THE UNIVERSITY OF HULL

ASSESSMENT AND IMPROVEMENT OF ACCESS AND QUALITY IN LOWER GASTROINTESTINAL ENDOSCOPY

**Being a thesis submitted for the degree of MD
In the University of Hull**

By

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SYNOPSIS

Quality assurance in lower gastrointestinal endoscopy (LGE) is gaining increasing attention. Simultaneously, there is an increasing demand for LGE. The overall aims of this thesis were to identify methods of improving both the availability and the technical quality of LGE in the National Health Service, United Kingdom.

This thesis attempts to bring some of these concepts together in a series of studies as listed below:

Study 1: The aim of this study was to assess patient satisfaction with LGE, and to determine factors that affect patient satisfaction. A new patient satisfaction questionnaire was developed and internally validated. The most important factors affecting patient satisfaction in this study were the technical skills of the endoscopist and the degree of discomfort/ pain experienced by the patient. This study has also shown that there are no differences between medical, nurse and non-medical endoscopists in terms of patient satisfaction with lower gastrointestinal endoscopy. Based on this understanding of factors affecting patient satisfaction with LGE, we performed the following studies (2, 3, 4 and 5) to determine methods of assessing technical quality of LGE and the best sedative regimen to ensure higher patient satisfaction.

Studies 2 and 3: The aims of these studies were to assess the technique of endoscopic clipping with follow up abdominal x-ray for objective validation of completion in colonoscopy and flexible sigmoidoscopy. Both studies have shown that this technique is useful not only for assessment of completion but also for validation of pathology miss rates in LGE. This is a proof of concept study and further validation against current standards would be required.

<u>Studies 4 and 5</u>: These two randomised controlled trials were performed to determine the best sedative/analgesic regimen for colonoscopy. The first study has shown that Entonox is associated with better pain relief, faster recovery of psychomotor function and higher patient satisfaction, as compared to conventional intravenous sedation. The second study has shown that there is no difference between Entonox and Propofol sedation in terms of pain relief, recovery of function, and time to discharge and patient satisfaction. However, propofol sedation is more resource intensive and makes patient manoeuvring more difficult. A further conclusion from the subset analysis of these studies is that there is no difference between doctors, nurses and non-medical colonoscopists in terms of patient satisfaction, pain relief, time for procedure or discharge and recovery of function.

<u>Study 6:</u> The aims of this study were to develop, train and validate artificial neural network (ANN) algorithms capable of accurately identifying individual patients attending routine colorectal clinics likely to have a positive diagnosis (cancer, polyp, or colitis) necessitating a lower gastrointestinal endoscopy. This study has shown that artificial neural networks offer the possibility of personal prediction of outcome for individual patients presenting in clinics with colorectal symptoms, making it possible to make more appropriate requests for lower gastrointestinal endoscopy.

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Abbreviations	
ANN	Artificial neural network(s)
ASA	American Society of Anaesthesiologists
AUC	Area Under the Curve
B.Sc	Bachelor of Science
BOC	Brins Oxygen Company
CCD	Charge Coupled Device
CT	Computerised tomography
EMI	Electromagnetic Imaging
ERCP	Endoscopic retrograde cholangiopancreatography
EudraCT	European Clinical Trial Database
FS	Flexible sigmoidoscopy
FOBt	Faecal Occult Blood test
GI Endoscopy	Gastrointestinal endoscopy
HAD	Hospital Anxiety and Depression
ISRCTN	International Standardised Randomised Controlled Trials Number
IV	Intravenous
ICH-GCP	International Committee for Harmonisation-Good Clinical Practice
JAG	Joint Advisory Group for endoscopy
L	Litre(s)
LGE	Lower Gastrointestinal Endoscopy

m-GHAA	Modified- Group Health Association of America
ml	millilitres
mg	milligrammes
mcg	microgrammes
MHRA	Medicines and Health Regulatory Authority
ME	Medical Endoscopists
MOAAS	Modified Observer's assessment of Alertness/sedation scale
NME	Non Medical Endoscopist
NE	Nurse Endoscopist
NHS	National Health Service
PCS	Patient controlled sedation
R&D	Research and Development
RCT	Randomised Controlled Trial
SPSS®	Statistical Package for Social Sciences
TCI	Target controlled infusion
USA	United States of America
UK	United Kingdom
VAS	Visual analogue scale
AUC	Area under the curve

DECLARATION

The planning, experimental design, execution of studies and technical work involved in this thesis were all performed by the candidate unless otherwise stated.

No part of this thesis has been submitted in support of an application for any degree or qualification in any other institute of learning.

AWARDS, PUBLICATIONS, AND PRESENTATIONS IN SUPPORT OF THIS

THESIS

Awards

1. John Farndon Prize (2010) for the best paper in the British Journal of Surgery for the Entonox paper.
2. Cardinal Health Prize (2007) for Best Oral Presentation at the Annual Meeting of the Society for Intravenous Anaesthesia, Cambridge, 2007.
3. Best Poster Prize at the United European Gastroenterology Forum, Copenhagen, 2005
4. Travelling Fellowship by the Coloproctology Section, Royal Society of Medicine, London, 2006
5. Travelling Fellowship by the United European Gastroenterology Forum, Copenhagen, 2006
6. Nominated for the Moynihan Prize at the Annual Meeting of the Association of Surgeons of Great Britain and Ireland, Edinburgh, 2006

Publications:

Papers:

1. S Maslekar, M Hughes, A Gardiner, B Culbert, JRT Monson, GS Duthie
   Randomised controlled trial of sedation for colonoscopy: Entonox versus Midazolam/ Fentanyl
   British Journal of Surgery 96 (4); 361-368

2. S Maslekar, P Balaji, M Hughes, A Gardiner, B Culbert, JRT Monson, GS Duthie
   Randomised controlled trial of patient controlled sedation for colonoscopy: Entonox versus modified patient maintained target controlled Propofol
   Colorectal Disease- *In Press*

3. S Maslekar, A Gardiner, JRT Monson, GS Duthie. Quality Assurance in colonoscopy: Role of endoscopic clips.
   Colorectal Disease –*DOI 10.1111/j.1463-1318.2009.01874x*

4. S Maslekar, A Gardiner, JRT Monson, GS Duthie. Quality Assurance in Flexible Sigmoidoscopy: Medical and non-medical endoscopists.
   Surgical Endoscopy - *In Press*

5. S Maslekar, A Gardiner, JRT Monson, GS Duthie. Patient satisfaction with lower gastrointestinal endoscopy: doctors, nurses and non-medical endoscopists.
   Colorectal Disease -*In Press*

6 S Maslekar, A Gardiner, JRT Monson, GS Duthie. Artificial Neural Networks to predict the presence of significant pathology in patients presenting to routine colorectal clinics. Colorectal Disease - *In Press*

Presentations:

1. Use of artificial neural networks to predict need for lower gastrointestinal endoscopy in outpatient clinics
   Maslekar S, Gardiner A, Duthie GS
   Moynihan Prize Paper at the Annual Meeting of the Association of Surgeons of Great Britain and Ireland, 3rd-5th May, 2006

2. Entonox for colonoscopy: results from a randomised controlled trial
   Maslekar S, Hughes M, Skinn E, Gardiner A, Culbert B, Duthie GS
   Six of the Best Prize Paper at the Annual Meeting of the Association of Surgeons Of Great Britain and Ireland, 3rd-5th May, 2006
   March 20-23, 2006

3. Non-medical endoscopists are safe and effective: results from randomised Controlled trial
   Maslekar S, Hughes M, Skinn E, Gardiner A, Culbert B, Duthie GS
   Presentation at British Society of Gastroenterology Meeting, Birmingham, March 20-23, 2006

4. Randomised Controlled Trial of sedation for colonoscopy: Inhaled Entonox is better than intravenous sedation
   Maslekar S, Hughes M, Skinn E, Gardiner A, Duthie GS
   Presented at the Society of Academic Surgery Annual Conference, Edinburgh, January 11-13, 2006

5. Patient satisfaction with lower gastrointestinal endoscopy: comparison between doctors, nurses and non-medical endoscopists
   S Maslekar, A Gardiner, GS Duthie
   Annual Meeting of American Society of Colon and Rectal Surgeons, Seattle, June, 3-7, 2006

6. Quality assurance in colonoscopy
   Maslekar S, Ramachadran M, Avery G, Duthie GS
   World Congress of Gastroenterology, Montreal, Canada, September 11-14, 2005

7. Randomised controlled trial of patient controlled sedation for colonoscopy: Entonox versus patient maintained target controlled propofol
   S Maslekar, P Balaji, JE Hartley, B Culbert, GS Duthie
   Digestive Diseases Week, Washington, May 19-24, 2007

1.1 Lower Gastrointestinal Endoscopy: an introduction

1.1.1 History of endoscopy development

The original gastrointestinal endoscopes were hollow reeds or bamboo canes that were illuminated by candles[1]. These developments have been attributed to both the ancient Greeks and the Egyptians[1]. The precise origin of endoscopy remains in doubt, although Hippocrates was responsible for the first proctoscopy recorded in around 460-370 BC[1, 2].

Although tubes of different types were subsequently designed, several hundred years passed before they could be made practical and useful. The next major advancements were the development of a rigid sigmoidoscope in 1795 by Philip Bozzini[3] and the development of the first rigid oesophagoscope in 1868[4] by Kussmaul. These instruments were extremely primitive in comparison with those in use today and only allowed a limited examination. The early pioneers faced two obvious albeit formidable problems: the gut is not straight and the colon is dark[5]. Although directly and immediately unrecognised at the time, the illumination problem was solved around 1878 by Thomas Alva Edison, who was able to make bulbs small enough to use inside the endoscope. This was followed by further sporadic episodes of open tube endoscopy procedures. For example, Killian (1898) used an open tube with illumination and a head mirror with topical anaesthesia[6]. The next crucial step was the development of Nitze optical system, which was incorporated into the first cystoscope[7]. However, the Nitze optical system suffered from serious limitations.

In 1954, the problem of illuminating the dark interiors of the gastrointestinal tract was solved by H.H. Hopkins with the development of a new optical system using

flexible fibres in 1954[8]. The first set of instruments based on this system were released in 1960s leading to a new epoch in rigid instrumentation[9]. This was the first of the two key inventions that led to dramatic improvements in the quality of endoscopy, leading us to the advanced endoscopes of the modern era. The only limitation remaining was the inability to negotiate the tortuosity of the gastrointestinal tract satisfactorily. The first approach to this problem was the development of an instrument with articulated lenses and prisms, which was incorporated into the first semi-flexible gastroscope by Wolf and Schindler[5].

The most notable development in the history of endoscopy then occurred in 1958: the flexible fibreoptic endoscope of Larry Curtiss, then a graduate student in physics, and Basil Hirschowitz, a trainee in gastroenterology[10]. What made this instrument possible was the availability of highly transparent optical quality glass. Over the next 30 years, the fibrescope evolved to a level of technical sophistication that seemed insurmountable.

However, obsolescence was assured subsequently with the invention of the charge coupled device (CCD) in 1969. Ten years later, this technology was incorporated into an endoscope[11]. Because the CCD produced an electronic image, endoscopy suddenly had a wider audience- a television audience. The construction of the endoscope initially was such that only the endoscopist saw mucosal images, and trainees could only view the image by adding a teaching aid to the endoscope. However, this resulted in a poor view of the mucosa for both the trainer and the trainee, and a significant increase in the weight of the endoscope. The development of video endoscopy by Welch-Allyn in 1983 using CCD produced high resolution images that ensured the territory previously the domain of the endoscopist could be

seen by trainees, assistants, and observers[12]. Moreover, the image was digital, and hence instantaneously an interface between the endoscope and the computer was established.

From 1968 to 1990 there was an explosion of technical achievements that transformed the practice of gastroenterology. The potential of the biopsy channel was exploited rapidly, and numerous therapeutic procedures followed – including the first snare polypectomy by Niwa in 1970[12]. This remarkable 22 year period from 1968 to 1990 was so formative that its been described as the golden era of gastrointestinal endoscopy[5].

For the purposes of this thesis, we define lower gastrointestinal endoscopy (LGE) as either colonoscopy or flexible sigmoidoscopy.

1.1.2 Indications

1.1.2.1 Indications for colonoscopy

Colonoscopy is now considered to be the gold standard exam and is superior to either CT colonography or double contrast enema alone[13]. Colonoscopy achieves more than barium enema or virtual colonography because of greater accuracy and its biopsy and therapeutic capabilities. Table 1.1 below shows the principal indications for colonoscopy.

Table 1.1 Colonoscopy: Indications and yield[13]

High Yield Indications	Low Yield Indications
Anaemia/bleeding/occult blood loss	Constipation
Persistent diarrhoea	Flatulence
Inflammatory disease assessment	Altered bowel habit
Genetic cancer risk	Pain
Abnormality on imaging	

1.1.2.2 Indications for flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) is preferred for many reasons. The foremost being the fact that it can be performed as an outpatient procedure without any sedation in a short period of time. In fact it can become part of the patients first outpatient visit, where after being assessed by the physician, the patient can go on to have FS at the same setting. Though some of the indications for FS can be similar to colonoscopy, it is important to remember that FS is limited to the left colon only. Hence, FS is not a suitable substitute for colonoscopy or barium enema.

There is increasing interest in the adoption of FS as the sole screening test for colorectal cancer. This comes from the evidence that nearly 70% of all colorectal cancers occur in the left colon. Atkin et al in a large multicentre randomised controlled trial have confirmed this and have suggested that FS should replace Faecal Occult blood testing as the screening tool. Table 1.2 shows the indications for flexible sigmoidoscopy.

Table 1.2 **Indications for flexible sigmoidoscopy**

Diagnostic	Therapeutic
Assessment of anal canal type bleeding	Therapeutic procedures such as endoluminal stenting, balloon
Assessment of diverticular disease when the diagnosis is in doubt	dilatation for strictures
Colorectal cancer screening	Decompression of sigmoid volvulus or pseudo-obstruction
Preoperative evaluation prior to anorectal surgery	Treatment of radiation proctitis
Surveillance of previously diagnosed left colonic cancer or polyp	Removal of foreign bodies
	Treatment of bleeding from left colon

1.1.3 Contraindications for colonoscopy and flexible sigmoidoscopy

Currently, there are remarkably few contraindications for colonoscopy (table 1.3).
The contraindications can be divided into absolute and relative contraindications.
Relative contraindications include situations in which risk is substantially increased.
In these conditions, it may be acceptable to perform the colonoscopy only if the
information thereby obtained is extremely vital for the ultimate outcome.

Table 1.3 Contraindications to colonoscopy and flexible sigmoidoscopy[14]

Absolute	Relative
Competent patients refusing consent	Acute diverticulitis (diagnosis established)
Known perforation of bowel	Haemodynamic instability
Fulminant colitis	Recent myocardial infarction (within 3 months) and Pulmonary embolism
Toxic megacolon	
Known colonic obstruction	
Acute peritonitis	Immediate postoperative phase
	Very large or symptomatic Abdominal aortic aneurysm
	Pregnancy
	Poor bowel preparation
	Lack of informed consent

There is no absolute contraindication to colonoscopy or FS in pregnancy[14], but is
best avoided in patients with a history of miscarriage, on commonsense grounds.
The contraindications for flexible sigmoidoscopy are similar to colonoscopy, and
hence discussed together.

Furthermore, a potential concern for with either colonoscopy or flexible
sigmoidoscopy is the use of the endoscopes in infected patients and hence the

possibility of subsequent transmission of infection to the next patient. However, if

universal precautions are adhered to and all recommended techniques used for

decontamination, then the risk of transmission is virtually negligible. Surprisingly,

very little data exists in this regard. In 1993 one report suggested that the reported

frequency was 1 in 1.8 million procedures[15]. There is also the potential for

transmission of infective particles with exceptionally long incubation periods[15]

(vCJD, for example). The British Society of Gastroenterology has published clear

guidelines on the decontamination of Equipment for Gastrointestinal Endoscopy[16]

and these must be adhered to all times for prevention of endoscopy related

transmission to infection. Hence, gastrointestinal infection is not necessarily a

contra-indication for either colonoscopy or FS.

Another concern with colonoscopy (and to lesser extent with flexible

sigmoidoscopy) is the occurrence of transient bacteraemia. There is no clear

evidence whether this can lead to clinically significant conditions like septicaemia,

and endocarditis. The British Society of Gastroenterology (BSG) has published

guidelines for antibiotic prophylaxis in patients undergoing gastrointestinal

endoscopy[17], which incorporate the National Institute of Clinical Excellence (NICE)

guidelines as well[18]. In general, antibiotic prophylaxis is no longer recommended for

the prevention of infective endocarditis in patients with cardiac risk factors who

undergo endoscopy. The arguments against routine prophylaxis include questionable

significance of bacteraemia from endoscopy, equivocal evidence regarding the role

of prophylactic antibiotics in prevention of endocarditis, risks of adverse effects,

evolving problems of resistant bacteria (e.g. MRSA) and practical difficulties in

patients with penicillin sensitivity. With regards to FS, there is no role for prophylactic antibiotics due to the limited nature of the procedure.

1.1.4 Complications of LGE

1.1.4.1 Complications of colonoscopy

Colonoscopy is generally a safe procedure and, fortunately, complications are rare. The most serious risk with colonoscopy is perforation of the colon. The quoted rate is around 1:500 to 1:1000, depending on whether it is a diagnostic or therapeutic colonoscopy[19]. Perforation usually occurs due to mechanical or pneumatic pressure or from biopsy. Some studies have shown that it is more common in patients who are either over-sedated or under general anaesthesia or in the presence of poor bowel preparation, or with acute bleeding[13]. The site of perforation is usually either areas of weakness of the colon wall (e.g., diverticulae, transmural inflammation) or distal to obstructing points[20] (e.g., neoplasm, stricture). Pneumatic perforation of the colon or ileum results from distension by insufflated air. Perforation secondary to polypectomy is usually due to thermal injury. Large perforations are rare and abdominal viscera become visible immediately. However, with smaller perforations, a high index of clinical suspicion is essential. Clinically perforation should be suspected if patients have disproportionate pain or marked and persistent abdominal symptoms. Delayed perforations are associated with minimal features like fever, raised white cell count or persisting abdominal pain. The management depends on the size of perforation, time interval post colonoscopy, degree of contamination, clinical features (peritonitis or not) and general health of the patient. In the absence of gross contamination, conservative treatment with intravenous antibiotics and close observation can be considered for most patients. Surgical intervention may

needed if there is gross contamination, peritonitis, perforation of tumours, or if conservative treatment fails.

The next common complication is bleeding which complicates approximately 1 of every 1000 colonoscopic procedures[13]. Most cases resolve spontaneously. Following polypectomy, bleeding may occur immediately, but, in 30-50% of cases[13], it can be delayed for 2-7 days until the eschar sloughs. It is common for such bleeding to stop spontaneously. Treatment options include transfusions, endoscopic therapy, angiography, and, rarely, laparotomy.

Documented instances of transmission of infection from one patient to another or to endoscopic personnel with either a colonoscopy or flexible sigmoidoscopy are extremely rare. Bacteria reported to have spread include *Salmonella* species, *Pseudomonas* species, and *Escherichia coli*[13]. To date, no reports of transmission of HIV have been made. Disinfection of scopes and accessories is the main preventive measure. Universal precautions against contact with patient's blood or bodily fluids should always be employed[13].

The combination of pain, peritoneal irritation, leukocytosis, and fever after colonoscopy may represent a post-polypectomy burn injury. This condition is called the post-polypectomy syndrome or post-polypectomy electro-coagulation syndrome[21]. Post-polypectomy syndrome was reported in six patients out of 16,318 colonoscopies performed between 1994 and 2002 in a large integrated health system[22]. Earlier reports estimated it to occur in 0.5 to 1.2 percent of patients undergoing polypectomy[21, 22]. Post-polypectomy syndrome develops when electrical current applied during polypectomy extends past the mucosa into the muscularis

propria and serosa, resulting in a transmural burn without perforation. Serosal irritation leads to a localised inflammatory response that manifests clinically as a localised peritonitis. Post-polypectomy syndrome occurs most often after the removal of large (>2 cm) sessile polyps, which usually require large amounts and long duration of thermal energy [23]. Inadvertent capture of a piece of normal adjacent mucosa within the snare loop during snare placement over a polyp can result in this condition when cautery transects both portions of tissue (mucosa and polyp). Plain abdominal radiographs are not useful in this setting. CT scan of the abdomen may reveal focal mural thickening and pericolic fluid at the site of recent polypectomy as well as soft-tissue stranding of the pericolic fat, without any evidence of pneumoperitoneum or large hematoma[24, 25]. Conservative management is generally successful and includes hospitalisation, intravenous fluids with or without antibiotics with good outcomes.

Although a truly uncommon complication, the presumed mechanisms of splenic rupture during colonoscopy include direct trauma to the spleen, marked angulation of the splenic flexure, excessive splenocolic ligament traction, and decrease in the relative mobility between the spleen and the colon[24]. Haemodynamic instability, clinical features of acute abdomen, leukocytosis, and/or acute anaemia in patients with persistent abdominal pain after colonoscopy demand immediate attention. Intestinal perforation or bleeding must first be excluded, after which CT scans can be used for further evaluation[25]. Splenic rupture is rare with flexible sigmoidoscopy, primarily because generally no attempts are made to pass the endoscope beyond the splenic flexure.

Sedatives used during colonoscopy may cause complications from allergic reactions or, more importantly, from doses that may be excessive for certain individuals and lead to respiratory depression. Serious events may complicate up to 0.5% of procedures[13]. More than 50% of deaths associated with endoscopy are related to cardiopulmonary events[26]. Adverse effects of benzodiazepines, other than respiratory depression, include anxiety and occasional injection-site reaction; the latter is more frequent with diazepam than with midazolam[27]. Other adverse effects of narcotics include nausea, vomiting, and hypotension[27]. Naloxone and flumazenil readily reverse the adverse effects of narcotics and benzodiazepines, respectively, within minutes. The proper technique and sequence of administration of these drugs, together with continuous monitoring of the sedated patient, can help minimize complications.

1.1.4.2. *Complications of Flexible sigmoidoscopy*

Potential complications of FS include perforation, bleeding, transmission of infection, colitis /diverticulitis and rarer complications like post-polypectomy syndrome. An expert review initially identified a serious complication rate of 1 in 10,000 whereas other series have shown rates of 0 to 4 per 1000. For screening FS, the rate of complications was shown to be around 21 per 100,000 procedures in a large study involving more than 100,000 participants.

Perforations are rarer with flexible sigmoidoscopy as compared to colonoscopy. The quoted rate for FS is around less than 1:10000 procedures. The large study mentioned above found a perforation rate of less than 1in 50,000 or even 1 in 100000. these rates are significantly lesser than colonoscopy perforation rates. The

mechanism of injury remains the same as in colonoscopy. The main difference between the two is that the bowel is generally unprepared in FS and hence the higher theoretical possibility of contamination. In practice, perforations are rare and management remains the same as in colonoscopy perforation.

Bleeding following FS has an incidence of <1:5000 procedures. The aetiology and management remains the same. Most bleeds settle spontaneously; however, it is usual to repeat the flexible sigmoidoscopy to ensure that the polyp base is not bleeding further. Therapeutic manoeuvres like endoscopic clipping, thermal probe or argon can be useful to arrest bleeding if it persists. Surgery is rarely indicated. Transmission of infection with FS is rare; the incidence and findings are the same as for colonoscopy. Universal precautions as suggested by the British Society of Gastroenterology should be adhered to at all times to minimise such complications. Colitis following FS has been reported but only in the form of case reports. The suggested mechanism is the contact of colonic mucosa with chemicals used for washing of endoscopes. Diverticulitis following FS is a recognised complication; but the incidence is very low and not established. Small, contained perforation of a diverticulum is the usual mechanism involved. Treatment generally remains conservative; gross contamination is usually the result of large perforation and should be dealt with accordingly.

Sedation is generally not administered during FS and hence sedation-related complications are rare. Even if sedation is required for FS, smaller doses are given, thereby minimising the risks.

1.2 Assessment of quality of LGE

1.2.1 Technical Quality of Lower gastrointestinal endoscopy (LGE)

LGE is the preferred method to evaluate the colon in most adult patients with bowel symptoms, iron deficiency anaemia, abnormal radiological studies of the colon, positive colorectal cancer screening tests, surveillance in inflammatory bowel disease and those with suspected masses. Although LGE has been performed for more than 30 years, there has been a recent surge of interest in the evaluation of its quality. This stems from the fact that there is growing evidence of variation in the quality of LGE. Rex et al first showed that the sensitivity of colonoscopy for cancer was 97% among gastroenterologists but only 87% among non-gastroenterologists in Indiana (USA)[28]. In a tandem colonoscopy study[29], in Indiana, involving 26 endoscopists, the range of miss rates for adenomas among different endoscopists ranged from 17% to 48%. However, the study with the biggest impact, especially in the United Kingdom, has been the study by Bowles et al[30], who showed that the average caecal intubation across a large region in the UK was only around 57%. This paper highlighted several variations in quality of colonoscopy and has been the trigger for improvements in quality of colonoscopy.

Not all the variations in quality of LGE impact outcomes. For instance, missing tiny hyperplastic polyps may not be important. On the other hand, some of the variations produce outcomes that are clearly adverse. Low completion rates result in both missed pathology as well as increased costs due to additional tests. Therefore, the

next obvious step is to perform continuous quality assessments and aim for improvements.

There are multiple indicators of quality of LGE including completion, pathology miss rates/ adenoma detection rates and others. The effectiveness of LGE depends on adequate visualization of the colon, diligence in examining this mucosa and interpreting the findings and patient acceptance of the procedure (patient satisfaction). In other words, the three key technical quality indicators of LGE include completion rates, pathology miss rates and patient satisfaction rates, though there are other factors as well.

1.2.1.1 Assessment of completion of colonoscopy

The aim of colonoscopy is to intubate the caecum and also ensure that the whole of the colon is carefully seen. Techniques of caecal intubation are described elsewhere[31] and are beyond the scope of this review. Caecal intubation is routinely documented by naming the identified caecal landmarks, which include the ileocaecal valve, tri-radiate fold and the appendiceal orifice. In cases of uncertainty, visualisation of the ileum may be necessary. However, despite using the technique of identifying all the three landmarks, the false positive rate is around 10-20%[32]. Tabibian and colleagues [32] using endoscopically placed clips showed that in 20% of the cases where the endoscopist believed that the caecum had been reached and used the clip for confirmation, the caecum had not been reached. In another study, using three-dimensional electromagnetic imaging, Adam and colleagues[33] showed that in

8 of 85 cases, where the endoscopist believed that a complete colonoscopy had been performed, the endoscope was shown not to have reached the caecum.

How do we objectively assess completion of colonoscopy to the caecum?

1.2.1.2 Objective assessment of completion of colonoscopy

Documentation of caecal intubation is essential for ascertaining completion and continuous quality improvement. This documentation needs to be objective and easily retrievable at a later date, if completion needs to be verified. Table 1.4 shows the different available options for objective documentation of completion of colonoscopy.

Photography of the caecum has been recommended by for documentation of completion and is perhaps the simplest available technique. However, still photography of the caecum may not be convincing in all cases because caecal anatomy can be variable and the quality of photographs can be poor. Furthermore, it may be difficult to interpret these photographs of caecum at a later date, making it impossible to confirm completion. A previous retrospective study[34] of consecutive caecal photographs taken by 6 different endoscopists demonstrated several relevant findings regarding caecal photography. First, there were marked differences between multiple expert endoscopists reviewing the same caecal photographs as to how convinced they were that the photographs represented the caecum. Second, the success of individual endoscopists in obtaining convincing caecal photographs was variable. However, these differences were not as great as the disparities between reviewers examining the same photographs. Finally, the study demonstrated that still

photographs of the caecum are only partially successful in documenting caecal intubation. However, caecal photography remains the most commonly used technique, primarily due to the ease of use, availability and a lack of a useful alternative.

The other established method of documenting completion in colonoscopy is the use of caecal videotaping. Caecal videotaping can be highly convincing as a method of documentation of caecal intubation. The advantages include low cost and relatively easy availability of the technology. On the other hand, videotaping seems impractical and tedious both in terms of recording and saving as well in retrieving the segments when required.

Routine ileoscopy/ intubation of the terminal ileum with either biopsy or photography has also been proposed as a method of objectively documenting completion in colonoscopy. However, there are concerns regarding a routine biopsy of the terminal ileum (TI) for the sole purpose of completion rate documentation. There is a theoretical risk of iatrogenic prion transmission with surgical and endoscopic instrumentation. In particular, variant Creutzfeldt-Jakob disease (vCJD) is resistant to conventional sterilization techniques and also has been shown to accumulate at a high concentration in the lymphoid-rich TI of patients infected with vCJD[35-37]. There are also considerable costs involved in obtaining, preparing, and analysing tissue samples, and 1 study estimated TI biopsy specimen–processing costs in the region of $430 (£240)[38]. This financial burden is unlikely to be offset by any additional diagnostic information generated from histologic assessment of TI biopsy specimens, because the diagnostic yield from routinely acquired TI biopsy

specimens is low. Data from prospective and observation studies suggest that the detection rate of significant pathology from routine TI biopsy in unselected patients is between 2% and 7%[39]. On the other hand, photographs of the terminal ileum are sometimes convincing if they show villi, circular valvulae conniventes, and lymphoid hyperplasia, but they are less likely to be effective compared with the above-mentioned photographs. Recently, Baraza et al[40] have shown that terminal ileal imaging is not a reliable mode of documenting complete colonoscopy. The overall accuracy of positive identification was only 53.4%. Though water insufflation and chromoscopy improved the accuracy to 68.3% and 63% respectively, the accuracy is still limited, and hence neither can be recommended for replacement of the use of the caecal landmarks.

Other techniques of confirmation of caecal intubation include transillumination of light through the abdominal wall and ballottement of the abdominal wall and identification of confluence of taeniae coli (Crow's foot or Mercedes Sign). The latter are extremely unreliable and are only suggestive of caecal intubation. Cirocco et al[41] showed that transillumination can be a very unreliable indicator of the colonoscope position, as the light seen in the right iliac fossa may be emitted from a colonoscope tip positioned in the sigmoid or transverse colon. These techniques are now considered obsolete and unreliable. In conclusion, none of the available techniques is practical for objectively documenting completion of colonoscopy. However, caecal intubation continues to be crucial for maximising the sensitivity of colonoscopy and convincing documentation of caecal intubation would provide a

way to monitor the quality of colonoscopy for the purposes of continuous quality improvement.

