered by the need to place the magnet behind the patient to attempt to pull the capsule along the supero-posterior axis in which the antro-duodenum tends to lie.(264) Therefore as a tool to enhance gastric transit time to optimise small bowel examination, it does not appear to be better than a standard protocol using prokinetic agents. For the purposes of gastric examination, however, retention of the capsule is desirable and the antro-pyloric region, a common site for pathology, was well visualised (*Figure 41*). Furthermore, peristaltic contractions, could, of course, be attenuated using anticholinergic agents such as hyoscine.(249, 265) Whether a combination of a pro-

motility agent and magnetic steering could be used together to enhance pyloric transit of the capsule would require further research.

Strength of attraction diminishes exponentially with increasing distance between magnets and several studies have suggested that this might hamper MACE in obese patients.(198, 202, 264) However, as magnetic control failed to offer any advantage over standard protocol when using CECR as the main outcome measure, it seems unlikely that this question has been adequately addressed and further study using different markers of control are needed.

Inflation of the stomach during OGD allows the endoscopist to distend the stomach and flatten rugal folds, maximising the chances of visualising the whole gastric mucosal surface and therefore minimising the risk of missed pathology. Such a facility is not an option in a remote technology like capsule endoscopy, but may be afforded indirectly by the ingestion of water or gas-producing substances. Our study shows that ingestion of a litre of water significantly improves gastric mucosal clarity and distension compared to a 200ml volume. Other studies have empirically used water volumes of 300ml (256) and 1300ml (in three divided doses over 75 minutes)(199, 200) alone, or 500ml (198) and 1000ml (202) with gas producing substances. The addition of simethicone as an anti-foaming agent may have contributed to opacity of the gastric content in other studies (198, 202) but appears to have been used in larger doses than in our protocol. Further investigation is needed to determine the optimal preparation, but the evidence from this study is that higher ingestion volumes improve the distension and visibility of the gastric mucosa and thus the overall quality of the examination.

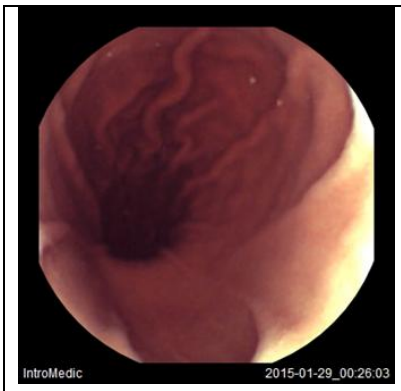
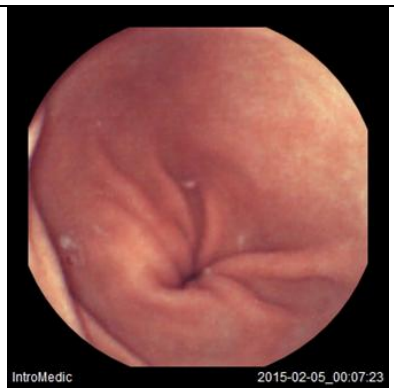
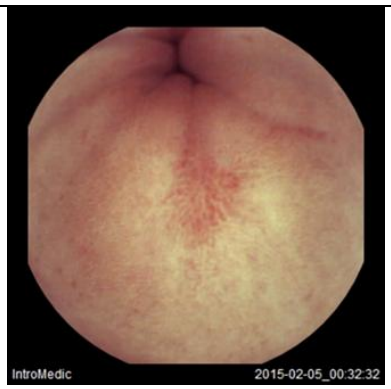
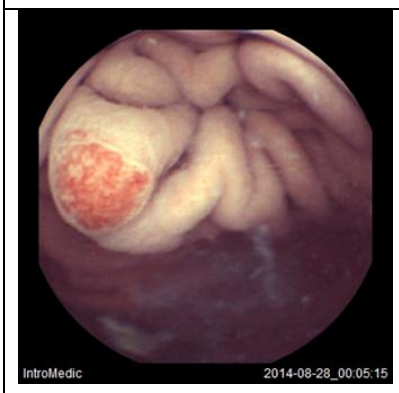
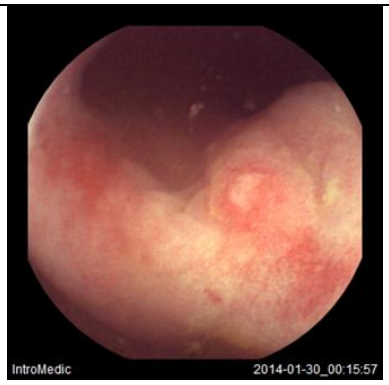
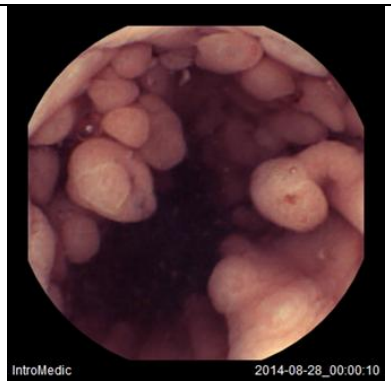
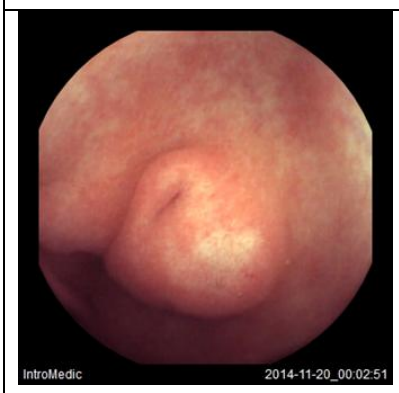
		
(a) Longitudinal view of the gastric body and lesser curve	*(b) Gastric antrum*	*(c) Pre-pyloric erosion*
		
(d) Angioectasia in the cardia	*(e) NSAID related erosive gastropathy*	*(f) Fundic gland polyps*
		
(g) Pancreatic rest		

Figure 41: Examples of mucosal views and gastric pathology identified during MACE of the stomach

The Siemens guidance system generates a magnetic field of varying strength and capsule movement is controlled using joysticks. It may, therefore, allow more subtle control than is afforded by a handheld magnet, which is reliant on the operator adjusting the distance of the magnet from, and location over, the skin surface. The magnet weighs 1.2Kg, so subtlety of control probably diminishes as the arm fatigues. However, endoscopists have long been used to learning complex procedures which require high levels of manual dexterity and the attraction of a handheld magnet is simplicity of operation, portability and comparatively minimal cost.

This study recruited a relatively high number of patients in order to ultimately prove a negative result. Although pursuing recruitment at this level may be considered a futile exercise considering it was clear from a fairly early stage that the outcome was likely to be negative. In fact, two original power calculationswere made aiming to detect a 10% improvement in small bowel CECR (requiring a population of 240patients to be recruited in total) and aiming to detect a 20%improvement in small bowel CECR (requiring a population of 120 patients to be recruited in total). Once 30 patients had been recruited to each group, interim analysis showed a likely negative outcome, however we felt we were still obtaining useful data regarding gastric mucosal visibility and distension and therefore we elected to complete the study at recruitment of 120 patients.

The manipulation of a capsule endoscope in the stomach using magnetic steering is feasible, but is unable to overcome pyloric contractions to enhance gastric emptying or improve CECR. Improved gastric mucosal clarity and distension are observed using higher volumes of ingested water and the addition of simethicone. Further work exploring the potential of this novel technology is recommended.

Chapter 7

Blinded comparison of magnetically assisted gastric capsule endoscopy and conventional endoscopy in recurrent and refractory iron deficiency anaemia: a pilot study

7.1 Abstract

INTRODUCTION: Magnetically assisted capsule endoscopy of the stomach has been demonstrated to be safe and feasible. The aim of this prospective trial was to compare diagnostic yield of magnetically assisted capsule endoscopy of the stomach to that of conventional flexible endoscopy in patients with recurrent or refractory iron deficiency anaemia.

METHODS: A total of 20 patients with recurrent or refractory iron deficiency anaemia were enrolled in this pilot study between January and November 2015. Magnetically assisted capsule endoscopy was performed using MiroCam Navi (Intromedic, Seoul, Korea) following conventional oesophagogastroduodenoscopy.

RESULTS: A total of 38 pathological findings were identified, of these, 16 were detected at both conventional endoscopy and MACE. Conventional endoscopy identified 14 additional lesions not seen at MACE, 9 of which were hiatal hernias. Conversely, 8 abnormalities detected by MACE were missed by conventional endoscopy. Satisfactory visualisation was achieved in 11% for the gastro-oesophageal junction, 21% for the cardia, 16% for the fundus, 79% for the anterior wall of the gastric body, 79% for the posterior wall, 79% for the greater curvature, 84% for the lesser curvature, 95% for the antrum and 89% for the pylorus. Patients experienced less pain, discomfort and distress during MACE compared to flexible endoscopy ($p=0.0009$, $p=0.0011$ and $p=0.006$ respectively). No adverse events occurred.

DISCUSSION: MACE of the stomachis safe, well tolerated and can detect a wide variety of gastric pathology. Improvements in gastro-oesophageal junction and proximal gastric visualisation need to be achieved before MACE could be accepted as an alternative to conventional endoscopy.

7.2 Introduction

Direct visualisation of the upper gastrointestinal mucosal surface provides far more useful information than the two dimensional images produced by radiology previously and thus flexible endoscopy has become the investigation of choice for diseases of the upper gastrointestinal tract.(266, 267) Currently 1% of the United Kingdom population per year will undergo flexible OGD(205) yet less than half of these reveal clinically significant pathology.(206, 207) The procedure is invasive and incurs the risks of intubation and potentially sedation. It is also anxiety provoking to patients and in some case this may be preventative to performing the procedure.(204, 241) A simple, non-invasive means of directly imaging the upper gastrointestinal tract would be beneficial to patients and clinicians.

Capsule endoscopy is considered the first-line investigation for disease of the small bowel, it avoids the risks of intubation and sedation and is well tolerated by patients.(263) However, the passive peristaltic motion utilised to propel a capsule endoscope through the tubular small bowel cannot be relied upon alone to accurately image all areas of the capacious gastric cavity, particularly in a collapsed, fasted state. Recently magnetic capsule navigation systems have been developed to allow some control over the capsule endoscope within the stomach. Promising results have been achieved using the systems developed by Siemens and Olympus (201) and Ankon technologies (202), both of which utilise an externally applied magnetic field to control an ingested magnetic capsule. However, the major drawback of both of these systems is that they require cumbersome, expensive equipment in order to function and thus widespread clinical application is likely to be limited.

The MiroCam Navi system (Intromedic, Seoul, Korea) overcomes this problem by using a handheld external magnet to gain control over a capsule endoscope containing magnetic material. We and others have previously demonstrated that this system is safe and feasible for examination of the gastric cavity.(255, 268, 269)Recurrent and refractory iron deficiency anaemia are common

indications for SBCE, but upper GI pathology within reach of a conventional flexible endoscope is identified in 10-37% of patients having repeat investigations.(251-253, 270, 271)For this reason national guidelines recommend repeat OGD and SBCE in such patients.(272)The aim of this prospective trial is to compare the diagnostic yield of MACE of the stomach to that of the conventional standard (OGD) in patients with recurrent or refractory iron deficiency anaemia.

7.3 Methods

Patients

Patients referred to our institution between January and November 2015 with recurrent or refractory iron deficiency anaemia, who required OGD and small bowel capsule endoscopy as part of their diagnostic investigation were invited to participate. Patients were recruited via a specialist face-to-face or telephone iron deficiency anaemia clinic. Exclusion criteria: patients who were younger than 20 years, pregnant, unable to speak or understand English or with permanent pacemakers, intra-cardiac devices or any other magnetically or electrically controlled devices.

Patient age, sex, height, weight and body mass index (BMI) were recorded. OGD and small bowel capsule endoscopy were performed successively on the same day after a 12 hour fast and ingestion of 2 litres of polyethylene glycol during the evening prior to the morning examination. Each participant completed a numeric rating scale questionnaire based on that used by Irvine et al (263) documenting their comfort before and during each procedure, plus a statement as to whether they would be willing to undergo a repeat procedure (*Appendix 6)*.

Study design

Prospective, blinded, controlled trial, approved by the local institution and regional ethical review board (NRES Committee Yorkshire & The Humber 14/YH/1010, Clinical trials number: NCT02282553).

Performing OGD

OGD was performed by two experienced, independent practitioners (KD and MK) in the standard fashion using Olympus GF-260 endoscopes (Olympus, Tokyo, Japan). Patients were able to choose whether to undergo the procedure with or without conscious sedation using midazolam and fentanyl. OGD was reported in a standardised way using a proforma reporting sheet to descriptively

document visualised abnormalities and their precise location(*Appendix 7)*. The aim of this means of reporting was to avoid the use of vague terms such as 'gastritis' and instead focus on a clear description of identified abnormalities to reduce inter-observer variability. Biopsies of the duodenal or gastric mucosa and any abnormalities were performed at the discretion of the endoscopist.

Performing MACE

MACE of the stomach was then performed using a handheld magnet (Navi Controller, Intromedic Ltd), 2 hours after OGD by a single operator (MFH) who remained blinded to the outcome of OGD. MiroCam Navi (Intromedic, Seoul, Korea), a small bowel capsule endoscope containing magnetic inserts (dimensions 24 x 11mm, weight 4.2g, field of view 170°, depth of view 30mm, operation time 8 hours) (*Figure 27*) was utilised. Images acquired from one end are captured at a rate of 3 frames per second and transmitted to a data recorder via electric field propagation. These images can be viewed in real-time via a wireless connection to an iPad (Apple Inc., Cupertino, CA) and subsequently in video format after downloading onto a computer workstation.

