# Improving the Quality of colonoscopy

MD thesis

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Abbreviations

| | |
|---|---|
| BCSP | Bowel Cancer Screening Programme |
| ADR | Adenoma Detection Rate |
| PDR | Polyp Detection Rate |
| gFOBt | Guaiac faecal occult blood test |
| CRC | Colorectal cancer |
| UK | United Kingdom |
| RCT | Randomised Controlled Trial |
| PEG | Polyethylene glycol |
| ASGE | American Society of Gastrointestinal Endoscopy |
| ACG | American College of Gastroenterologists |
| FIT | Faecal Immunochemical Testing |
| MSI | Micro- satellite instability |
| BBPS | Boston Bowel Preparation Scale |
| BCSS | Bowel Cancer Screening System |
| MGCS | Modified Gloucester Comfort Scale |
| NRCL | Nurse Rated Comfort Level |
| SSP | Specialist Screening Practitioner |
| VA-NRS | Verbally Administered Numerical Ratings Scale |
| IRAS | Integrated Research Application System |
| REC | Research Ethics Committee |
| HADS | Hospital Anxiety and Depression Scale |
| MHRA | Medicine and Health Regulatory Authority |
| ESGE | European Society of Gastrointestinal Endoscopy |
| NHS | National Health Service |

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**Declaration**

I confirm that the work within this thesis is my own work and has not been submitted for any other degree.

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**Abstract**

Colonoscopy has an important role in the assessment of colonic symptoms and screening for colorectal cancer. Studies suggest that the quality of colonoscopy is variable. The focus of this thesis is improvement of colonoscopy quality, in particular patient comfort and polyp detection which are both important measures of colonoscopy quality. The studies within this thesis examine current medication practices and attitudes towards these and then assess whether simple interventions can improve the quality of colonoscopy.

Discomfort during colonoscopy is common and influenced by many factors including the use of medication but practice varies between colonoscopists. Chapter three examines the relationships between medication practice and patient comfort during colonoscopy examinations performed within the English Bowel Cancer Screening Programme. Wide variation in patient comfort and medication use between colonoscopists are noted but with little apparent correlation. Deficiencies in the measurement of patient comfort are highlighted and strategies for improvement are suggested.

Many strategies are available to manage discomfort during colonoscopy. Entonox (50:50 combination of nitrous oxide and oxygen) has advantages associated with its rapid elimination but is used in only a minority of examinations. Chapter four examines perceptions and attitudes towards Entonox use among English Bowel Cancer Screening Colonoscopists and explores whether these may explain its low utilisation. Attitudes towards Entonox use varied widely but were generally positive although it appears that Entonox is often selected for patients expected to have little discomfort. Colonoscopists' attitudes towards Entonox use did not appear to explain its low utilisation.

The method of Entonox use during colonoscopy varies between previous studies. Obstetric studies report that the method of Entonox use may influence its efficacy but this had not been examined during colonoscopy. The efficacy and side effects of 'continuous' versus 'as required' Entonox

administration were compared in chapter five. Continuous Entonox administration did not increase potency but was associated with an excess of side effects.

Despite colonoscopy being the gold standard technique to examine the colon, polyps may be missed. This is of paramount importance since polyp removal is associated with colorectal cancer prevention.  Optimising polyp detection is therefore an important aim of colonoscopy.

Polyp detection is influenced by bowel cleanliness. There are many bowel-cleansing agents available including low-volume bowel preparations, which have been advocated as a means to improve patient experience, but their effect on bowel cleanliness is debated. A comparison of bowel cleanliness following a low volume and standard volume bowel preparation before screening colonoscopy is detailed in Chapter six. Minor differences in efficacy were found between bowel preparations in a single colonic segment but there were major differences according to whether the bowel preparation was administered as a single or split dose.

Previous studies have suggested position change may aid polyp detection but results are conflicting. Chapter seven compares routine patient position change, during colonoscope withdrawal, versus withdrawal in the supine position throughout. Routine position change significantly increased polyp and adenoma detection in the right colon.

The studies within this thesis explore the utility of simple interventions that could easily be adopted by all colonoscopists, and may therefore lead to changes in practice that improve colonoscopy quality.