Table 1.4 Methods of validating completion in colonoscopy

Technique	Accuracy/ Sensitivity	Advantages	Disadvantages
Caecal photography	51.4%[42]	Ease of use Current standard Easy to store	Low sensitivity and specificity Movement artefacts Difficult to interpret
Ileal biopsy	High	Very high accuracy	Needs ileal intubation Risk of vCJD transmission Increased workload for pathology Low yield of ileal pathology (7%)
Ileal photography (IP)	53.4%[40] (accuracy)	Permanent record of completion	Needs ileal intubation Difficult technique to learn Increased time
Underwater IP	68.3.%[40] (Accuracy)	Increased accuracy	Cumbersome Needs ileal intubation
IP with Chromoscopy	63% (accuracy)	Increased accuracy	Cumbersome Increased procedure time Needs ileal intubation
Caecal videotaping	-	Reliable Consistently convincing	Impractical Storage problems Cannot be accessed immediately
Scope guide			New technology Not yet available readily No proven results

			New technology
Quadrant coverage histogram			Not yet available readily
			No proven results

1.2.1.3 Use of endoscopic clips and follow-up abdominal x-ray for documentation of caecal intubation/ completion of colonoscopy

Tabibian et al[32] described the technique of applying endoscopic clips with follow on abdominal x-ray for objective documentation of completion. This study demonstrated that endoscopists were inaccurate in 34% of cases in terms of confirmation of caecal intubation. However, this technique has not been subsequently used or assessed further. As part of this technique, the endoscopists performing colonoscopy apply an endoscopic clip on the most proximal part of colon reached. This should ideally be the caecum in colonoscopy or the descending colon in flexible sigmoidoscopy. The endoscopist then documents his assessment of position in the colon. Subsequently, all patients undergo an x-ray of the abdomen whilst there is still air in the colon. A review of such an x-ray would reveal the exact location of the clip and hence the most proximal part of the colon reached with the endoscope. This can confirm completion in either flexible sigmoidoscopy or colonoscopy.

Endoscopic clips are commonly available, easy to use and are cheap. They tend to fall off in 2 weeks, and their safety record is excellent[43]. Currently, endoscopic clips have a number of uses and indications (table1.5).

Table 1.5 Indications for endoscopic clip therapy in GI disorders[44]

A) Arrest of GI bleeding from various lesionsa
      i. Peptic ulcer
      ii. Dieulafoy's lesion
      iii. Mallory-Weiss tear
      iv. Diverticular bleeding from duodenum
      v. Diverticular bleeding from colon
      vi. Post-polypectomy bleeding
      vii. Focal bleeding in ulcerative colitis

B) Secure tubes, catheters, and stents to the GI wall
      i. Jejunal feeding tube
      ii. Colon manometry catheter
      iii. Oesophageal metal stent

C) Close perforations and fistulas of the GI tract
      i. Oesophagus, stomach, duodenum, and colon after
         endoscopic therapy
      ii. Seal anastomotic leaks and fistulas after
         surgery

D) Cut the blood supply of a polyp
      i. Diminish the size of polyp to relieve gastric
         outlet obstruction
      ii. Before polypectomy of a giant polyp
         Clip-assisted biliary cannulation

E) Direct therapy or identify an anatomic landmark
      i. Assist interventional radiologists in embolisation
         of a bleeding vessel
      ii. Aid radiation oncologists in focusing radiotherapy
         of cancer
      iii Help surgeons in deciding the extent of resection
      iv. Facilitate physiologists to identify oesophageal landmarks
         during the evaluation of oesophageal function

The current thesis aims to assess the feasibility of using this simple technique to

objectively document completion. Further description of our modification of

technique appears in chapter 4.

1.2.2 Pathology Miss Rates in colonoscopy

The fundamental goal of colonoscopy in most instances is the detection of neoplastic lesions. However, there continues to be a disparity between different endoscopists in terms of pathology detection. Data from two U.S. practice groups[45,29], have indicated large disparities between gastroenterologists in their rates of detection of both small and large adenomas. With regard to cancer detection, one study demonstrated miss rates of 3% for gastroenterologists versus 13% for non-gastroenterologists[28]. However, miss rates for cancer were 5% for one group of gastroenterologists compared with 1% for all other gastroenterologists studied[28, 46]. Currently, regular calculation of the polyp detection rate is considered to be the standard technique used to assess pathology miss/ detection rates and this is accepted by the Joint Advisory Group for Gastrointestinal endoscopy (JAG). However, this technique is not entirely flawless. It is based on an assumption that the procedure was complete. If the endoscopist is inaccurate in assessment of completion, obviously pathology may be missed in segments of bowel, which have not been visualised.

Is there any other method of assessing pathology miss rates? The use of endoscopic clips with follow-up x-ray has been described above for detection of completion of colonoscopy. However, when these patients are audited at around 2 years, delayed pathology miss rates can be detected. We have also looked at the role of the technique of endomucosal clipping and follow up x-ray with audit at 2 years to objectively document completion as well as pathology miss rates.

1.2.3 Technical quality of flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) is a useful test to assess the left colon. Incomplete examination is an unfortunate drawback of FS, commonly occurring as the internal landmarks are not constant and clear. Furthermore, there is variability in defining completion of FS. The JAG has defined completion of FS as insertion of the endoscope to descending colon, and this should be achieved in 90% of examinations. However, generally endoscopists aim to examine as much of the distal colon as possible based on the limits of FS endoscope length or to the limits of patient tolerance. Studies[47] have shown that anatomical factors, preparation quality or variations in patient tolerance and gender all may limit insertion depth of insertion or completion of FS. Olynyk found that FS were incomplete in up to one-third of patients[48]. Painter et al[49] found that in up to a quarter of patients the descending colon was not intubated. Stewart at al[50] suggested a 25% incomplete examination rate and technical difficulty in up to a third of cases. Unlike colonoscopy, there are no constant landmarks in the left colon. Hence, documentation of completion of FS is difficult and unreliable. Furthermore, localising the depth of FS insertion by anatomical segment is also unreliable. The rectum is usually traversed by the distal 10-20 cm of the FS endoscope. Adam et al[33] have used a novel electromagnetic imaging (EMI) device to assess the position of the scope in the left colon. They showed that the endoscopists' assessment of position was correct in only 47 cases (50%), with over-estimation of length in 25% and underestimation in the remainder. EMI also showed that the splenic flexure was not reached in around 60% of cases.

However, the use of such an EMI device has not become popular, due to the lack of availability and time involved in using the same.

Lehman et al[51] used radio-opaque clips in the left colon and subsequent barium enema to document completion. This technique is very similar to the one described previously in the section under colonoscopy completion, with the exception of barium enema instead of plain abdominal x-ray. They showed that a 60cm examination reached the splenic flexure in only 33% of patients; 50-55 cm examination reached the sigmoid colon in most instances[51].

The technique of endomucosal clipping with follow up x-ray is a relatively simple and effective technique and can be adopted in all hospitals without the need for additional complex equipment or expertise.

1.2.4 Patient satisfaction with LGE

1.2.4.1 Introduction and definition of patient satisfaction

Patient satisfaction is an important aspect of quality assessment programmes in LGE. Interest in measuring satisfaction with healthcare has grown considerably in recent years and there is a large, diverse and expanding literature on the field. The term satisfaction itself comes from the Latin word "satis" meaning enough. However, it is generally agreed that patient satisfaction represents "a patients' cognitive or emotional evaluation of a health care providers' performance and is based on relevant aspects of the health care experience"[52, 53].

1.2.4.2 Why measure patient satisfaction?

Patient satisfaction is being increasingly measured for assessment of quality of healthcare. But is it important and if so, why?

It is obvious that satisfied patients are more likely to participate in their own treatment regime, and follow their schedules. Conversely, dissatisfied patients do not respond well and do not comply with interventions. Studies have shown that regular patient satisfaction assessments promote a useful mechanism of identifying areas that need improvement. It is therefore important to identify levels of satisfaction and factors affecting patient satisfaction, so that we could potentially work on them.

In countries like the United Kingdom, where the healthcare is delivered by the Government, the available resources remain finite, making it ever so important to identify patient perspectives and requirements, ensuring that the finances are utilised correctly. On the other hand, in countries like the USA, it is clear that customer satisfaction is the key to financial success and in having a bigger practice size and lesser litigation.

1.2.4.3 Problems with measuring patient satisfaction

Several problems arise when attempts are made to measure satisfaction. Broadly, this is either related to the inherent patient bias or problems with the actual instruments used in the measurement of satisfaction. Patients' marking of the satisfaction questionnaire can be tempered by their own expectations rather than the actual quality of care. Further, expressed satisfaction can actually be a reflection of patients' health outcomes and not necessarily level of care provided. A patient who has had a good outcome tends to rate the health service or provider much higher.

1.2.4.4 Methods of measuring patient satisfaction

There are many different methods of measuring and assessing patient's satisfaction with healthcare and several surveys have been published. Several factors affect the measurement method chosen and these include available resources and time, reasons for the study and the setting.

Previous studies[53] have demonstrated that there are broadly two different techniques of measuring patient satisfaction- survey methods and qualitative methods. Survey methods include either questionnaire administration or interviews. Questionnaires may be distributed by hand or at a computer terminal or be mailed. Personal interviews may be face to face, or by telephone. The advantages of questionnaires are that patients tend to be uninhibited in their responses, they are cheaper and there is no interviewer bias. However, the response rate can be low, and this in itself can introduce bias and it also disadvantages people with poor literacy skills.

A good satisfaction study should aim to minimise these biases and problems, thus making it more relevant and robust.

1.2.4.5 Need for measuring satisfaction with LGE

The satisfaction of patients with endoscopy is currently considered to be a key indicator of the quality of service provided and this is reflected in the fact that the Global rating scale (GRS) includes quality of patient experience or satisfaction as one of the important dimensions. GRS is currently the standard of practice in the UK endoscopy practice for the assessment of quality of endoscopy services.

Patient satisfaction will continue to remain an important outcome measure for GI endoscopy as screening initiatives intensify. With regard to colorectal cancer screening, to ensure that a substantial proportion of the eligible population is

compliant it will be necessary to focus on providing a satisfactory endoscopic experience. Moreover, in today's world, it has become increasingly important to establish the cost-effectiveness of various procedures. The patient's opinion is important in this process because expert views about procedures can be quite significantly different from those of the patients. Therefore, awareness of patients' opinion is crucial to improve endoscopy services.

Lin et al[54] have shown that a well-designed and implemented patient satisfaction system can help establish performance standards, improve risk management, increase accountability of endoscopy staff and ultimately improve quality of care. Satisfied patients are more likely to continue use endoscopy services and as we mentioned before, it is expected to increase compliance with both screening programmes and follow-up programmes for cancers and polyps.

Currently, there is no information on the factors associated with patient satisfaction, though various studies have concluded that waiting times, adequacy of explanation, sex of the patient and previous pelvic surgery are important factors[52].

Moreover, due to shortage of endoscopists, there has been an introduction of non-medical endoscopists (both nurse and non-medical non-nurse endoscopists). However, there has been no study to assess if patient satisfaction with the three different types of endoscopists (doctors, nurses and non-medical) is different. Non-medical endoscopy is discussed in detail in section 1.4.

1.3 Availability of LGE

1.3.1 Increasing demand for LGE

Limited availability of LGE has been considered as one of the biggest impediments for the successful introduction of 18-week pathway for colorectal diseases, primarily due to long waiting lists[55]. The National Bowel Cancer Screening programme in United Kingdom has further increased demand for LGE, putting enormous pressure on the provision of endoscopy services. It is estimated that around 60000 more colonoscopies [56] or one session per week (1 session=6 colonoscopies) for each district general hospital serving a population of 250 000 need to be performed annually to meet the demand arising from the screening programme. Price et al have shown that demand for colonoscopy activity increased by 31 per cent in Scotland and 21 per cent in England due to the investigation of faecal occult blood testing (FOBt) positive subjects [57]. There was a simultaneous increase in demand for non-screening colonoscopy as well. It was also predicted that a follow-up of patients with adenomas diagnosed due to screening programmes will result in a further increase of 28 per cent in the number of colonoscopies generated (over and above colonoscopy for FOBt-positive subjects), adding substantially to overall workload[57].

1.3.2 Potential solutions

What are the potential solutions for this increasing demand? We discuss three possible solutions in this work- increasing the number of endoscopists, decreasing demand for LGE and increasing turnover of colonoscopy by improving sedation.

At the outset, the simplest solution to the problem would be to increase the number of available endoscopists. However, it takes at least 15-16 years to train an individual to become a doctor and subsequently capable of performing colonoscopy. Hence, the Department of Health introduced the concept of nurse endoscopists, and, as a consequence, an increasing number of nurse endoscopists are being recruited in different hospitals across the United Kingdom. Despite this plan, there continues to be a high demand for endoscopists across the United Kingdom. Subsequently, the Department of Health then initiated a pilot project to train non-healthcare professionals to perform LGE[58]. These endoscopists will be called Non-Medical Endoscopists (NME) for the purposes of this thesis, though the term can generically be applied to all non-physician endoscopists. Further discussion follows in the next section.

Furthermore, studies in high-volume European endoscopy centres have shown that around 21% to 39% of LGE were inappropriate[59] or unnecessary. In other words, there is a potential to reduce the number of unnecessary LGEs, in which case the burden on colonoscopy services would be greatly decreased. However, the current clinical assessment techniques are not good enough to prevent these unnecessary or unhelpful procedures. In this thesis, we have, therefore, looked at the use of artificial neural networks to determine the presence of pathology in patients with colorectal symptoms, and the same has been discussed in section 1.6.

Currently, intravenous sedation using Midazolam with either Fentanyl or Pethidine is most commonly used for providing sedation for colonoscopy. However, NME are unable to prescribe and give intravenous sedation, and require a doctor or a nurse to

administer the same. This defeats the very purpose for which the NME are being introduced. Hence, we need to identify a sedative regimen that can be administered safely by NME, and at the same time should be effective and have a quick onset and recovery profile.

1.4 Non-Medical Endoscopy

1.4.1 Introduction

Lower gastrointestinal endoscopy (LGE), including both flexible sigmoidoscopy and colonoscopy is routinely provided by doctors. However, in 1977, Spencer and Ready[60] published first descriptions of endoscopy by non-medically qualified personnel (nurses) and since then there has been an increase in interest in this concept. Duthie et al first described the concept of nurse endoscopy in 1998 in United Kingdom [61] and since then the concept has become accepted practice in many hospitals across England.

The primary reason for these changes is the increasing demand for LGE and long waiting lists. A pilot study was undertaken in 2003 to evaluate the potential of training non-medical individuals to undertake flexible sigmoidoscopy, and this included a science graduate and a non-clinical member of hospital staff. These endoscopists are now defined as non-medical endoscopists (NME). For the purposes of this thesis, the term NME will be reserved for non-healthcare professionals undertaking endoscopy.

This concept has now been taken further and one member (science graduate) of this pilot group has now successfully completed colonoscopy training, and is now a JAG (Joint Advisory Group) - accredited endoscopist. This non-medical endoscopist has participated in the current study, which is included in this thesis.

The reasoning behind the pilot was to provide a workforce capable of coping with the increasing demands of endoscopy. With time, the senior non medical endoscopists would probably progress to performing colonoscopy. At the moment, they are limited by an inability to prescribe medications and administer sedation. This necessitates the presence of a suitably trained nurse or doctor to provide sedation, when the NME performs colonoscopy.

1.4.2 Training of non-medical endoscopists

There are unique issues related to the training of non-medical endoscopists. Firstly, there are educational differences between non-medical endoscopists and doctors. Secondly, doctors have a broad knowledge base and culture of decision making, which is certainly not the case with non-medical endoscopists. Hence the British Society of Gastroenterology has emphasised that "the training of non-medical endoscopists should be sufficiently broad to ensure that their endoscopic and attendance skills are equal to that of doctors, and their cognitive, interpretive and decision making skills are also balanced" [62].

This is reflected in the current training courses for the non-medical endoscopists. Based on the early experience with the pilot project of non-medical endoscopy, a three-year curriculum was developed at the University of Hull. During the first semester, students were trained and assessed in basic endoscopy skills which include cleaning of endoscopes, disinfection, and assisting at endoscopies. Themes include anatomy and physiology, endoscopy practice and theory, applied gastroenterology and professional practice. Hands-on practice was predominantly undertaken in the base NHS Trust under the supervision of a Joint Accreditation Group for GI Endoscopy (JAG) registered endoscopy trainer.

Table 1.6 Elements of practice and estimated timeframe for completion(from[63])

Year of Programme	Semester	Related practice module	Expected element of practice to be completed
1	1	Basic Endoscopic skills	Set-up & take down endoscopes Cleaning & disinfection
1	2	An introduction to Basic FS	Observation Simulated practice FS
1	3	An introduction to Basic FS	Simulated practice FS [Withdrawals]
2	1	The Practice of Diagnostic FS	Withdrawals [Full procedures]
2	2	Same as above	Full procedures [Std biopsy]
2	3	Same as above	Same as above

A basic overview of this course is that during the initial part of the course the participants are taught and encouraged to acquire basic knowledge of anatomy, physiology and pathology relevant to the training. As a continuum from year one, anatomy and physiology then take a more discipline specific approach, focusing on the GI tract in year two. Students extend basic understanding of general anatomy and physiology and applied concepts to the GI tract, with assessment being via written examination. Gardiner et al[64] have shown the range of methods applied to assess clinical practice elements in this course and this includes Observed Structural Clinical Examination and Direct Observation of Procedural Skills on real cases, patient stimulation and role play.

Simultaneously, hands-on training is carried out at the individuals' base hospital and there are additional sessions at the bigger centre for acquiring advanced skills. In fact it is a prerequisite for trainees joining this degree course that they have support at their own hospital for basic endoscopy training. Initially, observation of flexible sigmoidoscopy is commenced, with students recording observations undertaken. Following procedural observation, students undertake simulated procedures followed by endoscope withdrawal under direct supervision. Progression to full procedures commences once the student is deemed competent by the supervisor.

Table 1.7 Competency requirements for flexible sigmoidoscopy training[63, 64]

COMPETENCY ELEMENT	DESCRIPTION
HANDLING & CARE OF ENDOSCOPES	The trainee demonstrates appropriate care and handling of endoscopes, and can identify the anatomy of the endoscope
SAFETY IN ENDOSCOPY	The trainee works with the team to organise and maintain a safe environment for the patient in all aspects of endoscopy preparation and examination
COMMUNCIATION WITHIN ENDOSCOPY	The trainee demonstrates the ability to communicate with the patient, family and members of the endoscopy team
CONSENTING FOR FLEXIBLE SIGMOIDOSCOPY	The trainee demonstrates the ability to obtain and record consent for the FS examination
PATIENT PREPARATION	The trainee is able to safely prepare

	the patient for the FS examination
OBSERVATION OF ENDOSCOPY	The trainee, through observation, is able to describe the basic techniques and manoeuvres of FS and normal / abnormal anatomy of the colon and rectum
ENDOSCOPY SIMULATION	The trainee is able to perform FS examination on a patient simulator
ENDOSCOPE WITHDRAWAL	The trainee is able to withdraw the endoscope safely, identifying all anatomical landmarks and pathologies, following insertion by an experienced endoscopist
PRACTICE OF FLEXIBLE SIGMOIDOSCOPY	The trainee safely performs FS examination
THERAPEUTIC FLEXIBLE SIGMOIDOSCOPY	The trainee is able to demonstrate the safe removal of polyps, if appropriate, for histological assessment

The training of the non medical endoscopist who participated in the research in this thesis extended training beyond flexible sigmoidoscopy. The first 100 cases of flexible sigmoidoscopy were supervised and subsequent ones required the trainer to be present in the endoscopy unit. Once declared competent to perform flexible sigmoidoscopy, the NME went onto structured training for colonoscopy, based on the guidelines issued by the JAG.

In summary, the standards for training NME are the same as those for the training of doctors and nurses. These guidelines are developed and maintained by the JAG.

1.4.3 Results of NME with flexible sigmoidoscopy/ colonoscopy

Three hundred and twenty five patients, who underwent flexible sigmoidoscopy and colonoscopy by two non-medical endoscopists, were reviewed. The first 50 cases (total) were directly supervised by an endoscopy trainer and the next 50 required the trainer to be present in the endoscopy suite. The M: F ratio was 210:165 with a median age of 62 (range, 22-82) years. Indications for endoscopy included cases for symptomatic (220), follow-ups (80) and family history (25). Sedation with Fentanyl and Midazolam was given in 70 of the 75 colonoscopies and no sedation used for flexible sigmoidoscopies.

The median time for flexible sigmoidoscopy was 18 minutes (range, 5-40). The indications included symptomatic patients, family history clinic patients and follow up patients. The transverse colon was intubated in 85% of patients with flexible sigmoidoscopy and the caecum was intubated in 91% of patients undergoing colonoscopy. No sedation or procedure-related complications occurred. The findings included: normal (186 cases), polyps (97), malignancy (10), inflammatory bowel disease (26) and others (6). Six polyps and a malignancy were missed on initial endoscopy. These were picked up on repeat endoscopy, which were done because the first was deemed incomplete. Only 3 polyps were truly missed.

1.4.4. Medicolegal issues

Concern has been expressed about the legal implications of endoscopy practice and the need for full medico-legal cover in the event of complications. The common law of negligence requires "that at all times a reasonable standard of care is practiced. A person who holds himself/herself as possessing special skills will be judged by the standard of the specialist"[58].

Currently, the non medical endoscopists are not affiliated to a professional body but the Department of Health confirms that they are, however, covered under their local Trust Governance Frameworks under vicarious liability [65], and are all held on a voluntary list which will lead to regulation in the future. The issue of regulation is crucial and demands accelerated progress, not only to provide some reassurance to the endoscopy community but also to the public and the trainees alike.

1.5 Sedation for LGE

1.5.1 Introduction

Colonoscopy is generally performed in the United Kingdom as an outpatient procedure. However, it can be a difficult and painful procedure, sometimes resulting in acute pain. This necessitates the provision of analgesia and sedation during colonoscopy. Although colonoscopies can be performed without sedation, results of two studies showed that 16% to 56% of such procedures are terminated because of pain[66, 67]. As a result, the caecum is not reached in these patients and hence lesions can be missed.

Sedation is, therefore, routinely provided to patients during colonoscopy and is considered the standard of practice in the UK. In a multicentre study [30] conducted on over 9,000 colonoscopies, moderate sedation was used in 94.6% of patients, general anaesthesia in 0.2% and the remainder without any sedation.

Although there are many different techniques and medications to achieve sedation during colonoscopy, the ideal amount and type of sedation for a patient undergoing colonoscopy has not been established. Hence there is a wide variation in the provision of sedation and analgesia throughout the world. In France, about 90% of all colonoscopies are performed under general anaesthesia, usually supervised by an

anaesthetist[68, 69], while in Germany[70] and Finland[71] a number of procedures are carried out without any sedation.

The different types of sedation for colonoscopy include general anaesthesia, deep sedation and moderate sedation. However, there has been a general consensus that moderate sedation (formerly conscious sedation) as opposed to general anaesthesia, is adequate for the overwhelming majority of routine colonoscopies[72].

1.5.2 What is moderate/conscious sedation?

It is now clear that sedation provided by medications is usually a continuum, extending from minimal sedation to general anaesthesia. The British Society of Gastroenterology (BSG) recommends that "the doses of sedation and analgesics for colonoscopy should be kept to a minimum"[73]. Conscious sedation is defined by BSG[73] as "a technique in which the use of drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation. The drug and techniques used to provide conscious sedation should carry a margin of safety wide enough to render loss of consciousness unlikely**".**

1.5.3. Drugs for sedation

There are different types of sedation regimes available at the present moment, signifying the fact that none of them provide ideal sedation. The most commonly used regime is a combination of benzodiazepines with opioids[30]. Bowles et al have shown that 57.85% colonoscopies were performed with this combination in the UK[30]. The most commonly used regimens are midazolam with fentanyl and midazolam alone. The other sedative regimes include propofol, either on its own or in combination with opioids, and Entonox gas inhalation.

1.5.4. Safety, advantages and disadvantages of current sedation regimes for colonoscopy

Properties and dosing regimens for the most commonly used drugs in moderate sedation are summarised in table 1.8[27] below:

Table 1.8 Properties of commonly used sedative drugs for colonoscopy[27]

Drug	Pharmacolo-gical class	Effect	Onset of action	Duration of action	Adverse Effects
Midazolam	Benzodiazepine	sedation amnesia	1-5min	1-3hours	Hypotension, hypoventilation, increased respiratory rate and airway resistance, apnoea
Diazepam	benzodiazepine	sedation amnesia	1-5 min	20-60 min	Hypotension, Hypoventilation Apnoea
Mepiridine	Opioid	sedation analgesia	5 min	2-4 h	Same as above
Fentanyl	Opioid	sedation analgesia	<1 min	30-60 min	Respiratory depression, hypoventilation
Propofol	Sedative hypnotic	sedation analgesia	30-60 sec	3-10 min	Hypotension, hypoventialtion

There are a number of potential problems with available sedative agents. These include cardiorespiratory events, such as hypoxia, hypoventilation, arrythmias, and vasovagal episodes. In a retrospective study, it was estimated that the serious cardio respiratory complications and death rates from endoscopic sedation are unacceptably high at 54 and 3 per 10, 000 cases respectively [74, 75]. Moreover, benzodiazepines are lipid-soluble, and ,hence, repeat doses result in accumulation in adipose tissue which is subsequently released and leads to prolonged effects[27]. It is due to these persisting effects that the current recommendations in UK require the patient to be

accompanied home by a relative/ friend. Patients are advised not to drive for at least 24 hours, and also not to use heavy machinery or sign important documents for the same duration.

1.5.5. Properties of an ideal agent

The ideal agent should have certain properties to provide safe and effective minimal-to-moderate sedation. These include a consistent and predictable pharmacokinetic/pharmacodynamic profile, rapid onset of action, analgesic and anxiolytic effects. The agents should wear off immediately and leave no effects on mental and psychomotor function. The currently used combinations of benzodiazepines with opioids unfortunately do not meet these criteria.

1.5.6. Entonox

1.5.6.1 Entonox for sedation

Nitrous oxide (N_2O) gas has been known to have analgesic and sedative properties for over two hundred years ever since it was discovered by a Yorkshire chemist named Joseph Priestley[76]. The scientist Humphrey Davy inhaled the gas and found it gave him rapid pain relief from an infected tooth; on one occasion he reported momentarily losing consciousness, waking up laughing about the pleasurable feelings he had experienced: hence the term 'laughing gas' [76]. As a medicinal gas, it is available as a mixture containing equal parts of N_2O and oxygen (O_2). In many countries this is commercially available as Entonox, and in the UK it is also often known to patients and staff as 'gas and air'. Entonox is ideal in situations where pain is predictable and of a short duration. It can provide relief of pain during minor procedures such as wound dressing changes, debridement, removal of drains or sutures and even turning a patient with a fracture or a pressure ulcer[76]. The gas is

administered using a face mask or mouthpiece; gas flow is controlled by a sensitive demand-valve activated by the patient's inspired breath. This allows pressurised gas from the cylinder to flow through a pressure regulator into the lungs at a steady rate. Longer and deeper breaths allow greater volumes of gas to be taken into the lungs if necessary.

The gas is rapidly absorbed on inhalation, providing analgesia within minutes. It is excreted, largely unchanged, by the lungs and its rapid elimination from the body on cessation of inhalation makes it ideal for controlling pain during short procedures. There are no major incompatibilities with other drugs. Entonox will cause an enclosed air-pocket in the body to expand rapidly in volume as the gas mixture is absorbed from the blood into the space, resulting in a build up of pressure. It must therefore never be used if the patient has any conditions where air is trapped in the body and expansion would be dangerous; for example, it will exacerbate the onset and development of a pneumothorax (air inside the chest cavity but outside of the lung) and can increase the pressure of intracranial air following head trauma.

The following are general contraindications to the use of Entonox (from [77] and [76]):

- artificial, spontaneous or traumatic pneumothorax

- air embolism

- decompression sickness

- suspected bowel obstruction

- emphysema

- maxillofacial injuries

Repeated exposure to Entonox may result in megaloblastic anaemia owing to interference with the action of vitamin B_{12}.

1.5.6.2 Protocol for administration of Entonox

The protocol for Entonox administration is summarised below:

- **Practical considerations:** The first step is to obviously ensure the availability of the Entonox cylinders and mouthpieces. Also, it is important to ensure that the cylinder has sufficient gas in it to last the procedure.

- **Patient involvement:** Patients are then explained what the gas is for and what is required of them. The mouth piece is then given to the patient and he/she is instructed on the use. Patients generally practice a couple of breaths to ensure they are doing it correctly.

- **Documentation:** Nursing documentation will confirm that proper patient instruction took place, and record the time period in which the gas was used.

- **Procedure for administration:** The protocol is to encourage the patient to breathe the gas for around two minutes before commencing the procedure. The patient generally breathes continuously throughout the procedure. At all times the patient should be able to obey commands, but if a momentary loss of consciousness does occur, the seal around the mouthpiece will be lost as it falls away and the demand valve will fail to operate causing the flow of gas to stop.

1.5.6.3.Entonox for Colonoscopy

Entonox as described above is an inhalational sedative agent with analgesic properties and has a short onset and duration of action. In previous studies of inhaled Entonox versus placebo/intravenous sedation for colonoscopy, it has been shown to be associated with similar pain scores. Four studies[78-81] compared pain scores in

patients undergoing colonoscopy and sedated with either Entonox or conventional intravenous sedation (see table 1.8 below). Three studies have shown that Entonox is atleast as effective as either midazolam/fentanyl or midazolam/pethidine or Midazolam/ketobomidone or pethidine alone. The fourth study by Forbes and Collins[81] showed that pain scores were significantly lower in patients with conventional intravenous sedation as compared to Entonox, although the study was unblinded, with the possibility of bias. Despite these encouraging results, Entonox has not received widespread acceptance in colonoscopic practice. The probable explanation for such response is a lack of single, clear outcome, and the perceived difficulty in the use of Entonox.