Based on previous studies in humans and ex vivo porcine models we have found 1000mls of water containing 40mg simethicone to be an optimal preparation for adequate gastric distention and mucosal visualisation.(255) This preparation was ingested by the patient immediately prior to swallowing the capsule. The capsule was placed in the mouth of the patient and swallowed with water ad libitum in a sitting position. The external magnet was held at the sternum to capture oesophageal views as the capsule was swallowed. The complete protocol for examination is shown in *Appendix 8*. The patient ingested further water during the procedure, at the instruction of the operator, if gastric distention or mucosal visibility was sub-optimal. The visualisation of major landmarks was documented immediately on a 1-5 scale (5: excellent, 1: poor, *Table 9*). Pathologic findings were documented in a standardised descriptive fashion during the procedure using the same proforma described for OGD (*Appendix 7*).

We have already shown that MACE is unable to assist trans-pyloric passage of the small bowel capsule and thus once the operator was satisfied that a full and complete examination had been achieved the capsule was left in the pre-pyloric region to commence its passive motion through the small bowel.(269) Procedure duration was documented from the moment the capsule was ingested to the time a full examination was completed and MACE ceased.

Analysis

Based on the available literature and our local data, clinically significant upper gastrointestinal pathology is detected in up to 20% of patients with recurrent/refractory iron deficiency anaemia during small bowel investigation.(257, 258, 273) Assuming that the two methods on average detect the same number of pathologies, with a discordant proportion of 0.08, then in order to achieve 80% power to conclude non-inferiority of capsule endoscopy vs conventional OGD, with a "non-inferiority margin" of -0.05 (i.e. to reject the null hypothesis that the pathology rate using capsule is 5% below conventional or lower), the sample size required would be 270 patients. This pilot study aimed to recruit 20 patients as an initial feasibility assessment.Quantitative data are summarised with parametric statistics, the mean and standard deviation or with non-parametric statistics, the median and interquartile range. The small bowel capsule endoscopy videos were read and reported in the conventional manner, which included annotation of the anatomical landmarks (first gastric, duodenal and caecal images), by one of two experienced capsule endoscopists (KD, MEM). All MACE procedure videos were also reported by two reviewers A and B (MEM and MFH). MEM was blinded to the result of the OGD and MACE procedures. Overall gastric distension and mucosal clarity were documented using a 1-4 scale described previously,(269) mucosal visualisation at each major gastric landmark was documented on the same 1-5 scale used during this study (*Table 9*). Participants with pathologic findings detected during MACE, which were not found at OGD were subject to full review of both the capsule video and photographic documentation from the OGD by the small bowel multi-disciplinary team, in order to determine a consensus outcome.

Table 10: Grading scale for image quality at each landmark

Grade	Description
1	Poor view >75% obscured by debris/bubbles/poor image clarity/illumination
2	Sub-optimal view >50% obscured by debris/bubbles/poor image clarity/illumination
3	Reasonable view <50% obscured by debris/bubbles/poor image clarity/illumination
4	Good view, <25% obscured by debris/bubbles/poor image clarity/illumination
5	Excellent, 100% complete view of the landmark

Outcome measures

The primary outcome measure was diagnostic yield for upper gastrointestinal pathology of magnetically guided capsule examination compared to gastroscopy. Secondary outcome measures are: mucosal visualisation of major areas of the stomach during magnetically guided capsule examination as graded on a 1-5 scale and patient comfort scores.

7.4 Results

Demographic data and indication for procedures

A total of 20 patients were prospectively recruited between January and November 2015, 7 male, 13 female; mean age 65 years (±14.717, range 34-85 years). Mean BMI was 28 (±7.021, range 17-46). Six patients were referred with refractory iron deficiency anaemia, the remaining 14 had recurrent iron deficiency anaemia. Seventeen patients had other comorbid conditions such as; type 2 diabetes (5), cardiovascular disease (9), respiratory disease (2) and rheumatoid arthritis (1). Sixteen patients were taking regular proton pump inhibitor therapy. Other regular medications included warfarin (2), anti-platelet agents (3) and opiates (4). No patients reported using non-steroidal anti-inflammatory medication at the time of procedures. Mean haemoglobin measurement was 104g/L (±22.439, range 75-109g/L) with a median ferritin of 12ug/L (range 8-22ug/L). MACE was well tolerated by all patients and no adverse events were recorded.

Transit times and procedure completion rates

The mean duration of MACE was 21.84 minutes (±6.103, range 7-32 minutes). In two patients (both with a procedure duration of 7 minutes) the capsule could not be prevented from exiting the stomach due to strong antro-pyloric contractions, nor could the capsule be dragged back through the pylorus and thus a full, thorough examination could not be completed. In one patient a technical fault caused loss of the wireless image signal during the procedure, hampering a complete examination.

All patients underwent a complete OGD, with 7 patients requiring sedation with midazolam and 2 requiring both midazolam and fentanyl to undergo the procedure.

Pathology detection and final diagnosis

A total of 38 pathological findings were identified*, Table 10*. There were 11 hiatal hernias, 10 erosions, 7 areas of erythema, 3 polyps, 3 bile reflux, 2 bleeding lesions, 1 intestinal metaplasia and 1 angioectasia. Of these, 16 were detected at both conventional OGD and MACE. OGD identified 14 additional lesions not seen at MACE: 9 hiatal hernias, 3 erosions (1 fundal, 1 greater curve, 1 antrum), 1 polyp (body-anterior wall) and 1 bile reflux (antrum). Conversely 8 abnormalities detected by MACE were missed by conventional OGD: 4 erosions (1 greater curve, 1 lesser curve, 2 antrum), 1 bile reflux (antrum), 1 metaplasia (pylorus), 1 angioectasia (greater curve).

The single polyp and 3 erosions identified by OGD but missed by MACE were subsequently identified on review of the capsule video by an experienced observer (MEM). The 4 erosions, intestinal metaplasia and angioectasia were all identified on capsule video review but felt to be minor abnormalities which did not warrant repeat OGD at that time. The bleeding lesion identified at MACE but not OGD was thought to be a biopsy site after expert review of the capsule video and thus no further intervention was made.*Figure 42* shows a comparison of lesions detected at both MACE and OGD.

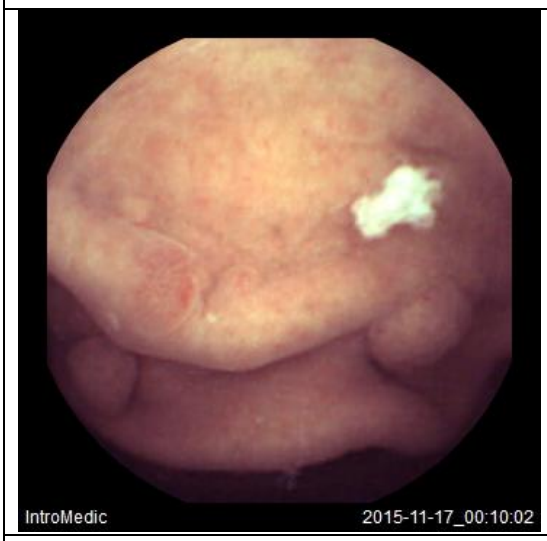
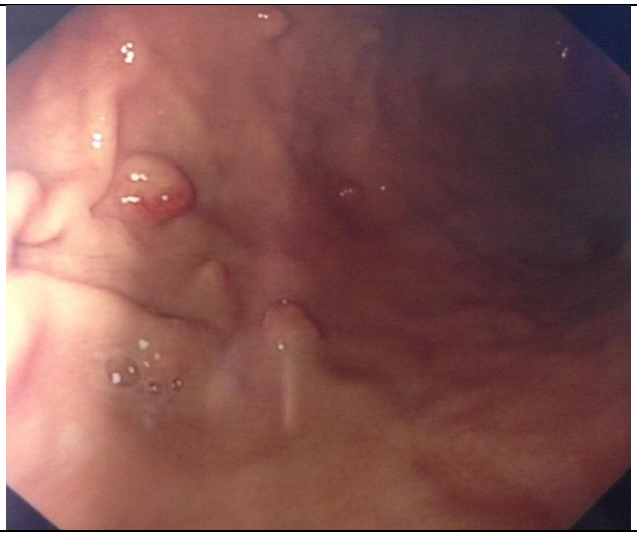
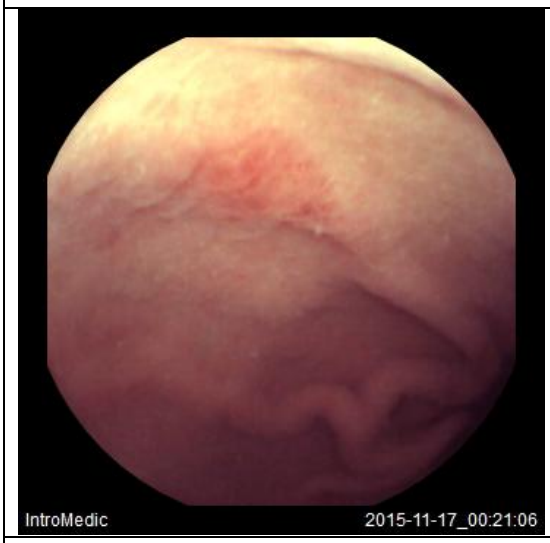
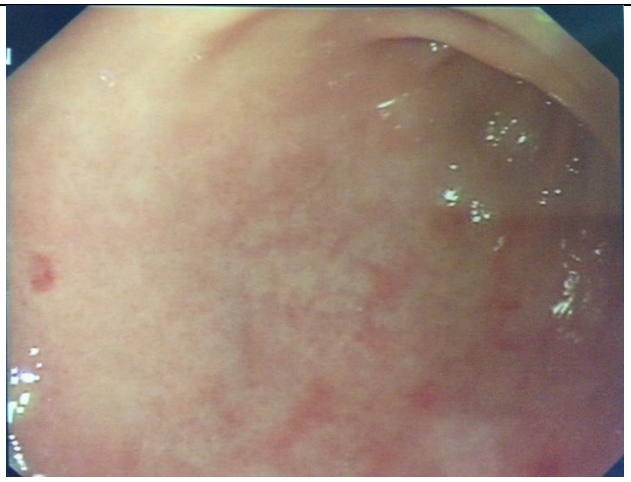
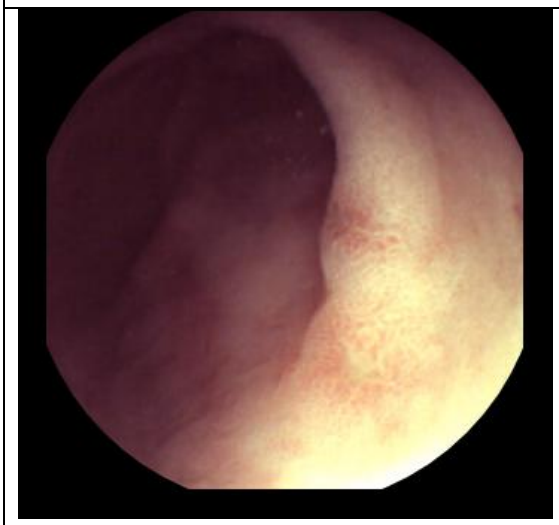
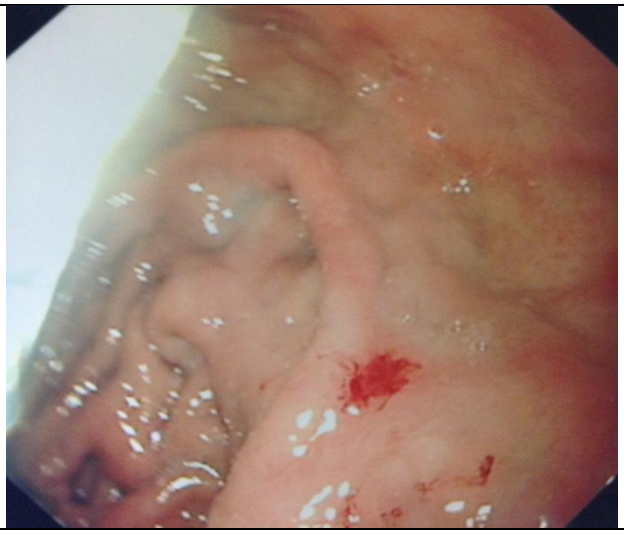
Table 11: Pathological findings detected during each procedure

Findings	**MACE only**	**OGD only**	**Both MACE & OGD**
Erythema	0	0	7
Bleeding	1	0	1
Hiatal hernia	0	9	2
Erosion(s)	4	3	3
Polyp(s)	0	1	2
Bile reflux	1	1	1
Metaplasia	1	0	0
Angioectasia	1	0	0
Total	8	14	16

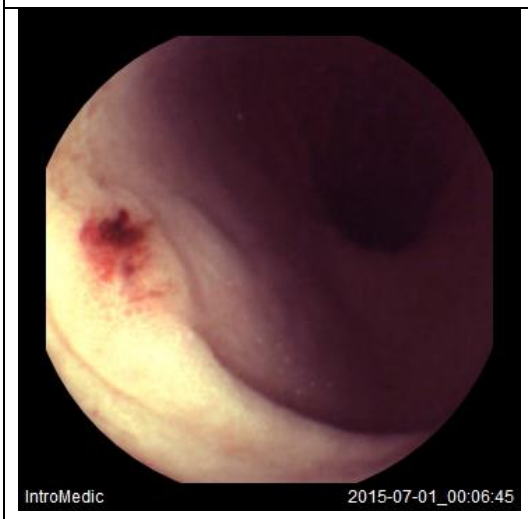
Abbreviations: MACE=magnetically assisted capsule endoscopy,