Publications arising that relate to background:

Ball AJ, Riley SA, Assessment of comfort during colonoscopy: a nurse- or patient-rated scale?

Gastrointes Endosc. 2013;78(4): 668

Ball AJ, Campbell JA, Riley SA. Position change during colonoscope withdrawal: Is it worth the effort?

Gastrointest Endosc. 2014;80(5):914-5.

**Chapter 1 - Literature review**

**1.1 Introduction**

**1.1.1 What is colonoscopy?**

Colonoscopy refers to a procedure whereby a flexible endoscope (colonoscope) is inserted via the anus to illuminate and visualise the colon and rectum. Colonoscopes, as they are recognised today, were initially developed in the 1960s as fibre-optic instruments.(1) Following significant technological improvements, modern day video endoscopes are capable of providing highly detailed images of the colonic mucosa in health and disease.

**1.1.2 The role of colonoscopy**

Colonoscopy is the investigation of choice for the assessment of patients with colonic symptoms and is widely used in screening for colorectal cancer. In the UK, over 20,000 colonoscopy examinations were performed during the two-week study period of the most recent national audit.(2) Colorectal Cancer (CRC) is the second commonest cause of cancer related death in the UK.(3)

**1.1.3 Natural history of colorectal cancer and screening**

Most CRCs progress over many years from precursor growths, called polyps. The most important polyp type is adenomas. A link between adenomas and carcinomas was proposed by Hill et al in 1978, and was referred to as the adenoma- carcinoma sequence.(4) Evidence for this association is indirect but overwhelming: Patients with untreated colonic polyps (greater than 10mm) are reported to have a high risk of subsequent CRC, with almost 24% developing CRC after 20 years of follow up.(5) On the other hand, patients who have undergone colonoscopy and had polyps removed are at very low risk of developing CRC.(6) Progression of the adenoma carcinoma is paralleled with an accumulation of genetic mutations, which occur in a multistep process.(7) Typical genetic alterations include mutations in the APC, p53, DCC and *k-ras* gene.

Progression of CRC is associated with invasion through the colonic wall in addition to lymph node and visceral, usually liver, metastases. As with all cancers, stage at the time of CRC identification is a determinant of survival. Early CRCs (Duke stage A) are associated with a 93% 5 year survival rate in

comparison to a 7% 5 year survival rate associated with late stage CRCs (Duke stage D).(8) Therefore, a strategy which detects CRC at an earlier stage may improve survival.

Several large randomised studies have assessed the benefit of screening colonoscopy following a positive faecal occult blood test (FOBt).(9-13) (FOBt detects microscopic amounts of blood in the faeces, which can be associated with bleeding lesions such as CRC.) Studies examining this approach have reported that CRC associated mortality is reduced by 10-21%. The improvements in survival have been attributed to the earlier stage at which CRC is detected: In a population undergoing screening colonoscopy following a positive FOBt, approximately two-thirds of the CRCs are at an early stage (Dukes stage A/B) whereas only one-third of CRCs are at an early stage in a symptomatic population (patients undergoing colonoscopy for reasons such as anaemia and change in bowel habit).

There are no randomised studies examining the benefit of CRC screening using colonoscopy alone. Observational studies however, have reported a 53% reduction in CRC associated mortality in a population of patients who had undergone screening colonoscopy and polypectomy compared to those who have not undergone screening colonoscopy.(14) It is believed that polypectomy interrupts the adenoma- carcinoma sequence thereby preventing CRC. The protective effect of screening and polypectomy appears to be protective against left, but not right, sided bowel cancer. The potential reasons for this are discussed later in the thesis. Given the protective effect of endoscopy against left sided bowel cancer, studies have examined the utility of screening flexible sigmoidoscopy (endoscopic examination limited to the left side of the bowel).(15-17). Randomised studies comparing flexible sigmoidoscopy screening against no screening have reported an 18% - 23% reduction in the incidence of CRC over a median follow up of 10.5 - 11.9 years. Screening flexible sigmoidoscopy also reduces CRC associated mortality by 22-31%. This could be further improved by increasing adherence to screening: As per protocol analyses, report a 31 - 33% reduction in the incidence of CRC and a 38 - 43% reduction in CRC associated mortality.