Table 1.9 Comparison of different studies involving Entonox sedation for colonoscopy

Studies	N*	Entonox(E) Versus	VAS[§]	Discharge time	Completion rates	Satisfaction scores
Lindblom et al[78]	50	Ketobomidone + midazolam (KM)	NS[¥]	E faster than KM	Equal	E>KM
Saunders[79]	89	Midazolam + pethidine (MP)	NS	Same	Equal	E>MP
Notini Gudmarsson[80]	40	Pethidine (P)	NS	E faster than P	Equal	E>P
Forbes[81]	102	Midazolam + meperidine (MM)	E worse than MM	E faster than MM	Equal	MM>E

§VAS=visual analogue scale.*N=total number of patients in the study.¥ NS=no significant difference in both groups.

1.5.7 Propofol

1.5.7.1 Introduction

Propofol (2, 6-diisopropylphenol) is a substituted alkyl phenol derivative that is believed to facilitate gamma-amino butyric acid activity in the brain[82]. It has an instantaneous onset of action, because of high lipid solubility. The recovery from propofol is rapid as it has a half-life of only 2 to 4minutes.These qualities make propofol an excellent sedative agent for use during short duration procedures. The major disadvantage of propofol is that the sedation produced can rapidly and easily convert inot general anaesthesia. This can be disastrous, especially in the setting of endoscopy if there is no anaesthetic support available immediately. Hence it is hugely important to titrate the doses of propofol. Moreover, propofol tends to cause deep sedation, which results in fewer propofol-treated patients being able to assist with the procedure (e.g. changing position). It has been reported in earlier studies that the greater level of sedation achieved with propofol potentially puts the patients at risk for perforation [83], though the evidence is not convincing. Also, there is a lack of a reversal agent for propofol, and over-sedation quickly leads to cardio-respiratory compromise.

Furthermore, it has a short-recovery time that makes it suitable as an intravenous agent for day-case anaesthesia and sedation. In practical terms, no matter how long the infusion period, recovery will occur within 10-20 minutes once it is discontinued. This is because propofol is rapidly metabolized, principally by conjugation in the liver[84].

All the studies have evaluated the use of propofol for ERCP or colonoscopy, and there has been no comparison with Entonox or Midazolam/ Fentanyl. Moreover, there has been only one study in the United Kingdom on the use of propofol for

colonoscopy, which used target controlled infusion of propofol for only 20 patients and concluded that patient maintained propofol is possible for colonoscopy[85].

1.5.7.2. Review of propofol versus traditional sedative regimes for colonoscopy

Among gastroenterologists, there is increasing interest in the use of propofol for endoscopic sedation, and the number of reports of endoscopist-administered propofol sedation for colonoscopy is growing[83, 86-91]. Currently, more than 25% of patients undergoing endoscopy in the United States receive propofol for moderate sedation. Several studies[92, 93] have been published showing propofol to be superior to traditional sedative regimens because of shorter recovery profile. In addition, propofol use has been shown to be overall cost-effective, even though additional trained personnel were required [93]. Despite these advantages, the use of propofol has been hampered by the understanding that it has a narrow therapeutic index and hence it is mandatory for an anaesthetist to administer it.

Qadeer et al [94] recently published the results of a systematic review comparing propofol with traditional sedative agents for gastrointestinal endoscopy (including ERCP and colonoscopy). Out of 1161 patients, 634 received propofol and the remainder received conventional intravenous sedation. The pooled odds ratio with the use of propofol for colonoscopy for developing hypotension or hypoxia was 0.4 (95%CI, 0.2, 0.79), as compared to traditional sedative agents. Qadeer et al[94] concluded that propofol sedation for colonoscopy is associated with lower odds of cardiopulmonary complications compared with traditional agents.

1.5.7.3. Target controlled infusion and Patient controlled propofol

New concepts in sedation for colonoscopy include enhanced mechanisms like target controlled infusion (TCI) and patient controlled systems for propofol.

Target controlled infusion systems for anaesthetic agents are computer –controlled infusion systems designed to deliver intravenous drugs according to the drugs pharmacokinetics[95]. Target controlled systems use complex mathematical models to compute the drug dosage, which account for various patient characteristics that alter the drug disposition. Because they frequently recalculate the appropriate dosage of drug to be infused, based on the computer's pharmacokinetic simulation of the drug concentration and ensuring that the correct concentration is infused at all times, TCI pumps address the limitations associated with delivery of drugs directly into the circulation. Propofol is commonly infused via TCI pumps, ensuring a titrated dose of the drug to be given, and this is particularly important due to the narrow therapeutic index of propofol. Published studies[96] have shown TCI propofol is associated with longer time to sedation, but is safer and results in higher patient satisfaction.

In PCS, the medication is self-administered by the patient in response to pain; therefore, the patient has to be conscious enough to press the handheld button. Specialised pumps are used that deliver a preset dose of medication in response to a patient pressing a handheld button. A lockout time is programmed into the pump to prevent the delivery of additional doses until the previous dose has taken its full effect. When rapid-acting drugs such as propofol and alfentanil are used for PCS, over sedation is unlikely to occur.

In order to minimise the possible side effects with propofol, there have been attempts to combine TCI pumps with PCS to deliver propofol. Campbell et al[85] experimentally modified a TCI pump to connect it to PCS, and used the system for colonoscopy. In this study, 20 patients undergoing colonoscopy were connected to the handset and modified TCI system. There was a significant drop in systolic blood

pressure and heart rate, and four patients became over sedated, and there was a delay

in recovery time, indicating this modification is still not optimal for use.

The above mentioned modification of the TCI pump is not commercially available.

Additionally, the manufacturer and the National Health Service trust were unable to

modify the pumps due to patent reasons. Hence, in the current thesis, two separate

pumps- PCS and TCI – have been used to achieve the target of delivering TCI-PCA

sedation during colonoscopy (chapter 6).

1.6 Artificial neural networks (ANN) for patients with colorectal symptoms

1.6.1 Introduction to ANN

Artificial neural networks (ANN) are special intelligent software programmes.

Inspired by the function of the human brain, they are able to learn and adapt

themselves based on the available data. As a result, ANN are able to analyse

complex relationships in databases. It is generally agreed that ANN are well suited

for solving non-linear problems. Non-linear problems are those problems "where the

relationship between the inputs and the outputs of the problem are not clearly

distinguishable"[97].

Structurally, ANN are networks of interconnected nodes or processing elements. The

most basic ANN has an input, processing and output node. So, the information or

data flows from the input node to the ouput node via the processing node. A

prespecified function or algorithm sits in the processing node and this analysis or

modifies the data and the result is fed to the output node. The connections between

the nodes are also important. These connections are constantly weighted and altered

in accordance with the learning of the programme. It is obvious that more compolex

networks will have hundreds of these nodes and the weights are constantly adapted to ensure accurate learning and output.

Figure 1.1 Example of MLP[98]

Artificial neural networks

Inputs

Output

An artificial neural network is composed of many artificial neurons that are linked together according to a specific network architecture. The objective of the neural network is to transform the inputs into meaningful outputs.
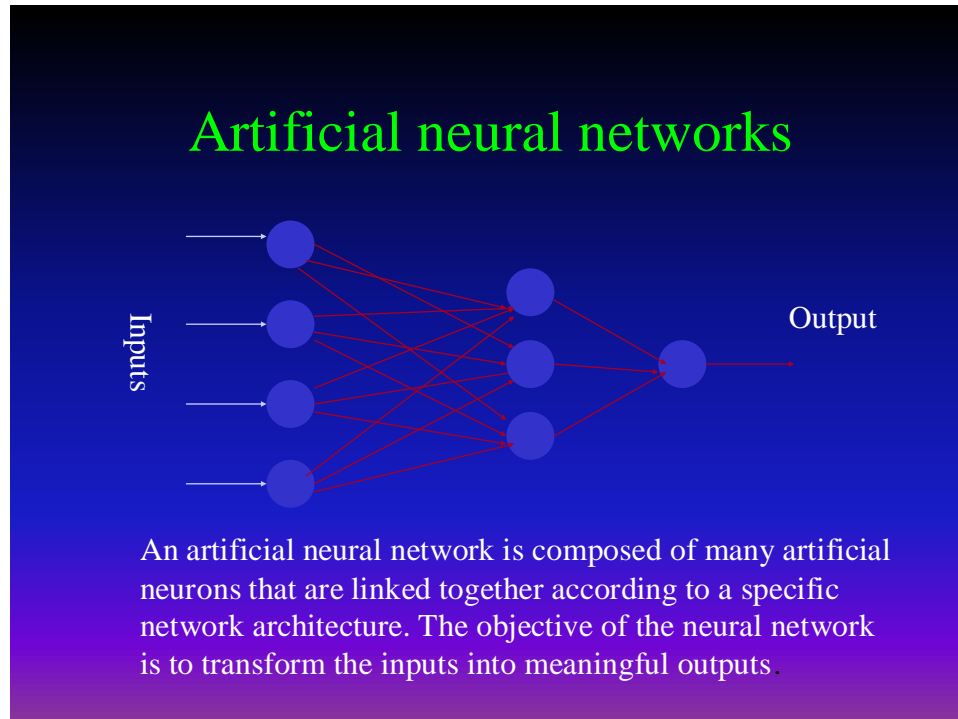
(modified from "Artficial neural networks- an introduction"[98])

ANN can be classified into feed-forward or feed-back networks. A different method of classification depends on the type of learning. This could be supervised learning or unsupervised learning networks. The feed-forward ANN is one in which the input signal is coming from the units of the previous layer and forwarded to the following; & the feed-back ANN which are characterised by retroactive connections carrying the output of a unit back as input of a unit of same or previous layer.

On the other hand, in the supervised learning networks, the ANN are trained by providing a data set which contains both inputs and outputs. The ANN learns from the outputs and designs itself by changing the connection to predict accurately. With

unsupervised learning, there is not a real training procedure since no target results for the input data are provided to the ANN. The input signals are treated like random variables and the network learns to find patterns in the data to produce outputs. ANN were pioneered by Rosenblatt, Widrow and Hoff and Widrow and Stearns [99]. However, Werbos in 1974 extended the network models beyond the elementary concept of perceptron [100](a single trainable layer of weights), to include models with two layers of weights that were trainable in a general fashion, and that accomplished nonlinear discrimination and nonlinear function approximation[101]. This computational method is called back-error propagation.

Among the different types of ANN, the most commonly used ones in medicine are the multilayered perceptron networks (MLP). The popularity of MLP comes from the fact that they are easy to use and can be trained by back-error propagation or other training methods. The MLP consists of multiple layers of artificial neurons, which are all connected to each other densely. As shown in figure 1.2, each input neuron is connected to all the neurons in the middle/ processing layer. The middle layer neurons have an activation function, which they apply to the input received from all the input neurons. The resultant output is then delivered to the output neurons, which further process this information to deliver the final outcome. The majority of clinical studies utilise such three layer networks in which the layers are fully interconnected[100, 102-105]. The interesting features of successful ANN models include the ability to perform accurately in the presence of heterogenous data (with some irregularities or measurement errors or unreliability), and the ability to detect and recognise complex non-linear relationships between the variables[100]. Thus, ANN

offer promise for improving the predictive value of traditional statistical data analysis.

1.6.2. Special features of ANN

The mathematical structure of ANN makes it capable of simultaneously handling an exceptionally high number of variables characterising the data such as that collected in a clinical field. This is an enormous advantage as compared to the classical statistical models. ANN are not limited by certain fixed assumptions regarding the type and number of variables in the data. This is a distinct advantage as compared to traditional statistical approaches. The important component of ANN is that during the training of a network, 3 overlapping sets of data are used. Typically, a data set is divided into three subsets, usually randomly: the training, testing and validation sets. The training set is used to adjust weights during training. The testing set is used to determine when to stop training. A different subset is used to report the performance of the network, and this is called the validation set.

On the other hand, disadvantages of ANN include: (a) difficulty in understanding how the relationships are being developed, (b) many methodological issues remain to be solved, (c) models prone to over-fitting, but this can be prevented by careful adjustment and establishment of stopping rules, and (d) there is conflicting evidence as to whether or not they are better than traditional regression statistical models for either data classification, or for predicting outcome.

1.6.3 Training of ANN

The majority of biomedical studies utilise three-layer networks, in which layers are fully connected. Each layer has a pre-defined set of nodes. There are additional

hidden nodes as well. The training of ANN broadly involves two activities :1.

adjustment of weights and 2. activation of hidden nodes.

Any ANN has a random weight assigned to each of the connections. As part of

training, when the data is presented to the network, weights are adjusted on a

constant basis. This is done once again on the basis of pre-determined algorithms

like gradient descent etc. The knowledge gained from this process is then passed

onto the next set of nodes until it reaches the output nodes. The results are then

checked with the actual result and error rate is calculated. The process continues

forwards and backwards until the error rate is minimized and generally below the

preset acceptable level.

However, it is important to realise that there should be patterns in the data for the

ANN for identify and learn and hence successfully predict in the future.

The time taken for a network to learn and adapt depends on the number of nodes and

inputs and examples provided. For instance, a network with 200 inputs trained on a

few hundred examples needs around 4 hours to train on an average computer.

1.6.4 Measurements of performance and reliability

There exist many different performance measurements for neural networks. Simple

performance measure can be employed to demonstrate how well the neural network

output matches data with known outcomes. Performance metrics include the Mean

squared error (MSE) and root mean squared errors (RMS). Occasionally percent-

correct is used as a performance measurement. The area under the receiver operating

characteristic (ROC) plot (AUC) is a more comprehensive performance measure to

use with classification neural networks than either MSE or RMS. The area under the

ROC [in which sensitivity is plotted as a function of (1 - specificity)] is an

acceptable performance measure to use with a single output classification neural network[106]. AUC gives a definitive measure of the classifier's discrimination ability that is not dependent upon the choice of the decision threshold[101]. It is essentially the ability of the network to differentiate a positive case from a negative case when both are presented to it.

Other measures of the network's performance include the kappa value and the information given[101]. Unlike the AUC, these measures require an output threshold to be chosen. Kappa is the actual improvement in classification rate over the chance rate divided by the maximum possible improvement over the chance rate[101]. A value of 1 indicates perfect classification, and a value of 0 indicates classification at the chance rate.

A comparison with experts can be conducted to measure performance- does the network predict an outcome as often as a trained expert does?

1.6.5. Literature review of use of ANN in medicine

Medical decision support with neural networks is an area of medicine which is increasing exponentially in the last two decades. Table 1.9 shows the different published applications of neural network in medicine.

Table 1.10 Applications of neural networks in medicine[100]

Diagnosis
  Appendicitis
  Dementia
  Myocardial infarction
  Prostate cancer
  Sexually transmitted diseases (STD)
Histology
  Pap smear
  Imaging
  Nuclear Medicine scans
  Perfusion scans

Positron Emission Tomography (PET) scans
X-rays
Outcome predictions
Cancer
Cardiopulmonary resuscitation (CPR)
Surgery
Waveforms
Arrythmias
Electroencephalograms (EEG)
Electrocardiograms (ECG)

ANN have been used in the clinical diagnosis, image analysis in radiology and histopathology, and data interpretation in intensive care setting.

Stamey et al [107] developed a neural network derived classification algorithm called ProsAsure Index, which can classify prostates as benign or malignant. This model was subsequently validated in prospective studies and had diagnostic accuracy of 90%. PAPNET, a computerised automated screening system based on neural networks, has been developed to assist the cytologist in cervical screening and is one of the ANN models which is promoted commercially[108]. Prognostication is a vital area of medicine. Accurate identification of high risk patients and early targeted treatment is essential. ANN have also been shown to perform better than expert colorectal surgeons in predicting outcome in patients with colorectal cancer [102].

1.6.6 ANN as a clinical decision tool to determine the need for LGE

As discussed above, clinicians are not particularly accurate in determining if patients presenting for the first time in the clinic have significant lower gastrointestinal pathology. Hence, it is currently difficult to assess accurately which patients need a LGE. ANN have the ability to resolve complex relationships in data and have proven to be useful in various other clinical scenarios. Hence we decided to explore the

feasibility of using ANN for clinical decision making in colorectal/gastroenterology

clinics.

Chapter 2 Aims and Materials/methods of the study

2.1 Aims of the study:

This study has been performed with the following aims:

1. To assess patient satisfaction of LGE, and determine factors associated with patient satisfaction.

2. To assess the feasibility of using the technique of endoscopic clipping with follow- up x-ray as an objective measure of completion and miss rates in LGE.

3. To identify and assess methods of improving availability of LGE in the NHS by

A. developing and assessing the feasibility of using artificial neural networks in accurately identifying patients presenting in colorectal clinics who need LGE

B. Assessing the safety and efficacy of non-medical endoscopists (NME) in providing LGE services thereby enabling an increase in the number of endoscopists

C. determining the best method of providing sedation for colonoscopy in order to reduce the time to discharge, and enabling NME to perform LGE independently (Entonox versus Midazolam/Fentanyl and Entonox versus Propofol).

2.2   *Materials and Methods*

The materials and methods used in this thesis have been described in detail in the individual chapters.

2.3   *Ethics and trust approvals*

Ethical and trust approvals were obtained prior to commencement of recruitment.

(South Humber Research Ethics Committee: 04/Q1105/41: Randomised Controlled Trial of Sedation for Colonoscopy: Entonox versus Midazolam/Fentanyl (23/01/2006) and 05/Q1105/8: Assessment of lower gastrointestinal endoscopy (07/02/2005). York Research Ethics Committee: Randomised controlled trial of patient controlled sedation for colonoscopy: Entonox versus target-controlled patient maintained propofol (31/08/2007)). Approval was also sought from the Clinical Trials Department, Medicines and Health Regulatory Authority, London for both the Randomised Controlled Trials. All studies were monitored by the Clinical Trials Monitor, R&D, Hull and East Yorkshire NHS Trust, in accordance with the ICH_GCP guidelines.

Chapter 3 Patient satisfaction with lower gastrointestinal endoscopy

3.1 Introduction

Patient satisfaction is a crucial measure of performance standards and accountability of the endoscopists. Monitoring satisfaction is essential for quality assurance, evaluation of treatments and also possibly as it affects health outcomes. The American Society of Gastrointestinal Endoscopy has included patient satisfaction as an important indicator in all quality assurance programmes for endoscopy [109]. It is a valuable tool in assessing endoscopists' performance, identifying areas of concern and planning optimal health care delivery[53]. For example, if we identify areas of concern and act upon them, it should theoretically lead to enhanced patient care and satisfaction. Previous patient satisfaction surveys[52, 110] in endoscopy have attempted to analyse predictors of patient satisfaction and these have included endoscopists' technical skills, adequacy of sedation and patient anxiety. However, there is still insufficient information related to both patient satisfaction with endoscopy as well as factors determining patient satisfaction.

Moreover, as mentioned in the previous chapters, the Department of Health, United Kingdom introduced a pilot programme to train non-healthcare professionals to perform endoscopy[111]. These non-healthcare professionals performing LGE are termed non-medical endoscopists (NME). Though they have been shown to perform LGE safely, there are no studies comparing patient satisfaction between doctors, nurses and non-medical endoscopists.

The aim of our study, therefore, was to determine patients' satisfaction in our endoscopy unit, and identify factors related to patient satisfaction. A second objective was to compare doctors, nurses and non-medical endoscopists in terms of patient satisfaction.

3.2 Methods:

3.2.1 Study participants and data collection

This study was performed in the endoscopy unit at Castle Hill Hospital, Cottingham, United Kingdom from August, 2004 to December, 2005. The study was approved by the South Humber Research Ethics Committee, United Kingdom. All patients undergoing LGE were included in the study, except patients undergoing both lower and upper gastrointestinal endoscopies in the same session and patients not willing to participate. Patients were sent invitation letters 3 weeks prior to the procedure, and this included a patient information leaflet (approved by the Ethics committee) outlining the aims of the study and what it entailed**.** The principal investigator was present to answer patient questions.

Once patients agreed to participate in the study, they signed a consent form. The research co-ordinator handed two questionnaires to the patients- one before the procedure (pre-procedure questionnaire) and the second one after the procedure (patient satisfaction questionnaire).

Subsequently, all patients had their LGE and were allowed to recover as per the existing protocols in the unit. The participants then completed the specifically designed satisfaction questionnaire at the point of discharge, but before they were informed the results of their endoscopy (to prevent any bias). These anonymous questionnaires were deposited in a dedicated collection box.

Participants were also given a second satisfaction questionnaire similar to the previous patient satisfaction questionnaire, and this was meant to be completed 24 hours after the procedure and sent back to the endoscopy unit. Phone calls were made approximately 2

weeks after the procedure to all the non-respondents. These calls were repeated at 4 weeks in case of further non-responders. No further telephone calls were made to these patients.

3.2.2 Pre-procedure Questionnaire

This questionnaire consisted of demographic questions as well as the Hospital Anxiety and Depression scale (HAD). The HAD scale was used for the assessment of pre-procedure anxiety, and it has been previously validated for use in this setting. This is a self screening test for depression and anxiety[112]. It consisted of 14 questions, seven for anxiety and seven for depression. Although it was designed for hospital general outpatient assessment, it has been extensively used in primary care[113], and now in endoscopy research[114].

3.2.3 Patient Satisfaction Questionnaire (PSQ)

The American Society for Gastrointestinal Endoscopy (ASGE) modified the GHAA-9 satisfaction questionnaire to produce the instrument (m-GHAA 9) for measuring patient satisfaction with endoscopy[109]. The original Group Health Association of America (GHAA) satisfaction instrument[115] is a commonly used patient satisfaction questionnaire and has been in existence for nearly 20 years. This questionnaire has been validated in other patient groups over the years. This mGHAA-9 is based on 6 aspects of patient care, and the remaining 3 questions in the questionnaire include an overall rating of the visit and inquiries into whether the patient would have the same procedure at the same hospital. We modified this questionnaire further to reflect the endoscopy process in the National Health Service in the United Kingdom. The development and validation of the new questionnaire for this study was done in stages: literature review and item generation, pilot study & initial validation, and concurrent validation in the main study.

With regards to item generation, all the questions from the mGHAA-9 were included. A detailed review of literature was carried out to identify instruments for measuring patient

satisfaction for endoscopy. An expert panel consisting of colorectal surgeons, nurses, surgical trainees and other endoscopists assessed the items and developed a final questionnaire. The questions included in the questionnaire were constructed to encompass issues of high priority for endoscopists and relevant to the current problems with endoscopy and National Health Service. Sedation is a key factor associated with patient experiences in endoscopy, as sufficient sedation-analgesia can minimise the pain/ discomfort and, hence, probably optimise satisfaction[52, 110]. This is reflected in several questions regarding satisfaction with sedation (measured on a 100 mm visual analogue scale (VAS)). Patient satisfaction with endoscopic procedure in general was also assessed by a 100mm VAS.

A pilot study was then undertaken wherein the questionnaire was administered to patients undergoing LGE in the unit. Patients were asked to suggest any further questions of relevance and also those which were difficult and ambiguous. Patients were also asked to rank the 21 items on the questionnaire in decreasing order of importance to them. The aim was to determine which of the 21 questions were most relevant to patients with regard to a good experience of endoscopy.

The content validity and the items' face validity were tested by the above mentioned core group of experts and endoscopy staff. Items that were not answered by at least 10% of patients were deleted. Acceptability was assessed by the response rate. All patients reported that the questionnaire included all relevant items, proving the questionnaires' face validity.

Three questions were deleted from the final questionnaire, based on the analysis of the 100 respondents. These patients were not included in the study. Internal consistency was assessed with Cronbach's alpha. Factor analysis of 21 items revealed high consistency:

skills and hospital factors (α=0.81), pain reported after LGE (α=0.86), attitudes and information given (α=0.70).

3.2.4 Endoscopists

All the LGE in the study was carried out by three different types of endoscopists- medical endoscopists (ME), nurse endoscopist (NE) and non-medical endoscopists (NME). The doctors included in the study were consultants or senior colorectal trainees (JAG certified). The NE was a fully trained, JAG certified endoscopist, who is also a trainer on different endoscopy courses. The NME was the first fully trained non medical non nurse endoscopist. The individual was a science graduate, and was trained to perform lower gastrointestinal endoscopy, under the pilot programme started in 2003 by the Department of Health. The details of non-medical endoscopist training have been published elsewhere[116].

The patient satisfaction questionnaire was also administrated to the endoscopists, who were asked to rank the items in terms of how important they felt each question from a patient satisfaction perspective.

In addition to above, demographic and clinical features recorded from all patients included age, gender, weight, height, clinical indications, past and family history, results and procedural findings.

3.2.5 Statistical Analysis

All the data was analysed using SPSS (v14.0) software. Patient satisfaction and satisfaction with sedation was compared between the three groups using the Mann Whitney U test. Demographic and baseline characteristics were compared with the use of Mann Whitney U test for continuous data and Chi Squared test for categorical data. All other factors were compared between the groups using Independent samples T-test, with

p<0.05 being significant. The weighted kappa test was used to correlate the answer provided immediately after endoscopy with those provided in the mail questionnaires. Descriptive statistics like frequency, medians and inter-quartile ranges were performed. Univariate analysis was performed to test the relation between different variables and the primary outcome (patient satisfaction and pain scores). In order to determine factors determining patient satisfaction with endoscopy, multivariate regression analysis was performed and p<0.05 was considered significant.

3.3 RESULTS

A total of 561 patients undergoing lower gastrointestinal endoscopy were invited to participate in the study. However, only 503 patients were included. Out of the 58 excluded patients, 36 marked the questionnaire incompletely, and the remainder gave multiple responses to the same question.

3.3.1 General results

Out of 503 procedures, 332 were colonoscopies and 171 were flexible sigmoidoscopies. Doctors performed 151 colonoscopies and 44 flexible sigmoidoscopies, whereas NC performed 110 colonoscopies and 51 flexible sigmoidoscopies. NME performed 76 flexible sigmoidoscopies and 71 colonoscopies in the study period. General patient characteristics, including demographic features across all groups, are shown in table 9.1. In the colonoscopy group, 90 patients received Entonox and 242 patients received intravenous sedation (midazolam with fentanyl). Only 3 patients in the flexible sigmoidoscopy group received sedation.

Table 3.1 Baseline characteristics in the three groups

	Doctors	Nurses	NME	P*
Age (median) in years	62	60	63.5	-
Gender (Male:Female)	104:87	87:68	88:67	-
Intravenous - Midazolam - Fentanyl Entonox	2.5mg 75mcg prn[§]	2.0mg 75mcg prn[§]	3.0mg 100mcg prn[§]	0.96 0.88 -
Endoscopy type Flexible sigmoidoscopy Colonoscopy	44 151	51 110	76 71	0.091 0.142
Pre-procedure Anxiety scores[¥]	5	6.5	5.4	0.925

* Mann-Whitney U test. [§] = as required. [¥] =measured on Hospital Anxiety and Depression scale (as described in text)

The indications for colonoscopy were rectal bleeding (33%), change in bowel habit (25%), polyp follow up (22%), colorectal cancer follow-up (12%) and abdominal pain (8%).

The pre-procedure anxiety scores in the flexible sigmoidoscopy and colonoscopy group as well in all groups are shown in the table 3.1.

3.3.2 Correlation between direct and postal questionnaires

Out of 503 questionnaires, only 412 patients returned the questionnaires at 24 hours. The inter-rater agreement (weighted kappa) between the question on overall satisfaction for the direct and postal questionnaires was 0.82. This signifies strong agreement between the two scores. The weighted kappa between the question on pain score when asked immediately post-endoscopy, and at the 24-hour follow up, was 0.72.

3.3.3 Patient satisfaction questionnaire results

The overall satisfaction with lower gastrointestinal endoscopy was a median 94 (range, 38, 100). However, it is difficult to assess an isolated single satisfaction score, though a score above 90 is usually indicative of very good performance[52]. The median satisfaction score in the colonoscopy group was 96 (range, 88-100) and the median score for the flexible sigmoidoscopy group was 91 (range, 82, 98). These differences were not statistically significant (p=0.4).

We defined adverse endoscopic experience as a satisfaction score of less than 50mm on the VAS, a pain score more than 50mm on the VAS, or a lack of willingness to repeat the endoscopy again. This definition was adopted for the study and is not based on any previous studies. Among 503 patients, only 41 patients (8%) had an adverse endoscopic experience. 12 such patients had endoscopy under a doctor, whereas 15 and 14 patients respectively had the procedure under a nurse and a non-medical endoscopist. Once again, these differences were not statistically significant (p=0.3). The majority of patients, 84%, rated the endoscopists' manner as excellent, followed by 8% very good, 7% good and 1% fair. Similarly, 88% of the patients rated the endoscopists' technical skill as excellent, 2% very good, 8% good, 1.5% fair and 0.5 % poor. Only 18% of patients rated the bowel preparation experience excellent, whereas 22% rated very good, 38% good, 10% fair and 12% poor (table 3.2).

98% of the patients agreed to undergo the procedure in the same hospital (endoscopy suite) and 2% did not agree to the same. 99% of patients agreed to undergo the procedure again if necessary under the same endoscopist, and 4% did not agree. The median pain score was 20.6 (range, 0-60), on a scale of 0-100.