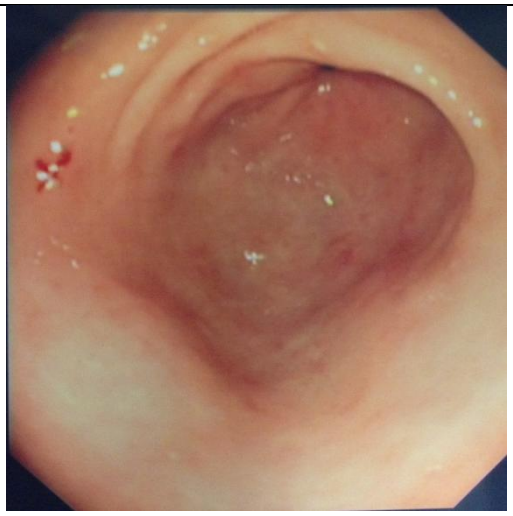
OGD=oesophagogastroduodenoscopy

Figure 42: Examples of pathology identified at both MACE and OGD

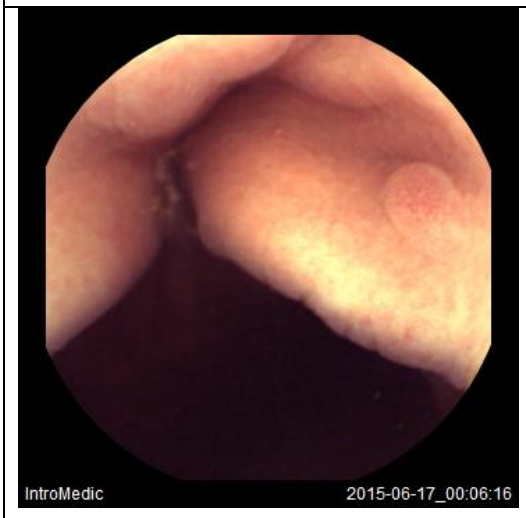
MACE	*OGD*
	
(a) Multiple benign gastric polyps	
	
(b) Patch of erythema in the gastric body	
	

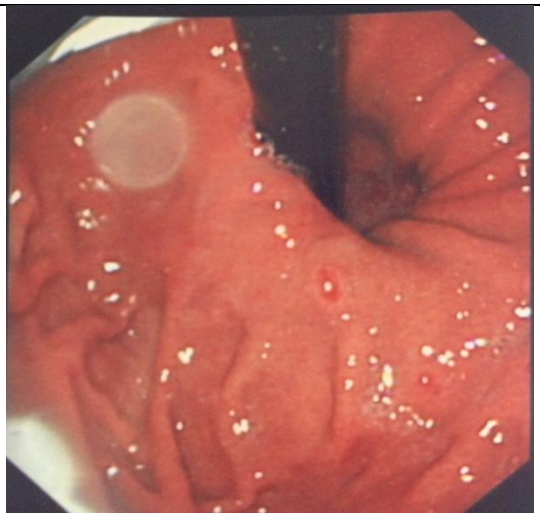
(c) Erosion on the incisura, there is fresh oozing of blood during OGD



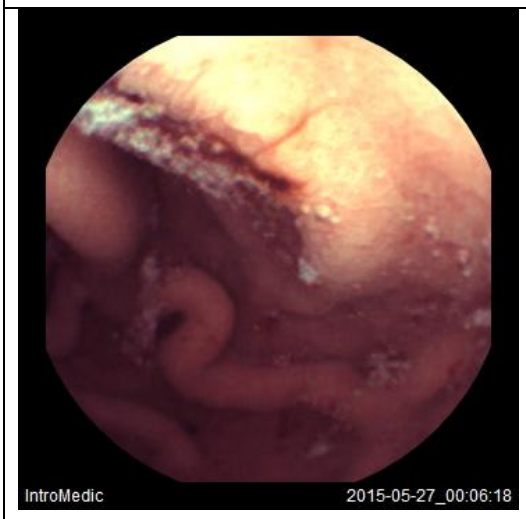


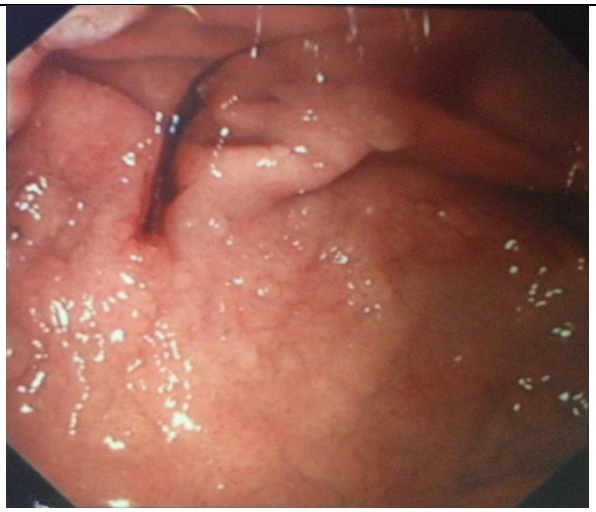
(d) Angioectasia in the gastric antrum





(e) Small benign gastric polypin the fundus





(f) Bleeding gastric erosion with adherent clot

Gastric landmark visualisation

Results of visualisation of major gastric landmarks recorded during MACE are illustrated in *Table 11*. Satisfactory visualisation (score of 4 or 5) was achieved in 11% for the gastro-oesophageal junction (GOJ), 21% for the cardia, 16% for the fundus, 79% for the anterior wall of the gastric body, 79% for the posterior wall, 79% for the greater curvature, 84% for the lesser curvature, 95% for the antrum and 89% for the pylorus.

Incomplete observation of the oesophagus was caused by a combination of rapid transit, inability to hold the capsule at the GOJ to enable thorough observation and loss of wireless transmission. The proximal stomach (cardia and fundus) was poorly observed in the majority of patients due to a combination of inadequate distension and adherent debris, however rapid transit through the stomach also prevented clear observation in 2 patients. The pylorus was not clearly seen in 1 patient due to mucous and debris which could not be adequately mobilised.

On retrospective review of the MACE videos, adequate visualisation of the GOJ occurred in only 5-10% of procedures (*Table 11*). There was significant disparity between the reviewers in visualising the proximal stomach with adequate cardia views documented in 65% by operator A, but only 10% by operator B (in real-time during the procedure this was 21%). Similarly the fundus was seen satisfactorily in 40% by operator A and only 25% by operator B (16% during the real-time procedure). In the distal stomach there was more agreement between both retrospective reviewers and the retrospective reviewers and the real-time results, *Table 11*.

Visualisation of the first and second parts of the duodenum was not conducted during the real-time examination, however on retrospective review D1 was seen poorly by both reviewers (40% and 45%). This was not the case for D2, which showed significant variation between the reviewers with reviewer B achieving satisfactory views in 90%, but reviewer A in only 40%.Overall gastric mucosal clarity and distension was deemed adequate in 80% or more procedures by both reviewers.

The agreement of mucosal visualisation scoring between reviewers was calculated using Spearman's rho. Overall there was statistically significant correlation between the mucosal visibility scores of each retrospective reviewer ($p<0.0001$, $r=0.594$) and the retrospective reviewers and real-time MACE procedural scores and ($p<0.0001$, $r=0.507$ and $p<0.0001$ and $r=0.640$).

Patient tolerance

Patient comfort during MACE was deemed to be good in all patients, as noted by the operator, with none reporting any pain or discomfort. Comfort scores assessed by the patient themselves were formally documented in a questionnaire format. Patients reported significantly more procedural pain, discomfort and distress during OGD compared to MACE, but despite this, all patients were willing to undergo either procedure again if clinically indicated (*Table 12*).

Table 12: Gastric mucosal visualisation during real-time (RT) MACE and on retrospective review of MACE videos by reviewers A & B

			Gastric landmark visualisation on 1-5 scale					**Overall visualisation**
			1	2	3	4	5	
Gastric Landmark	GOJ	RT	17	0	0	1	1	11% (2)
		A	16	1	2	0	1	5% (1)
		B	15	2	1	1	1	10% (2)
	Cardia	RT	8	4	3	2	2	21% (4)
		A	15	1	2	1	1	10% (2)
		B	0	2	3	8	7	65% (13)
	Fundus	RT	7	6	3	2	1	16% (3)
		A	7	6	2	3	2	25% (5)
		B	2	2	8	6	2	40% (8)
	Body-anterior	RT	0	0	4	5	10	79% (15)
		A	0	1	1	4	14	90% (18)
		B	0	0	6	4	10	70% (14)
	Body-posterior	RT	0	0	4	5	10	79% (15)
		A	0	2	3	3	12	75% (15)
		B	0	0	4	6	10	80% (16)
	Greater curve	RT	0	0	4	5	10	79% (15)
		A	0	1	1	4	14	90% (18)
		B	0	0	4	6	10	80% (16)

	Lesser curve	RT	0	0	3	4	12	84% (16)
		A	1	1	2	2	14	80% (16)
		B	0	0	2	7	11	90% (18)
	Antrum	RT	0	0	1	7	11	95% (18)
		A	0	2	3	1	14	75% (15)
		B	0	0	1	5	14	95% (19)
	Pylorus	RT	1	0	1	5	12	89% (17)
		A	1	1	0	3	15	90% (18)
		B	0	0	1	5	14	95% (19)
Duodenal Landmark	D1	A	2	5	5	6	2	40% (8)
		B	0	3	8	9	0	45% (9)
	D2	A	0	0	2	3	15	90% (18)
		B	0	1	11	7	1	40% (8)

Abbreviations: RT=real time review, MACE= magnetically assisted capsule endoscopy, GOJ=Gastro-oesophageal junction, 1-5 Scale: 5=Excellent view, 4=Good, 3=Reasonable, 2=Sub=optimal, 1=Poor. Satisfactory visualisation classed as grade 4 or 5.

Table 13: Patient comfort scores prior to and during each procedure

	MACE	**OGD**	**P value**
Pre-procedural discomfort Median (IQR)	3 (1-5)	4 (3-5)	0.18
Pre-procedural pain Median (IQR)	2 (1-5)	3 (3-6)	0.60
Expected discomfort Median (IQR)	0 (0-1)	0 (0-1)	0.87
Expected pain Median (IQR)	0 (0-1)	0	0.62
Procedural pain Median (IQR)	0	2 (0-3)	0.0009
Procedural discomfort Median (IQR)	0	2 (0-4)	0.0011
Procedural distress Median (IQR)	0 (0-1)	2 (0-5)	0.0060
Repeat procedure (%)*	100	100	

Abbreviations: IQR=interquartile range, MACE=magnetically assisted gastric capsule endoscopy, OGD=oesophagogastroduodenoscopy

*Willingness to undergo a repeat procedure

7.5 Discussion

This pilot study has provided a preliminary assessment of the diagnostic yield for MACE of the stomach compared to conventional endoscopy. The procedure was highly acceptable to patients and no adverse events occurred.

Accurate steering of the capsule was best achieved by manipulating the hand-held magnet at specific external locations to cause tilting and rotation of the capsule from a static point. However we found wide anatomic variation between patients and thus the external magnet locations suggested in *Appendix 8* are best utilised as a basis for systematic examination rather than a rigid protocol. Dragging the capsule over shorter distances was occasionally successful, but more often this was prevented by mucosal folds or loss of magnetic force due to increasing distance between the capsule and external magnet. Positional change facilitated movements of the capsule over a greater distance by allowing it to follow the flow of the distention volume as it filled the new dependent area of the stomach and overall this approach was more reliably effective than discrete magnetic manipulation.

Visualisation of the proximal stomach and oesophagus was clearly challenging and this has been recognised in other studies. Rahman et al, in their study of 26 volunteers using MiroCam Navi, were able to obtain clear views of the fundus and cardia in only 47% and 65% of patients respectively. While clear views of the incisura, antrum and pylorus were obtained in 88%, 88% and 100% of patients respectively.(268) Previous CT modelling studies in patients without hiatal hernias have shown that the mean distance between a capsule lying in a fundal dependent position and the ventral skin surface is 16.5cm (±2.5) compared to 9.0 cm (±2.3) from the antral dependent position.(264) Since magnetic force decreases exponentially with increasing distance this, together with the high prevalence of hiatal hernias observed in our study may explain the difficulties we experienced in the proximal stomach.

Even the larger external magnetic guidance systems, with the potential for much greater magnetic forces, have encountered difficulties in this region. Liao et al found that the capsule could not be guided to the cardia and fundus in 5 of the 34 patients they examined with the Ankon Technologies Co. Ltd. system, (202) and although Rey et al were able to view the cardia in 88.5% of the patients they examined, they did report that closer, steady examination might be achieved by an increase in magnetic force.(200)

Conversely, Keller at al used a magnetically manoeuvrable capsule and hand held magnet (Given Imaging, Yoqneam, Israel) with a similar magnetic force to MiroCam Navi (256g/cm) in their study of ten healthy volunteers, but found that opaque luminal contents contributed to the limited fundal views observed in 1 participant, rather than difficulties manoeuvring the capsule in this region.(198) Debris, adherent mucous and pooling of opaque fluid is a common issue during MACE since the capsule endoscope is unable to suction luminal contents or lens-wash unlike conventional endoscopy. Although this could be an issue in any gastric location, it does appear to be particularly problematic in the proximal stomach, possibly due to difficulties adequately distending this region or achieving sufficient illumination when viewing from a distance as is common during MACE.

We used the addition of an antifoaming agent (Simethicone) to cleanse the mucosa of bubbles and mucous debris, but others found that this hampered examination by increasing fluid opacity, although this could be due to the smaller distension volumes utilised (500-800mls compared to 1000mls in our study).(198, 268) Rey et al avoided the use of an anti-foaming/mucolytic agent completely by utilising 1300mls of ingested water in divided doses and light exercise, although still encountered problems with resistant mucous impeding the mobility and visual field of the capsule.(200) Liao et al used ingestion of water (1000mls) and a gas producing powder in their preparation protocol but despite this, gastric distension was inadequate in 14.7% and one patient described abdominal pain after ingesting the powder.(202) The optimal protocol combining adequate cleansing, distension and patient acceptability remains to be defined, however this study

has shown 1000mls of water and 40mg of simethicone to be effective for visualising the gastric body and distal stomach with excellent patient tolerability.