The UK population is screened for CRC with a one off flexible sigmoidoscopy at the age of 55 years, in addition to being screened with a FOBt biennially between the ages of 60- 74 years. Those with a positive FOBt are offered screening colonoscopy.

### 1.1.4 The limitations of colonoscopy

Colonoscopy has many limitations including the potential to cause pain and embarrassment. The consumption of bowel preparation may also be challenging and sometimes unsuccessful. The procedure is technically demanding, may cause serious complications and although widely considered to be the most sensitive colonic investigation, pathology may be missed.

Many of the limitations may relate to differences in colonoscope technique or practice, which vary between colonoscopists. The caecal intubation rate of colonoscopy examinations, for example, varies widely between colonoscopists.(2, 18) To raise the quality of care for patients undergoing colonoscopy, standards have been set against which colonoscopists may compare their performance against peers.(19) These may be used to identify potentially low-performing colonoscopists for whom it may be possible to target additional training.

### 1.1.5 Assessing the quality of colonoscopy

Assessing the quality of colonoscopy is complex and cannot be adequately summarised using a single parameter. The American Society of Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) Taskforce for Quality in Endoscopy devised 14 evidence-based indicators of colonoscopy quality(20) (see figure 1). Four of these relate to or are major determinants of adenoma or polyp detection. More recently, the European Society of Gastrointestinal Endoscopy (ESGE) devised 15 key similar key quality indicators on the quality of screening colonoscopy, which also strongly feature polyp detection or surrogates (e.g. 'adenoma and cancer detection should be audited', 'colonoscope withdrawal time should be audited' and 'the state of bowel cleansing should be audited').(21)

It could be argued that the measure of colonoscopy quality that has the greatest clinical relevance is the frequency of CRC in the period following colonoscopy, referred to as interval cancer rate. Robertson et al performed a pooled analysis of eight studies assessing the factors associated with interval CRC after colonoscopy and clearance polypectomy(22). Interval cancers were most often

| Quality Indicator |
| --- |
| **1** Appropriate indication |
| **2** Informed consent is obtained, including specific discussion of risks associated with colonoscopy |
| **3** Use of recommended post-polypectomy and post-cancer resection surveillance intervals |
| **4** Use of recommended ulcerative colitis/Crohn's disease surveillance intervals |
| **5** Documentation in the procedure note of the quality of the preparation |
| **6** Caecal intubation rates (visualization of the caecum by notation of landmarks and photo documentation of landmarks should be present in every procedure) |
| **7** Detection of adenomas in asymptomatic individuals (screening) |
| **8** Withdrawal time: mean withdrawal time should be >6 minutes in colonoscopies with normal results performed in patients with intact anatomy |
| **9** Biopsy specimens obtained in patients with chronic diarrhoea |
| **10** Number and distribution of biopsy samples in ulcerative colitis and Crohn's colitis surveillance. Goal: 4 per 10-cm section of involved colon or approximately 32 specimens per case of pancolitis |
| **11** Mucosally based pedunculated polyps and sessile polyps < 2 cm in size should be endoscopically resected or documentation of unresectability obtained |
| **12** Incidence of perforation by procedure type (all indications vs. screening) is measured |
| **13** Incidence of post-polypectomy bleeding is measured |
| **14** Post-polypectomy bleeding managed non-operatively |

**Table 1 -** Indicators of quality during colonoscopy proposed by the ASGE/ACG taskforce on quality in endoscopy.

classified as being missed cancers (52%), and a minority were attributed to being new cancers (24%), incomplete polyp resection (19%) or failed biopsy detection (5%). Interval cancers in the right colon were more likely to be designated as missed cancer than those in the left colon (66% vs. 38%, p=0.04). Several factors have been reported to influence the likelihood of interval cancer, including the presence of diverticulosis,(23, 24) adenoma at the index colonoscopy,(25) a family history of CRC(25) and increased patient co-morbidity.(24) The frequency of interval cancers is reported to vary according to the endoscopists' ADR (adenoma detection rate),(26, 27)and their speciality(23) suggesting a dependency on colonoscopic technique.