Table 3.2 Summary of patient satisfaction questionnaire results

Wait for the procedure	
-Excellent	75
-Very good	18
-Fair	5
-Poor	2
Convenience of appointment time	
-Excellent	68
-Very good	23
-Fair	7
-Poor	2
Length of time at endoscopy suite	
-Excellent	85
-Very good	10
-Fair	4
-Poor	1
Instructions for the bowel prep	
-Excellent	78
-Very good	12
-Fair	4
-Poor	6
Bowel prep experience	
-Excellent	18
-Very good	22
-Good	38
-Fair	10
-Poor	12
Personal manner	
-Excellent	84
-Very good	8
-Good	7
-Fair	1
Technical skills	
-Excellent	88
-Very good	2
-Fair	8
-Good	1.8
-Poor	0.15
Time spent	
-Excellent	81
-Very good	13
-Good	4
-Fair	1
-Poor	1

Explanation of procedure	
-Excellent	77
-Very good	15
-Fair	7
-Good	1
Personal manner of nurses	
-Excellent	72
-Very good	16
-Good	10
-Fair	2
Pain score$*^{\S}$	20.6 (0-60)
Overall satisfaction$*^{\S}$	94 (40-100)
Overall rating of visit	
-Excellent	71
-Very good	18
-Fair	10
-Poor	1
Will revisit same endoscopy suite	
-Yes	98
-No	2
Will undergo endoscopy by same endoscopist?	
-Yes	99
- No	01

*Results quoted are in percentages except *where the result is quoted in median and range in brackets. $^{\S recorded\ on\ 100}$ mm visual analogues scales where 0=worst and 100=best or 0=no pain and 100=worst imaginable pain*

3.3.4 Comparison between doctors, NE and NME

There was no difference in colonoscopy completion rates (table 3.3) between the three

groups (p=0.3). The time to caecum was slightly higher in the NME group, as compared to

the nurse and doctor groups, but the differences did not reach statistical significance

(0.09). No differences were detected between the endoscopists in patient rating (table 3.3)

for overall satisfaction (p = 0.6), technical skills of the endoscopist (p = 0.58),

communication skills (p = 0.61) or interpersonal skills of the endoscopist (0.59). The

median satisfaction scores for the three different types of endoscopists were 96, 95 and 97

respectively for doctors, nurses and non-medical personnel. Furthermore, a total of 416

patients responded to the repeat questionnaire at 24 hours, and we lost 87 patients to

follow up despite telephonic reminders. Importantly, there were still no differences in

patient satisfaction between the three groups when marked at 24 hours post-procedure.

Table 3.3 Outcomes in the three different endoscopist groups

	Doctors (n=195)	*Nurses (n=161)*	*NMC (n=147)*	P*
Overall patient satisfaction	96 (40-100)	95 (55-100)	97 (48-100)	0.1
Patient satisfaction at 24 hours	95 (45-100)	95 (50-100)	98(55-100)	0.1
Median pain scores -at discharge -at 24 hours	21(0-60) 22 (0-50)	18 (10-60) 20 (10-45)	23 (10-60) 21 (5-60)	0.3 0.1
Median pain scores in different sedation groups: - Entonox group - IV$^¥$ sedation group	12 (0-40) 34 (0-50)	18 (10-45) 28 (10-60)	16 (10-40) 32 (10-60)	0.9 0.8
Adverse experience†	12	17	14	0.3
Caecal intubation§	142 (94.5 %)	105 (96%)	66 (93.5%)	0.30
Completion of FS §,†	40 (90.9%)	47 (92%)	70 (92.2%)	0.10
Median time to caecum (min)	14 (10-21)	12 (8-20)	16.8 (12-29)	0.09
Median completion time (min)	21 (18-45)	19 (13-38)	21 (19-40)	0.1
Median time to discharge (min)	36 (20-70)	43 (15-60)	38 (15-90)	0.09
Technical skills$^\$$	1.72	1.66	1.72	058
Communication skills$^\$$	1.5	1.44	1.52	0.6
Interpersonal skills$^\$$	1.54	1.49	1.55	0.59

Values in parentheses are ranges, except §*where* values are in percentages. †=completion defined as insertion up-to descending colon. *Mann-Whitney U test. $where 1=excellent, 2=very good, 3=fair and 4= poor.

3.3.5 Multivariate analysis to determine factors affecting patient satisfaction and pain perception

Among all the variables tested in the univariate analysis, pre-procedure anxiety, age, sex of the patient, history of pelvic surgery/ hysterectomy, higher pain scores, pre-existing pain and type of endoscopy were associated with poor satisfaction scores. However, on multivariate analysis, higher pre-procedure anxiety, history of pelvic surgery/hysterectomy and higher pain scores were associated with adverse patient satisfaction (table 3.4).

Table 3.4 Multivariate regression analysis of factors affecting patient satisfaction

	Hazards Ratio (95% Confidence Interval)	**p-value**
Age	1.95 [0.64,2.96]	0.3
Female sex	0.92 [0.67, 1.96]	0.1
H/o pelvic procedures	0.60 [0.31, 0.82]	**0.04**
Type of procedure	4.5 [2.56,6.65]	0.9
Pre-test anxiety scores	2.1 [1.4, 4.94]	**0.042**
Procedural pain	1.19 [1.1,2.89]	**0.03**
Colon resection	3.4 [0.8, 5.6]	0.95
Endoscopist type	1.6 [0.62,3.1]	0.913

In the case of pain scores, pre-procedure anxiety, history of pelvic surgery/ hysterectomy and female sex were associated with higher pain scores on multivariate analysis.

3.3.6 Patient and endoscopists' preferences

Patients scored pain control as the most crucial factor affecting their satisfaction with lower gastrointestinal endoscopy. The next two critical facets for the patients were the technical skills of the endoscopists and the waiting time for the appointment. The endoscopists, on the other hand, marked the personal manner of the endoscopists, followed by the attitude of the endoscopists as the two most important markers of possible patient satisfaction. Notably, endoscopists ranked the pain/ discomfort levels as the third priority, and the personal manner of the nurses and supporting staff as subsequent component influencing patient satisfaction.

3.4 Discussion

Patient satisfaction has gained increasing importance and is at the forefront of healthcare outcomes measurements in recent years[52]. Monitoring patient satisfaction is an integral part of quality assurance of healthcare. It is already known that patient satisfaction can affect health outcomes [117]. Fitzpatrick has shown that satisfied patients are more optimistic about their situation and are more compliant with their treatment regimens [118]. Screening programmes for colorectal cancer have been introduced in different countries, including the United Kingdom in 2006. It is essential for patients to have a satisfactory experience of colonoscopy or flexible sigmoidoscopy, if they are to be compliant with screening programmes [119]. With increasing demand for lower gastrointestinal endoscopy, monitoring of patient satisfaction and integration of feedback plays a pivotal role in providing quality assurance.

In this study, we have found that patient satisfaction with LGE was high. There are 2 key findings from the study: identification of factors that influence satisfaction with LGE, and

that there was no difference between doctors, NME or nurses in terms of patient satisfaction.

Identification of factors that determine satisfaction is critical, because it provides a theoretical opportunity to modify these factors to ensure a better clinical outcome. Several factors have been proposed as predictors of decreased endoscopic satisfaction. These factors can be further categorised as either procedure related or patient related[54]. Raymond et al found that prior use of benzodiazepines and females were independently associated with low satisfaction rates[120]. However, the majority of these endoscopies were upper gastrointestinal endoscopies and were performed without sedation. Ko et al[121] have shown that procedural pain, bedside manners, technical skills, physical environment and communication with the patient are factors that affect patient satisfaction. In our multivariate analysis, we found that higher pre-procedure anxiety scores, pain during the procedure and a history of pelvic surgery/hysterectomy were associated with the lowest patient satisfaction scores. Higher pain scores were associated with poor patient satisfaction. It is interesting to note that patients receiving intravenous sedation experienced greater pain, as compared to those receiving Entonox gas. Consequently, satisfaction scores were lower in the IV group as compared to the Entonox group. These findings are similar to our previous randomised controlled trial comparing Entonox with Midazolam/Fentanyl for sedation for colonoscopy[122]. Other studies have shown that bowel preparation process has been associated with poor satisfaction[123]. However, we found no correlation between bowel preparation and satisfaction scores. Though other studies have shown baseline patient anxiety[124], female patients[125] and higher socioeconomic status[125] to be associated with poor satisfaction, we found no such correlations. The other items looked at included instructions for bowel preparation, waiting time for endoscopy and the

attitude of the reception staff. Del Rio et al[126] also found that waiting time for endoscopy is an important component of patient satisfaction. However, these factors did not reach any significance in our study; this is possibly because the number of unsatisfied patients was remarkably low, and the number of patients rating waiting times poor was also low. Furthermore, we noted differences in patient and endoscopists' perception of factors associated with satisfaction. Adequacy of pain control was the number one relevant factor for the patients, followed by the technical skills of the endoscopists and waiting time for appointment. Endoscopists, however, prioritised the personal manner of the endoscopists followed by the attitude of the endoscopists as the most important markers of possible patient satisfaction. Surprisingly, pain/discomfort associated with the procedure was the third most important factor for the healthcare professional. In a previous study [127], patients marked friendliness of the endoscopists as the most important factor. However, Yacavone et al found that 16% of all patients in their study ranked adequacy of pain control as the number one factor influencing their satisfaction, and this item was ranked overall number two [52]. It is, therefore, important to address these issues in any quality assurance programmes on endoscopy.

Having identified the key factors that affect patient satisfaction, the obvious next step is to enhance the patient's experience. Currently, there are long term efforts to improve the quality of LGE by the Department of Health, United Kingdom and other speciality organisations. The development of the Global Rating Scale (GRS) to monitor the performances of endoscopists and endoscopy units, and improve patient experiences is expected to produce rich dividends in the form of increased satisfaction. The GRS provides a simple, web based, unified opportunity to continuously quality assure endoscopy services. It is a tool that enables endoscopy units to determine how well a

patient centred endoscopy service they are providing. The various domains of the GRS include clinical quality, quality of patient experience, training and workforce domains. These domains are completed twice a year in April and October. The patient satisfaction domains include equality of access and privacy, timeliness (eg. waiting times etc), booking and choice, privacy & dignity, aftercare and ability to provide feedback. These seem to encompass all the previously discussed factors that affect patient satisfaction.

Patient satisfaction is usually assessed by questionnaires, but there are numerous pitfalls with respect to validity and reliability of questionnaires[54]. We therefore tested our questionnaire for both internal validity (content and face validity) and reliability (Cronbach's alpha), and found the questionnaire performed well on both the tests. Criterion validity cannot be assessed because there is no universal standard to measure it against[54]. The most commonly used questionnaire for assessment of patient satisfaction in endoscopy is the m-GHAA-9 questionnaire which we modified in our study. This questionnaire on its own suffers from the fact that it does not ask about procedural pain or bowel preparation process. Moreover, scores on the questionnaires can be affected by the method and timing of administration[54]. In order to overcome this potential bias, patients in our study completed the questionnaires anonymously, deposited it in a box and filled out another anonymous questionnaire 24 hours later.

The second important finding of the study is that we found no difference between NME and doctors and nurses in terms of patient satisfaction. Moreover, patients did not find any significant difference between the 3 groups in terms of technical skills, time spent and explanation given by the endoscopists, endoscopists' attitudes and other aspects of the endoscopy service. Patients were asked if they would undergo the procedure again (if they had to) under the same endoscopists. It is interesting to see that once again the number of

patients agreeing was similar in the three groups. We believe that these findings are extremely important. The current study is the first study of this size to evaluate patient findings comparing medical, nurse and non-medical endoscopists. Though this study is not a randomised controlled trial, the findings are reassuring in terms of patient satisfaction. Notably, there were no complications, either endoscopy-related or sedation-related in any of the groups.

The current study was carried out in a single institution and, hence, reflects the views of a particular cross-section of population. We believe that assessment of satisfaction should be carried out in multiple centres, and indeed this forms part of the United Kingdom Government initiative in using the Global Rating Scale [128].

In conclusion, we have identified several factors affecting patient satisfaction including procedural pain, pre-procedure anxiety and history of pelvic surgery. This study has also shown that there are no differences between medical, nurse and non-medical endoscopists in terms of patient satisfaction with lower gastrointestinal endoscopy.

Chapter 4 Technical quality assurance in colonoscopy: role of endoscopic clips

4.1 Introduction:

As discussed before, for colonoscopy to remain an effective diagnostic tool, it is necessary to perform a complete procedure with meticulous visualisation of mucosa, ensuring that no significant lesions are missed. However, it remains a technically difficult and lengthy procedure, which results in differing quality at different centres. Significant complications of colonoscopy are thankfully uncommon and thus difficult to use for assessment of quality. Documented completion rates and low long-term pathology miss rates could therefore be recognised as key indicators of technical quality.

A complete colonoscopy is usually defined as the passage of the endoscope to the caecum or terminal ileum. The current recommendations are that the caecum should be intubated in at least 90% of cases[129]. A recent review of endoscopic practices indicated that the average caecal intubation rate was only around 57%[130], which was far less than that recommended. Furthermore, it is not just enough to do a complete colonoscopy. It is equally important to visualise the mucosa of the entire colon adequately, ensuring that all pathologies are identified. These TWO key principles should, therefore, underpin any quality assurance programmes in colonoscopy.

There have been recent multifaceted efforts to improve the quality of LGE by the gastroenterology societies and royal colleges as well as the Department of Health, United Kingdom. A result of such quality assurance programmes is the creation of the Joint Advisory Group for endoscopy (JAG) and the Global Rating Scale (GRS). The JAG (www.thejag.org.uk) is responsible for the training of endoscopists and for setting up of standards for endoscopy. The GRS (www.grs.nhs.uk), on the other hand, is a web-based

tool that enables endoscopy units assess regularly how well they are offering a patient centred endoscopy service. The GRS consists of different dimensions and one of them is the technical completion rates of colonoscopy. Though the current requirements are for a colonoscopy completion rate of 90% and above, there is no stipulation regarding how this should be objectively recorded. The American Society of Gastrointestinal Endoscopy (ASGE) Taskforce on Quality in Endoscopy[46] still recommends photo-documentation for the confirmation of caecal intubation, despite recognized limitations with this method[131] (see chapter 1). The documentation of completion in the GRS is based on the endoscopists' own assessment of completion, and there is no objective method of identification of caecal landmarks. It is recognized that the 3 caecal landmarks (ileocaecal valve, appendicular orifice and the tri-radiate fold) are relatively constant and the best method of identification of caecum. However, as discussed in chapter 1, there is still no single consistent method of objectively documenting caecal intubation.

The technique of applying endoscopic clips followed by abdominal x-ray to confirm completion is a relatively easy to use method of documenting completion. The technique has previously been used in a small study to check if endoscopists have reached the caecum or not[32]. We aimed to evaluate this technique to objectively document both completion of colonoscopy and determination of pathology miss rates.

4.2 Methods

All patients undergoing colonoscopy by a single trained endoscopy team (consultant and nurse endoscopist) at a tertiary referral hospital between January 1998 and December 1999 were included in the study. The exclusion criteria included emergency colonoscopies,

pregnant females, post-surgical resection, patients not willing to participate and patients on endoscopy lists when the consultant was not available.

The study was approved by the Local Research Ethics Committee and the hospital research and development department. All patients undergoing colonoscopy were sent letters inviting them to participate in the study two weeks before the procedure. The study was explained to patients on their arrival to the endoscopy suite. Participating patients subsequently signed an approved consent form. Both the participating endoscopists were fully trained and independent endoscopists.

Colonoscopy was then performed in a routine manner using Pentax 160cm video-colonoscopes with a 3.6mm biopsy channel. Intravenous sedation with Midazolam and Fentanyl was given to all patients. During the procedure, patients were monitored in accordance with the British Society of Gastroenterology guidelines[132]. When the endoscopist was convinced that the caecum was reached (with positive recognition of 2 of the 3 above mentioned caecal landmarks), a clip was applied on the most proximal mucosa using an Olympus Titanium Endoclip applicator. Clips were attached to the mucosa at maximum endoscope insertion as near to the instrument tip as possible. The working length of the clip applicator was 1650mm (Olympus HX-200L-135) with a standard clip length and a clip angle of 135 degrees. The clip applicator was inserted into the biopsy channel of the colonoscope and advanced until the tip appeared within the endoscopic field of view. The jaws of the clip were opened and the clip was pushed at the target mucosa. The slider was then pulled firmly to close the clip. The slider was then pulled up to the thumb ring to detach the closed clip from the coil sheath. The endoscopist identified

where the clip had been placed in the colon, and the same was recorded by the attending nurse.

All the patients were allowed to recover and were discharged as per the existing protocols in the unit (table 3.1). However, at the time of discharge, all the participants had an abdominal x-ray to determine the position of the clip. No excess air was left behind to facilitate the identification of clips. Only one patient required a repeat abdominal x-ray because the first film had limited exposure (not for inability to identify clip). A consultant radiologist reported the x-rays blinded to the procedure and the clip position. The colonoscopy completion rate was determined using this and then compared with the endoscopist findings. All incomplete endoscopies were repeated over as soon as possible.

Patients were then followed for a median of 6 (range 4-7) years. Subsequently, the endoscopy database was reviewed to identify participants who underwent repeat colonoscopies in the follow up period. The hospital pathology database was also reviewed for any other positive histological results for all the participants over the five year period. All patients' case notes were reviewed and those who did not have a repeat colonoscopy were contacted to check whether they had a repeat procedure elsewhere or had persisting colorectal symptoms. The aim was to look for missed pathology.

For the purposes of this study, missed lesions were defined as all those lesions identified in repeat colonoscopies within a median interval of six years.

Data was entered into SPSS v14.0 for statistical analysis. Differences in proportion were tested using the Pearson chi-squared test, with $p < 0.05$ considered significant.

4.3 Results

Eighty two patients underwent colonoscopy with endoscopic clipping and follow-up abdominal x-ray during this study from January to December 1999. The patient characteristics are detailed in table 4.1.

Table 4.1 Patient and procedure characteristics

Number of patients	82
Median age (range in brackets)	58 (21-92) years
Sex (male:female)	50:32

The indications for colonoscopy included symptomatic cases (n= 39), polyps (n=13), cancers (n=4), colitis assessment (n=15) and others (n=11). All patients received intravenous conscious sedation with median doses of Midazolam of 4mg and Fentanyl of 75mcg. There were no procedure or sedation related complications. There were no 30-day procedure-related mortality (determined by medical records- no patient died in the median 6 year period) or documented procedure-related re-admissions within this period.

4.3.1 Position of the clips and completion rates

The position of the endoclip as reported on abdominal x-ray is shown in table 4.2. Thus, the colonoscopy was complete in 76 (93%) of patients. In the remaining 6 patients, the clips were found to be at varying places including ascending colon (n=3), hepatic flexure (n=1) and splenic flexure (n=2). The caecal intubation rate was 100% as judged by the endoscopists, but 93% as judged by the radiologists. The adenoma detection rate was 22%.

Table 4.2 Position of the endoscopic clip on abdominal x-ray

Position of the clip	Number of patients (percentage)
Caecum	76 (93%)
Ascending Colon	3 (3.6%)
Hepatic flexure	1 (1.2%)
Splenic flexure	2 (2.4%)

4.3.2 Endoscopist assessment versus imaging

The endoscopists' assessment was then compared with the x-ray findings. The endoscopist opinion was inaccurate in 6 (7%) procedures, despite using at at-least two out of three endoscopic landmarks to identify the caecum (table 4.2 and figure 4.1). All these patients subsequently underwent repeat colonoscopies as soon as possible thereafter.

Figure 4.1 X-ray abdomen showing a clip in the caecum (correctly identified by endoscopist)

Clip in the caecum
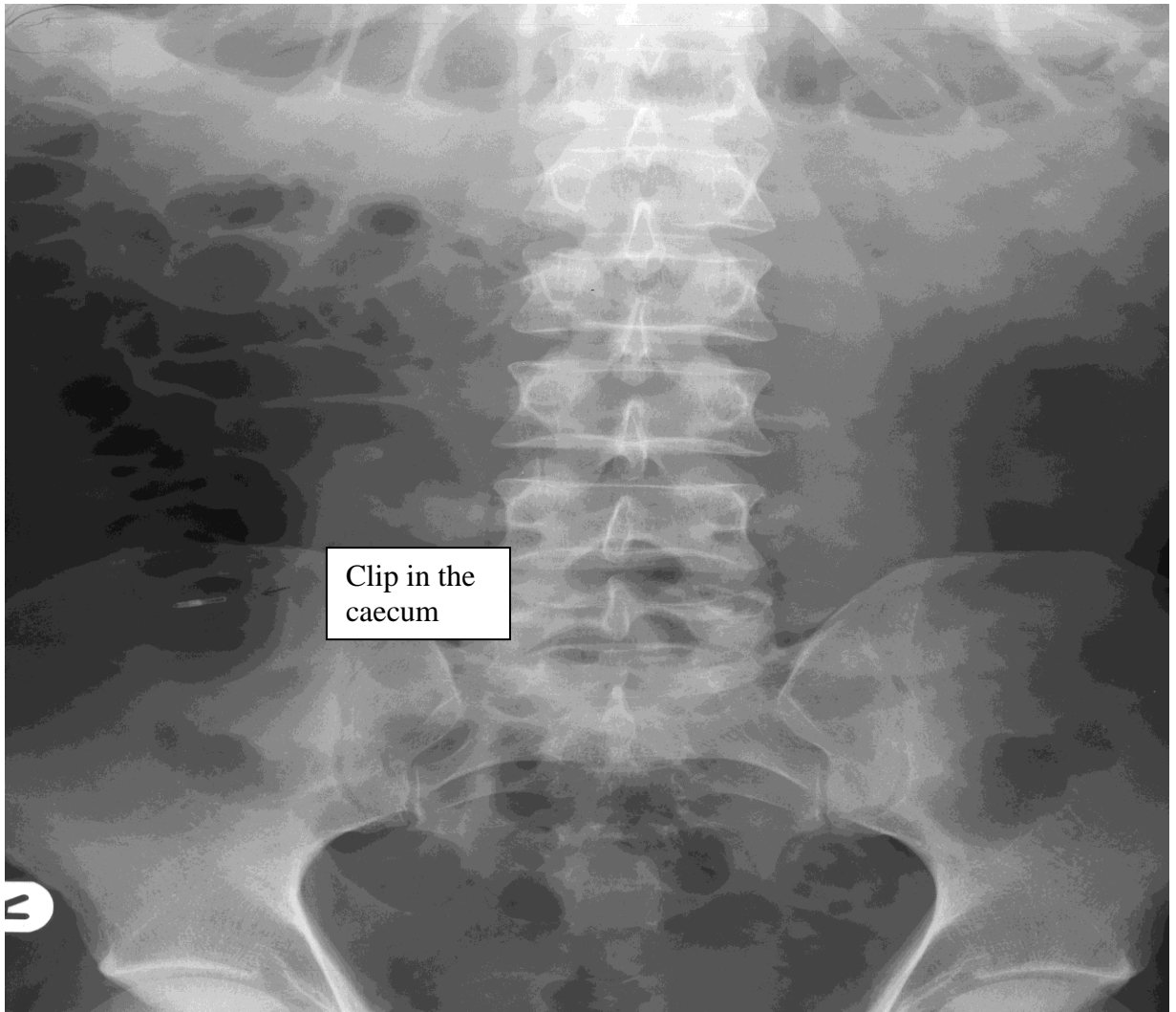
4.3.3 Follow up results and pathology miss rates

3 adenomas and 1 cancer were missed in the group of patients who were originally deemed to have a complete colonoscopy (table 4.3 and 4.4). The endoscopist considered the procedure complete in all these cases, but the use of the endoscopic clip and abdominal x-ray revealed an incomplete colonoscopy and subsequently these patients underwent

repeat colonoscopy. All the lesions were proximal to the site of clip application. Therefore, these are technically missed lesions; most likely missed because the procedures were incomplete. The missed cancer was located in the proximal ascending colon. It was subsequently identified on a repeat colonoscopy done in 10 days time. The patient underwent a right colonic resection and is currently free from recurrence.

Table 4.3 Missed pathology in complete and incomplete colonoscopies

	Incomplete Colonoscopy (n=06)	Complete Colonoscopy (n=76)
Adenoma missed	3(50%)	1(1.3%)
Cancer missed	1(16%)	0(0%)

Furthermore, at median 6 years-follow up, 33 patients had undergone repeat colonoscopies for various indications. The procedure was normal in 23 patients, and the diagnosis of inflammatory bowel disease/ diverticular disease was confirmed in further 9 patients. 1 adenoma was found in a patient who had undergone colonoscopy previously within median duration of 6 years. This lesion was missed during the first colonoscopy and subsequently detected on repeat procedures. Thus, 1 lesion was missed in complete colonoscopies at a median follow up of 6 years (1/76 complete colonoscopies).

Therefore, it is clear from table 4.3 that significant lesions are missed in nearly 66% (4/6) of incomplete colonoscopies, as compared to only 1.3% (1/76) of complete colonoscopies.

Table 4.4 Incomplete Colonoscopies and Outcomes

No.	Actual Level reached	Endoscopist Opinion	Lesion missed	Site of missed
1	Distal ascending colon	Complete	Adenoma	Caecum
2	Transverse colon	Complete	Cancer	Ascending colon
3	Hepatic flexure	Complete	Adenoma	Caecum/Ascending colon
4	Splenic flexure	Complete	Adenoma	Caecum
5	Ascending colon	Complete	None	N/A
6	Hepatic flexure	Complete	None	N/A

4.4 Discussion:

Technical success is a crucial feature of quality of colonoscopy and has enormous significance for the patient. The two fundamental components of procedural success include completion to caecum and successful identification of all pathology. This is particularly pertinent as incomplete endoscopies are associated with extremely high pathology miss rates, as demonstrated in our study (67% in incomplete procedures v/s 1.3% in complete colonoscopies) and others[133]. There are 3 findings from our study: experienced endoscopists can over estimate the proximal extent of colonoscopy which can lead to serious pathology being missed, and the technique of endoscopic clips with x-ray can help in objective documentation of completion, in some cases.

If we have to provide stringent quality assurance of colonoscopy, then indisputable evidence of caecal intubation will need to be provided[54]. Currently accepted identification markers of caecal intubation are a combination of images of the tri-radiate fold,

appendicular orifice and the ileocaecal valve. The JAG and the ASGE recommend caecal

photography (to capture images of atleast 2 of the above 3 landmarks) for objective

documentation of caecal intubation. It is easy to obtain and store images of the caecum

showing the above mentioned landmarks, especially with the advent of the modern

reporting systems. However, Thuraisingam et al[42] have recently shown that the sensitivity

(51.4%) and specificity (89.2%) of caecal photography is too low to be used for reliably

documenting colonoscopy completion. The difficulty lies in recording a moving image.

Several studies have also shown similar results[134, 135]. The current study has shown that

even experienced endoscopists can over estimate the position of the endoscope during

colonoscopy, despite using the reliable caecal landmarks. The colonoscopists were

inaccurate in around 7% of cases and 66% of these cases had significant pathology

proximal to the tip of the endoscope. This emphasises the need to use accurate methods of

identifying and objectively documenting caecal intubation in colonoscopy. If photography

of caecal landmarks is not enough, then what are the other options?

There are several other methods of documenting completion of colonoscopy, which have

been discussed earlier in chapter 1. Ileal intubation with ileal biopsy is considered to be the

gold standard for confirmation of completion of colonoscopy. However, without clinical

indication, ileal biopsy is not cost-effective as there is only 2-3% yield of significant

pathology. Additionally, there is a potential risk of vCJD transmission. Therefore, the

Royal College of Pathologists actively discourage ileal biopsy and suggest ileal

photography instead. However, Baraza et al[40] have shown that ileal photography, either on

its own or with additional enhancement by a pool of water or indigo-carmine dye, is an

unreliable method of confirming ileal intubation. In our study, we have assessed the

technique of application of endoscopic clip (with a follow-up abdominal x-ray) to assess

completion. The results confirm that the technique is useful and easy to practice. There are potential uses for the clip technique- endoscopic clips with abdominal x-ray could be used in a random number of procedures for every endoscopist each year and their completion rates determined. Additionally, all such procedures could be audited at an interval of 2 years to determine the true miss rates for each endoscopist. Furthermore, there are 3 possible scenarios with the identification of caecum on colonoscopy in terms of quality assurance and outcomes. First, the endoscopist is confident about completion and has identified two of the above landmarks and he is correct. Second scenario is where the endoscopist has a doubt regarding the completion and, therefore, performs a repeat colonoscopy. The third is where the endoscopist is confident about completion, but he/she is incorrect. It is the third scenario which is crucial for quality assurance as it could easily result in missed lesions. We emphasise the role of endoscopic clips with follow-on abdominal x-rays for resolving these scenarios. In this study, six patients were found to have incomplete colonoscopies, based on the results of endoscopic clipping and follow on x-ray. Based on these findings, the patients had a repeat procedure and missed lesions were detected in 4 out of 6 patients (67%). Three adenomas and one cancer were missed in these procedures. However, as they were deemed incomplete at the end of the procedure, and hence underwent repeat scoping, they cannot be classified as true misses. On the other hand, only one adenoma was missed in the remaining patients and this happened despite the procedure being complete. The pathology miss rate for this series of colonoscopies would have been 5/82 (around 6%). However, as patients underwent endoscopic clipping with x-ray, incomplete procedures were immediately identified and repeated, leading to a reduction in final miss rate to 1.3% (1/76) only. This technique aids in objective determination of completion, and, at the same time, is safe and easy to use. Moreover,

when this is combined with an audit of the procedures in two years, missed lesions thus determined reflect the true miss rates, once again emphasizing the usefulness of the technique.

The salient feature pertinent to quality assurance is that the technique of endoscopic clipping and follow on x-ray enables the determination of the accuracy of the intra-procedural opinion of the endoscopists, with regards to the identification of caecum and hence completion of colonoscopy. In other words, it quantifies the accuracy level of each endoscopist's assessment of completion. The implication is that if an endoscopist is of a high quality as demonstrated by the use of endoscopic clips, it follows that there is a high degree of accuracy in his assessment of completion of colonoscopy.

However, though the technique of endoscopic clipping with x-ray is useful, it has not yet been validated against the current criterion standard which is ileal intubation and biopsy. Moreover, identification of the exact position of the clip on an abdominal x-ray could be difficult in some cases though we did not find the same in our study. This could be possibly due to the small number of patients in our study. We believe that future studies are required to validate this useful technique against the technique of ileal biopsy, and also to validate the accuracy of abdominal x-rays (in locating the clip) against reliable radiological imaging methods, for instance, computerised tomography of the abdomen.

The adenoma miss rate for this series was 4/82 (4.8%). Out of 4 adenomas missed complete colonoscopies, 2 were lesser than 1cm in size and the other two were greater than 1cm. A systematic review[136] has shown that the pooled miss rate for polyps of any size was 22% (95% CI: 19–26%; 370/1,650 polyps) after colonoscopy. Adenoma miss rate by size was, respectively, 2.1% (95% CI: 0.3–7.3%; 2/96 adenomas ≥10 mm), 13% (95% CI: 8.0–18%; 16/124 adenomas 5–10 mm), and 26% (95% CI: 27–35%; 151/587

adenomas 1–5 mm). For non adenomatous polyps, the miss rate was: zero of eight non-adenomatous polyps ≥10 mm were missed (0%; 95% CI: 0–36.9%), and 83 of 384 non-adenomatous polyps <10 mm were missed (22%; 95% CI: 18–26%). Pabby et al[137] in the Polyp Prevention Trial showed that 13 patients (n=2079) had cancer detected during follow-up at 1-4 years after a clearing colonoscopy and that 3 cancers were missed at baseline colonoscopy.