In contrast to the study by Rahman et al, (268) we achieved images of the distal oesophagus in only a very small proportion of patients due to a combination of rapid oesophageal transit of the capsule and transient loss of image transmission by the capsule. With the external magnet held at the sternum in an upright seated position, magnetic attractive forces did not appear strong enough to overcome oesophageal peristaltic contractions. A comparative study between a specifically designed oesophageal capsule (PillCam ESO2)and the magnetically manoeuvrable capsule (MMC) produced by Given Imaging showed that although oesophageal transit time was longer in the MMC group (111-1514 seconds vs 47-1474 seconds), Z-line identification was better in the PillCam ESO2 group (73% vs 33%). This suggests that features specific to PillCam ESO2, such as a dual head camera and high image capture rate are of more value for obtaining high quality oesophageal images than longer oesophageal transit and thus such facilities should be considered in future technological improvements to capsules designed for gastric examination.

Retrospective review of the MACE procedure videos showed a similar outcome to real-time reporting overall with good correlation between the two reviewers. However reviewer A documented better visualisation of the proximal stomach than reviewer B and the real-time outcome. Since reviewer A had also performed the real-time MACE examinations we can perhaps conclude that the benefit of slow-motion review and freezing individual frames provided by retrospective review helps improve mucosal visualisation. Secondly, reviewer A was experienced at performing MACE of the stomach compared to reviewer B, who had limited experience. In conventional endoscopy the shaft of the endoscope traversing the GOJ allows orientation when retro-flexing, together with air insufflation. Without this, as occurs during MACE, the operator must become accustomed to the more collapsed appearance of the cardia and fundus and therefore the differing experience of the reviewers may explain the disparity seen in the proximal stomach

particularly. Both performing MACE while interpreting 'real-time' images from the i-pad viewer is challenging, but I feel necessary in order to appropriately guide the capsule to unseen areas of the stomach or focus on a particular area of interest. Retrospective review of the capsule video should perhaps be considered the gold standard of reporting however, since more thorough visualisation can be conducted without the distraction of also performing the procedure.

Sixteen pathological abnormalities were detected by both MACE and OGD. OGD detected 14 abnormalities not seen at MACE, of these 9 were hiatal hernias. Taking into account the difficulties we experienced obtaining GOJ views, it is unsurprising MACE failed to identify these. However, unlike MACE, patient discomfort and retching commonly occur during OGD which may emphasize the presence of a hiatus hernia due to an increase in intra-abdominal pressure.Bile reflux was identified at OGD but not MACE in one patient and vice versa. Since this a dynamic process it may not be visible at the prior/subsequent procedure, especially during MACE when a cleansing volume of water has been ingested. All the other lesions identified at OGD but not during MACE (3 erosions and 1 polyp) were identified on retrospective review of the capsule videos. Without the distraction of simultaneously performing and reporting the procedureand the added benefit of slow a play-back mode diagnostic yield may further improve, although this would be at a cost of longer reporting times.

MACE identified 8 lesions not seen at OGD: 4 four erosions, 1 angioectasia, 1 patch of intestinal metaplasia and 1 area of fresh blood. On secondary expert review of the bleeding lesion it was felt it looked typical of a biopsy site from the prior OGD. The erosions, angioectasia and patch of intestinal metaplasia, well defined at MACE due to the depth of field and image resolution, were small and could easily have been overlooked at OGD. Of course trauma from the previous endoscopy could also be accountable for the erosions and represents one of the limitations of this study. Finally, neither procedure can be completely free of error, in the case of OGD this is well documented.(252, 274)

In this study procedural tolerance scores were significantly better for MACE than OGD. Since MACE is a non-invasive procedure this is not entirely unexpected, however almost half of the patients in this study underwent OGD with midazolam sedation. In the study by Denzer et al, all patients preferred magnetic capsule endoscopy over OGD, even though propofol sedation was utilised for the endoscopic procedure.(201) Presumably, this reflects a patient preference for non-invasive procedures, potential fears about sedation and a desire to avoid restrictions to normal activity (e.g. driving) in the recovery period.

Taking this forward to a full study, some modifications to the protocol are recommended. We would advise that MACE be performed before OGD to avoid trauma inflicted during OGD being interpreted as pathology during subsequent MACE. Both procedures should also be accurately timed to allow for comparison in procedure duration.

In conclusion this pilot study demonstrates that MACE of the stomach using MiroCam Navi is both safe and feasible and well tolerated by patients. MACE was able to identify a wide range of gastric pathology but struggled to adequately visualise the proximal stomach and oesophagus. Capsule technological developments are likely to improve this issue in the near future with the introduction of dual head gastric capsule and illumination advances. Further work to explore the potential of this developing technology is recommended.

Chapter 8 Discussion

8.1 Summary of work conducted

The work described in this thesis has attempted to answer the question as to whether magnetically assisted capsule endoscopy of the stomach, using MiroCam Navi, is a viable alternative to conventional upper gastrointestinal endoscopy. This has been approached via four main studies.

The first feasibility study,outlined in Chapter 4, explored practical aspects of utilising thisnovel equipment by experiments in ex vivo porcine stomach models. The strengths of this approach are that multiple replicate experiments could be conducted, allowing the operator to become intimately familiar with the subtleties of the system while developing a robust experimental protocol. The final study in this initial series entailed the operator performing repeated gastric MACE procedures on the same stomach with the aim of identifying all implanted beads in the shortest possible time. The outcome of this study showed that a learning curve was clearly evident with the first 23 procedures taking significantly longer to perform than the latter 23 (10.28 minutes vs. 6.26 minutes, $p<0.001$). Furthermore, no beads were missed after the first 25 procedures and all procedures were completed in less than four minutes after 39 procedures, when a plateau was reached. This study played an important role in the development of our MACE examination protocol and laid the foundations for a further study using ex-vivo models.

Building on the work from the initial feasibility study the second study was designed to move a step forward by comparing the ability of MACE to accurately examine the gastric cavity compared to flexible endoscopy (Chapter 5). Beads implanted into major locations of ex-vivo porcine stomachs were used as surrogate markers of gastric examination in this blinded randomised trial. This was designed as a non-inferiority study using flexible endoscopy as the conventional gold-standard for which MACE would be measured against. MACE was proven to be non-inferior by identifying 89% (80/90) of the beads compared to flexible endoscopy, 88% (79/90) beads, with a difference in

sensitivities of 1.11, 95% Confidence Interval (0.06, 28.26). MACE was clearly a success for the examination of ex vivo stomach tissue, however for real clinical utility this needed to translate into human populations and thus the subsequent studies attempted to evaluate this.

The first human study, discussed in Chapter 6, aimed to investigate whether MACE could optimise conventional small bowel capsule endoscopy by enhancing gastric transit of the capsule and therefore improving capsule endoscopy completion rates. A similar gastric preparation protocol to that used in the ex vivo studies was used, but with the addition of simethicone to act as an anti-foaming agent. Similarly, the principles developed for MACE examination of the ex vivo stomach were applied to the human anatomy to standardise examinations.

122 patients were randomised to either a conventional protocol using mobilisation and metoclopramide to attenuate gastric emptying or MACE. No significant difference in capsule endoscopy completion rate between the two groups was noted (p=0.39). The first pyloric image was seen significantly sooner in the MACE group (p=0.03) despite gastric transit times being equivalent (p=0.12), suggesting that magnetic manipulation enhanced capsular transit to the gastric antrum but could not hasten pyloric transit. The lack of adverse events and excellent patient tolerance during the study supported our assumption that MACE was a safe intervention and comfortable for patients. Although MACE seemed unable to overcome pyloric contraction to enhance gastric emptying, the mucosal visualisation achieved within the stomach was excellent and the external magnet was clearly able to affect movements of the capsule within the gastric cavity, suggesting feasibility for the technique in human populations. Finally, the preparation protocol was suitable and tolerable, providing satisfactory gastric cleansing and distension in the majority of patients.

The final study, discussed in Chapter 7, aimed to evaluate the diagnostic ability of MACE compared to the conventional standard of flexible endoscopy. A population of patients with recurrent or refractory iron deficiency anaemia were utilised.A total of 38 pathological findings were identified;

11 hiatal hernias, 10 erosions, 7 areas of erythema, 3 polyps, 3 bile reflux, 2 bleeding lesions, 1 intestinal metaplasia and 1 angioectasia. Of these, 16 were detected at both conventional OGD and MACE. OGD identified 14 additional lesions not seen at MACE, conversely 8 abnormalities detected by MACE were missed by conventional OGD.Satisfactory visualisation of the gastric mucosa during MACE (score of 4 or 5) was achieved in 11% for the gastro-oesophageal junction, 21% for the cardia, 16% for the fundus, 79% for the anterior wall of the gastric body, 79% for the posterior wall, 79% for the greater curvature, 84% for the lesser curvature, 95% for the antrum and 89% for the pylorus.

The outcome of this study again supports the hypothesis that MACE is safe and feasible, but also demonstrated that MACE is capable of identifying a wide variety of gastric pathology. We also showed that MACE was better tolerated than OGD, with patients reporting significantly more procedural pain, discomfort and distress during OGD compared to MACE ($p=0.0009$, 0.0011 and 0.0060 respectively for each variable).

The performance and clinical application of MACE has evolved rapidly during the production of this body of work with numerous relevant papers published. In the sections below I will discuss some of the important aspects of MACE revealed through my own research and contextualise them into the advancing published knowledge of MACE.

8.2 Mucosal cleansing &Gastric distension

A clean, well distended stomach, free from debris with well-flattened mucosal folds is one of the most important factors for accurate MACE of the stomach. For this reason the preparation protocol prior to gastric MACE has two aims: firstly to remove all traces of luminal content and mucous and secondly to adequately distend the stomach to ensure rugal folds are smoothed out. Gastric capacity is highly variable, depending on body habitus and eating habits and therefore the optimal distension volume is likely to vary from individual to individual. An average gastric capacity is 1000mls, thus forming the basis for our protocol, however it can expand to hold up to 4000mls, 50 times its empty capacity and thus higher volumes may be necessary.(275, 276) Following the successful feasibility studies in ex vivo models using 1000mls of water, the only modification was to add an anti-foaming agent (40mg simethicone) in an attempt to reduce luminal mucous and bubbles which could hinder mucosal visualisation. In Chapter 6 we demonstrated that this pre-procedural protocol of 1000mls of water and 40mg simethicone significantly improved gastric mucosal clarity and distension compared to 200mls of water and 40mg simethicone ($p<0.0001$ and $p<0.0001$ respectively). Furthermore in Chapter 7 we graded gastric mucosal clarity and distension satisfactory (Grade 1 and 2 on a 1-4 scale) in 80% of patients undergoing MACE using this protocol. Poor proximal gastric distension and adherent debris accounted for the majority of the remaining 20% of patients with inadequate mucosal clarity and distension.

Various different approaches for gastric preparation have been adopted by others, using alternative capsule systems. Keller et al found that the addition of 5mls simethiconeto 500mls water impaired visualisation by increasing the opacity of the fluid and thus 500mls of water alone, taken 60 minutes prior to the procedure, was used in their protocol.(198) Once the capsule had entered the stomach the patient ingested 5.8g of sherbet powder with the aim of augmenting gastric distension through the release of carbon dioxide. Further sherbet could be administered if distension appeared sub-

optimal. Despite these efforts, complete gastric examination was prevented in 70% of the participants due to fluid obscuring the apical fundal region or insufficient distension of the mucosa to flatten all folds.

Larger ingested liquid volumes together with a gas producing powder were utilised by Liao et al and Zou et al in their studies using the large external magnet system produced by Ankon technologies Co. Ltd. 500mls of water was ingested 60 minutes prior to the procedure, followed by a further 500mls 15 minutes before, with the aim of cleansing the stomach effectively. Six grams of 'air-producing powder was then taken with 5mls of water, 5 minutes before capsule ingestion. The powder was expected to release approximately 540mls of carbon dioxide. A further 5mls of water was allowed to ease ingestion of the capsule. Additional water or air-producing powder could be ingested depending on whether adequate distension was achieved, as graded by the operator. Mucosal cleanliness was deemed 'moderate' in 11.8% of participants and 'good' in the remaining 88.2%. Whereas gastric distension was graded 'moderate' in 14.7% and 'good' in 85.3%.(202)The authors felt that the main limiting factor to a complete examination in this study was difficulties navigating to the proximal stomach (5 patients), rather than poor preparation. This issue seemed to be resolved with increasing operator experience in the subsequent study using the same protocol. Although gastric visibility and distension was not individually assessed in that study,difficulties manipulating the capsule occurred in only 3 of the 68 patients and this was due to adherent mucous rather than inadequate mucosal cleansing or distension.(203)

Rey et al used water alone in their protocol using the large magnetic guidance system produced by Siemens and Olympus. The patient was requested to drink 500mls of water approximately 90 minutes prior to the procedure. This was followed by a further 400mls of water 60 minutes later and 15 minutes of light exercise. These steps were aimed at achieving a clean stomach before a further 400mls of water was ingested to act as the distending volume. The greater preparation volume yielded good resultsoverall, with sub-optimal distension reported in only 2 patients, although

mucous remained a significant issue with reduced manoeuvrability of the capsule secondary to resistant mucous noted in 7 of the total 61 study patients.(200)

For the purposes of the study outlined in Chapter 5 we collaborated with a group investigating the same capsule system, MiroCam Navi. Recently they have published their independent work using the system in 26 healthy volunteers. A mixture of 20mg metoclopramide syrup, 20 000 units of pronase and 40mg simethicone was ingested with 100mls of water 15-30 minutes prior to the procedure in order to cleanse the stomach. Rather than ingesting a specific distension volume the volunteers were instructed to ingest water throughout the procedure, depending on the views obtained. Overall a mean volume of 800mls was required (range 200-1500mls). This regime was less effective for the proximal stomach, with only 56% achieving 'good' mucosal visualisation, compared to 85% in the distal stomach.(268) Similar to the study by Keller et al, they found opaque luminal contents impeded views in the proximal stomach. We did not encounter this problem with the use of simethicone during the studies described in this thesis, but perhaps this could be explained by the higher dilution volumes of water used in our studies (1000mls vs 500-800mls).(198, 268)

Despite a multitude of different preparation protocols, no head-to-head trials have yet been conducted and the present published studies show significant heterogeneity which makes drawing meaningful conclusions difficult. Large ingestion volumes of water are troublesome for patients, while the use of gas-producing substances can increase abdominal discomfort, produce bubbles which can distort capsule images and only remain effective within a limited time period. Anti-foaming agentssuch as simethicone are of benefit for MACE of the stomach in our experience and have been shown to improve visibility at OGD in a meta-analysis,(53) but others have found them to increase fluid opacity hindering mucosal visualisation.