Although interval cancers are an important outcome measure of colonoscopy quality, these are generally uncommon with a reported risk of only 1.1-2.7 per 1000 patient years.(28) Interval cancer rate is therefore an insensitive measure of an individual colonoscopists quality. Surrogate measures of interval cancer risk including adenoma detection rate (ADR) have therefore been employed. Two key studies have shown that ADR is closely related to interval cancer risk.(26, 27) Kaminski et al used a multivariate hazard regression model to examine the relationship between ADR and the risk of interval cancer among 186 screening colonoscopists (45,027 examinations) and reported an increased risk of interval cancer among endoscopists with an ADR <20% (hazard ratio >10).(26) More recently, Corley et al similarly found an inverse association between ADR and the risk of both interval cancer and CRC associated mortality among 314,872 examinations performed by 136 colonoscopists, between 6 months and 10 years post procedure.(27) ADR is now widely employed as a marker of colonoscopy quality.

A further indicator of colonoscopy quality is the occurrence of patient discomfort, the frequency of which also varies between colonoscopists. Lee et al reported that the frequency of colonoscopy examinations associated with moderate (0-31.1%) and severe discomfort (0-10.4%) within the English BCSP varied widely. Discomfort is usually caused by stretch of the colonic mesentry, which most often reflects the presence of loops in the shaft of the colonoscope.(29) While the levels of discomfort are acceptable for most patients, for some this can be severe, limit procedural completion and negatively associates with their satisfaction(30)and willingness to undergo a repeat colonoscopy examination.

There are currently no standards to compare and assess the quality of colonoscopy based on patient comfort. In their absence, the NHS Bowel Cancer Screening Programme (BCSP) quality assurance (QA) guidelines and the ESGE guidelines on screening colonoscopy have suggested that comfort should be measured and audited.(19, 21)  The lack of defined standards to assess quality based on patient comfort may relate to the many difficulties associated with its measurement. First, the time

course and severity of discomfort is variable with some patients having only moments of discomfort whilst others have more prolonged pain. A single descriptor or rating is therefore unlikely to adequately summarise the experience. Second, comfort is a very subjective phenomenon, which is often difficult for patients to convey and observers to understand and quantify. Third, comfort is influenced by the attitudes and expectations of patients, with the priority of some being to have a completely pain-free procedure whereas others are willing to have some discomfort if they can view the examination or can have the reduced inconvenience associated with no medication[31]. Fourth, the tolerance of discomfort varies between patients. Finally, many patients have amnesia related to the use of sedation. Given these complexities, it is perhaps unsurprising that the optimal technique to measure comfort is uncertain. It is also unclear whether a clinician or patient is best placed to perform these ratings. Ratings scales have also undergone only limited validation and are nurse rather than patient rated.[32, 33]

The following section gives a detailed but non-systematic review of polyp detection and patient comfort during colonoscopy.

## 1.2 Colonic polyps

### 1.2.1 What are colonic polyps?

Colonic polyps are abnormal growths of colonic epithelium, which can be categorised according to their histological and endoscopic appearance. Their importance relates to the potential to transform into CRC and the ability to prevent CRC through colonoscopic polypectomy.

### 1.2.2 Histological subtypes

Most colonic polyps are categorised histologically as either adenomatous (dysplastic) or hyperplastic (metaplastic). There are other histological subtypes but these are less common and will not be discussed further. Dysplasia refers to an excess of immature cell types, which is recognised histologically by the presence of cellular and architectural abnormalities. Metaplasia refers to the abnormal change of one mature cell type into another.

Adenomatous polyps are further characterised histologically according to the extent of tubular and villous changes. The importance of villous change was demonstrated by Atkin et al, who reported that patients with tubulovillous or villous rectal adenomas, who did not undergo surveillance colonoscopy, following rigid sigmoidoscopy had an increased risk of subsequent cancer (standardized incidence ratio = 3.6) whereas those with only small tubular adenomas had a lower risk (standardized incidence ratio = 0.5)(34). Adenomas may be further characterised according to the extent of dysplasia. A meta-analysis of studies examining the incidence of advanced adenomas (≥10 mm, villous, high grade dysplasia, or invasive components) at follow up colonoscopy reported that high grade dysplasia significantly increased subsequent cancer risk (OR = 1.84).(35)

A characteristic histological feature of hyperplastic polyps is the presence of serrations. Hyperplastic polyps comprise several histological subtypes including sessile serrated adenoma, traditional serrated adenomas and mixed polyps but further description of these is beyond the scope of this thesis.