Once technical quality is quantified using this technique and subsequent areas of deficiency identified, the only direction for endoscopists (and units) is to improve the quality by achieving higher completion rates and removing all polyps on index colonoscopy. Obviously, other aspects of quality of colonoscopy including adenoma detection rates, patient satisfaction and rate of complications need to be assured on a regular basis. It is, therefore, evident that any quality assurance in colonoscopy based on technical aspects should form part of a bigger programme to evaluate colonoscopy globally and include other criteria such as patient satisfaction, and adenoma hit rates.

4.5 Conclusions:

We have shown in this study that even experienced endoscopists over estimate the proximal extent of colonoscopy despite the use of standard caecal landmarks, and that there is a higher chance of missing lesions if the colonoscopy is incomplete. The study has also shown that the technique of endoscopic clipping with follow-on abdominal x-ray is a feasible method of objectively documenting colonoscopy completion, but there is a need for further validation before it can be routinely applied in clinical practice.

Chapter 5 Technical quality assurance in flexible sigmoidoscopy: role of endoscopic clips

5.1 Introduction

Flexible sigmoidoscopy (FS) is a straightforward and relatively safe procedure, which is generally well tolerated without any sedation. Previous studies[138, 139] have shown that the use of FS results in a 59-80% reduction in mortality from cancers arising in the distal colon and rectum. It is widely used a first line investigation for assessment of rectal bleeding[140], colitis and is now being advocated for screening for colorectal cancer[141]. The limitation of FS is that the depth of insertion and hence the completion rate is variable. The internal landmarks are not constant and distinct in the left colon, and there is no reliable marker of completion, as compared to colonoscopy. Some believe that the splenic flexure is a reliable landmark. However, visualisation of the splenic flexure is possible in only around 50% of examination and if the examination stops short of the splenic flexure, it cannot be used as a reliable landmark[51]. The Joint Advisory Group (JAG) in Endoscopy has defined completion of flexible sigmoidoscopy as insertion of the endoscope to the descending colon, and this should be achieved in 90% of examinations. A previous study has shown that the examination of the entire sigmoid colon was not achieved in 25% of cases and the descending colon was intubated in a minority of cases[142]. Currently, there is no universally established method of objectively validating completion in FS. The technique of applying endoscopic clips with a follow- up abdominal x-ray was previously shown to be an objective marker of completion in colonoscopy[51, 143] (as shown in the previous chapter). This method has not been previously applied to FS.

Further, in view of increasing demand for endoscopy and the introduction of screening programmes, the Department of Health in the United Kingdom has begun to train non-

healthcare professionals to perform endoscopy[58]. However, there have been no studies to establish their accuracy and completion rates in FS.

We, therefore, performed this study with the following aims: to determine the accuracy of the endoscopists' clinical impression regarding the actual position of the endoscope in the colon during FS, to compare ME and NME in terms of such clinical accuracy and to determine the role of endoscopic clips with follow-up x-rays in objectively documenting completion.

5.2 Methods

This was a prospective study performed in the Endoscopy unit at Castle Hill Hospital, Cottingham, United Kingdom from June 2006 to January 2008, and was approved by the South Humber Research Ethics Committee, United Kingdom. It was undertaken according to International Conference on Harmonisation Good Clinical Practice standards (ICH-GCP), including on-site monitoring and source data verification.

All patients undergoing elective FS were invited to participate in the study. They were also given detailed information leaflets (approved by the Ethics committee) about the trial two weeks before the procedure and then had an opportunity to discuss the trial with the co-coordinator, throughout the 2-week period as well as before the FS. The exclusion criteria included emergency FS, pregnancy, post-surgical resection, patients not willing to participate, patients on endoscopy lists when the consultant was not available and patients having an immediate barium enema as part of one- stop assessment.

All patients had the study explained in detail upon their arrival in the endoscopy suite and then participating patients signed a consent form. FS was subsequently performed in a routine manner using Pentax 160cm video-colonoscopes incorporating a 3.6mm biopsy channel. Only one patient requested sedation (midazolam-2.5 mg) and the remaining

procedures were done without any sedation. During the procedure, the patients were monitored in accordance with the British Society of Gastroenterology guidelines[132]. The endoscopists were asked to insert the flexible sigmoidoscope at least up to the descending colon for completion, except when they had to abandon the procedure or it was technically not feasible. Once the most proximal part of the colon was reached, the endoscopist clipped the colonic mucosa, using an Olympus Titanium Endoclip applicator. The endoscopist identified where the clip had been placed in the colon and the same was recorded by the attending nurse.

Post-procedure patients were allowed to recover as per existing protocols (chapter 5). Prior to discharge, participants underwent an abdominal x-ray to determine the position of the clip. A consultant radiologist reported the x-rays and the clip position. The completion rate was determined using the radiology findings and then compared with the endoscopist findings. All incomplete endoscopies were repeated subsequently.

The two endoscopists taking part in the study were a surgical registrar and a non-medical non-nurse endoscopist (called as non-medical endoscopists-NME, for the purpose of this study). Both endoscopists had performed more than 100 FS prior to the study and regularly perform FS. The NME was a non-healthcare professional who was currently working in the capacity of an Assistant Endoscopy Practitioner. This NME, who was also pursuing a degree (B.Sc.) in Coloproctology from the University of Hull, was part of the Pilot project initiated by the Department of Health to train non-healthcare professionals to perform endoscopy. Further details of non-medical endoscopist training are described elsewhere[58]. For the purposes of this study, we defined the procedure complete when the flexible sigmoidoscope reached the descending colon. All procedures were included in the study even if the descending colon was not reached, because the aim of the study was to

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determine the accuracy of the endoscopists' assessment of the position of the endoscope in the colon.

Data was entered into SPSS v14.0 for statistical analysis. Differences in proportion were tested using the Pearson chi-squared test, with $p < 0.05$ considered significant.

5.3 Results

Fifty one patients underwent endoscopic clipping during FS in this study from June, 2006 to January, 2008. The patient characteristics, indications and findings of FS performed in this study are detailed in table 5.1. There were no procedure or sedation related complications. There was neither any 30-day procedure-related mortality nor any documented procedure-related re-admissions within this period.

The medical endoscopist performed 25 procedures and the NME performed the remainder (26). We found no correlation between the length of the endoscope inserted and the position of the endoscope in the colon ($p = 0.14$).

Table 5.1 Demographic details

	Overall	ME	NME
Number of patients	51	25	26
Sex (Males: Females)	28:23	10:15	14:12
Median age * in years	55 (37, 69)	53 (33, 71.5)	57.5 (40, 65)
Median time for completion*	12 (10,16)	11 (10,14)	13 (12,16)
Overall Accuracy	74.5% (38/51)	80 % (20/25)	70 % (18/26)
Findings on FS			
- Normal	34 (66.7%)	15	19
- Cancer	01 (2%)	01	00
- Polyp	05 (9.8%)	02	03
- Colitis	07 (13.7%)	04	03
- Diverticular disease	04 (7.8%)	03	01
Indications			
- Rectal bleeding	34 (66.7%)	16	18
- Polyp on barium enema	4 (7.8%)	01	03
- Change of bowel habits	8 (15.7%)	06	02
- Diarrhoea (with bleeding)	3 (5.9%)	01	02
- Colitis assessment	2 (3.9%)	01	01

* range in brackets

Figure 5.1 X-ray abdomen showing a clip at the splenic flexure (incorrectly identified by endoscopist)

5.3.1 Accuracy of endoscopists' assessment and completion rates

Of 51 patients included in the study, the descending colon was reached in 18 patients and splenic flexure or beyond in a further 20 patients. The scope reached upto the sigmoid colon in the remaining 13 patients (26%). However, in 6 out of these 13 incomplete flexible sigmoidoscopies, the procedure was terminated in sigmoid colon because of pain (2) or poor bowel preparation (3) or severe proctitis (1). This gives a crude completion rate of 74% and a corrected completion rate of 84%.

The endoscopists' assessment of the position of the scope in the colon was accurate in 38/51 cases, giving an overall accuracy of 75%. This compares favourably with previous studies where the accuracy rates were around 50%[33]. The ME was inaccurate in 4

procedures. There was over estimation of the position of the endoscope in 2 out of 4

procedures and under estimation in the remainder. The NME was inaccurate in 8

procedures, over estimating the position in 4 cases and under estimating in the remainder.

All patients who had incomplete FS subsequently underwent repeat procedures and no

significant pathology was found.

Table 5.2 Analysis of inaccurate predictions of position

	Endoscopist opinion regarding position of the endoscope in colon	**Actual position of the endoscope in left colon**
Medical endoscopist		
1	Distal Descending colon	Sigmoid colon
2	Splenic flexure	Sigmoid colon
3	Sigmoid colon	Proximal descending colon
4	Distal Descending colon	Transverse colon
5	Sigmoid colon	Proximal descending colon
Non-medical endoscopist opinion		
1	Splenic flexure	Proximal Descending colon
2	Splenic flexure	Sigmoid colon
3	Sigmoid colon	Distal Descending colon
4	Distal Descending colon	Splenic flexure
5	Proximal Descending colon	Sigmoid colon
6	Transverse colon	Descending colon
7	Sigmoid colon	Proximal Descending colon
8	Descending colon	Transverse colon

5.3.2 Medical versus non-medical endoscopists

The demographic features were similar in both groups (table 5.1). There was no difference between the two groups in terms of ability to reach the transverse colon flexure, completion rates, total procedure time and depth of insertion. The medical endoscopists' impression regarding the position of the scope in the colon was accurate in 20 out of 25 procedures (80% accuracy) as compared to the non-medical endoscopist's impression (18 accurate out of 26; 70%). These differences did not reach any statistical significance (Fisher's exact test, P=0.09). The medical endoscopist's opinion was inaccurate in 5 examinations. Table 4.2 gives details of sites of inaccuracies with both medical and non-medical endoscopists. The ME over-estimated the position in 2 examinations and under-estimated the position in further 3 patients. On the other hand, the NME over-estimated the position in 3 patients and under-estimated in 5 procedures. The median procedure time and depth of insertion were similar in both groups (table 5.3).

Table 5.3 Medical versus non medical endoscopists: outcomes

	Medical endoscopist	Non-medical endoscopist	P value
Numbers to descending colon	8	10	-
Numbers to splenic flexure	9	4	-
Numbers to transverse colon	4	3	-
Sigmoid colon only	4	9	-
Completion rate	22/25 (88%)	21/26 (85%)	0.54
Overall accuracy	80% (20/25cases)	70%(18/26cases)	0.09
Mean procedure time (range) in minutes	12 (8,14)	14 (10,18)	0.9
Mean insertion depth in cm	75 (67.5, 82)	67.5 (55,71	0.34

5.4 Discussion

We have shown in this study that the endoscopists' impression regarding the position of the scope in the left colon during flexible sigmoidoscopy is accurate in only 75% procedures. The technique of endoscopic clip application and follow-up x-ray is a feasible method of assessing completion. Furthermore, the study has shown that were no differences between the medical and non medical endoscopists with regards to accuracy and FS completion rates.

The JAG defines a complete FS as intubation of the descending colon. However, technically incomplete examination is an unfortunate drawback of FS. Using radio opaque clips, Lehman et al[51] noted that the splenic flexure was reached in only 33% of flexible sigmoidoscopies. The implications of incomplete examination are enormous in that this may result in missed polyps and cancers[47]. Additionally, both the patient and the endoscopist may be falsely reassured regarding the findings on the background of a potentially incomplete FS.

Anatomical factors, preparation quality, variations in patient tolerance and female gender all play a role in limiting depth of insertion and are hence more likely to be associated with incomplete FS[144]. Inaccurate assessments of the anatomical segment of the colon reached by the endoscopist can also potentially lead to incomplete FS. However, there is a serious problem with this failure- if the endoscopist does not recognise that a procedure is incomplete and assumes he/she has identified sufficient left colon, not only do lesions tend to be missed, but patients might be falsely reassured as well. This makes quality assurance

of endoscopists performing flexible sigmoidoscopy with regards to the accuracy of their assessment of position in colon particularly important.

How do we objectively assess an endoscopist's accuracy in determining completion in flexible sigmoidoscopy? Due to the lack of consistent anatomical landmarks in the left colon, there is no universally agreed technique of objectively documenting completion in flexible sigmoidoscopy. There are a couple of previous studies that attempt to address this question. Adam et al[33] used an electromagnetic imaging device (EMI) to identify the position of the endoscope in the left colon and compared with the endoscopists own assessment of the position. The study showed that the endoscopists' assessment of position in the left colon was accurate in around 50% of cases. The splenic flexure was not reached in 60% of cases. However, the EMI device is cumbersome to use and impractical. This technique cannot be used on a routine basis and has also not been validated. A second study[145] used a video assessment scoring method to determine the accuracy of endoscopist performance at flexible sigmoidoscopy. The aim of this study was to develop a valid and reliable objective scoring method using video footage of screening flexible sigmoidoscopies[145]. The final parameters used for scoring included time spent viewing the mucosa, re-examination of poorly viewed areas, suctioning of fluid pools, distension of the lumen, lower rectal examination, and overall quality of the examination. Though the technique was used to assess overall quality of FS, there is no specific focus on completion itself. Moreover, this technique necessitates video recording of the procedure making it impractical and cumbersome. We, on the other hand, have shown that the technique of applying endoscopic clips with follow-on abdominal x-ray to determine the accuracy of the endoscopists' assessment of the position of the endoscope is feasible and safe. The

application of an endoscopic clip does not add significantly to the procedure time. Endoscopic clips with abdominal x-ray could probably be used in a random number of procedures every two years for each endoscopist to determine their completion rates as well as their accuracy of assessment of position in the colon. These results could be re-audited in two years to determine if any lesions have been missed. This technique can also be used when the endoscopist performing the flexible sigmoidoscopy is not sure about his/her position in the left colon. The limitation of this technique is that it has not been validated. However, there is no criterion standard against which the technique can be validated. A second limitation is that the ability of the abdominal x-ray to accurately identify the position of the clip has not been validated against a standard radiological imaging technique like computerized tomography of the abdomen (CT). The future plan is to validate this technique against CT abdomen and also video footage of the procedure.

This study has also shown that localization of the segment of colon reached by depth of insertion of the endoscope is not as accurate as the endoscopists' impression. When the endoscope was inserted up to 60cm, the splenic flexure was reached in only 25% of cases, and the descending colon was reached in 60% of cases. However, it was not possible to exactly correlate the depth of insertion with the anatomical segment of the left colon, though we could probably estimate that when the endoscope is inserted for 60cm, there is a 60% probability that the descending colon will be reached.

We also compared the accuracy of the medical and the non-medical endoscopist. While the medical endoscopist was accurate in 20/25 cases, the non-medical endoscopist was accurate in 18/26 cases. These differences were not statistically significant. There were no differences between the two endoscopists in terms of mean insertion depth (75cms versus

67.5 cms; p=0.34) and completion rates to descending colon (22/25 versus 21/26 cases; p=0.54). It is important to note that this is not a randomised controlled trial and was not powered to detect any differences. However, the findings are reassuring regarding both the medical and the non-medical endoscopists.

In conclusion, this study has shown that the clinical impression of endoscopists is accurate in only around 75% of cases, implying the need for quality assurance. The technique of endoscopic clipping with follow up abdominal x-ray is a feasible method of objectively documenting completion. However, there is a need for further validation of the technique before it can be routinely applied. Finally, this study has shown that non-medical endoscopists can perform FS with similar accuracy, completion rates and depth of insertion, as compared to medical endoscopists.

Chapter 6 Randomised controlled trial of sedation for colonoscopy: Entonox versus Midazolam/Fentanyl

6.1 Introduction

With screening programmes shown to reduce mortality from colorectal cancer, and their subsequent introduction in the United States and recently in the United Kingdom, it is obvious that referrals for colonoscopy have increased. A prerequisite for successful colonoscopy is good analgesia and sedation during the procedure. Colonoscopy is usually performed with the patient sedated using a combination of benzodiazepines and an opioid[74, 146-149], mostly midazolam and fentanyl or pethidine (mepiridine), which is the standard practice in most countries. Although such intravenous sedation provides varying degrees of pain relief, it is associated with a small but definite risk of cardiopulmonary complications of 0.1% to 0.54%[75], and mortality of 0.03%[74]. Oxygen desaturation seems in part to be due to medication, even when an attempt is made to titrate the dose[74, 150-152]. Patient controlled Nitrous oxide mixed with oxygen (50:50; Entonox[®], BOC gases, Guildford, UK) has been shown to be safe and effective, even under adverse cardiac conditions. This weak inhalation agent has anaesthetic, sedative and anxiolytic properties. Entonox[®] has a low blood/gas solubility ratio and, therefore, has a rapid onset and clearance time. It is used to alleviate pain in dental treatment, in ambulatory care including ischaemic heart disease, and during prolonged labour.

The aim of this randomised controlled trial was to evaluate the role of Entonox[®] as a sedative-analgesic in colonoscopy compared with intravenous midazolam-fentanyl, in terms of analgesic efficacy, depth of sedation, rate of complications, recovery of psychomotor function and time to discharge.

6.2 METHODS:

6.2.1 Study Design

This trial was performed in the endoscopy unit at Castle Hill Hospital, Cottingham, United Kingdom between April, 2005 and March, 2006. The study was approved by the South Humber Research Ethics Committee, and the Clinical Trials Unit, Medicines and Health Regulatory Authority, and preregistered with the European Clinical Trials Database (EudraCT number 2004-004890-26) and the International Standard Randomised Controlled Trial Number Register (ISRCTN 81142957). It was undertaken according to International Conference on Harmonisation good clinical practice standards, including on-site monitoring and source data verification.

6.2.2 Inclusion and Exclusion Criteria

All patients undergoing elective colonoscopy were invited to participate in the trial. They received detailed information leaflets (approved by the Ethics committee) about the trial two weeks before the procedure and also had an opportunity to discuss the trial with the co-ordinator. Informed written consent was obtained from all patients before they were randomised. Patients with a history of pneumothorax or severe bronchial asthma, previous colonic resection, intolerance to any of the drugs, those undergoing upper gastrointestinal endoscopy and colonoscopy simultaneously, and those taking opiates were excluded from the study.

6.2.3 Randomisation and allocation concealment

Block randomisation was used, with stratification based on the types of colonoscopist: doctors, nurse colonoscopists and non-medical non-nurse colonoscopists (also known as non-medical colonoscopists). A block size of six was used to help concealment of allocation. The assignments were held in sequentially numbered, opaque sealed envelopes.

The envelopes were opened sequentially and only after the participant's name, address, date of birth and other details were written on the appropriate envelope at a central location, by a person unrelated to the trial. Neither the patients nor the colonoscopists were blinded to the treatment modality.

6.2.4 Interventions

Patients were randomly assigned to receive either intravenous Midazolam (2mg/ml; Hypnovel®, Roche, UK) and Fentanyl (50mcg/ml; Sublimaze®, Janssen-Cilag, High Wycombe, UK) or inhaled Entonox®. They were informed about the relevant procedure, the reasons for sedation and the technique.

Patients randomised to intravenous sedation 0.75-1mg Fentanyl, followed by 1-mg incremental doses of midazolam (2mg/ml) up to a maximum of 10 mg. All patients received supplemental oxygen at the rate of 2-3 l/minute during the procedure. Colonoscopy was performed 5 minutes after the last dose of Midazolam. The colonoscopist was allowed to administer further doses of midazolam, if warranted throughout the procedure.

Those randomised to Entonox® inhaled the gas through a mouthpiece for a full 120 seconds initially, for a further period until the caecum was reached, and as required thereafter. If the patient found the procedure too uncomfortable or the colonoscopist judged that the patient was in discomfort, intravenous sedation was given, but only after a washout of 4-5 minutes.

All patients were assessed continuously throughout the procedure, in accordance with the guidelines of the British Society of Gastroenterology[130] (see table 6.1). The aim of conscious sedation was that the patient should be able to obey commands at all times.

Patients were allowed to recover after the procedure and discharged by recovery room nursing staff according to pre-existing discharge criteria (table 6.1).

Table 6.1 Monitoring of patients and discharge criteria

Monitoring

1. 2-3L oxygen given to all patients

2. Intravenous cannulae in situ before the procedure in all patients

3. Pulse oximetry

4. Clinical monitoring- including heart rate, blood pressure. This was continued into recovery area, and it was the responsibility of both the endoscopists as well as the nurses to monitor these physiological variables.

5. Full resuscitation equipment available within easy reach in the endoscopy suite.

Discharge Criteria

1. Patient responded appropriately to questions and was able to communicate clearly.

2. Patient was able to sit upright for at least 5 minutes and was able to tolerate liquids/solids. Patient was able to dress independently and use the toilet.

Modified Observer's Assessment and Alertness/Sedation Scale (MOAAS)

SCORE	RESPONSIVENESS
5	Responds readily to the name spoken in normal tone
4	Lethargic response to the name spoken in normal tone
3	Responds only after the name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

6.2.5 Colonoscopy

All colonoscopies were performed according to a standard operating procedure with the Pentax video colonoscopes (Pentax, Hamburg, Germany). Colonoscopy was carried out by three different types of colonoscopists: doctors (colorectal consultants), senior nurses with experience of more than 5000 colonoscopies, and non-medical colonoscopists. Completion to the caecum was documented based on two of three landmarks- ileocaecal valve, appendiceal orifice and/or the tri-radiate fold.

6.2.6 Data collection and outcomes

Demographic and clinical features recorded for all patients included age, sex, weight, height, clinical indications, past and family history, results and procedural findings.

All participants completed a Hospital Anxiety and Depression questionnaire, baseline letter cancellation test and scored pain on a 100-mm visual analogue scale before randomisation, but after giving consent to be included in the trial. Patients who refused to participate were asked their reasons for doing so, such as experience with any of the drugs or frightened by the idea of deciding own sedation. These patients also completed questionnaires before and after the procedure.

The primary end-point was the degree of pain experienced by the patient during the procedure assessed on a 100-mmvisual analogue scale (VAS). Measurements were taken immediately, and at15-min intervals after the procedure until discharge (table 6.2). Patients also marked a VAS at 24 hours after colonoscopy after allowing recovery from sedation.

The secondary end-points included degree of sedation, patient, nurse and endoscopist satisfaction, complication rate, time taken to reach caecum and total colonoscopy time, completion rate, degree of psychomotor recovery and time to discharge (table 6.2).

The degree of sedation was measured on the Modified Observer's Assessment of Alertness/Sedation scale (MOAAS; table 6.1), at 1-min intervals throughout the procedure and 5-min intervals during recovery.

Patient satisfaction was measured at discharge and 24 hours after colonoscopy by means of a 100-mm VAS, which was incorporated into a previously validated patient satisfaction questionnaire for colonoscopy[109]. Nurse and Endoscopist satisfaction was measured using a similar 100-mm VAS, as part of a different questionnaire.

Psychometric tests were administered immediately upon arrival of the patient to the recovery area and then at 15-min intervals until discharge. Inability of the patient to perform the tests immediately on return to the recovery room was noted. Psychomotor recovery was assessed using the Letter cancellation test[153], which measures concentration and perception. The patient was presented with a sheet of paper containing a printed paragraph of 20 rows of 40 randomly arranged letters, and then asked to read from left to right and top to bottom, simultaneously marking through all occurrences of a pre-designated letter. The number of lines completed in 120 seconds and the number of times the pre-designated letter was correctly identified were recorded. Post-procedure scores were compared with baseline values and results presented as percentage recovery of psychomotor function. This test has previously been shown to be an accurate means of measuring psychomotor recovery in the post-endoscopy setting[153, 154].

The efficacy of sedation was evaluated by colonoscopists in terms of the rate of caecal intubation, time taken to reach the caecum, total colonoscopy time and complication rate. The colonoscopists also completed a questionnaire concerning the degree of sedation, difficulty of colonoscopy and difficulty in manoeuvring the patient. After the procedure the attending nurses completed a questionnaire for each colonoscopy concerning the

perceived adequacy of sedation, ability of the patient to assist with moving during the procedure, and maximum depth of sedation.

Table 6.2 **Administration of questionnaires to participants**

  A. Pre-colonoscopy (after consent and before randomisation)

      1. Hospital Anxiety and Depression Scale

      2. Letter Cancellation Test

      3. 100 mm Visual Analogue Scale

  B. Post colonoscopy

      1. Visual Analogue Scale- immediately after the procedure and at 15-minute intervals up to and including at discharge; repeated at 24-hours post colonoscopy

      2. Letter Cancellation Test – immediately after the procedure and at 15-minute intervals up to and including at discharge

      3. Patient satisfaction questionnaire- at discharge and at 24 hours post colonoscopy

6.2.7 Statistical Analysis and sample size calculation

The required sample size was estimated from the results of a pilot study in which the degree of pain experienced by 20 patients undergoing colonoscopy under Entonox® or intravenous midazolam-fentanyl sedation (10 patients in each group) was measured on a 100-mm VAS. Using a power of 80 percent and a 2-sided level of significance of 0.05 (based on Wilcoxon-Mann-Whitney statistic appropriate for a two-group comparison), it was calculated that a total sample size of 120 would be required to determine a difference of 15 points on a 100-mm VAS between groups. The 20 patients in the pilot study were not included in the final analyses for the randomised controlled trial.

All analyses followed the intention to treat principle. No interim analyses were performed before analysis of the primary endpoint. Demographic and baseline characteristics were compared by two-way ANOVA for continuous data and Fishers exact test for categorical data. Differences in proportion were tested using the chi-squared test, or Fisher's exact test for smaller samples. VAS scores, sedation scores, postoperative time to discharge and results of the letter cancellation test were evaluated using the Mann-Whitney U test. All P values are two tailed.

6.3 Results

6.3.1 General characteristics

Of a total of 176 patients assessed for eligibility, 45 were excluded (*Fig.6.1*):13 were ineligible (seven had undergone surgical resection, two had a combined upper and lower gastrointestinal endoscopy, and four had severe asthma) and 32 patients refused to participate (20 patients did not want to participate in any trial as they were too anxious, and the remainder had inhaled Entonox[®] in the past and were not happy to participate). The remaining 131 patients were included in the trial, of which 65 were randomized to receive Entonox[®] and 66 intravenous sedation with midazolam–fentanyl.

Figure 6.1 Flowchart of patients in the randomised controlled trial

176 patients were assessed for eligibility

45 patients were excluded
1. Not meeting inclusion criteria (n= 15)
2. Refused to participate (n=30)

Randomised
N=131

Randomly assigned to Entonox® group
N=65

Randomly assigned to Intravenous sedation
N=66

65 patients completed trial

66 patients completed trial

Analysed n=65
No exclusions

Analysed n=66
No exclusions
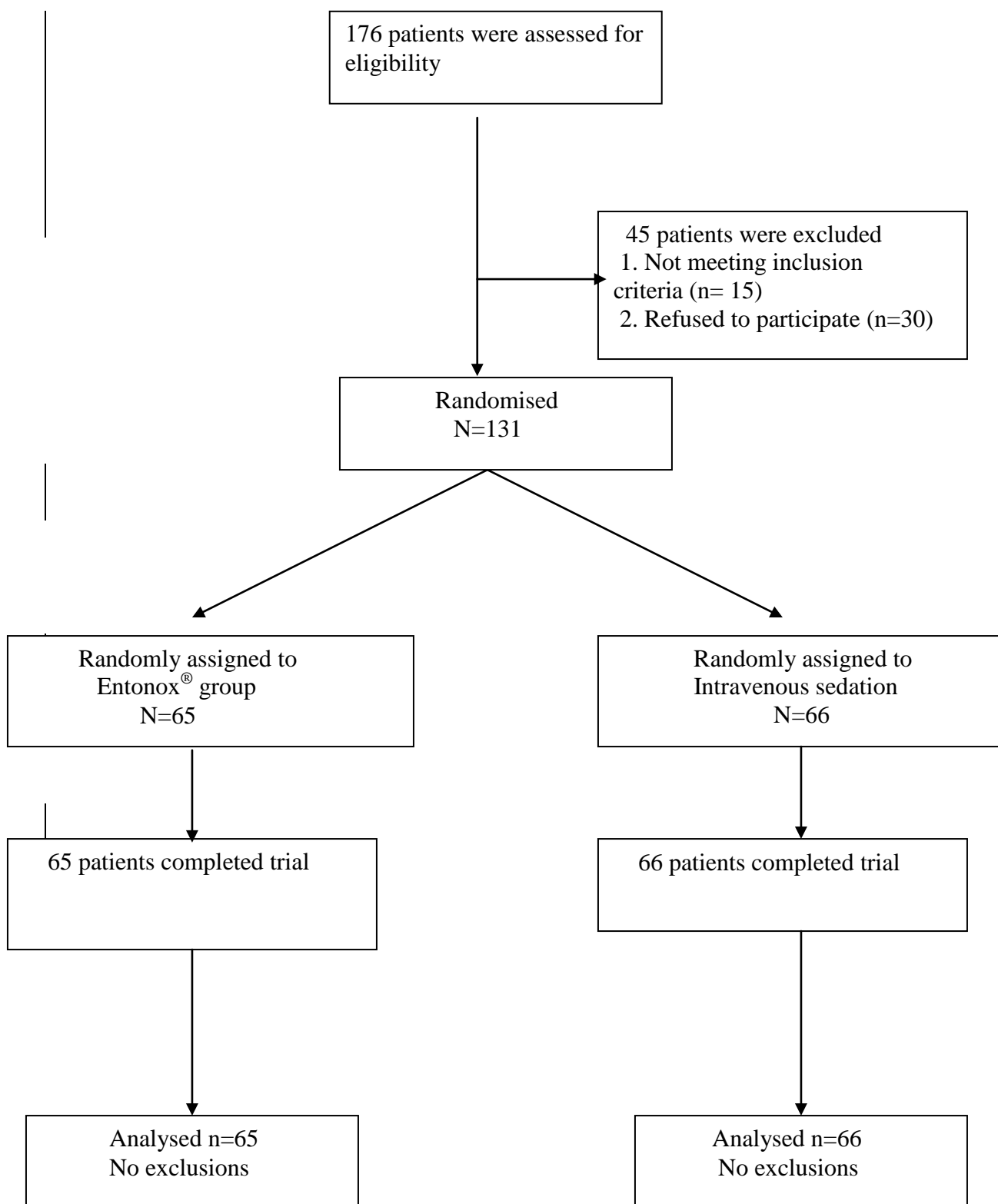
The two groups had similar demographic characteristics and American Society of

Anesthesiologists (ASA) grades, and there was no difference in pre-procedure anxiety

scores (7·5 (range 3–10) *versus* 6.0 (range 2–12); *P* = 0.143) (*Table 6.3*).