Although adequate preparation is imperative to successful MACE, it should clearly not compromise patient acceptability, since this remains the major advantage of MACE over conventional endoscopy.

The evidence drawn from this body of work suggests that a protocol of 1000mls of water with 40mg simethicone ingested immediately prior to MACE confers excellent gastric mucosal visualisation and distension in the majority of patients with a limited impact on patient comfort. Unlike other investigators (200, 203)we found adherent mucous could obscure the field of view, but did not prevent magnetic mobilisation of the capsule. In view of the improved proximal gastric visualisation seen by Rey et al using 1300mls of water, increasing the distension volume should be a primary consideration in any future work. Further studies exploring the benefits of the addition of light exercise, differing mucolytic agents and gas producing powders should also be considered, with particular emphasis on enhancing visualisation in the proximal stomach.

8.3 Is manoeuvrability really necessary?

The premise of capsule endoscopy of the small bowel, oesophagus and colon relies on the passive intrinsic peristaltic motion of the gut to propel the capsule forwards. The tubular nature of these structures ensures the capsule obtains circumferential luminal views without the need for external intervention. It has been assumed that capsule endoscopy of the stomach could not be approached in this way, since its large capacity and rugal folds would preclude a complete examination, hence the introduction of capsules with steering capabilities. However, studies have shown that small bowel capsule endoscopy in patients with recurrent or refractory iron deficiency anaemia identifies pathology in the stomach in up to 20% of cases.(257, 258)This raises the question as to whether steering of the capsule is really necessary at all and whether a complete enough capsule examination of the stomach could be achieved by passive motion alone.

Kobayashi et al addressed this by conducting a trial comparing the diagnostic yield of small bowel capsule endoscopy to OGD for gastric pathology in 55 patients with obscure gastrointestinal bleeding or iron deficiency anaemia. Patients followed a standard protocol for SBCE, without additional gastric cleansing or distension steps, but the video of the stomach obtained was carefully read and reported in the same way as for the small bowel. The sensitivity and specificity of CE for diffuse lesions (e.g. gastritis, gastric antral vascular ectasia) was considerably better than for localised lesions (sensitivity 70% vs. 28%, p=0.002, specificity 82% vs. 63%, p=0.17, respectively). As expected, a longer gastric transit time was associated with better concordance between OGD and CE for both localised and diffuse lesions. Both gastric cancers identified at OGD were missed at SBCEand taking this into account, together with the poor sensitivity for gastric focal lesions reported in this study, led the authors to conclude that passive CE could not be recommended in the diagnosis of gastric diseases.(277)

PillCam ESOcontinues to transmit images of the stomach and duodenum for up to 30 minutes after capsule ingestion and has two imagers with a high frame acquisition rate which could improve the sensitivity of passive CE for the detection of gastric pathology. Marelli et al exploredthis concept in a comparative pilot study of 49 patients with uncomplicated dyspepsia.(256)All patients underwent conventional upper GI flexible endoscopy and capsule endoscopy of the oesophagus, stomach and potentially duodenum (termed Cap-OGD in their study) using PillCam ESO. Two protocols were used for Cap-OGD, the first 25 patients followed the 'simplified ingestion protocol', which involved swallowing the capsule in the right lateral position using sips of water through a straw every 30 seconds for 7 minutes, the patient was then free to mobilise for 15 minutes. The second group of patients swallowed the capsule while standing and then mobilised at their leisure for the remaining 30 minutes battery life of the capsule.

All major pathology identified at OGD was also identified at Cap-OGD, however Cap-OGD struggled to identify minor pathology such as mucosal erythema and fundic gland polyps. This contrasts with our findings and those of others, discussed in *section 8.6* of this chapter. Potential reasons identified by the authors included the lack of gastric distension achieved and the improved image quality of flexible endoscopes with high definition lenses. Only 61% of capsules reached the duodenum within 30 minutes in this study and thus significant pathology was missed in the distal stomach and proximal duodenum. However, this could be overcome by newer capsules with better power conservation strategies and longer operating times.

A more complex protocol was developed by Jun et al in their study of 8 patients undergoing oesophago-gastric capsule with PillCam ESO. All patients had endoscopically diagnosed gastric cancer and underwent capsule endoscopy within 48 hours of their OGD. Prior to capsule endoscopy patients received an anti-muscarinic agent (cimetropium bromide 5mg intramuscularly) and 200mg simethicone in 10mls of water. The capsule was swallowed with 100mls of water in a seated position. Two minutes after ingestion the patient changed position every 30 seconds in the following

order: supine, left lateral, prone, left lateral, supine, right lateral, supine, right lateral, head up tilt and right lateral head down tilt. This was then repeated after ingestion of 4g sodium bicarbonate to act as an effervescent agent.

Despite this protocol only 50% of gastric lesions were identified at CE by the blinded reporter viewing the downloaded video after the examination. A further two were identified by second review of the capsule videos after un-blinding. On retrospective review the authors felt that lesions were missed most commonly when hidden between mucosal folds due to inadequate distension. Difficulty identifying the fundal region was found to be secondary to a combination of incomplete expansion and shallow penetration by light, which potentially could be resolved by real-time viewing and positional change at the time of procedure.(278)

Taking these three studies into account it seems unlikely that passive capsule examination alone, can be relied upon to accurately visualise all major locations of the stomach and identify relevant pathology. However, overall study participant numbers remain small and certainly the dual imager PillCam ESO seemed to be more successful at identifying pathology, than the single head small bowel capsule camera, if gastric distension was adequate. Technological advancements such as a longer capsule battery life, brighter illumination and high definition lenses together with a defined optimal preparation protocol may improve the technique, however to represent a valid alternative to conventional endoscopy some element of real-time capsule steering is likely to be necessary to allow mobilisation of adherent debris, targeted examination of blind spots and careful inspection of detected abnormalities.

8.4 Optimal protocol for manoeuvrability

During our studies using the MiroCam Navi system we have observed a number of specific points of interest regarding manipulation of the capsule that warrant further discussion. Firstly the operating distance between the capsule and the external magnet is imperative to accurate control and although this was easily modifiable in ex-vivo studies this was more problematic in humans and led to some difficulties, predominantly in the proximal stomach. Secondly, tilting and rotational movements were particularly successful and easy to intuitively perform by the operator. Thirdly, dragging translational movements of the capsule were challenging. We experienced this not only in humans where mucous, mucosal folds and anatomical variants could be to blame, but also in simple experiments using smooth water containing vessels. Our protocol of employing the tilting and rotational movements of the capsule from strategic fixed points and then positional change for larger translational movements was specifically to overcome these issues.

Others have reported similar findings using handheld magnet systems. Although Keller et al did not describe a sequential protocol for movements of the external magnet in their feasibility study, they did observe difficulties with dragging the capsule and found rotating and tilting movements to be far more successful, together with positional change.(198)

Rahman et al followed a well-defined sequence of positional change in conjunction with specific movements of the external magnet controller held at designated anatomical locations in their study using MiroCam Navi. In contrast to our study, described in Chapter 7, the patient ingested the capsule in a supine position with a 10° tilt and sips of water through a straw. Holding the external magnet at the sternum, they were able to stabilise the capsule in the distal oesophagus for 1 minute in 92% of patients, but a clear gastro-oesophageal junction view was observed in only 46%.(268)We found oesophageal views particularly difficult to obtain with the patients in a seated position to

ingest the capsule and clear gastro-oesophageal junction views were obtained in only 11% ofpatients (chapter 7).

Keller et al have previously shown that despite being able to delay oesophageal transit with a magnetically controlled capsule, this did not confer better views of the gastro-oesophageal junction compared to using the specifically designed oesophageal capsule (PillCam ESO) (complete gastro-oesophageal junction view 73% vs. 33%, $p<0.01$).(279) In this study both capsules were ingested in the right lateral position, during MACE the magnet was placed on the patients back in a location determined by MRI to be 3-4cm proximal to the gastro-oesophageal junction. Since the major advantage of the hand-held MACE systems are their portability, if this technique were to spread into routine clinical practice it would be unfeasible to require MRI guidance for positioning of the external magnet. Even with this assistance it seems that adequate gastro-oesophageal junction views may be best achieved by the dual imagers and increased frame rate offered by a specifically adapted capsule, rather than prolonging oesophageal transit by magnetic control.

We and others found the proximal stomachparticularly challenging to examine, partly due to difficulties with distension and adherent debris as previously described. In our protocol we used the supine and left lateral positions to allow distension of this part of the stomach. The external magnet was then placed in the left and right pectoral regions, epigastrium and left upper quadrant to steer the capsule to scan the mucosa of the opposite wall of the stomach. Adequate views of the cardia and fundus were achieved in 21% and 16% patients respectively, which improved when the videos were viewed retrospectively by reviewer A (Chapter 7). In their study, Rahman et al obtained a clear view of the cardia in 65% of patients and the fundus in only 46%.(268) They also used a supine position and the external magnet in the left pectoral and xiphisternal area to view this region, but in contrast to our studythe left lateral position was not employed. Instead an additional external magnet location in theright upper quadrant location was used, together with the right lateral position if adequate views were not obtained. As a last resort the prone position was utilised with

the magnet held over the upper back. Despite these measures proximal gastric visualisation failed to achieve the level of clarity and completeness required to rival OGD. Using the Siemens/Olympus external magnet system, Rey et al found the left lateral position was better than supine or right lateral for viewing the proximal stomach, enabling complete visualisation of the cardia in 72% and the fundus in 58% (*Figure 43*).(200)

One of the major issues with viewing the proximal stomach is that there are a number of factors which are preventative to adequate capsule examination and until they are resolved individually it is difficult to tease out the exact contribution of each factor and thus make recommendations. During conventional gastroscopy the cardia and fundus are easily identified by the shaft of the endoscope traversing the gastro-oesophageal junction and gross air distension. During MACE this assistance is not possible and one must become accustomed to the appearance of a more collapsed proximal stomach, which can be easily confused with the distal stomach in practice. It is also worth mentioning that even the large external magnetic guidance system used by Liao et al had some difficulties manoeuvring in the proximal stomach, despite greater magnetic strengths and capsule localisation data.(202) Current protocols have yet to achieve optimal mucosal distension, luminal debris can be an issue and finally capsule illumination over the longer distances required to view the fundus is sub-optimal. With this in mind, until further work is done to resolve each of these issues, the most effective means of steering the capsule in this region will be difficult to ascertain. Considering the findings of the above described studies, together with our own experience we would recommend the left lateral and supine positions to be considered initially when attempting to obtain proximal gastric views, perhaps reserving the right lateral and prone positions for if views were especially troublesome.

The gastric body and distal stomach was much more straightforward to examine with MACE, in particular we found we could achieve excellent views of the lesser curvature and angulus by holding the capsule against the anterior gastric wall with the magnet in the xiphisternal region, tilting the

capsule to scan the opposite wall. In our experience the supine position and external magnet locations of the left and right upper quadrants, xiphisternum and umbilicus provided adequate gastric body views. Following this, the right lateral position and external magnet positions of epigastrium, right of the umbilicus and right upper quadrant and finally the right pectoral region were effective for the antrum and pylorus. This enabled 'good' or 'excellent' visualisation of the gastric body in 79%, lesser curve 84%, antrum 95% and pylorus in 89% of cases (Chapter 7). We did not find holding the magnet over the patients back, while in the right lateral position was useful for visualising the antrum and pylorus.

Rahman et al used only one external magnet position (umbilicus) but supine, right lateral and prone positioning to view the gastric body, followed by a return to the supine position with the magnet held 1-18cm to the right of T5-L3 vertebrae and finally these steps repeated in the right lateral position to view the gastric antrum and pylorus. Using this technique, clear views of the body were obtained in 73%, incisura 88%, antrum 88% and pylorus 100%.(268)Rey et al also found the right lateral position was optimum for examining the antrum and pylorus, achieving a complete view of the antrum in 70% and the pylorus in 72% of patients in this position*(Figure 43)*.(200)

The challenge in trying to define a standardised examination protocol for MACE is that it is a dynamic procedure which relies somewhat on intuitive movements of the external magnet by the operator in response to feedback from the real-time viewer. Gastric anatomy can vary enormously from individual to individual and therefore, much like when performing colonoscopy, manoeuvres are made within a framework of guidance while responding to the individual eccentricities of the patient. Repeated positional changing is likely to increase the duration of the procedure and is more troublesome for patients, particularly ifreduced mobility is an issue, therefore it should be kept to the minimum required to achieve a complete examination. Both the protocol used during our studies and that by Rahman et al have been shown to be effective for examination of the mid-distal stomach. For the purposes of future studies, we would recommend a modified protocol combining

the routine used during our studies with that by Rahman et al for examining the whole stomach *Figure 44*. We would advocate further work though, to explore strategies to improve MACE in the proximal stomach and this should be an important focus for future studies.