Table 6.3 Baseline characteristics

	ENTONOX[®] (N=65)	*Midazolam-fentanyl* (N=66)
Gender (M:F)	29:36	34:32
Median age (years)(range)	56.1 (39-70)	60.4 (41-69)
ASA class 1	53	55
* 2*	12	11
Pre-procedure Anxiety (median)	7.5 (3-10)	6 (2-12)
Doses		
* Midazolam*	-	4 mg
* Fentanyl*	-	100 mcg

Indications for colonoscopy included symptoms (79 patients), family history (28) and

follow-up (24). Colonoscopy findings included colorectal cancer (five), polyps (26),

normal (53) and other pathology (47). Median doses of midazolam and fentanyl were 4

(range 3–5) mg and 0·1 (range 0·05–0·1) mg respectively. There were no complications in

either group, although one patient in the intravenous group complained of nausea which

settled spontaneously. None of patients in the Entonox[®] group required additional sedation

or conversion to intravenous sedation. Twenty-one patients had undergone colonoscopy

previously, and another 11 had had flexible sigmoidoscopy. Of the former 21 patients, 19

had received midazolam with fentanyl or pethidine, whereas two had received pethidine

only. Nine of these patients were randomized to Entonox[®] in the present trial and found

the current sedation better. The remaining 12 patients received intravenous sedation during

this study, of whom six found the current regimen better, two described no difference and the remaining four thought the current regimen was worse.

6.3.2 Primary outcome - Pain

Patients in the Entonox® group recalled significantly less pain during colonoscopy than those receiving midazolam–fentanyl (mean VAS score 16·7 *versus* 40. 1; $P = 0·001$; 95 per cent confidence interval (c.i.) of the difference 21·5 to 29·1). These differences persisted at different points after the procedure and also after 24 h (*Table 6.4*).

Table 6.4 Pain scores on visual analogue scores

Pain scores on VAS	*Entonox®*	*IV*	*Significance (p-value)*
At discharge	16.7 (0-24)	40.1(18-91)	0.001
15 min	16.5 (0-24)	39.6 (18-91)	0.001
30 mins	16.6 (0-25)	40 (18-92)	0.001
At 24- hours post procedure	15.0 (0-25)	38 (15-94)	0.001

6.3.3 Depth of sedation

The median depth of sedation measured using the MOAAS was 4 (range 4–5) and 3 (range 3–4) in patients receiving Entonox® and midazolam–fentanyl respectively ($P = 0·163$).

6.3.4 Intubation rates and completion time

Caecal intubation rates were 94 and 92 per cent respectively ($P = 0·513$). Two patients in the Entonox® group had an impassable stricture/cancer and one patient had poor bowel preparation. In another patient, it was not technically possible to complete the colonoscopy beyond the hepatic flexure. In the intravenous sedation group, three patients had poor bowel preparation, one patient had a technically difficult colon and one patient had a

distally obstructing cancer. There was no difference between the groups in time to reach the caecum or total completion time (*Table 6.6*).

6.3.5 Psychomotor recovery and time to discharge

Patients in the Entonox® group had recovered 92·2 (range 89·5–96·0) per cent of their baseline psychomotor function immediately upon return to the recovery area, whereas recovery in the intravenous sedation group could not be calculated as most patients were unable to answer the letter cancellation test due to the effects of sedation. Values at 15 min after the procedure were 94 (range 92·5–100) and 68 (range 60·8–71·1) per cent respectively. At the time of discharge, significant differences remained and psychomotor function had fully recovered only in the Entonox® group (*Table 6.5*). Patients undergoing colonoscopy under intravenous sedation had a longer time to discharge.

Table 6.5 Recovery of psychomotor function and time to discharge

Variables	**Entonox®** *(95%confidence intervals)*	*Midazolam-fentanyl (95%confidence intervals)*	*Significance p-value (Mann Whitney U test)*
Recovery of function Immediate 15 min Discharge	92% (89.5,96) 94% (92.5,100) 100%	- 68% (60.8,71.1) 87% (82,94.6)	- p=0.001 p=0.003
Time to discharge (Mean)	28 min	51 min	p=0.001

6.3.6 Patients' assessment

All patients completed the satisfaction questionnaire before being given their results so that the colonoscopy findings did not affect the satisfaction scores. The median

satisfaction score was significantly higher in patients who received Entonox® (96 *versus*

89; *P* = 0·024; 95 per cent c.i. of the difference 4 to 12) (*Table 6.6*). These differences

persisted when patient satisfaction was assessed 24 h after the procedure. More patients in

the Entonox® group would agree to a repeat colonoscopy under the same sedation (89

versus 73 per cent; *P* = 0·011. Sixty per cent of patients who received Entonox® reported

requiring additional sleep compared with 95 per cent of those who had intravenous

sedation (*P* = 0·032). Median time to return to normal activities after the procedure was

1·5 (1–4) h and 9·5 (8–12) h respectively (*P* = 0·011) in Entonox® and intravenous groups.

Table 6.6 Patients', endoscopists' and nurses' assessment

Patient assessment	**Entonox®** (n=65)	*Midazolam-fentanyl (n=66)*	*Significance (p-value)§*
Median Satisfaction score†	96.4 (90-100)	89 (20-95)	0.001
*Agree to repeat use of same sedation**	58 (89)	48 (73)	0.011¥
Endoscopists' assessment			
*Caecal intubation**	61 (94)	61 (91.7%)	0.513¥
Median time to caecum (min)	18 (6-24)	20 (5-23)	0.812
Median completion time (min)	26.5 (18-47.5)	31.9 (20.4-51.8)	0.761
Median difficulty of colonoscopy‡	17 (10-31)	14 (12-30)	0.714
Median Satisfaction Score†	95 (90-100)	90 (70-100)	0.061
Nurses' assessment			
Median satisfaction score†	95 (30-100)	90 (20-100)	0.168
*Adequate sedation-analgesia**	56 (86)	50 (76)	0.013
*Difficulty in manoeuvring**	3 (5)	14 (21)	0.001

*Values in parentheses are ranges, except *Values are percentages. †On a 100-mm visual analogue scale. ‡On a 100-mm visual analogue scale, where O is the easiest, and 100 is*

the most difficult ever seen- 50 is very difficult. §Mann-Whitney U test, except ¥chi-squared test.

6.3.7 Endoscopists' assessment

The endoscopists assessed the technical difficulty of procedures carried out with the two types of sedative. Median scores for difficulty were similar, as were satisfaction scores for sedation (*Table 6.6*). Analysis of the endoscopists' perception of difficulty in manoeuvring patients during colonoscopy showed that more patients sedated with midazolam–fentanyl were difficult to move as compared to the patients receiving Entonox®.

6.3.8 Nurses' assessment

There was no difference in nurses' assessment of satisfaction with either type of sedation (*Table 6.6*). Only three patients in the Entonox® group were difficult to manoeuvre during the procedure compared with 14 patients in the intravenous sedation group.

6.3.9 Effect of type of colonoscopist

The baseline characteristics were similar for the three types of colonoscopists.

Table 6.7 Baseline characteristics in the 3 groups

	Doctors N=44	Nurses N=44	Non-Medical N=43
Age (median) in years	62	60	63.5
Gender (M:F)	26:18	29:15	25:18
Intravenous -Midazolam -Fentanyl	2.5mg$ 75mcg*	2.0mg$ 75mcg*	3mg$ 100mcg*
ASA grade Grade 1 Grade 2	32 12	31 13	32 11

*= microgrammes. $ = milligrammes.

Subgroup analysis revealed no differences between the three types of colonoscopist in terms of pain scores, patient and nurse satisfaction.

Table 6.8 Patient and attending nurse assessments

	Doctors N=44	Nurses N=44	Non-Medical N=43	Significance P

Pain Scores
  -discharge
  -24 hours
	21
	22
		24
		24
			18
			19
				0.9
				0.9

Patient satisfaction	96	95	95	-
Nurse Satisfaction	4.1/5	4.3/5	4/5	0.76

There were no differences in the groups in terms of time to reach the caecum, completion and complications rates, sedation or pain scores and recovery times (table 6.9).

Table 6.9 Primary and secondary outcomes for all the groups

	Doctors N=44	Nurses N=44	Non-Medical N=43	Significance (p-value)
Completion Rates	95%	97.5%	92.5%	0.3
Time to Caecum	14 min	16 min	16.5 min	0.2
Total time	18 min	19 min	21 min	0.09
Time to discharge	38 min	43 min	36 min	0.08

6.4 Discussion

This randomised controlled trial has shown that sedation with Entonox® effective for colonoscopy. Both diagnostic and therapeutic procedures were performed efficiently, with a high completion rate with no complications. Patients experienced less discomfort and

pain, recovered earlier from sedation and are discharged home faster than those given intravenous sedation. Use of Entonox was also associated with higher patient, endoscopist and nurse satisfaction scores.

Colonoscopy can be uncomfortable, necessitating the administration of analgesics and sedatives. The commonly used benzodiazepine -opioid combination can cause cardio-respiratory depression and occasionally death, especially in elderly patients. An important reason for this is the lack of a clear dosing regimen and difficulty in dose titration. As intravenous sedation causes cardio-respiratory depression, the alternative would be to use brief analgesia (with sedation) that offers fast recovery without risk of complications. Entonox® clearly seems to fit the bill. It is effective and easy to administer; the patient inhales through a special mouthpiece attached to a cylinder and this obviates the need to administer additional oxygen through a different nasal cannula. The onset of action is rapid, and the effect is apparent within 1-2 minutes. Patients tend to become slightly drowsy, but remarkably more relaxed in the initial 2 minutes, which contributes to pain relief.

The primary outcome measured in this study was pain perceived by the patient, which was measured at different times after the procedure. Measurement of pain after 24 hours is important as the effects of sedation are minimised by then. Pain perception at 24 hours also influences patient's decision to attend for repeat colonoscopy if necessary.

There were no complications in either group. There is virtually no risk of overdose with Entonox® as the patient's level of consciousness governs his/her ability to maintain the flow of gas. There is no risk of inhalation of the gas by colonoscopy staff, as it flows through a one-way valve and does not leak into the environment.

The total procedure time was similar in both groups. However, psychomotor function recovered more rapidly in patients sedated with Entonox®, owing to rapid elimination of the gas from the body, usually within 30-45 seconds after stopping inhalation. These patients were discharged earlier and were able to return to routine activities more quickly than those receiving intravenous sedation. With 100% recovery of psychomotor function after the use of Entonox® , as also noted previously[155], there is no apparent reason to stop patients from driving home immediately after discharge. The manufacturer has now issued guidelines indicating that patients can drive immediately after discharge from the endoscopy unit after undergoing any procedure under Entonox®.

Patient satisfaction is another area where current practice is suboptimal and the use of Entonox® also addresses this issue. Higher patient satisfaction with Entonox® was related to the reduced pain and faster recovery. Entonox® sedation is essentially patient controlled, and this probably contributed to greater patient satisfaction as well. Inhalation of the gas as necessary, with longer and deeper breaths allowing greater volumes in the lungs, not only helps in relieving discomfort and pain, but alleviates anxiety as the patient is in control of their own pain relief. The latter contributes to the often discussed and possible placebo effect with Entonox®.

Currently, there is a low uptake of colorectal cancer screening by patients in the USA[156]. It is, therefore, essential to optimise the experience of colonoscopy, by minimising discomfort and allowing early resumption of normal activities. This will lead to an increase in the number of patients willing to undergo the procedure for screening.

The present results differed from previous studies[78, 81, 157] on the use of Entonox® for colonoscopy in that Entonox® was shown to be superior to intravenous agents. The dose of midazolam used in this trial (median 4mg) was comparable to that used in previous

studies. Forbes and Collins[81] used a median of 4.7 mg midazolam, but still concluded that intravenous sedation was better than Entonox®. Importantly, the doses of midazolam in the participant and non-participant groups in our study were similar, hence confirming the absence of any bias.

A limitation of this study is that patients and colonoscopists were not blinded to the type of sedation. Even though it has been shown previously that the noise made by Entonox® cylinders can be masked[78, 157], the pilot study demonstrated that this is difficult to achieve. However, even without blinding, it was possible to address the issues of whether Entonox® is able to provide sufficient sedation-analgesia and whether it could be adopted in a busy endoscopic unit. None of the colonoscopists had previously used Entonox® for sedation, and this should reduce any bias. Furthermore, the person collecting the data was blinded to the treatment offered. Another limitation of the trial is that the primary outcome was measured using a VAS, as no absolute pain scoring systems are available for colonoscopy. However, it was possible to compare VAS scores between the two groups and to establish that Entonox® was associated with less pain. Baseline scores were also collected to determine whether patients were already in pain before the procedure. Furthermore, there are contraindications to the use of Entonox® in patients with history of pneumothorax or severe emphysema, limiting the use of Entonox®. However, only a small proportion of patients fall into this category- 7% in our series. Routine intravenous sedation or propofol sedation can be offered to these patients.

In the current global financial scenario, hospitals look for cost-effectiveness in the products they choose, as well as safety, efficacy, ease of use and efficiency. The cost of a single cylinder of Entonox is around £110. Each cylinder can be used for around 65 patients, as seen in our study. This works out to around £1.60 per patient per colonoscopy.

On the other hand, the cost of intravenous sedation is around £1 per patient for every colonoscopy (Midazolam- £0.73 and Fentanyl £0.23). However, we have shown that patients undergoing sedation with Entonox recover faster and can be discharged earlier, thereby saving time and bed stay costs. Patients can drive home 30 minutes after Entonox® sedation. These are potential economic benefits for the patients because they no longer require taking additional time off work, and do not need an escort to go home after the procedure. Entonox® is easy to use and can be administered by nurses or healthcare assistants. This potentially lowers treatment costs by avoiding more resource-demanding options.

An agent with shorter duration of action would be desirable for providing sedation in colonoscopy; one that permits more rapid recovery of function, while providing good patient comfort during the procedure and with a safety profile equivalent to that of medications currently in use. We conclude that the use of Entonox® for colonoscopy sedation is associated with better sedation-analgesia and faster recovery and discharge than intravenous sedation. Furthermore, non-medical endoscopists would be able to perform independent colonoscopy (when fully trained) without depending on either nurses or doctors for sedation, realising their full potential. We believe that Entonox® can potentially be used routinely for providing sedation for colonoscopies, except in patients with contraindications to the use of Entonox®.

Chapter 7 Randomised controlled trial of patient controlled sedation for colonoscopy: Target controlled patient-maintained propofol versus Entonox

7.1 Introduction

Colonoscopy is characterised by short intervals of discomfort, mostly related to stretching of colonic mesentery[158]. Patient controlled analgesia/sedation (PCA) is ideally suited to manage this type of pain. PCA is accomplished with a specific pump that delivers a preset dose of the medication in response to either the press of a button or, in case of inhaled gases, a deep breath through the face mask. There is a growing interest in patient controlled sedation for colonoscopy. Several studies[159-161] have shown that patients receiving PCA experience procedure-related satisfaction that is comparable with and in some cases, better than, conventional sedation. This satisfaction is partly because it allows patients to be in control of their pain relief. The total dosage of drug used tends to be lower than that used in conventional sedation, and, thus recovery is reported to be faster.

For a drug to be effective in a PCA system, it should have rapid-on and rapid-off pharmacokinetic properties[158]. In the previous randomised controlled trial (chapter 6), we have shown that Entonox® is superior to midazolam/fentanyl for providing analgesia during colonoscopy. Entonox® is now the standard of practice in our unit for sedation during colonoscopy, and is normally delivered as a patient controlled analgesia.

Propofol is another drug that has been used most frequently either as a PCA, or target controlled infusion (TCI), especially in the endoscopy setting. This sedative agent has been shown to be superior to benzodiazepines and narcotics with regard to rapid induction of sedation[162], faster recovery[163, 164] and equivalent levels of amnesia[165, 166]. However, as discussed previously, Propofol has a narrow therapeutic index and can produce deep sedation, resulting in respiratory depression and even apnoea. Because the depth of

sedation is a continuum, the doses required for conscious sedation as used in colonoscopy is markedly lower than those used for induction of anaesthesia[167]. Deeper sedation can also make patient manoeuvring difficult during colonoscopy. Propofol is typically delivered as a target controlled infusion (TCI) for various indications. TCI of Propofol enables an exact amount of the drug to be delivered, maintaining a preset concentration of Propofol in the blood or brain. This technique has previously been used in colonoscopy and Campbell[85] et al modified a TCI pump to achieve patient maintained sedation. However, this modification is experimental and its efficacy is not proven in large studies.

We devised a new protocol for delivering propofol for colonoscopy in our unit, combining a target controlled infusion with patient controlled sedation (TCI-PCA). Under this protocol, Propofol sedation was initiated with a TCI pump to achieve a preset effect site concentration, and subsequently sedation was maintained by the patients using a simple patient controlled analgesia pump (PCA) delivering Propofol on demand.

Though there have been studies[167-169] comparing Propofol with conventional intravenous sedation, there are none comparing it with Entonox®. Further to out previous study on Entonox®, we currently use Entonox® for all colonoscopies. Around 25% of all colonoscopies in the United States are now performed using propofol. Therefore, the aim of this randomised controlled trial was to evaluate the role of TCI-PCA propofol as a sedative-analgesic in colonoscopy compared with Entonox®, in terms of analgesic efficacy, depth of sedation, manoeuvrability, rate of complications, rate of psychomotor recovery and time to discharge.

7.2 METHODS:

7.2.1 Study Design

This trial was performed in the endoscopy unit at Castle Hill Hospital, Cottingham, United Kingdom between January, 2005 and June 2006. The study was approved by the South Humber Research Ethics Committee, UK, and the Clinical Trials Unit, Medicines and Health Regulatory Authority, and preregistered with the European Clinical Trials Database, as well as the International Standardised Randomised Controlled Trials Database. It was undertaken according to International Conference on Harmonisation good clinical practice standards, including independent on-site monitoring and source data verification.

7.2.2 Inclusion and Exclusion Criteria

All patients undergoing elective colonoscopy were invited to participate in the trial. They received information leaflets (approved by Ethics Committee) two weeks before the intended procedure, and also had the opportunity to discuss the trial with the co-ordinator. Patients with chronic pulmonary disease, history of colonic resection, intolerance to any of the drugs, ASA class IV, those with an allergy to soyabeans/eggs, those with history of seizure disorder, sleep apnoea, or difficult intubation, short thick neck or inability to open mouth widely, and those unwilling to enter the trial, were excluded from the study

7.2.3 Randomisation and allocation concealment

Participants were randomised using the technique of block randomisation. A block size of five was used to conceal allocation. The assignments were held in sequentially numbered, opaque sealed envelopes. These envelopes were opened sequentially and only after the participant's name, address, date of birth and other details were written on the appropriate envelope. The colonoscopists were not aware of the location of the envelopes. Neither the patients nor the colonoscopists were blinded to the treatment modality after the allocation.

7.2.4 Interventions

After informed written consent was obtained, patients were randomly assigned to receive either inhaled Entonox® or TCI-PCA propofol. They were informed about the relevant procedure, the reasons for sedation and the technique.

Patients randomised to TCI-PCA propofol were administered propofol through an intravenous cannula using our modified system. The system consisted of a Graseby® (Watford, Herts, UK) 3400 TCI pump, controlled by a microprocessor system. The microprocessor in this pump is pre-programmed with the pharmacokinetic data describing the distribution and elimination of Propofol[170]. The anaesthetist entered the patient's age and weight into the microprocessor, and the system displayed the target blood concentration and calculated effect site (brain) concentration. The anaesthetist was able to manually override the system to alter the concentration in the event of over sedation. Patients were given Propofol through the pump to achieve a target concentration of 1.2 µg/ml/hr. Simultaneously, patients were connected via a Y-connector to another PCA (patient controlled analgesia-Graseby, Watford, Herts, UK) pump containing Propofol. Patients were given a handset connected to this PCA pump. The press of this handset delivered a bolus of 200mcg/kg/ml, with a lockout period of 2 minutes. Patients were encouraged to press the button during the procedure, if they wanted to feel sleepier.

Those randomised to Entonox® were administered the gas through a mouthpiece connected to an Entonox® cylinder. This mouthpiece has a one-way demand valve system, which is operated by the act of inhalation of the patient and closes down when the patient ceases to inhale[77]. Details of delivery of Entonox® are described in chapter 6.

In both groups, colonoscopy was started once a sedation score (Modified Observer's Assessment of Alertness and Sedation Scale- MOAAS) of 4 was reached. This policy was adopted to ensure comparability of both groups. The aim of conscious sedation was that at

all times the patient should be able to obey commands, and hence an MOAAS score of 4 was the target. The anaesthetist was allowed to give intravenous Fentanyl, if patients were too uncomfortable during the procedure.

All patients were assessed continuously during the procedure, as per the guidelines of the British Society of Gastroenterology[130]. Patients were allowed to recover normally after the procedure and discharged by the recovery room staff in accordance with the existing protocols (table7.1).

Table 7.1 Discharge criteria, sedation and manoeuvrability scoring

Discharge Criteria

1. Patient responds appropriately to questions and is able to communicate clearly.

2. Patient is able to sit upright for at least 5 minutes and is able to tolerate liquids/solids.

3. Patient is able to dress independently and use the toilet.

Sedation Scoring (ASA/MOAAS)

5- responds readily to name spoken in a normal tone

4- lethargic response to name spoken in a normal tone

3- responds only after name is called loudly and/or repeatedly

2- responds only after mild prodding or shaking

1- responds only after painful trapezius squeeze

0- no response after painful trapezius squeeze

Degree of manoeuvrability (Manoeuvrability scoring)

1. Patient was awake and responded to all verbal commands

2. Drowsy and responded to most of the commands to move (>50%)

3. Patient was able to move to some commands (<50%)

4. Quite difficult to manoeuvre and/or no response to verbal commands to move (<10%)

7.2.5 Colonoscopy

All colonoscopies were performed according to a standard operating procedure with the Pentax video colonoscopes (Pentax, Hamburg, Germany). Colonoscopy was carried out by three different types of colonoscopists: doctors (colorectal consultants), senior nurses with experience of more than 5000 colonoscopies, and non-medical colonoscopists. Completion to the caecum was documented based on two of three landmarks- ileocaecal valve, appendiceal orifice and the tri-radiate fold.

7.2.6 Data collection and measurements

Demographic and clinical features recorded for all patients included age, sex, weight, height, clinical indications, past and family history, results and procedural findings.

All participants completed a Hospital Anxiety and Depression questionnaire, baseline letter cancellation test and scored pain on a 100-mm visual analogue scale before randomisation, but after giving consent to be included in the trial. Patients who refused to participate were asked their reasons for doing so, such as past experience with any of the drugs or frightened by the idea of deciding own sedation. These patients also completed questionnaires before and after the procedure.

The primary end-point was the degree of pain experienced by the patient during the procedure assessed on a 100-mmvisual analogue scale (VAS). Measurements were taken immediately, and at15-min intervals after the procedure until discharge (table 6.2). Patients also marked a VAS at 24 hours after colonoscopy after allowing recovery from sedation.

The secondary end-points included degree of sedation, patient, nurse and endoscopist satisfaction, complication rate, time taken to reach caecum and total colonoscopy time, completion rate, degree of psychomotor recovery and time to discharge (table 6.2). The degree of sedation was measured by the anaesthetist on the Modified Observer's Assessment of Alertness/Sedation scale (MOAAS; table 7.1), at 1-min intervals throughout the procedure and 5-min intervals during recovery (by the research co-ordinator).

Patient satisfaction was measured at discharge and 24 hours after colonoscopy by means of a 100-mm VAS, which was incorporated into a previously validated patient satisfaction questionnaire for colonoscopy[109]. Nurse and Endoscopist satisfaction was measured using a similar 100-mm VAS, as part of a different questionnaire.

Psychometric tests were administered immediately upon arrival of the patient to the recovery area and then at 15-min intervals until discharge. Inability of the patient to perform the tests immediately on return to the recovery room was noted. Psychomotor recovery was assessed using the Letter cancellation test[153], which measures concentration and perception. The patient was presented with a sheet of paper containing a printed paragraph of 20 rows of 40 randomly arranged letters, and then asked to read from left to right and top to bottom, simultaneously marking through all the occurrences of a predesignated letter. The number of lines completed in 120 seconds and the number of times the pre-designated letter was correctly identified were recorded. Post-procedure scores were compared with baseline values and results presented as percentage recovery of psychomotor function. This test has previously been shown to be an accurate means of measuring psychomotor recovery in the postendoscopy setting[153, 154].

The efficacy of sedation was evaluated by colonoscopists in terms of the rate of caecal intubation, time taken to reach the caecum, total colonoscopy time and complication rate. The colonoscopists also completed a questionnaire concerning the degree of sedation, difficulty of colonoscopy and difficulty in manoeuvring the patient. The difficulty in manoeuvring was measured using a manoeuvrability scoring system (table 7.1).

After the procedure the attending nurses completed a questionnaire for each colonoscopy concerning the perceived adequacy of sedation, ability of the patient to assist with moving during the procedure, and maximum depth of sedation.

Sedation complications were defined as a prolonged drop in oxygen saturation below 85%, with the need for positive pressure ventilation using a bag-valve system. Other complications recorded include prolonged drop in blood pressure and heart rate.

7.2.7 Statistical Analysis and sample size calculation

This was an equivalence study. The estimates of sample size were based on the primary outcome measure, which was the degree of pain experienced by the patient and measured using the 100-mm VAS. The variance was assumed to be similar in both groups to be around 30 points, as determined by previous studies[87] as well as our own randomised controlled trial[171]. The hypothesis was that the two drugs could be considered equivalent if the 95% two-sided confidence interval for the treatment difference fell wholly within the interval +/- 15mm. If the difference between Propofol and Entonox groups is less than this predetermined equivalence margin (-15 mm to +15 mm), then the treatments would be considered equally equivalent.

Using a statistical power of 80% and a 2-sided level of significance of 0.05, it was calculated (based on formula from Jones and colleagues[172]) that a total sample size of 96 patients would be required to test the hypothesis.

All analyses followed the intention to treat principle. No interim analyses were performed before analysis of the primary endpoint. Demographic and baseline characteristics were compared by two-way ANOVA for continuous data and Fishers exact test for categorical data. Differences in proportion were tested using the chi-squared test, or Fisher's exact test for smaller samples. VAS scores, sedation scores, postoperative time to discharge and results of the letter cancellation test were evaluated using the Mann-Whitney U test. All P values are two tailed.

7.3 Results

7.3.1 Patients

During the study period, a total of 112 patients were assessed for eligibility (figure 7.1), out of which 12 patients were excluded after eligibility assessment: 8 were ineligible (7 patients were post-surgical resection, 1 patient had severe chronic obstructive airways disease) and 4 patients refused to participate. Among those patients who refused to participate, 2 patients said that they did not want to participate in any trial as they were too anxious and the remainder said that they had inhaled Entonox® in the past and were not happy to participate. The remaining 100 patients were included in the trial, of which 50 each were randomised to receive either TCI-PCA propofol or Entonox®.

Figure 7.1. Participants in the study and randomisation

```
                    ┌─────────────────────────────┐
                    │ 112 patients were assessed   │
                    │ for eligibility              │
                    └─────────────────────────────┘
                                 │
                                 │        ┌──────────────────────────────┐
                                 │        │ 12 patients were excluded     │
                                 ├───────▶│  1. Not meeting inclusion      │
                                 │        │ criteria (n= 8)               │
                                 │        │  2. Refused to participate     │
                                 │        │ (n=4)                         │
                                 ▼        └──────────────────────────────┘
        ┌──────────────────┴──────────────────┐
        ▼                                       ▼
┌───────────────────────┐          ┌───────────────────────┐
│ 50 randomly assigned   │          │ 50 randomly assigned   │
│ to Entonox            │          │ to Propofol sedation  │
└───────────────────────┘          └───────────────────────┘
        │                                       │
        ▼                                       ▼
┌───────────────────────┐          ┌───────────────────────┐
│ 50 patients completed  │          │ 50 patients completed  │
│ trial                 │          │ trial                 │
└───────────────────────┘          └───────────────────────┘
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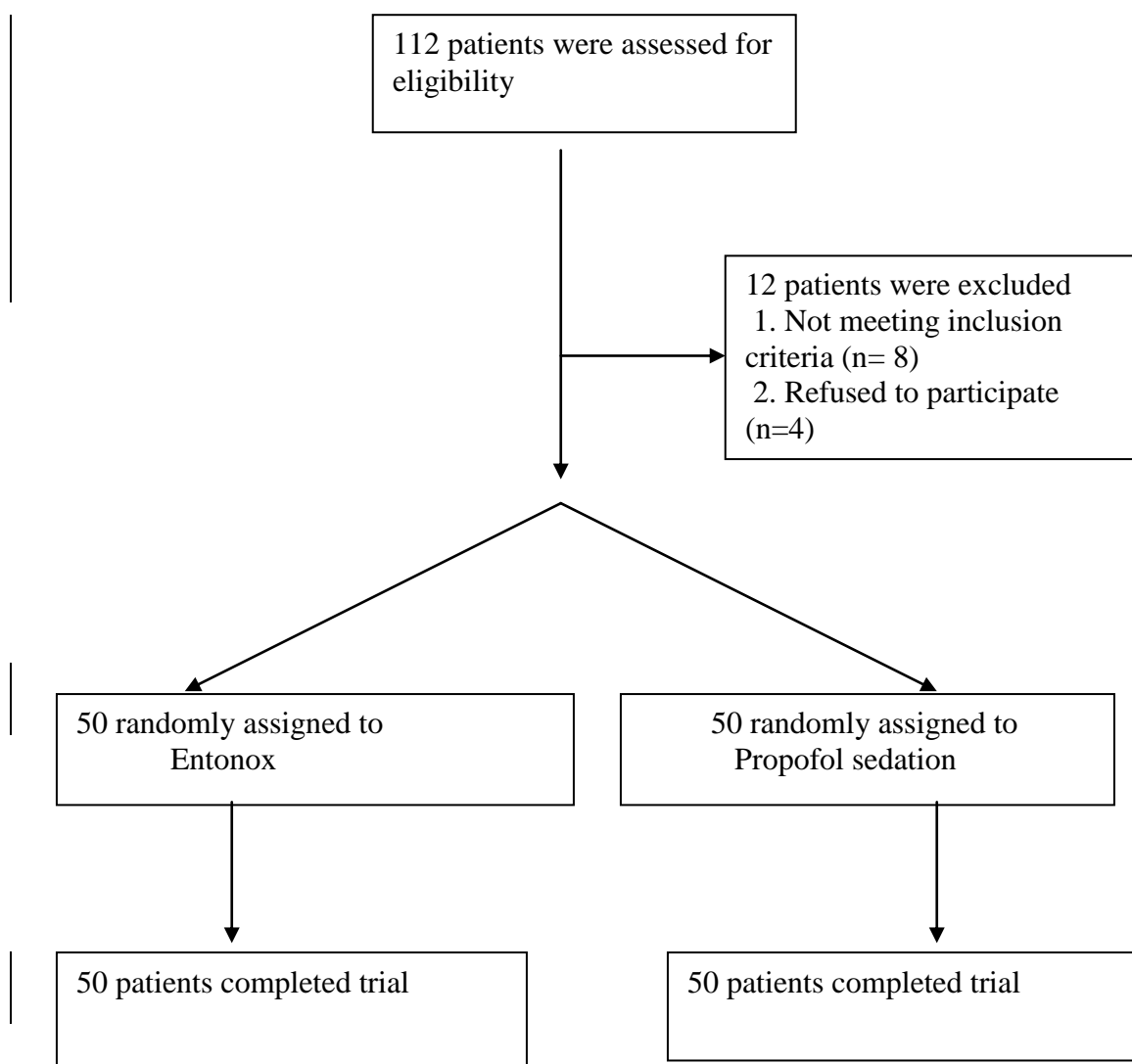
The two groups had similar baseline characteristics, ASA grades, and there was no

difference in pre-procedure anxiety scores (7.5 (range 4-11) versus 8.4 (range 3-10);

P=0.214) (table 7.2). There were no complications in either group.

7.3.2 Medication

The median doses of TCI, PCA and total propofol were 37mg, 137mg and 174.8mg (range

148,210). Patients pressed the PCA handset button for a median of 4 times (range: 1-7)

during each procedure, and 96% of these attempts were successful. In the Entonox® group,

patients inhaled the gas until the caecum was reached and thereafter only 30% (15/50) continued to inhale Entonox®.

Table 7.2 Baseline characteristics of patients in both groups

	Entonox®	*TCI-PCA propofol*
Gender (M:/F)	29:21	24:26
Median age in years (range)	56.1 (42, 66)	60.4 (40,71)
ASA class 1	08 (16%)	10 (20%)
* 2*	33 (66%)	29 (58%)
* 3*	09 (18%)	11 (26%)
Median Pre-procedure Anxiety score (median)	7.5 (4-11)	8.4 (3-10)
Diagnosis		
* Colorectal Cancer*	6	4
* Colorectal Polyp*	12	16
* Diverticulitis*	8	12
* Colitis*	7	3
* Others/normal*	21	16

7.3.3 Primary Outcome- Pain Scores

The pain score at discharge was 15.38 (range:14-20) in the Entonox® group versus 17.31 (range:10-20) in the TCI-PCA propofol group (odds ratio, 1.03; 95 percent confidence interval, -0.89 to 5.02; P = 0.16). At 24 hours, the pain scores were 16.14 (range 14, 21) with Entonox® and 17.89 (range: 10,20) with TCI-PCA propofol. (P=0.16). The 95 percent confidence interval for the absolute difference in pain scores was -0.89 to 5.02 (table 7.3). This difference was well within the preset limit of +/- 15. The similarity in the overall pain scores remained consistent across all points of measurement.

Table 7.3 Visual Analogue Scores (Primary outcome measure)

Pain scores on VAS	*Entonox*	*Propofol*	*Significance (p-value)*
At discharge	15.38 (IQR14,20)	17.31 (IQR 10,20)	0.16 (-0.89,5.02)
15 minutes	15.78 (IQR 12,20)	16.54 (IQR 10,20)	0.16 (-0.93, 5.06)
At 24- hours post procedure	16.14 (IQR 14,21)	17.89 (IQR 10, 20)	0.16 (-0.88, 5.03)

7.3.4 Secondary Outcomes

7.3.4.1 Depth of sedation

The median depth of sedation was 4 (IQR 5-4) and 3 (5-3) in the Entonox® and TCI-PCA propofol groups respectively (P=0.091).

7.3.4.2 Manoeuvrability during the procedure

The median manoeuvrability scores were 1 (range 1-2) and 2 (range 1-3) in the Entonox® and TCI-PCA groups respectively (P=0.2).

7.3.4.3 Completion Rates and procedure time

Caecal intubation rates were 96 and 98 percent respectively in the Entonox® and TCI-PCA propofol groups (P=0.551) (table 7.4). One patient in the Entonox® group had an impassable stricture, and another had poor bowel preparation leading to incomplete colonoscopy. In the TCI-PCA propofol group, the single incomplete colonoscopy was due to an obstructing lesion in the hepatic flexure.

There was no difference between the groups in time to reach the caecum or total completion time (table 7.4).

Table 7.4 Patient assessment

Endoscopist Assessment	*Entonox*	*Propofol*	*Significance (p-value)*
Caecal intubation (%)	48/50 (96%)	49/50 (98%)	0.55
Median time to caecum (min)	13 (10,16.25)	14 (12, 23.25)	0.18
Median completion time (min)	22.6 (18,28)	20.4 (17,23)	0.09
Median difficulty of colonoscopy	24	22	0.79
Satisfaction	96 (95,98)	98 (96,100)	0.26
Nurses assessment			
Median satisfaction score (out of 100)	95 (93.4,98)	97 (95, 99)	0.34
Adequate sedo-analgesia	56	54	0.2
Maneouvrability Score	1	2	0.2
Patient Assessment			
Median Satisfaction score	94	96 (94,98)	0.10
Agree to repeat use of same sedation	46	48	0.56
Remember start of procedure	39/50	42/50	0.39
Remember end of procedure	41/50	45/50	0.35

*Interquartile range in brackets

7.3.4.4 Psychomotor recovery and time to discharge

Patients in both groups demonstrated rapid recovery of psychomotor function after the

procedure (table 7.5). However, patients in the Entonox[®] had complete recovery of

psychomotor function at discharge compared to the TCI-PCA propofol group, where the

median recovery was 96% (IQR, 94,100; P=0.04). The median time to discharge was

27.86 min (22, 30.5) and 28.08 (23,32) in the Entonox® and TCI-PCA propofol groups respectively (P=0.86).

Table 7.5 Recovery of psychomotor function and time to discharge

Variables	Entonox (IQR)	Propofol (IQR)	Significance
Recovery of function			
Immediate	92% (89.5,96)	90% (84,92)	p=0.79
15 min	99% (98.5,100)	94% (91,99)	p=0.08
Discharge	100%	96% (94,100)	p=0.02
Time to discharge (Mean)	27.86 min (22,30.5)	28.08 min (23,32)	p=0.86

7.3.4.5 Patient, Nurse and Endoscopist satisfaction

All patients marked their satisfaction questionnaire before being given their colonoscopy results so that the findings of colonoscopy did not affect the satisfaction scores. The median satisfaction scores were 96 (range: 95-98) and 98 (96-100) in the Entonox® and TCI-PCA propofol groups respectively (P=0.261) (table 7.4). The attending nurses and endoscopists found no differences in their assessment of satisfaction with either Entonox® or TCI-PCA propofol sedation-analgesia (table 7.4).

7.3.4.6 Amnesia and Additional sleep and return to normal activities

All patients completed a satisfaction questionnaire at 24 hours after the colonoscopy. This questionnaire also included questions regarding the number of additional hours of sleep required and the time taken to get back to routine work. The resumption of normal activities was at a median of 2-4 hours and 6 hours respectively in the Entonox® and TCI-PCA propofol groups (P=0.021). 54 percent patients in the Entonox® group reported

requiring additional sleep, as compared to 96 percent in the TCI-PCA propofol group (p=0.03).

7.4 Discussion

The chief finding of this trial is that TCI-PCA propofol is equivalent to Entonox® in analgesic efficacy. Furthermore, in terms of depth of sedation, manoeuvrability, rate of completion, complication rates, satisfaction rates, completion rates and time to discharge, the results of TCI-PCA propofol are similar to Entonox®.

Propofol is a rapidly acting sedative drug with a short duration of action and has attracted increasing attention as it is well tolerated by patients and dramatically reduces recovery time after successful sedation, in comparison to routine intravenous sedation[173, 174]. However, three primary concerns have been expressed and this has led to a relatively lesser uptake of propofol for sedation during colonoscopy in the United Kingdom. These relate to its narrow therapeutic range, lack of an antidote in cases of over-sedation and difficulty in manoeuvring patients during colonoscopy. In order to overcome these problems, we modified the technique of propofol administration to make it a TCI-PCA propofol regime. The aim was to ensure that a low dose of Propofol was used; simultaneously providing effective pain relief and ensuring that the patient was awake enough to move as required during the colonoscopy. The current protocol for propofol administration has enabled these goals to be achieved in this trial. There were no complications with the use of Propofol; verbal communication was not lost in any of the patients, and haemodynamic stability was maintained, even in the elderly patients.

Entonox® provides effective sedation and analgesia for colonoscopy and is very safe. We chose to compare Propofol with Entonox because we have previously demonstrated that the latter is more effective than routine intravenous sedation, including opiates and benzodiazepines[171].

We found in our study that recovery of psychomotor function was initially similar with both Entonox® and modified TCI Propofol. However, at discharge, only Entonox® patients had complete recovery of psychomotor function. Currently, the manufacturer recommends that patients having colonoscopy under Entonox® can drive home after discharge. However, restrictions exist on patients having propofol for colonoscopy, in terms of requiring to be accompanied home and a need for an adult carer for 24 hours after the procedure. Though both Entonox® and TCI-PCA propofol are equally efficacious and allow comfortable colonoscopy, Entonox® is easy to administer, provides faster recovery (both immediate and subsequent 24 hour recovery) and permits patients to drive home after the procedure, as compared to propofol. Furthermore, the current guidelines require anaesthetist presence when patients are being sedated with propofol. This need for an additional doctor seems non-feasible in the current budgetary constraints of most hospitals in the United Kingdom. There is increasing data, especially from the United States, that nurses can safely monitor and administer propofol during colonoscopy. However, the evidence is not sufficient enough yet. We believe, based on these advantages, that Entonox® should be used routinely for all colonoscopies (except patients with contraindications) whereas TCI-PCA propofol could be used for patients needing higher sedation.

Both Entonox® and propofol are associated with higher patient satisfaction and pain relief. There are suggestions that a placebo effect (due to patient control) could explain the better

outcomes. We do agree that a placebo effect contributes partly to the effects of both Entonox® and propofol.

A limitation of this study is that patients and colonoscopists were not blinded to the type of sedation. However, even without blinding, it was possible to address the issues of whether TCI-PCA propofol was as efficacious as Entonox®, and whether both sedation regimes could be adopted in a busy endoscopic unit. Secondly, we started colonoscopy when the MOAAS score of 4 was reached, rather than wait for the target concentration of Propofol to be achieved. We adopted this methodology to enable comparability in both groups and also because the aim of all sedation in colonoscopy is to provide conscious sedation.

As discussed before, hospitals seek cost-effectiveness in the products chosen for patients. The cost of a single cylinder of Entonox® is around £110. Each cylinder can be used for around 65 patients, resulting in a cost per patient of £1.60. On the other hand, the cost of each 20ml ampoule of propofol is around 4.18, which is the cost per patient per colonoscopy. There is a further expense with propofol in that an additional anaesthetist (or a suitably trained nurse) is required per colonoscopy, which is impossible to achieve in the current financial criteria.

We chose to adopt the model of equivalence testing for this study. We have already demonstrated that Entonox® is superior to conventional midazolam/fentanyl sedation for colonoscopy (refer chapter 5) and, hence, Entonox® is the standard sedation practice in our unit. In this study, we, therefore, aimed to determine if propofol is as efficacious as Entonox® and hence the equivalence protocol.

In summary, both our novel method of administering Propofol as well as Entonox® inhalation provide effective sedation-analgesia, and are associated with a high degree of patient and endoscopist satisfaction. The depth of sedation seems appropriate, allowing

patients to be easily manoeuvred during the procedures. However, there is a need for further randomised controlled trials to compare different methods of delivering propofol, and a direct comparison with different agents for sedation.

Chapter 8 Artificial Neural Networks to predict the presence of significant pathology and subsequent need for lower gastrointestinal endoscopy in patients presenting to routine colorectal clinics

8.1 Introduction

The question most frequently asked in a clinic when seeing patients with colorectal symptoms is "Does this patient have any significant colorectal pathology and does he/she need a Lower Gastrointestinal Endoscopy (either colonoscopy or flexible sigmoidoscopy-LGE)?" Clinicians are currently unable to predict accurately which patients with colorectal symptoms will have polyps, cancer or colitis, and hence warrant referral for LGE.

The current available methods for such prediction are clinical assessment and linear statistics. Clinical assessment suffers from a degree of inaccuracy leading to around 21%-39% of unhelpful/unnecessary colonoscopies[59], as shown in high-volume European centres. The two week criterion[175, 176], which was developed in order to overcome this, has not been entirely successful. Chohan et al[177] have shown in a review of fast track referrals under the two week criterion that overall only 14% of the fast-track patients were diagnosed with colorectal cancer. The majority, therefore, had no abnormal findings. Algorithms based on expert systems are cumbersome and have not been shown to be better than clinical decision making [102, 178].

Artificial neural networks (ANN) have previously been used for a number of medical classification tasks[179-181]. These are computational methodologies that perform multi-factorial analyses. One of the desirable aspects of these dynamic software programmes is the ability to determine complex relationships between variables in biological data, based on weighting of these variables when presented, while not requiring any background

knowledge of diagnostic rules[181]. Our own previous work has shown that ANN are capable of accurately predicting outcomes in patients treated for colorectal cancer[102] and also in patients who underwent anal sphincter repair[103]. In both these studies, ANN were shown to be more accurate than clinicians and statistical programmes. However, ANN have previously not been applied for diagnostic triage of patients with colorectal symptoms. The aim of the present study was to develop, train and validate ANN algorithms capable of identifying accurately individual patients attending routine colorectal clinics likely to have a positive diagnosis (cancer, polyp, or colitis) necessitating a lower gastrointestinal endoscopy, to externally validate the networks in the primary care and to compare them with clinicians' diagnostic accuracy.

8.2 Methods

This is a prospective study on the use of ANN to identify patients attending for lower gastrointestinal endoscopy (LGE) at high risk for colorectal cancer, polyps or colitis. The study was based at the Academic Colorectal Unit, Castle Hill Hospital, Cottingham, United Kingdom from April 2004 to March 2005. Research Ethics Committee approval was obtained. The study was monitored by and conducted according to the International Committee on Harmonisation -Good Clinical Practice (ICH-GCP) standards.

8.2.1 Participants and study design

300 consecutive patients undergoing lower gastrointestinal endoscopy (including colonoscopy and flexible sigmoidoscopy) were recruited for the study. All participants (aged 18 and over) were initially seen in a colorectal clinic with lower gastrointestinal symptoms. The Consultant team then made the clinical diagnosis and referred these patients for LGE. These patients were recruited for the study. Those patients from the clinic who were not referred for further investigations included patients who were deemed

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to have anal canal type lesions (eg. fissures, haemorrhoids) and those who did not warrant any further investigations.

The exclusion criteria included patients with previous colorectal cancer resection, past history of inflammatory bowel disease, colorectal polyps or diverticular disease and those refusing to participate in the study. Patients were sent an invitation letter with a detailed information leaflet two weeks before recruitment and had the option of discussing the study with the trial conductors before the procedure.

All participants then signed an approved consent form and answered a symptom questionnaire specifically developed for this study. After the procedure, patients were discharged as per the existing protocols in the unit. The results of the LGE were then collated with the questionnaires. Demographic and clinical data was also collected for all participants on a separate data collection form. All such data including the responses from the questionnaire were then entered into a database.

8.2.2 Development of the questionnaire

The questionnaire used for this study was specifically developed and internally validated using peer review method. The peer review group included colorectal consultants, senior colorectal fellows, colorectal specialist nurse and non-medical colonoscopists, as well as nurses. Pilot studies were conducted with the first three versions of the questionnaire and modifications introduced based on both patient feedback as well as network performance. The fourth questionnaire incorporated all the changes from the previous versions and eventually was adopted for use in this study.

The questionnaire was constructed on the basis of a typical clinical interview with the patient who presents for the first time in a colorectal clinic with lower gastrointestinal symptoms. It does not include advanced laboratory blood tests or imaging results or

endoscopy outcomes. Each questionnaire takes around 4-5 minutes to answer and contains

typically 40 yes/no/not applicable type responses.

8.2.3 Development and internal/external validation of the ANN

The following figure provides an overview of the ANN training and validation:

Figure 8.1 ANN training and validation
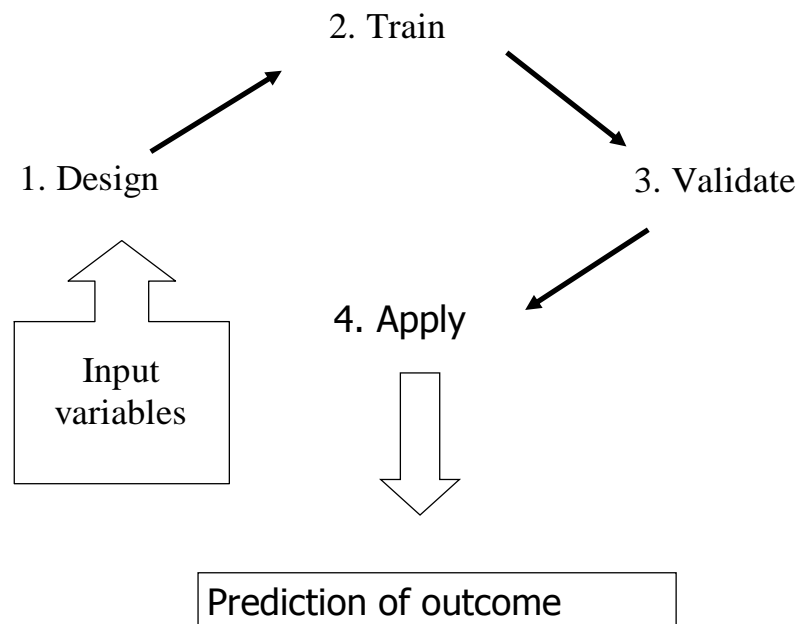
8.2.3.1 Design

We used a fully connected multilayer feed forward network since the analytical power of

this type of network has already been proven in different studies[102, 182]. A more

comprehensive description of neural networks can be found elsewhere[183-185]. The networks

were constructed by means of two general-purpose neural-network software programmes –

Brainsheet[®] and Neuro XL Predictor for Excel[®] (version 1). The number of units in the

input layer was determined by the number of input data values. The number of units in the

middle layer was chosen by experimentation. Several different networks were constructed containing varying numbers (two to 15) of units in the middle layer. The output was coded as either the presence (1) or absence (0) of any one the following three conditions: polyps, colorectal cancer or colitis. These three conditions are the most common yet significant findings in patients presenting to any colorectal clinic.

8.2.3.2 Training

Data from the first 100 patients during the initial study period were used to train the ANN. These were a separate set of 100 patients and were not included in the study. Subsequently, data from the next set of 100 patients was used to train and test the ANN. During training, the input variables were entered as either continuous or categorical data, whereas the output variables were entered as binary variables. The network was allowed to run and make a prediction; subsequently, the software correlated the network output with the actual outcome. If the network was incorrect, then a process of back propagation readjusted the hidden weights within the network until the correct prediction was achieved. This process was automatically repeated, and after thousands of such repetitions the network was trained (table 8.2). In order to decide when to terminate the training process to achieve optimum performance and to avoid overtraining, the training was terminated when the sum of squares error with respect to the validation data set was at a minimum.

Figure 8.2 *ANN training by back-propagation*

Mean Error: Given Results vs. Neural network prediction
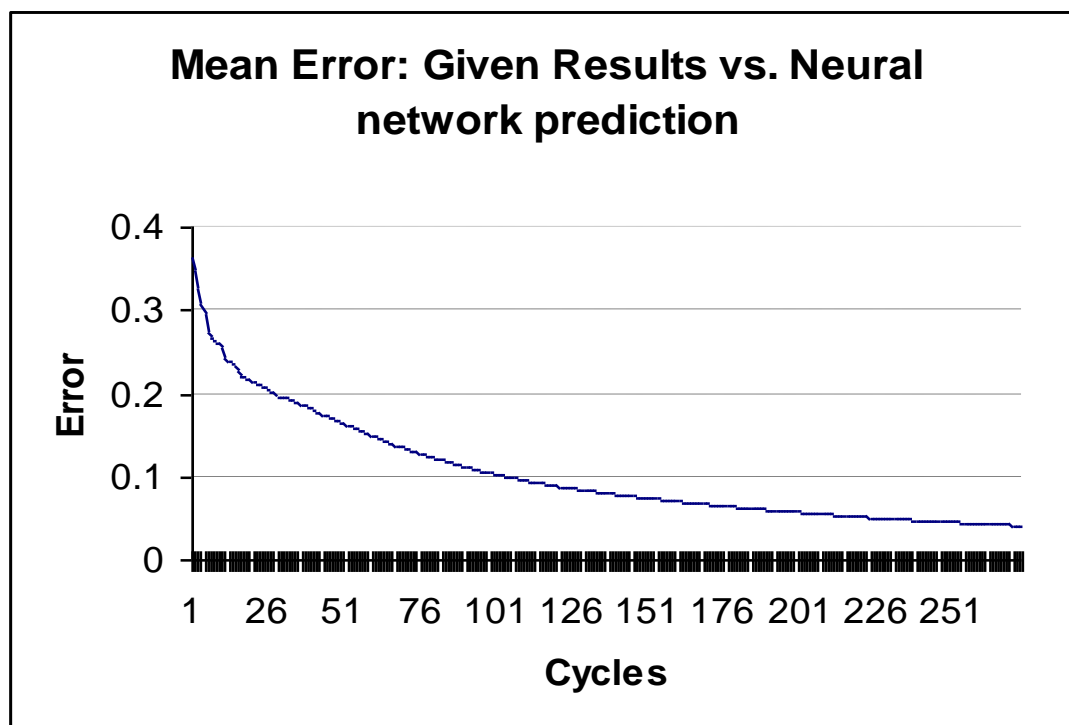
8.2.3.3 Internal validation

Data from the next set of 200 patients was then used for internal validation. Patients in this group were recruited after the end of first recruitment in order to achieve temporal staggeration. During validation, the actual outcome was concealed from the networks, and the predictive accuracy was compared with the actual outcome.

8.2.3.4 External Validation

Once the network was internally validated, it was presented to the community medical practice for external validation. A primary care practice (general practice) in Hedon, Hull was chosen because this practice offered independent LGE services. 50 consecutive patients presenting at this practice with colorectal symptoms, and subsequently posted for LGE were recruited for the study. These patients completed the validated questionnaire

before their LGE. The data from these questionnaires were fed into the trained network

and the predictions made by the trained network were then compared with actual results.

8.2.4 Comparison with clinicians

Four clinicians were then provided with the completed questionnaires, and asked to predict

for each patient the presence/absence of a positive colorectal pathology, and if present,

which one of the four diagnoses mentioned above was applicable. The clinicians'

predictions were then compared with the actual findings. These clinicians were either

senior colorectal trainees or post-training fellows or consultant colorectal surgeons.

Personal data and the results of the neural networks were not available to the clinicians.

8.2.5 Statistical Analysis

The results of comparison between the performance of the ANN and the actual findings, as

well as that of the clinicians is expressed in terms of overall accuracy, sensitivity,

specificity, positive and negative predictive values.

Receiver operating characteristic (ROC) curves were computed for training, internal

validation and external validation data. Their areas (area under ROC curve- AUC) were

calculated using the ROC web-based calculator. Standard errors were calculated according

to the method of Hanley and Mc Neill.

Sensitivity was defined as true positives/(true positives + false negatives), specificity as

true negatives/(true negatives + false positives), positive predictive value as true

positives/(true positives + false positives), and negative predictive value as true

negatives/(true negatives + false negatives).

All statistical analyses will be done using SPSS$^®$ 14.0 for Windows.

8.3 Results

The demographic characteristics including findings of LGE are shown in table 1. The data

from the first group was used to train the ANN (April to September, 2004; n=100). Data

from the second group was used for internal validation (September, 2004 to April 2005;

n=200). The two groups were similar in terms of demographic features and distribution of

diagnoses (table 8.1).

Table 8.1 Demographic features in all the groups

	Group 1 (training) N= 100	Group 2 (prediction) N= 200	External validation N= 50
Age*	58.2 (38-84)	60.4 (29-78)	54.6 (32-58)
Males:Females	42:58	106:94	22:28
Diagnosis			
-Normal	49 (49%)	88 (44%)	25 (50%)
-Colitis	14 (14%)	28 (14%)	06 (12)%
-Polyp	22 (22%)	48 (24%)	11 (22%)
-Cancer	10 (10%)	26 (13)%	05 (10%)
-Miscellaneous/ Diverticular disease	05 (5%)	10 (5%)	03 (6%)

* in years and range in brackets.

8.3.1 Internal Validation of the ANN

The best ANN models selected for analysis achieved an accuracy of 90% in predicting the

presence of significant pathology- polyps, colitis, or colorectal cancer at internal validation

(table 8.2). The ability of the ANN to determine accurately the absence of any significant

pathology (NPV) was 95%. In other words, the network wrongly predicted in 5% patients

that there was no significant pathology. All these patients had either colitis or polyps. All

colorectal cancers were accurately diagnosed.

Table 8.2 Results of Internal and External Validation

INTERNAL VALIDATION				
	Accuracy% (95% CI)	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV	NPV
Test N=100	95%	94%	96%	95%	94%
Predict N=200	90% (180/200) 87-94	88.2% (85.3, 91.1)	91.8%	96%	98%
EXTERNAL VALIDATION				
GP-EV* n=50	89.6% (45/50) (82-96)	86.4% (84.3, 88.5)	92.9%	90.4%	89.65%

* External validation group at General practitioner's clinic

Table 8.3 compares the performance of the 40, 35, 25 and 20 factor models on the training

and test data. It is clear that the performance of the models deteriorates significantly with

reduction in the number of variables to less than 40. Hence, the 40-factor model was

selected, in view of its good calibration and best fit.

Table 8.3 *Performance of the ANN models on training data*

Measure	Number of factors		
	35	*40*	*45*
Area under The ROC	*0.812*	*0.954*	*0.96*
Sensitivity	*76.4*	*88.2*	*89.1*
Specificity	*81.6*	*91.8*	*91.5*

The ANN model was reasonably well calibrated and accurate as shown in table 8.4. The table also shows the mean square error statistics, along with 95% confidence intervals, supporting the hypothesis that the fit is robust across the range of operation.

Table 8.4 *Comparison of ROC curves for all groups*

	ROC curve (Area under the curve)	**Standard Error**	**95% Confidence intervals**
Internal validation	0.954	0.0152	0.92, 0.98
External validation	0.932	0.017	0.90,0.962
Clinician	0.836	0.026	0.8,0.868

The following ROC curves (figure 8.3) for the selected ANN model in internal validation and external validation show an area under curve consistently above 0.90, indicating a high degree of accuracy and reliability.

Figure 8.3 –*ROC curves for all data sets*

A. ROC curve for test and train data (area under the curve = 0.98)

ROC for test-train data
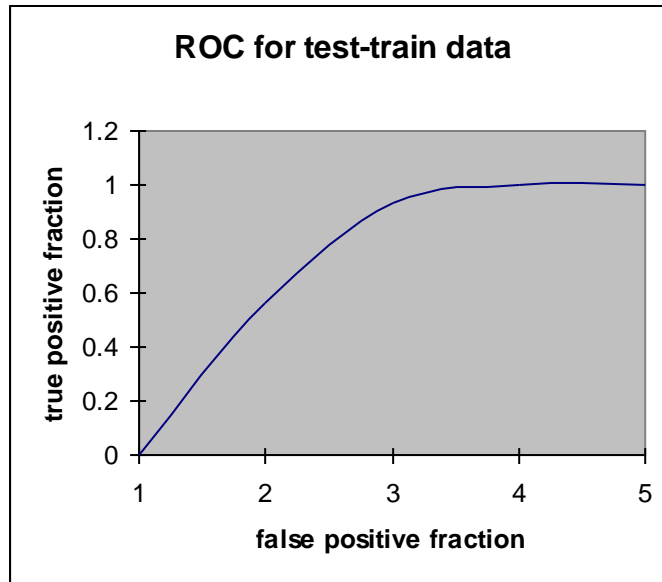
B. ROC curve for internal validation data set
    (Legend: 1. Middle line (blue) - ROC curve; 2. Top (yellow) & bottom (pink) lines-95% confidence interval of the ROC curve)

ROC Curves for internal validation
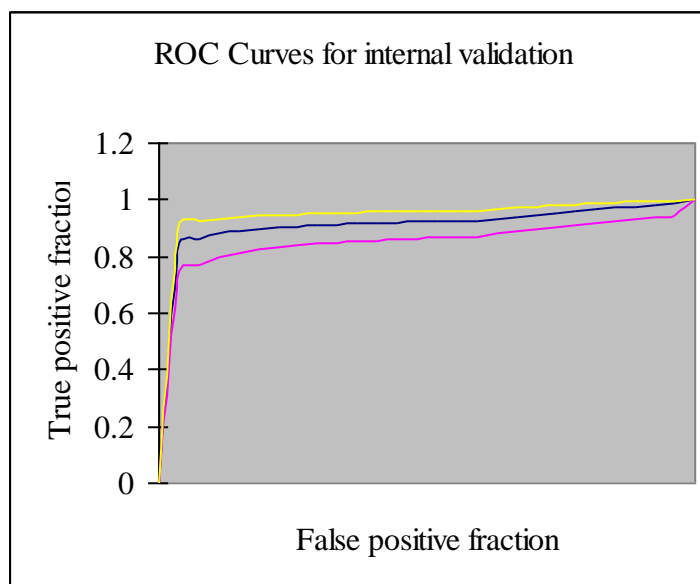
C. *ROC curves for external validation (area under curve = 0.932)*

ROC curves for external validation

false negative fraction (y-axis): 0, 0.2, 0.4, 0.6, 0.8, 1, 1.2

false positive fraction (x-axis)
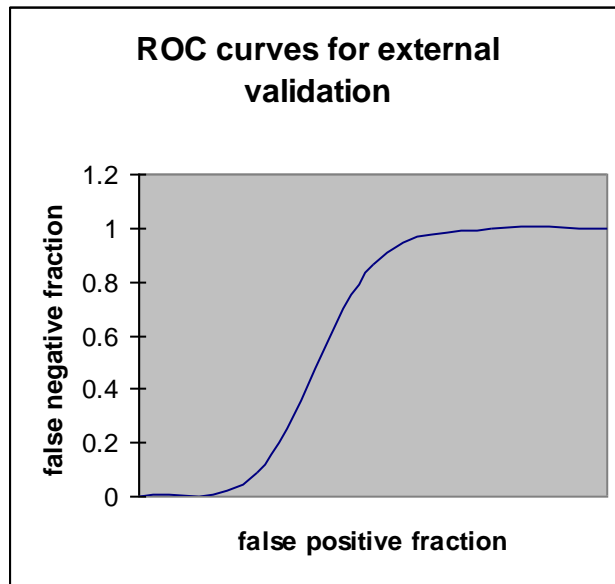
8.3.2 ANN versus Clinicians

The overall accuracy of the clinicians was 75% (95% CI; 59, 87), which was significantly lower than the accuracy of the ANN (table 8.5). The AUC for ANN for prediction of the outcome variables were significantly superior to the Clinicians. Similarly, the ANN proved superior in terms of NPV, PPV, sensitivity and specificity.

Table 8.5   Clinicians versus ANN

	Accuracy (95%CI)	Sensitivity	Specificity	PPV	NPV
ANN* (n=200)	90% (87-94)	88.2% (85.3, 91.1)	91.8%	96%	98%
Clinician* (n=200)	75% (69-83)	72.5%	76.5%	77%	73%

* 95% confidence intervals in the brackets

8.3.3 External Validation

The details of the demographic features and diagnosis in patients in the external validation group are shown in table 8.1. The predictive accuracy of the ANN model in the external validation group was similar to the internal validation group and so were the sensitivity, specificity, positive and negative predictive value (table 8.2). The individual accuracies for the ANN in the external validation group were 100%, 87% and 92% respectively for colorectal cancer, colitis and polyps. Figure 8.3 demonstrates the AUC for ANN in the external validation group.

8.4 Discussion

The current study has shown that ANN programmes can be trained to predict the presence of significant pathology in patients presenting with colorectal symptoms to routine clinics. The algorithm performed equally well in the external population and was clearly superior to Clinicians.

There are two salient aspects of the current study- the development of the questionnaire and the training of the ANN. The questionnaire is an essential component of such artificial intelligence programmes and has to be clinically relevant as well. The questionnaire that was developed for this study was modelled on simple physician-patient clinical encounter scenario. It is based on the belief that any predictive instrument can only be useful if it uses exactly the same data that is available to the clinicians, as the possible future application of such a decision tool is either in primary/general practice or the first clinical consultation in tertiary care. Our ANN model used only data from clinical history and physical examination. Commercially available ANN software can be used in any standard laptop or desktop computer. We envisage that when patients first present to a family doctor (General Practitioner), the use of this tool after clinical assessment should support

the doctor in making a decision whether the patient needs to be urgently referred to the specialist colorectal / gastroenterology services. Likewise, a colorectal surgeon or gastroenterologist should be able to use this tool to aid his decision regarding further investigations for the patient. In patients who present with obvious sinister symptoms (for e.g. Change of bowel habits, weight loss and pr bleeding), it is generally easy to make a clinical decision. However, in patients with borderline symptoms (for e.g. a 45 year old man with fresh per rectal bleeding or change of bowel habits), it becomes difficult to decide whether the symptoms are sinister enough to warrant an urgent LGE. It is such scenarios where the presence of accurate decision tools will play an important role. The clinician could ask the patient to complete the questionnaire while waiting to be seen, and the same could be fed into the computer, aiding decisions to be made.