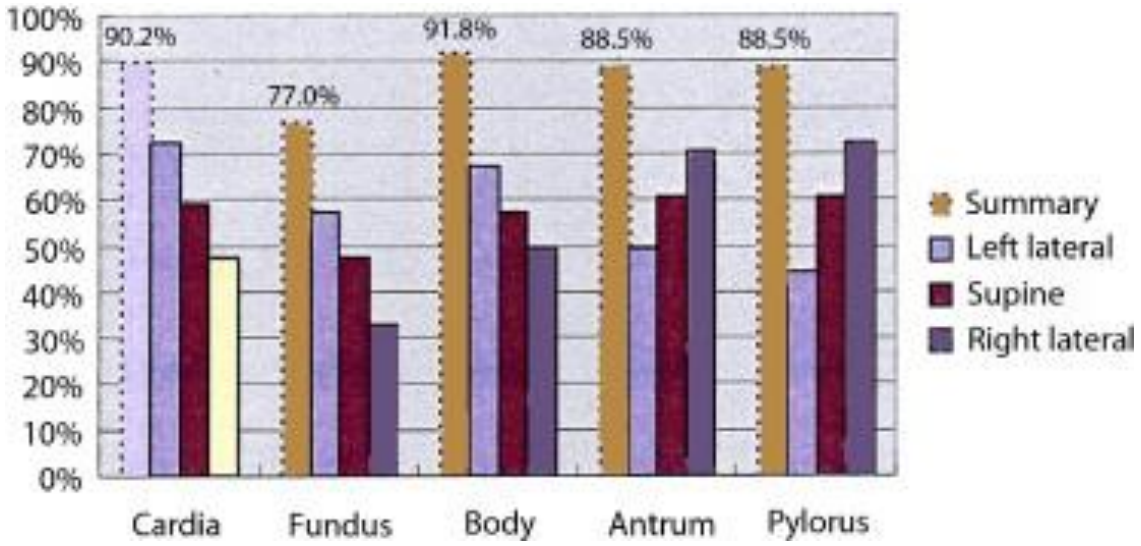
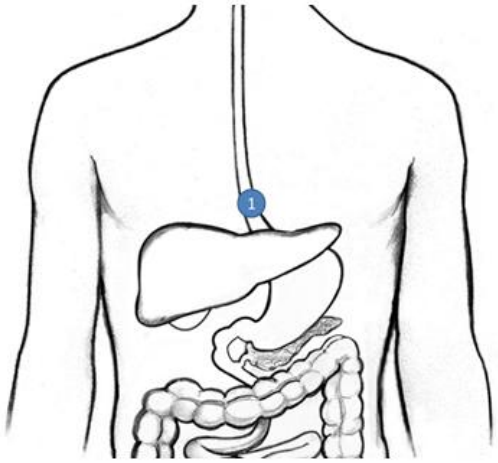
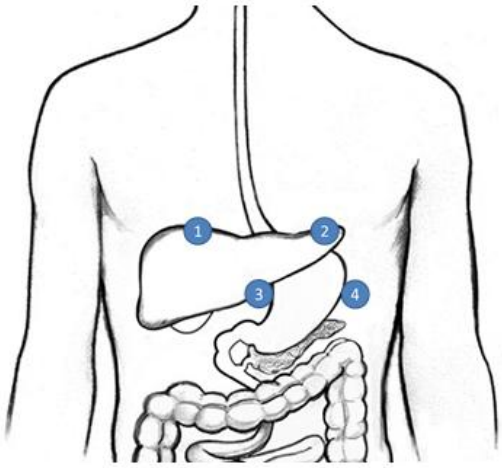
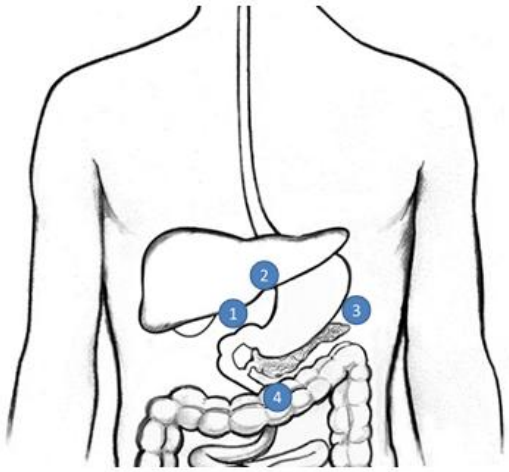
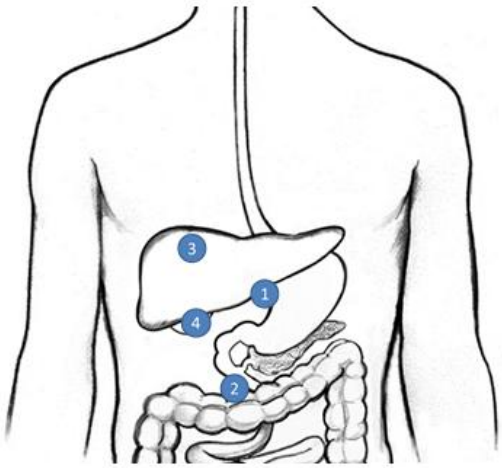


Figure 43: Proportion of complete observations in each stomach area, taken with permission from Rey et al.(200)Summary column represents the total number of adequate visualisations of each area of the gastric cavity in all positions combined.

Figure 44: Modified protocol for MACE examination	
	**POSITION 1: OESOPHAGEAL VIEWS** SUPINE 10° TILT Patient swallows capsule with sips of water through a straw. 1. Hold external magnet over the sternum
	**POSITION 2: FUNDAL & CARDIAL VIEWS** SUPINE POSITION 1. Right pectoral region 2. Left pectoral region 3. Epigastrium 4. Left upper quadrant IF INADEQUATE VIEWS ACHIEVED: -repeat above in left lateral position -repeat above in right lateral position -prone position with magnet over upper back

	**POSITION 3: GASTRIC BODY** SUPINE 1. Right upper quadrant 2. Xiphisternum 3. Left upper quadrant 4. Umbilicus
	**POSITION 4: ANTRUM/PYLORUS** RIGHT LATERAL 1. Epigastrium 2. Right of umbilicus 3. Right upper quadrant 4. Right pectoral region
https://catalog.niddk.nih.gov/imagelibrary/lightbox.cfm	

8.5 Patient comfort

Patient comfort and compliance with investigation is one of the major themes driving this research. Conventional flexible endoscopy is perceived as intrusive and distressing to patients and may be preventative to performing the procedure in 2-5%(280, 281) or lead to an incomplete procedure in up to 13%.(282)High anxiety levels, young age and pronounced gag reflex are all associated with reduced tolerance of upper GI endoscopy. Measures to improve tolerability including psychological support,(283) hypnosis(284) and acupuncture(285) have unfortunately only achieved limited success.

Sedation using intravenous benzodiazepines or opiates, alone or in combination, does facilitate endoscopy procedures and improves patient tolerance and acceptability.(286) But this comes at a cost of increased risk, particularly in high doses, in elderly patients or those with cardiovascular disease.(241, 287, 288)Recognised complications include: respiratory depression, agitation, hypotension and allergic reactions. Studies suggest that half of all complications and deaths associated with OGD are secondary to cardiovascular problems and thus, in many cases, sedation related.(289)

Sedation is also associated with practical inconveniences both to the patient and the endoscopy service. Patients are unsafe to drive for 24 hours after the procedure and often need to delay return to work. Whilst within the endoscopy unit more nursing staff and monitored bed-space is required to care for semi-conscious patients after the procedure andmanage any side effects, complications and unexpected admissions. Longer procedures and recovery time also reduce procedural capacity within the department with associated financial losses.(290)Reducing the risks of upper GI endoscopy while maintaining patient comfort is favourable to both patients and clinicians and thus many researchers have looked for alternatives to sedation including; background music, local anaesthetic throat swabs rather than spray, the addition of pre-procedure analgesia and adopting a

trans-nasal approach.(291-299) While some approaches were well-received by patients, adoption of these adjuncts within regular clinical practice has been limited.

Capsule endoscopy of the small bowel is well tolerated by patients due to its non-invasive nature. However, for clear, accurate mucosal visualisation, preparation to remove luminal debris and distend the bowel is paramount and this cannot be facilitated during the procedure since there is no suction or wash ability, unlike conventional endoscopy. For the small bowel this can be achieved successfully with fairly low volumes of bowel preparation and thus patient tolerance is not significantly affected. For colon capsule endoscopy however, preparation is more rigorous, although there is hope that more patient-friendly regimes could be adopted in the future.(300-302) The optimal preparation for gastric MACE remains unclear, although it is worth considering that controversy still remains over the best preparation for SBCE, despite its introduction over 15 years ago. While the importance of adequate preparation cannot be overemphasised for all types of capsule endoscopy, including MACE, it is important that this does not compromise the overall patient experience or become preventative to performing the procedure.

I have prospectively collected data on patient tolerance over the two human trials conducted as part of this body of work. The questionnaire utilised was based on one developed during a large study on patient tolerance of endoscopy procedures within our institution.(232, 263)A combination of visual analogue and numeric rating scales were utilised to give patients the best chance of accurately documenting their feelings and experiences. The data collected included information about pre-procedural anxieties and post-procedural experience. This allowed comparisons to be drawn between the patient tolerance of MACE compared to a protocol to enhance gastric emptying in chapter 6 and between MACE and OGD in chapter 7.

Firstly in chapter 6 we can see that MACE was extremely well tolerated with 98% of patients happy to undergo a repeat procedure. In comparison to the control group (protocol of mobilisation for 30

minutes, followed by intramuscular metoclopramide if the capsule had failed to enter the duodenum), there were no significant differences in patient tolerance between the two protocols. There was no negative feedback from participants regarding the water ingestion protocol and since this was also demonstrated to be an effective preparation, it was taken forward and used in the second human trial described in Chapter 7.

In Chapter 7 we can draw direct comparisons between the tolerability of MACE compared to OGD. Interestingly there were no significant differences in pre-procedural expected pain and discomfort for either procedure. This might be due to the fact that MACE is a novel procedure and patients had little reference point to base their expectations on. Additionally, all patients had previously had an OGD and nearly half of patients (9/20) requested sedation, possibly reflecting a previously positive experience with sedation and hence lower expected discomfort levels. Reviewing the post-procedure data, MACE was tolerated significantly better in all three measures, pain, discomfort and distress ($p<0.001$, $p=0.001$, $p=0.006$ respectively). Despite this,100% of patients stated they would be happy to undergo either procedure again if clinically indicated and no post-procedure symptoms were reported. Our findings are supported by the only other published trial of MACE in humans using MiroCam Navi. Of the 26 patients included in this study, none reported any significant discomfort and overall the procedure was tolerated well, although this was not formally assessed.(268)

Other studies of MACE using different devices have reported similar findings, though again in a less formalised manner. In their study of the handheld magnet device produced by Given Imaging, Keller at al reported 9 of the 10 subjects had no complaints at all during the procedure, while one described a feeling of mild abdominal pressure. In two patients mild abdominal fullness and distension was reported during the post-procedure follow up.(198)

There are three published studies using the Siemens/Olympus device and a protocol of 1300mls of water, the largest volume of all of the studies of MACE. The first in 2010, described 2 patients (of 29) experiencing abdominal pain during the procedure. In 1 patient, this was subsequently diagnosed as diverticulitis.(199) In the second study in 2012, 2 patients were excluded initially due to inability to swallow the capsule (1 patient with previous nasopharyngeal carcinoma and 1 began to vomit) and again 2 patients experienced abdominal pain during the procedure, presumably included from the initial feasibility study since 1 was diagnosed with diverticulitis.(200) In the most recent study of 189 patients using this equipment, all preferred MACE rather than OGD under propofol sedation.(201) Although propofol sedation allows for excellent tolerance of procedures due to its heavily sedating properties the drawbacks for patients are its perceived invasiveness, a fear of anaesthesia and the inability to drive or work for 24 hours after the procedure.

Two studies are reported using the Ankon Technologies Co. Ltd. device with a preparation of 1000mls of water and 6g of air producing powder. In the first, all 34 patients graded their tolerance of the preparation as 'good' or 'very good' while 100% described their comfort during the procedure as 'very good'. 1 participant described mild abdominal distension after ingesting the air producing powder.(202) During the follow-up study of 68 patients, 2 patients complained of self-limiting abdominal pain the day following the procedure.(203)

Overall these and our studies support the hypothesis that MACE of the stomach is a very well tolerated procedure with few adverse events. In fact MACE using MiroCam Navi seems to be particularly patient friendly, with none of the 168 patients examined so far reporting any discomfort or pain. Finally our data from chapter 7 suggests that MACE is better tolerated than conventional flexible endoscopy, while the study by Denzer et al showed patients preferred MACE over standard OGD, albeit with propofol sedation. As larger studies using MACE are conducted, we would recommend formally assessing patient tolerance and preference as part of the investigative protocol in order to enable meaningful conclusion regarding patient comfort to be drawn.

8.6 Pathology detection

In our final study (Chapter 7), we have explored the ability of MACE to identify gastric pathology compared to conventional OGD. Both procedures identified 16 findings, OGD detected 14 abnormalities that MACE did not, while MACE found eight lesions that OGD did not. Exploring this in more detail, nine of the 14 findings detected by OGD but missed by MACE were hiatal hernias, not surprising considering the gastro-oesophageal junction and proximal stomach were poorly visualised during our study. The other findings missed by MACE were erosions (3), gastric polyp (1) and bile reflux (1). Bile reflux is obviously a dynamic process and MACE identified another case which OGD missed. The gastric preparation for MACE could have potentially washed any bile residue away, whereas on the other hand we have observed bile refluxing through the pylorus in patients undergoing MACE (two patients in this study and others during the study outlined in Chapter 6). Other lesions identified at OGD but missed at MACE (3 erosions and 1 polyp) were identified on retrospective review of the capsule videos.