The second crucial feature of the study was the development and training of the ANN. As shown in the results section, the final version of the ANN performed well in terms of ability to identify the presence of significant pathology. The network was highly accurate in diagnosing colorectal cancer, polyps and colitis. The models generated were well calibrated and performed well on data prospectively collected at a later date at the same institute as well as an external practice. For a diagnostic algorithm to be performing well and be useful, it should be robust enough to be used in different clinical settings. The ANN model developed in our study proved reasonably portable and performed well in the external data set derived from a primary care practice. The AUC as well as sensitivities and specificities were comparable in both groups of data.

Mean negative predictive values were high for the ANN model in predicting the presence of significant pathology in both internal and external data. This implies that the ANN can be relied upon to identify patients who do not have sinister pathology and, hence,

conceivably such patients can either be discharged or arranged for more routine clinical follow up. This strategy can have a positive impact on health-care resources and lead to more efficient utilisation of endoscopy services, though the current study does not focus on this aspect.

This is the first study of this kind to assess the role of ANN in reducing endoscopy workload. In this study, 162 patients had a procedure wherein the colon was normal. The ANN was able to accurately predict this in 158 patients. Hence, a large number of LGE were preventable with the use of ANN, though it is difficult to determine the exact number. Previous use of ANN in endoscopy have been for different aetiologies, like predicting outcomes after GI bleeds[104, 186], classifying dyspepsia[187], discriminant analysis of atrophic gastritis[188] and others.

Furthermore, with the introduction of screening programmes, there is a different set of patients (asymptomatic) presenting for endoscopies. In order to assess the role of ANN in this group, we are currently setting up a new trial involving different hospitals, and aim to include these patients as well.

In retrospect, we agree that there are few limitations in our study. Firstly, the clinicians were supplied data in the form of completed questionnaires and were not able to interview and examine the patients themselves before making their own predictions. This denied them the full use of their diagnostic skills. The number of patients in the external validation group was low as compared to the internal validation group. We would prefer to increase the number of patients in the external validation group.

Finally, only those patients with colorectal symptoms and subsequently referred for LGE were invited to participate, possibly introducing some selection bias. We deliberately chose this select group of patients because these are the patients most likely to harbour

serious pathology (on clinical assessment), and, yet most difficult to diagnose accurately enough to be able to triage into those needing LGE and those not needing LGE. The purpose of developing the ANN in this study was to be able to perform accurately this triage function. The remainder of patients presenting in the clinics and not included in the study would either be those seen as follow up or clinically diagnosed with conditions not requiring a LGE. These patients are not a diagnostic dilemma and, hence, do not need the help of the ANN.

This paper does not contend that neural networks are the substitute for clinical judgment. We also do not claim that ANN should they be considered as an answer for all complex data analysis or all complex clinical decisions. In fact, careful clinical judgement is required to ensure that the information entered is correct and the ANN produces meaningful results. We also do not imply that all the decisions should be based on ANN output only. It was not developed to diagnose all abdominal pathologies, but to focus specifically on the three conditions mentioned previously.

8.4 Conclusion

Artificial neural networks offer the possibility of personal prediction of outcome for individual patients presenting in clinics with colorectal symptoms, making it possible to make appropriate requests for lower gastrointestinal endoscopy.

CHAPTER 9 SUMMARY OF CONCLUSIONS

The overall aims of this thesis were to determine methods of assessing the quality of LGE, and improving both the availability and technical quality of LGE in the National Health Service. Having reviewed the literature, we conducted six different studies to achieve these goals.

Quality and availability of LGE are issues gaining unprecedented attention in recent years. The American Society of Gastroenterology[46] and others[189] have defined different aspects of quality of LGE. However, we chose to look only at the technical aspects of quality assurance in this thesis both because a review of all the quality indicators would be impossible in one work, and also because technical quality is an important part of LGE, as indicated by patients in most studies[52] including the current one. The three principal aspects of technical quality assurance of lower gastrointestinal endoscopy (LGE) include completion rates, pathology miss rates and patient satisfaction. We developed and validated a patient satisfaction questionnaire to specifically assess patient satisfaction in our unit and to identify factors associated with the same. This study showed the levels of satisfaction in our unit in both non-medical and medical endoscopists to be high. A multivariate analysis of all questions from the patient satisfaction questionnaire, as well as demographics and clinical features, has shown that higher pre-procedure anxiety scores, pain during the procedure and a history of pelvic surgery/hysterectomy were associated with lowest patient satisfaction scores. Patients marked pain and technical skills as the most important factor affecting their satisfaction. These findings are important; a theoretical advantage is that modification of such patient and procedure-related factors should lead to better patient experience in the future. Armed with this knowledge of patient needs, we looked at methods of improving technical quality of LGE and patient

experience of colonoscopy in terms of pain/discomfort, and performed two randomised controlled trials on sedation for colonoscopy.

We assessed the role of the technique of endoscopic clipping (with follow-up abdominal x-ray) in quality assuring both colonoscopy and flexible sigmoidoscopy. Both studies have shown this technique to be safe and feasible. The major advantage of this technique of objective validation is that it enables assessment of both completion and miss rates. The current method of validation of completion is the use of photographs of caecal landmarks, but studies have shown them to be difficult to interpret and equally susceptible to errors[134, 135]. Does the technique of clipping perform better? We believe that it is a simple and feasible technique, but the current study should be interpreted as a pilot study. Further validation by comparing it with different modalities like caecal photography or ileal biopsies is mandatory. Another shortcoming of the study was the lack of validation of the accuracy of the abdominal x-ray in identifying the position of clips. A future study of this kind should include a comparison with current standards, and also a computerised tomography scan on a random number of patients should be performed.

With regards to improving methods of pain relief, the first randomised controlled trial has shown that Entonox[®] provides better relief than conventional intravenous sedation, and is associated with better patient satisfaction and faster discharge. The second study showed no difference between Entonox[®] and propofol in terms of pain relief, time to discharge/recovery and patient satisfaction. These two studies provide evidence for the role of Entonox[®] in routine sedation for colonoscopy. However, there is a possibility that the beneficial effect of Entonox[®] arises from a placebo effect- the act of controlling sedation makes the patient feel empowered and in control. The second problem with Entonox[®] sedation is that in around 7-10% of patients, it is contraindicated. The option

therefore is to use either intravenous sedation or propofol in this small group of patients. A multi-centre randomised controlled trail to evaluate all three types of sedation (conventional intravenous, propofol and Entonox®) with both patients and endoscopists blinded to the treatment modality would be an ideal method of answering the questions.

The current NHS targets (two week wait, 62 days for urgent treatment, 31 days for all from the decision to treat to treatment and the 18-week pathway) are difficult to achieve and sustain for most NHS trusts, mainly because, in most places, the primary diagnostic test (LGE) is not directly accessible to GPs, and partly because of the long waiting time, and complex pre-treatment pathway for bowel cancer patients. In addition, the two week wait (TWW) criteria are not a particularly reliable predictor of the presence of bowel cancer. In most reported series, only about 10% of TWW patients were found to have bowel cancer and only a quarter of patients who turn out to have cancer come through the Two Week Wait pathway[190]. Furthermore, there is a prediction for further increase in demand due to the introduction of screening programmes and long-term surveillance schedules to prevent recurrence of benign and malignant tumours.

In this thesis, we assessed two possible solutions to shortening the interval to LGE: introduction of non-medical endoscopists (NME) and the role of artificial neural networks (ANN). In order to increase the number of available endoscopists (and, hence, the availability of LGE), the Department of Health trained non-medical personnel to perform LGE. We have shown that NME can perform diagnostic LGE procedures, with similar completion rates and patient satisfaction to medical endoscopists. However, NME cannot provide intravenous sedation on their own, and are dependant on doctors or suitably trained nurses to prescribe sedation. The use of Entonox® for routine sedation can obviate the need for a doctor or nurse to prescribe sedation. We have also shown that NME can

colonoscope with equal effectiveness using Entonox sedation, as compared to both doctors and nurses. This is a key finding for this study, as it enables NME to perform LGE independently. However, we need to remember that none of these studies were powered to directly determine differences between non medical endoscopists and nurses/doctors in terms of technical quality of LGE.

Lastly, we used artificial neural networks to predict which patients with colorectal symptoms will have polyps, cancer or colitis. Clinicians are currently unable to accurately identify such patients in the outpatient setting and therefore a large number of unnecessary LGE are ordered for. Our study has shown that ANN programmes can be trained to predict the presence of significant pathology in patients presenting with colorectal symptoms to routine clinics. The algorithm performed equally well in the external population and was clearly superior to Clinicians. We envisage that either a general practitioner or a colorectal surgeon should likewise be able to use this tool to aid his decision regarding further investigations for the patient. This study was applied to symptomatic colorectal patients, who were already screened in a clinic. However, it would be interesting to assess the ability of ANN to predict in asymptomatic patients, particularly those being screened for colorectal cancer.

9.1 FUTURE DIRECTIONS:

Quality assurance of LGE will continue to be of paramount importance in the future. GRS could be the skeletal framework around which all quality improvements could be based. Within this framework, there is further opportunity for objective assessment of quality of LGE. Several interesting areas of work can be identified from this thesis to pursue in the future.

We plan to validate the technique of endoscopic clip application with follow-up abdominal x-ray in the assessment of both completion and pathology miss rates of LGE against current standards, like ileal photography and biopsy, and caecal photography.

We have shown that patient satisfaction with LGE can be predicted by several factors. These include pre-procedural anxiety and intra-procedural pain. There is, therefore, scope for a randomized controlled trial of pre-emptive interventions aimed at improving the patients' experience of colonoscopy. This thesis already includes 2 trials showing that Entonox® is associated with lesser pain/discomfort during colonoscopy, leading to higher patient satisfaction. It would also be interesting to see if the findings in this thesis especially regarding Entonox® can be replicated in other hospitals.

We have shown that non-medical endoscopists can perform LGE with similar completion rates, and patient satisfaction, as compared to medical endoscopists. We anticipate a bigger role for non medical endoscopists in providing endoscopy services in the future, more so in the face of an increasing demand. The use of Entonox® for sedation for colonoscopy could mean more trained NME providing independent LGE services than is feasible currently. Larger multicentre studies could be designed to compare doctors with non-medical endoscopists in different settings and hospitals, especially with a long follow-up period.

The results on the use of artificial neural networks to accurately predict outcomes in patients with colorectal symptoms are hugely encouraging and exciting. We are currently setting up a trial to assess their usefulness in asymptomatic patients who are undergoing screening for colorectal cancer. Multicentre studies could clarify more precisely how ANN can be applied to both symptomatic and asymptomatic patients.

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Appendix for the thesis titled

ASSESSMENT AND IMPROVEMENT OF QUALITY AND ACCESS
IN LOWER GASTROINTESTINAL ENDOSCOPY

Appendix 1: **Visual Analogue Scale**

Thank you very much for participating in this trial. We would like you to indicate on this scale how much pain you had during the procedure. This scale is marked from 0 to 100, where 0 represents no pain and 100 represents worst pain ever. Please mark the appropriate number and write the number in digits as well.

Thanks once again.

0(no pain)   100 (worst pain ever)

Example only- not for use---

The above is an example of VAS used in the study. We used single VAS on single page each time they were assessed.

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Appendix 2:   **Visual Analogue Scale -24 hours post procedure**

Thank you very much for participating in this trial. It is now 24 hours since the colonoscopy. We would like you to indicate on this scale given below how much pain you had **during** the procedure. This scale is marked from 0 to 100, where 0 represents no pain and 100 represents intolerable pain. Please mark the appropriate number and write the number in digits as well.

0   100

We now request you to send us this scale in the prepaid envelope. This information is extremely important to us and enables proper conduct and analysis of the trial.
Thank you once again.

Appendix 3: Letter cancellation test:

Thanks for participating in the trial. Given below is a jumble of randomly arranged letters. We request you to identify and cross-out the letter **C** each time it appears. You have a maximum of 120 seconds to do so. At the end of 120 seconds, please stop the test and put your pen down. Thanks once again.

B E I F H E H F E G I C H E I C B D A C H F B E D A C D A F C I H C F E
B A F E
D C F G H E C C A H E F A C D C F E H B F C A D E H A E I E G D E G
H B C A E C
G I C E H C I E F H I C D B C G F D E B A E B C A F C B E H F A E FE G
C H G C
D E H B A E G D A C H E B A E D G C D A F C B I F E A D C B E A C G
C C D C A A
G A C H E F B C A F E A B F C H D E F C G A C B E D C F A H E H E F
D I C H A C
 B I E B C A H C D E F B A C B C G B I E H A C A F C I C A B E G F B E
F A E A E
 B G C G F A C D B E B C H F E A D H C A I E F E G E D H B C A D G E
A D F E F W
B E I G A C G E D A C H G E D C A B A C F B C H D A C G B E H C D F
E H A E I Q
E D G C D A F C B I F E A D C B E A C G C C D G A C H E F B C A F E
A B F C H A
D E F C G A C B E D C F A H E H E F D I C H B I E B C A H C D E F B A
C B C G C
B I E H A C A F C I C A B E G F B E F A E A B G C G F A C D B E B C H
F E A D H
C A I E F E G E D H B C A D G E A D F E B E I G A C G E D A C H G E
D C A B A F
E F B C H D A C G B E H C D F E H A E I C E H C I E F H I C D B C G F
D E B A E
B G C G F A C D B E B C H F E A D H C A I E F E G E D H B C A D G E
A D F E R S

B E I G A C G E D A C H G E D C A B A C F B C H D A C G B E H C D F
E H A E I A
G A C H E F B C A F E A B F C H D E F C G A C B E D C F A H E H E F
D I C H A C
B I E B C A H C D E F B A C B C G B I E H A C A F C I C A B E G F B E
F A E A E
B G C G F A C D B E B C H F E A D H C A I E F E G E D H B C A D G E
A D F E F W
B E I G A C G E D A C H G E D C A B A C F B C H D A C G B E H C D F
E H A E I Q
E D G C D A F C B I F E A D C B E A C G C C D G A C H E F B C A F E
A B F C H A

Thanks once again for participating in this study.

Appendix 4:

Confidential questionnaire for Colonoscopy

You have now finished your procedure and are about to go home. We request you to kindly fill in the following questionnaire about what and how you felt regarding the whole procedure. Please read each question carefully before answering. We are interested in finding about your experiences during the procedure.

Thanks for taking out time for filling this questionnaire.
In terms of your satisfaction, how would you rate each of the following?

1. The length of time you waited to get an appointment

Excellent □   Very good □   Good □   Fair □   Poor □

2. Convenience of the appointment time for endoscopy

Excellent □   Very good □   Good □   Fair □   Poor □

3. Length of time spent waiting at the endoscopy suite for the procedure

Excellent □   Very good □   Good □   Fair □   Poor □

4. How were the instructions for the bowel preparation?

Excellent □   Very good □   Good □   Fair □   Poor □

5. Attitude of the reception staff

Excellent □   Very good □   Good □   Fair □   Poor □

6. **The personal manner (courtesy, respect, sensitivity, friendliness) of the endoscopist who**

performed your procedure

Excellent □   Very good □   Good □   Fair □   Poor □

7. The time spent by the endoscopist with you

Excellent □   Very good □   Good □   Fair □   Poor □

8. The manner in which the procedure was explained by the endoscopist

Excellent □   Very good □   Good □   Fair □   Poor □

9. The technical skills (thoroughness, competence) of the endoscopist (your perception)

who performed your procedure

Excellent □   Very good □   Good □   Fair □   Poor □

10. General satisfaction with the endoscopist's attitude and behaviour

Excellent □   Very good □   Good □   Fair □   Poor □

11. How much pain did you have during the procedure? (Please mark on the following scale from none to intolerable)

0   **100**

 None   **Intolerable**

12. How satisfied are you with this type of pain relief and sedation (please mark on a scale of 0-100)

   0 (Dissatisfied)   100(Very satisfied)

13. How satisfied are you with the endoscopist who performed your procedure? (please mark on a scale of 0-100)

   0 (Dissatisfied)   100(Very satisfied)

14. Would you consider having this procedure done again under this type of sedation and pain relief?

       Yes □   No □

15. Overall rating of the visit

Excellent □   Very good □   Good □   Fair □   Poor □

16. Would you have the procedure done again by this endoscopist?

       Yes □   No □

17. Would you consider having this procedure done again at this hospital?

       Yes □   No □

18. Would you refer friends/ family to this hospital again for this procedure?

Yes □   No □

Appendix 5 (Randomised controlled trials):

Confidential questionnaire for Colonoscopy :24 hours post procedure

Thank you very much for answering this questionnaire. It is now more than a day since you had your colonoscopy. We request you to kindly fill in the following questionnaire about what and how you felt regarding the whole procedure. Please read each carefully before answering. We are interested in finding about your experiences during the procedure.

Thanks for taking out time for filling this questionnaire and sending it to us. Your answers are extremely vital to determine the quality of sedation.

In terms of your satisfaction, how would you rate each of the following?

1. **The personal manner (courtesy, respect, sensitivity, friendliness) of the endoscopist who performed your procedure**

Excellent □   Very good □   Good □   Fair □   Poor □

2. The time spent by the endoscopist with you

Excellent □   Very good □   Good □   Fair □   Poor □

3. The manner in which the procedure was explained by the endoscopist

Excellent □   Very good □   Good □   Fair □   Poor □

4. The technical skills (thoroughness, competence) of the endoscopist (your perception) who performed your procedure

Excellent □   Very good □   Good □   Fair □   Poor □

5. How much pain did you experience during the procedure? (Please mark on the following scale from none to intolerable)

1   **100**

6. How satisfied are you with this type of pain relief and sedation (please mark on a scale of 0-100)

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<div align="center">_____</div>

Dissatisfied   Very satisfied

7. Would you consider having this procedure done again under this type of sedation and pain relief?

Yes □   No □

8. How satisfied are you with this endoscopist? (please mark on a scale of 0-100)

<div align="center">_____</div>

Dissatisfied   Very satisfied

9. Did you require additional sleep during the day after your procedure?

Yes □   No □

10. How much sleep did you require?

None   □   less than 2 h □   2-4h □   4-6h □

11. When did you resume your normal daily activities?

<2hours □   2-4h □   4-6h □   >6h □

12. How did the sedation you receive compare with previous endoscopic procedures you have undergone?

Better □   Same □   Worse □   Not applicable □

13. Overall rating of the visit

Excellent □   Very good □   Good □   Fair □   Poor □

14. Would you have the procedure done again by this endoscopist?

Yes □   No □

15. Would you consider having this procedure done again at this hospital?

Yes □   No □

16. Would you refer friends/ family to this hospital again for this procedure?

Yes □   No □

Thanks once again for your time.

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Appendix 6: Endoscopists' assessment of the procedure and sedation

Name:
Designation:
Patient name: DOB: Unit No.:

_____

1   Degree of ease   1   2   3   4   5
         Of colonoscopy   (Very difficult)   (Very easy)

2   Patient pain   1   2   3   4   5
         tolerance   (intolerant)   (very tolerant)

3   level of sedation   0   1   2   3   4   5
         (average for the procedure)*

4.   How do you think the patient will rate this procedural experience?
         Excellent/ Good/ Fair/ Poor

5.   Did you have difficulty manoeuvring the patient?
                 a.   patient was awake and responded to all commands
                 b.   patient responded to most of the commands(>50%)
                 c.   patient was able to move to some commands(<50%)
                 d.   quite difficult (<10%)

6.   How satisfied are you with this sedation?

_____

0(not satisfied at all)   100 (very satisfied)

∗ Sedation scoring is as per the following:
         0-   no response to painful trapezius squeeze
         1-   responds only after painful trapezius squeeze
         2-   responds only after mild prodding or shaking
         3-   responds only after name is called loudly and/or repeatedly
         4-   lethargic response to name spoken in normal tone

5- respnds readily to name spoken in normal tone

Appendix 7:

Nurse's assessment of the procedure and sedation

A. Data collection:

Name: Designation:
Patient name: DOB:
Unit No.:

Sedation:
Time sedation started?
Time stopped:
Time scope inserted:
Time caecum reached:
Was caecum reached: YES/ NO   If no, was it deliberately stopped: Y/N
Time scope came out:

B. Assessment of sedation
Please select the best answer for each of the following questions.

1. Do you feel the patient had adequate sedation/ pain relief? YES/ NO

2. Which of the following best describes the patient's sedation:
             Too heavy/ Just right/ Too light

3. Do you believe the patient had discomfort? YES/ NO

4. Was the patient difficult to sedate? YES/ NO

5. Was the patient alert before the completion of the procedure: YES/ NO

6. Was the patient able to assist with moving during the procedure: YES/ NO

7. Did you have difficulty manoeuvring the patient?
        e. patient was awake and responded to all commands
        f. patient responded to most of the commands(>50%)
        g. patient was able to move to some commands(<50%)
        h. quite difficult (<10%)

8. What was your perception of the depth of sedation?

     level of sedation   0   1   2   3   4   5
     (average for the procedure)*

9. How satisfied are you with pain relief and sedation:

0(not satisfied at all)   100 (very satisfied)

10. How satisfied are you with the endoscopist?

     1   2   3   4   5
(not satisfied)   (very satisfied)

Thank you very much for your time.

∗ Sedation scoring is as per the following:
     0- no response to painful trapezius squeeze
     6- responds only after painful trapezius squeeze
     7- responds only after mild prodding or shaking
     8- responds only after name is called loudly and/or repeatedly
     9- lethargic response to name spoken in normal tone
     10- responds readily to name spoken in normal tone

Appendix 8:

COLONOSCOPY QUESTIONNAIRE

(For the ANN study)

PRE-INVESTIGATION HEALTH AND SYMPTOM ASSESSMENT

We are currently doing a study to determine if we can accurately identify which patients would need flexible sigmoidoscopy/ colonoscopy in our unit. We would like to invite you to participate and would be grateful if you could take the time to answer the following questions. You would only need to fill this questionnaire and there is no additional procedure/visit.

Thank you very much for your time.

Please note: this questionnaire will remain private and confidential. Any data used from this questionnaire will remain anonymous.

This questionnaire should be completed prior to your consultation and returned to the nurse. Thank you once again for being part of the study.

Could you please answer **all** the questions as they are all very important, thank you.

PART ONE:

NAME:	
DATE OF BIRTH:	
AGE:	
SEX:	

PART TWO:

		YES	NO	NA
2.1	Do you smoke	1	2	0
2.2	Have you ever smoked regularly	1	2	0
2.3a	Do you take Aspirin tablets	1	2	0
2.4	Do you take regular painkillers	1	2	0
3.1a	Does your bottom bleed when you open your bowel	1	2	0
3.1b	If yes, is it bright red	1	2	0
3.1c	Has it ever been dark red	1	2	0
3.2	If it has happened, has it been more than once	1	2	0
3.3	Has it been happening for longer than 6 weeks	1	2	0
3.4	Have you passed any mucous or slime from your bottom in the last 6 weeks	1	2	0
3.5	Have you passed any pus from your bottom in the last 6 weeks	1	2	0
3.6	Does your stomach feel swollen before you open			

		YES	NO	NA
	your bowel	1	2	0

PART FOUR:

		YES	NO	NA
4.1a	Has your bowel habit changed over the last 6 weeks	1	2	0
4.1b	If yes, are you more constipated	1	2	0
4.1c	If yes, have you become more loose / watery	1	2	0
4.1d	Does your bowel habit change between constipation and diarrhoea	1	2	0
4.2	If no, has it happened to you within the last 12 months	1	2	0
4.3	Do you feel that you completely empty your bowel after you have had it open	1	2	0
4.4	Do you need to strain to open your bowel	1	2	0

PART FIVE:

5.1   Have you had any pains in your back passage in the last 6 weeks

                    YES1   NO2

5.2   Have you had any stomach pains in the last 6 weeks

                    YES1   NO2

		YES	NO	NA
6.1	Have your weight been steady	1	2	0
6.2	Have you been losing weight	1	2	0

6.3	Have you gained any weight			
		1	2	0
6.4	Has you appetite been	HIGH	NORMAL	LOW

PART SEVEN:

		YES	NO	NA
7.1	In the last 6 weeks, have you felt tired or had very little energy	1	2	0
7.2	Have you been short of breath when walking up stairs	1	2	0
7.3	Have you been short of breath in general	1	2	0
7.4	Have you been told you are anaemic	1	2	0

PART EIGHT:

		YES	NO
8.1	Have YOU ever had any polyps in the bowel	1	2
8.2	Have YOU ever had any BOWEL cancers	1	2
8.3	Have YOU ever had any OTHER forms of cancer	1	2
8.4	If yes, how old were you when you were diagnosed		

PART NINE:

		YES	NO
9.1	Have YOUR mother, father, brothers or sisters ever had any polyps in the bowel	1	2

		YES	NO
9.2	Have YOUR mother, father, brothers or sisters ever had any BOWEL cancers	1	2
9.3	Have YOUR mother, father, brothers or sisters ever had any OTHER forms of cancer	1	2
9.4	If yes, how old were they when they were diagnosed		

PART TEN:

		YES	NO
10.1	Have any other members of your family (aunts, uncles etc) ever had any polyps in the bowel	1	2
10.2	Have any other members of your family (aunts, uncles etc) ever had any BOWEL cancers	1	2
10.3	Have any other members of your family (aunts, uncles etc) ever had any OTHER forms of cancer	1	2
10.4	If yes, what relationship to you were they		
10.5	If yes, how old were they when they were diagnosed		

PART ELEVEN:

		YES	NO
11.1	Have YOU ever been diagnosed with inflammatory bowel disease (ulcerative colitis or crohns' disease)	1	2
11.2	Has anyone in your family ever been diagnosed with inflammatory bowel disease	1	2
11.3	If yes, what relationship were they to you		

Thank you very much for completing this questionnaire.