MACE identified eight lesions not seen at OGD, however all of these were felt to be minor in nature and did not warrant repeat OGD. One area of fresh blood was missed by OGD, but on secondary expert review of the capsule video it was felt this looked typical of a biopsy site from the prior OGD. As mentioned previously, bile reflux was also identified in one patient during MACE, but not at prior OGD. Four erosions, one angioectasia and one patch of intestinal metaplasia were overlooked at OGD, but well defined and easily identifiable at MACE.

This raises the question as to whether MACE has an advantage over OGD for identifying subtle mucosal lesions, whether localised or diffuse. The reduced gastric distension may make vascular lesions appear more prominent, whereas the depth of view and focussing capabilities of capsule endoscopes are specifically designed for viewing lesion close-up and thus very clearly defined images of smaller lesions are obtained.

MACE identified 10 erosions/inflammation not seen by OGD in the study by Rey et al, whereas only a single erosion was identified by OGD and missed by MACE. Interestingly though, MACE also identified 11 polyps missed by OGD, although these were mainly small, hyperplastic polyps with limited clinical relevance.(200) One potential reason for MACE identifying more of these very small lesions is the increased duration of procedure compared to OGD. Also, similar to our study (Chapter 7), the OGD was performed first and thus the erosions identified by subsequent MACE could reflect trauma from the initial intubational endoscopy. However, the procedures were performed in this sequence during the prior feasibility study(199) and this discrepancy was not noted.

In an attempt to avoid this problem, Zou et al perfomed MACE first followed by OGD 4-24 hours later. Fifty-three of the 68 identified pathological lesions were found by both techniques, giving an overall agreement of >90%. Again, MACE seemed to be slightly better than OGD in finding minor erosions (6 vs. 3).(203) This contrasts with the study by Rahman et al where all pathologic lesions found during MACE were also identified by subsequent gastroscopy, with the exception of a 5mm sub-mucosal lesion identified by OGD alone.(268) The Given Imaging MACE system has not been evaluated for its ability to detect upper GI pathology.

Finally, all lesions identified at OGD but missed at subsequent MACE (except hiatal hernias) in our study were identified on second review of the capsule video by an expert blinded reviewer. Without the distraction of performing and reporting MACE simultaneously the reviewer can devote their full attention to the capsule video, which is important since abnormalities may be evident in only a small number of frames. Moreover the reporting software has slow-motion play back functions and allows the operator to move between individual image frames of areas of interest. Taking this into account, retrospective review of capsule videos may improve the diagnostic yield of MACE, but would be time consuming and prevent immediate patient feedback of results.

8.7 Practical and financial perspectives

For MACE to be considered a viable alternative conventional endoscopy it needs tonot only be an accurate means of visualising the gastric cavity and diagnosing pathology, but also to be competitive in terms of price and the practicalities of performing the procedure.

MACE using the external magnetic guidance units described, although promising in terms of diagnostic yields, would require a dedicated room with the installed equipment which is large and cumbersome. This is likely to represent a significant initial financial outlay, not taking into account the training and practice of specially trained operators to continue the service. In contrast, MiroCam Navi requires simple portable equipment and therefore could be performed in any clinical unit, including within a primary care setting. However, there is still a need for adequately trained operators and the exact time and training required is not yet clear.

Our ex vivo study outlined in Chapter 4 suggested 39 consecutive procedures were required to gain competence in the ex vivo model. The complexity of the procedure within humans is increased and therefore this number is likely to be higher, although there is yet no evidence to guide where this threshold should lie or specific training methodologies which should be utilised. Rey et al describe using in vitro plastic models to gain initial experience with their equipment before conducting a pilot study on 24 patients.(200) In vitro and ex vivo models provide a simple means of gaining familiarity and practice with the equipment and thus would be easy to implement in any training schedule.

Of course conventional endoscopy also requires formal training of practitioners. Current guidelines from the Joint Advisory Group for endoscopy in the UK specify a minimum of 150 upper GI procedures are required before formal competence is considered. Practitioners are not isolated to medically trained staff either, with nurse endoscopists fulfilling significant service provision in many trusts. There is no reason why this could not be extended to MACE procedures since nurses have been shown to read and report SBCE to the same quality of consultant gastroenterologists.(303)

Like the larger MACE systems, conventional endoscopy requires a dedicated space for procedures to be conducted, but also a recovery space to accommodate sedated patients afterwards. The equipment required is initially financially burdensome but has ongoing costs in terms of maintenance, disinfection and medications together with staffing costs for appropriately trained nurses. Simple hand-held MACE systems avoid such expenditure, although the larger guidance systems are likely to require some element of maintenance.Of course the major expense for capsule systems is the cost of the capsules themselves, ranging between £360-422 plus value-added tax. There are also additional costs such as reporting software, bowel preparation and the cost of time to read and report the procedures.As with all new technologies we would expect the cost of the capsules to reduce as use becomes widespread, although this will require negotiation with the production companies.

All investigators have shown MACE to be more time-consuming than OGD. In Chapter 5 we demonstrate that MACE took significantly longer than OGD in our study of ex vivo models (3.34 minutes vs. 9.90 minutes, $p<0.0001$). In the human study of MACE (Chapter 7) the mean procedure duration was 22 minutes, similar to the other published study of MACE using MiroCam Navi (24 minutes),(268) but considerably longer than the average duration of an upper GI endoscopy procedure. MACE using the Olympus/Siemens system took anaverage of 30 minutes during the feasibility study,(199) decreasing to 17.4 minutes in their blinded comparative study, while OGD only took 5.3 minutes.(200) The operators of the Ankon system took an average of 43 ±10.0 minutes to perform a MACE examination of the stomach,(202) reducing to 29.1 ±8.5 minutes in their second study but still significantly longer than mean OGD duration 5.0 ±1.0 minutes ($p<0.001$).(203) It is clear from these results that procedure duration reduces with increasing operator experience.

Considering MACE is still a fairly novel procedure there is still likely to be further room to hasten procedure times as more is understood about the technique and practical experience accumulates.Furthermore with automated reporting systems on the horizon for small bowel capsule

endoscopy, it is not beyond the realms of possibility that the entire procedure could be performed and reported in an automated fashion in the future. On the other hand a recent meta-analysis has shown 11.3% of upper GI cancers are missed at endoscopy up to three years before diagnosis and therefore we should also consider whether OGD procedures are being performed too quickly.(304) The Japanese have long set a precedent for quality in endoscopy and in a recent review considering quality assurance of upper GI endoscopy the authors suggest drawing on this experience to improve quality by setting a standard minimum procedure time of 8 minutes.(305) The importance of this notion has been recognised by the British Society of Gastroenterology Endoscopy Committee, who are now considering ways of improving and standardising the quality of OGD procedures in the UK.(306)

Finally, since MACE is viewed as a highly acceptable investigative means by patients, compliance with early investigation of symptomatic patients could potentially be enhanced. This is particularly relevant for screening populations, where uptake for conventional endoscopy is disappointingly poor,often due to procedural anxieties. In the case of colon capsule endoscopy, it has been demonstrated that if the uptake for bowel cancer screening was increased by 30% by offering a non-invasive means of investigation, such as CCE, thiswould offset the higher costs of performing the procedure leading to significant cost savings.(307)

8.8 Strengths& Limitations

Strengths

During this thesis we have attempted to answer the research question by following a logical, well-thought out process of investigation. In fact, the systematic progression of the studies described in this thesis is not dissimilar to the initial work performed following the introduction of small bowel capsule endoscopy.

In order to ensure safety and reduce inconvenience to patients, considerable feasibility work was performed prior to the human studies in order to guide protocol development. Additionally, the assessment of patient comfort during procedures was based on previous successful work performed in this department.

Independent statistical advice from the University of Sheffield Maths and Statistics Department was sought for preliminary power calculations for each study and also to check the methods and validity of the statistical data analysis and conclusions drawn following data collection and analysis.

The first study of MACE in human subjects in this thesis, described in Chapter 6, included relatively large numbers of patients, with no adverse events recorded. This concurs with the only other published study of MACE using MiroCam Navi,(268) although this study was smaller in number (26 patients recruited).

In both of the human studies of MACE described in this thesis we attempted to reduce selection bias by defining relatively few exclusion criteria.

This is a novel, exciting area of research reflected in the volume of peer-reviewed publications and presentations accomplished during the course of the thesis.

Limitations

The human studies recruited from one tertiary centre in the UK and therefore the conclusions drawn may not be applicable to all populations. Although, on the other hand Sheffield Teaching Hospitals NHS Foundation Trust is a large centre with a diverse population, drawing referrals from the surrounding regions in Yorkshire and therefore is likely to represent a good mix of simple and more complex patients.

During this thesis I was the sole operator performing MACE. This obviously reduces inter-observer variability but assumptions regarding learning curves and gastric mucosal visualisation and pathology detection may not be generalizable to a wider population of operators.

Although we aimed to recruit 20 patients for the pilot study described in Chapter 7, it would have been advantageous to recruit more if time had allowed. This may have strengthened the conclusions drawn during this pilot study, however valuable information was acquired in order to improve the methodology of the study going forwards.

Finally, during Chapter 7, we focussed on a very specific group of patients with recurrent/refractory iron deficiency anaemia. Expanding the inclusion criteria to include patients with other upper gastrointestinal conditions may enhance patient recruitment and enable more generalizable conclusion to be made.

8.9 Recommendations for future research

Further work to explore the optimal preparation protocol would be of benefit. Specifically, studies designed to evaluate the best volume of water to achieve adequate gastric distension without reducing patient tolerance and the utility of other measures such as mucolytics, gas producing powders and exercise would be helpful.

The most effective protocol of positional change and external magnet locations has yet to be clearly defined, although in future work we would encourage the utilisation of the modified protocol described in *Figure 43* in the first instance.

The most effective means of distending and evaluating the proximal stomach remains the major challenge following the work conducted in this thesis and in my opinion should be the main focus of future efforts to improve the technology.

Newer upper gastrointestinal capsules with better illumination and dual head cameras are on the horizon and may significantly improve gastric visualisation in MACE and enhance diagnostic yield. Studies to evaluate the potential of these novel technological developments should be a priority once they are available.

In view of the encouraging results obtained from the pilot study described in Chapter 7, we would recommend continuing this study, with minor modifications, to completion.

Finally a formal cost-analysis of MACE of the stomach compared to conventional flexible endoscopy would be of value to determine the potential niche of this technology within the current framework of upper gastrointestinal investigational procedures.

Conclusion

To conclude this body of work I will return to the initial research question: is magnetically assisted capsule endoscopy a viable alternative to conventional flexible endoscopy of the stomach? The Oxford English Dictionary definition of viable is quoted as 'capable of working successfully; feasible'.(308) During the course of this thesis I believe I have shown MACE to be capable of working successfully in both ex vivo porcine stomachs, but also more importantly, within humans. The final studies have shown MACE of the stomach to be safe and feasible within humans and have also allowed us to understand more clearly the advantages and challenges of MACE compared to conventional flexible endoscopy. Clearly there are hurdles to overcome before MACE of the stomach is considered equivalent to, or even superior to conventional endoscopy, however as a feasible alternative, I believe the studies outlined in this thesis support this assertion and allow us to reject the null hypothesis. In real terms within the foreseeable future, MACE is more likely to occupy a complementary position to standard intubational endoscopy rather than superceding it, providing a more patient friendly non-invasive alternative. Ultimately of course, MACE remains in the very early stages of its development and thus there are challenges ahead and much more to learn within this exciting field, but I look forward to this with great anticipation.

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APPENDIX 1: Abstracts and Publications

Abstracts and publications derived from this body of work.

Abstracts

Hale MF, Sidhu R, McAlindon ME. Randomised comparison of a standard protocol using metoclopramide versus a hand held magnet to enhance gastric emptying of the small bowel capsule. Gut 2015; 64: Suppl 1 A223 doi:10.1136/gutjnl-2015-309861.47

Holmes G, Hale MF, McAlindon ME, Anderson S. Mapping the gastric mucosal surface: image mosaicking for capsule endoscopy. Gut 2015; 64: Suppl 1 A490 doi:10.1136/gutjnl-2015-309861.1073

Hale MF, Rahman I, Drew K, Sidhu R, Riley SA, Patel P, McAlindon ME. Magnetically steerable gastric capsule is equivalent to gastroscopy for the identification of beads in a porcine stomach model: double blind randomised controlled trial. Gut 2014 ;63: Suppl 1 A53 doi:10.1136/gutjnl-2014-307263.108

Hale MF, Drew K, Baldacchino T, Anderson S, Sanders DS, Riley SA, Sidhu R, McAlindon ME. Gastroscopy without a gastroscope! Feasibility in a porcine stomach model using a magnetic capsule. Gut 2013; 62: Suppl 1 A156 doi:10.1136/gutjnl-2013-304907.351

Publications

Hale MF, Drew K, Sidhu R, McAlindon ME. Does magnetically assisted capsule endoscopy improve small bowel capsule endoscopy completion rate? A randomised controlled trial. Endosc Int Open. 2016 Feb;4(2):E215-21.

Hale MF, Rahman I, Drew K, Sidhu R, Riley SA, Patel P, McAlindon ME. Magnetically steerable gastric capsule endoscopy is equivalent to flexible endoscopy in the detection of markers in an excised porcine stomach model: results of a randomized trial. Endoscopy. 2015 Jul;47(7):650-3. doi: 10.1055/s-0034-1391329. Epub 2015 Jan 27

Hale MF, Davison C, Panter S, Drew K, Sanders DS, Sidhu R, McAlindon ME. Review: Practical aspects of delivering a small bowel endoscopy service in the UK. Frontline Gastroenterol 2015; 6: 2 132-140 doi:10.1136/flgastro-2015-10055

Hale MF, Sidhu R, McAlindon ME. Capsule endoscopy: Current practice and future directions. World J Gastroenterol. 2014 Jun 28;20(24):7752-7759.

Hale M, McAlindon ME. Capsule endoscopy as a panenteric diagnostic tool. Br J Surg. 2014 Feb; 101(3):148-9

Book Chapters

Hale MF, McAlindon ME. Future Development of Capsule Endoscopy. In Li Z, Liao Z, McAlindon M (ed.) Handbook of Capsule Endoscopy. Springer, Netherlands.

APPENDIX 2: Consent form for Study 3

Study Number: STH17268

Patient Identification Number for this trial:

CONSENT FORM

Title of Project:Randomised comparison of a standard protocol using metoclopramide versus a hand held magnet to enhance gastric emptying of the small bowel capsule.

Name of Researcher: Dr M E McAlindon Please initial all boxes

1. I confirm that I have read and understand the information sheet dated**05/09/10** (version**2.0**) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for theseindividuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

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

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

APPENDIX 3: Consent form for Study 4

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Study Number: STH18317

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Pilot Study: Diagnosis of upper gastrointestinal pathology in patients with recurrent/refractory iron deficiency anaemia: magnetically guided capsule endoscopy versus conventional gastroscopy.

Name of Researcher: Dr M E McAlindon Dr M F Hale

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 29/01/14 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

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

APPENDIX 4: Study 3 Patient Information

Steerable Capsule Endoscopy Research
Patient Information Sheet

Study: Randomised comparison of a standard protocol using metoclopramide versus a hand held magnet to enhance gastric emptying of the small bowel capsule.
Investigators: Dr Melissa Hale, Dr Mark McAlindon

We are inviting you to take part in a research study. Before you decide whether to participate or not it is important for you to understand why the research is being done and what it will involve. One of our team will go through the information with you when you arrive for your examination. We suggest this should take 25 minutes. Please take time to read the following information carefully and to decide whether or not you wish to be involved.

What is the purpose of this study?
Capsule endoscopy is a swallowable pill camera which passes through the gastrointestinal tract by the action of the musculature of the gut. The capsule is completely passive and is therefore reliant on the natural action of the gut muscles to move through the bowel.

To enter the small bowel the capsule must first pass through the stomach which can take a prolonged period of time in some people, expending the valuable battery life of the capsule in the process. If the battery runs out before all of the small bowel has been imaged, the procedure may need to be repeated. Incomplete examinations occur in up to 20 % of procedures (i.e. 1 in 5).

Currently, to try and avoid this problem a nurse checks on the progress of the capsule 30 minutes after it has been swallowed. Medication can be used to increase movements of the stomach if the capsule remains there after this time period.
We have now developed a hand held magnet which can exert some control over the capsule while it is in the stomach. The magnet is moved over the abdomen to try and direct the capsule into the small bowel without the need for medication. We hope that using this approach will be more comfortable for patients and increase the likelihood of a complete examination.

In order to know which method works best we plan to compare the standard practice (capsule check at 30 minutes +/- medication) versus the magnet approach.

Why have I been chosen?
Any patient over the age of 16 years attending for a small bowel capsule endoscopy examination is eligible to take part in the study. Patients who are pregnant or have implantable cardiac devices cannot take part in the study.

Do I have to take part?
It is up to you to decide whether or not to take part. You are free to withdraw at any time and without giving a reason. This will have no bearing on the medical treatment you receive or upon your legal rights.

What do I have to do?
If you agree to participate you will be randomly allocated to either the current (standard) protocol or the research protocol using the magnet. Both groups will have their height, weight and waist circumference measured on arrival for the procedure. If you did not enrol in the study you would just have you height and weight measured. A questionnaire regarding your comfort during the procedure will be given to you on arrival to complete before and after you test. If you did not enrol in the study you would not be requested to complete this.

If you are assigned to the standard protocol then the test will be conducted in the standard fashion. If you are allocated to the research protocol you will be asked to drink 1000mls (just under 2 pints) of water prior to swallowing the capsule. The data recorder (usually worn in a bag around the waist) will be connected to a small lap top computer. After you swallow the capsule you will be instructed to lie on your right side. The researcher (Dr Melissa Hale) will move the magnet over your abdomen and back until the capsule has left the stomach and moved into the small bowel. Once the capsule is in the small bowel you will continue the test in the standard way. If, after 30 minutes, the capsule remains in the stomach you will transfer onto the standard protocol where medication can be administered to encourage the capsule to pass into the small bowel.

What are the possible benefits of taking part?
Whilst there are no financial benefits of being a part of this study, participation will enable us to obtain important information about the best way to perform capsule endoscopy examinations.

Will my taking part be kept confidential?
All patient information is stored on password protected computer databases or in locked filing cabinets. You will be allocated a study number and staff not directly involved with you will know you only by this number. When the results of the study are reported, individuals who have taken part will not be identified in any way.

What if I change my mind about taking part?
If you decide to withdraw from the study, your standard of care will not be affected.

What if there is a problem?
Complaints: If you wish to complain formally, you can do this through the NHS Complaints Procedure, (contact The Patient Services Team at the Royal Hallamshire Hospital by telephone: 0114 271 2400, by email: PST@sth.nhs.uk, or in person at thePatient Partnership Department on B Floor, Royal Hallamshire Hospital)or you can find further information on

ethics in research on the National Research Ethics Service website (http://www.nres.nhs.uk/).

How will the information I provide be used?
We plan to publish the results in a health journal so others can read about and learn from the results of the study.

Who has reviewed this study?
This study has been reviewed and given a favourable opinion by the South Yorkshire NHS Research Ethics Committee.

Thank you for reading this. If you have any questions or would like any more information please contact Dr Melissa Hale, Clinical Research Fellow on 01142261180 or melissa.hale@sth.nhs.uk
Please keep this information sheet for your records.
If you agree to enter the study, please sign the enclosed consent form and we will return a copy to you.

APPENDIX 5: Study 4 Patient Information

Steerable Capsule Endoscopy Research
Participant Information Sheet

Study: Diagnosis of upper gastrointestinal pathology in patients with recurrent/refractory iron deficiency anaemia: magnetically steerable gastric capsule endoscopy versus conventional gastroscopy.

Investigators: Dr Melissa Hale, Dr Mark McAlindon

We are inviting you to take part in a research study. Before you decide whether to participate or not it is important for you to understand why the research is being done and what it will involve. One of our team will go through the information with you when you arrive for your examination. We suggest this should take 15 minutes. Please take time to read the following information carefully and to decide whether or not you wish to be involved.

What is the purpose of the study?

Gastroscopy is the usual way to examine the upper gastrointestinal tract (oesophagus and stomach) and consists of a flexible camera introduced through the mouth. However many patients find this procedure uncomfortable and anxiety provoking.

Capsule endoscopy is a swallowable pill camera which passes through the gastrointestinal tract by the action of the musculature of the gut. It is traditionally used to image the small bowel.

Questionnaire based studies on our unit have shown that in general, patients tolerate capsule endoscopy very well and find it a more comfortable procedure than gastroscopy.

We have now developed a hand held magnet which can exert some control over the capsule while it is in the stomach. The magnet is moved over the abdomen to direct the capsule to all areas of the stomach. This is used together with changing the patient position to enable all areas of the stomach to be viewed by the capsule.

We would like to compare whether this new method, using the capsule, magnet and positional change is as good as conventional gastroscopy for identifying abnormalities in the stomach.

Why have I been chosen?

Any patient who needs to undergo both a gastroscopy and small bowel capsule endoscopy as part of their diagnostic investigations is eligible to enter the study. Since this is a comparison study you are only eligible to enter if you are undergoing two procedures, **BOTH**

gastroscopy and small bowel capsule endoscopy. Often such patients have recurrent or refractory iron deficiency anaemia. Patients under the age of 20 years, patients who are pregnant or who have implantable electronic devices cannot take part in the study.

Do I have to take part?

No, it is up to you to decide whether or not to take part. You are free to withdraw at any time and without giving a reason. This will have no bearing on the medical treatment you receive or upon your legal rights.

What do I have to do?

You will be asked to complete a comfort questionnaire (expected to take 5 minutes) before and after both procedures. We will endeavour to ensure both procedures are performed on the same day but in some cases this may not be possible and thus you will be required to attend the hospital on **two** occasions.

When you attend for your small bowel capsule endoscopy we will measure your height, weight, waist and hip circumference. You will then be asked to drink 1000mls (just under two pints) of water prior to swallowing the capsule. The data recorder will be connected to a small laptop computer showing live real-time images from the capsule. Dr Melissa Hale will move a hand held magnet over your abdomen and back to view all areas of the stomach**. You may be requested to adopt certain positions (lying on your back/right/left hand-side).** This process can take 20-30 minutes. Once the capsule has viewed all areas of the stomach the capsule will be left to complete its examination of the small bowel as usual. This ends your participation in the study.

What are the possible benefits of taking part?

Whilst there are no direct benefits of being a part of this study, participation will enable us to obtain important information about the usefulness of this new technique.

Will my taking part be kept confidential?

All participant information is stored on a password protected computer database or in locked filling cabinets. You will be allocated a study number and staff not directly involved with you will only know you by this number. When the results of the study are reported, individuals who have taken part will not be identified in any way.

What if I change my mind about taking part?

If you decide to withdraw from the study, your standard of care will not be affected.

What if there is a problem?

Complaints: if you wish to complain formally you can do this through the NHS Complaints Procedure, (contact the Patient Services Team at the Royal Hallamshire Hospital by telephone; 011427124000, by email: PST@sth.nhs.uk, or in person at the Patient Partnership Department on B Floor) or you can find further information on ethics in research on the National Research Ethics Service website (http://wwww.nres.nhs.uk).

How will the information I provide be used?

We plan to publish the results in a health journal so others can read about and learn from the results of the study.

Who has reviewed this study?

This study has been reviewed and given a favourable opinion by the South Yorkshire NHS Research Ethics Committee.

Thank you for reading this. If you have any questions or would like more information please contact Dr Melissa Hale, Clinical Research Fellow on 0114 226 1180 or Melissa.hale@sth.nhs.uk
Please keep this information sheet for your records.

APPENDIX 6: Patient comfort questionnaire

Endoscopy Patient Comfort Questionnaire

STH18317 31/3/14 version 1.0

This information is being collected as part of a research study looking at a new way of performing capsule endoscopy. All data will be treated as confidential. Please complete sections 1.0 before your endoscopy and 2.0 and 3.0 after your procedure.

Thank you for taking the time to complete this questionnaire.

Section 1.0: Please complete this section ***before*** your endoscopic test:

Date of procedure:

Date of birth:

For the following questions please score your feelings from 0-10 where 0 is none and 10 is the worst imaginable.

How anxious are you about the procedure? (Please place an X on the line)

0 ——————————————————— 10

How much abdominal discomfort are you expecting during the procedure?

0	1	2	3	4	5	6	7	8	9	10

No discomfort — Worst discomfort imaginable

How much abdominal pain are you expecting during the procedure?

0	1	2	3	4	5	6	7	8	9	10

No pain — Worst pain imaginable

How much abdominal discomfort are you currently in?

0	1	2	3	4	5	6	7	8	9	10

No discomfort — Worst discomfort imaginable

How much abdominal pain are you currently in?

0	1	2	3	4	5	6	7	8	9	10

No pain — Worst pain Imaginable

Section 2.0: Please complete this section ***after*** your endoscopic test

Overall how much abdominal pain did you experience during the procedure?

0	1	2	3	4	5	6	7	8	9	10

No pain — Worst pain imaginable

Overall how much abdominal discomfort did you experience during the procedure?

0	1	2	3	4	5	6	7	8	9	10

No discomfort — Worst discomfort Imaginable

Overall how distressed were you throughout the procedure?

0	1	2	3	4	5	6	7	8	9	10

No distress — Worst distress Imaginable

If a doctor advised you to, would you have a repeat examination? Yes O No O

Section 3.0: Please use this space to record anything you feel is important regarding the procedure.

APPENDIX 7: Study 4 Pathology Reporting Form

Please tick the box(es) that correspond to the findings at gastroscopy

	Tick (or state number)	*Location**
Oesophagitis		
Mallory-Weiss tear		
Gastric antral vascular ectasia (GAVE)		
Portal hypertensive gastropathy		
Small ulcer <1cm		
Large ulcer ≥1cm		
Ulcer with visible vessel		
Ulcer with active bleeding		
Dieulafoy lesion		
Erosion		
Nodules		
Erythema		
Oedema		

Bile reflux		
Angioectasia		
Tumour without ulceration		
Tumour with ulceration		
Polyp		
Diverticulum		
Varices		
Fresh blood or clots		
Haematin/old blood		

*Please report location as follows:

Oesophagus: proximal, mid, distal

Stomach: cardia, fundus, body: greater/lesser curvature or anterior/posterior wall, antrum, pylorus

APPENDIX 8: MACE Protocol for Study 4

POSITION 1: OESOPHAGUS	Patient in a seated position. Patient swallows the capsule with a glass of water. Magnet held at sternum to capture GOJ view.
POSITION 2: CARDIA & FUNDUS	Patient adopts a supine position. Magnet held successively at: • Right pectoral region • Left pectoral region • Epigastrium • Left upper quadrant If inadequate views obtained, repeat the above in the left lateral position.
POSITION 3: GASTRIC BODY	Patient remains in a supine position. Magnet held successively at: • Right upper quadrant • Left upper quadrant • Xiphisternum • Umbilicus
POSITION 4: ANTRUM & PYLORUS	Patient remains in a supine position Magnet held successively at: • Epigastrium • Right of the umbilicus • Right upper quadrant • Right pectoral region If inadequate views obtained, repeat in the right lateral position. If inadequate views obtained, hold the magnet over the upper back, to the right of the thoracic and lumbar spine.