Adenomatous polyps are believed to be the precursors to 70-80% of all CRCs, the natural history of which can be modified through colonoscopic polypectomy. The United States National Polypectomy Study compared patients who had undergone polypectomy with a matched population and reported that these patients had a 53% reduction in CRC associated mortality.(6, 14)

Hyperplastic polyps were previously regarded as unimportant but recent studies have indicated that these may be the precursors to 20-30% of CRCs(36, 37). However, the natural history of hyperplastic polyps is not as well understood as that of adenomatous polyps and studies confirming a benefit of removing hyperplastic polyps are lacking. Much of the evidence regarding the relationship between hyperplastic polyps and CRC comes from the shared epigenetics and histological features with serrated adenocarcinomas.(38) It has also been suggested that these polyps may be responsible for a significant proportion of interval cancers. This may relate to their subtle appearance and predilection for the proximal colon, which is a common site for interval cancers.(39)

Colonoscopic studies differ as to whether they present adenoma detection rate, polyp detection rate (PDR) (generally adenomas and hyperplastic polyps) or present both. When the studies within this thesis refer to polyps, it is referring to any adenomatous or hyperplastic polyp.


### 1.2.3 Morphological description of polyps

Polyps come in many shapes and sizes and there are a variety of systems available to describe the endoscopic morphology of polyps. The Paris classification is widely used and has recently being adopted by the English BCSP database.(40) This system broadly describes polyps according to whether they are elevated or flat. Elevated lesions are further subdivided into pedunculated (1p) or sub-pedunculated (1sp) and sessile (1s) and flat lesions are further described according to whether they are slightly raised (2a), completely flat (2b), depressed (2c) or a combination of these (2c/a and 2a/c). Standardising morphological description allows colonoscopists to describe and compare polyps using a common language, guiding resection techniques and sometimes giving clues to the

presence of malignancy. Furthermore, there are differences between these morphologies with regards to the ease of visualisation with elevated lesions being easier to identify whereas flat lesions are often subtle in appearance.(41)

**1.2.4 Variation in polyp detection**

Although most large and some small polyps are seen during colonoscope insertion, the majority of polyps are detected during colonoscope withdrawal when mucosal visualisation is the main focus. Chen et al reported that the endoscopist was a greater determinant of adenoma detection than patient age and gender and the detection of one or more adenomas varied between 15.5% to 41.1%.(42) As already discussed, variation in adenoma detection has clinical relevance due to its association with interval colorectal cancers(43, 44).

In routine practice it is impossible to know whether all polyps have been seen during colonoscopy examinations. In a research setting, however, it is possible to assess polyp miss rate by measuring the additional yield of polyps from either a repeat colonoscopy (referred to as tandem or back to back examinations) or a radiological investigation.

Back-to-back colonoscopy examinations may be used to examine polyp or adenoma miss rate, although this may be criticised as polyps/adenomas may also be missed during the second examination. Studies have reported miss rates of 15-28% during back-to-back examinations, with small polyps being missed more often than large polyps.(45-47)

The radiological examination most commonly compared to colonoscopy is CT colonography. Benson et al compared the yield of neoplasia using colonoscopy and CT colonography and reported a similar sensitivity for polyps > 6mm, but CT colonography was less sensitive for polyps < 6mm.(48) Studies of colonoscopy and CT colonography also provide useful insight into the typical location of the polyps that are missed during colonoscopy, which are often at flexures and behind mucosal folds.(49)

In routine practice, polyp miss rate is measured indirectly using the adenoma and polyp detection rate. A low ADR or PDR being taken as an indicator of missed polyps. This measure does not take account of the variation in the prevalence of polyps, which varies between patient groups. Although ADR is an imperfect measure, its ease of measurement and inverse relationship with interval cancer risk make it clinically useful. However, Saini et al recently published a modelling study, which suggested that solely relying on ADR as a means of identifying low performing endoscopist (adenoma miss rate) has significant limitations, due to differences in case mix.(50) They modelled differences in adenoma prevalence and miss rates based on previously published data and suggested that using an ADR threshold of 16.5% would detect only half of the low performing endoscopists. Furthermore, nearly 80% of the endoscopists below the 16.5% threshold would not have been low performers.

**1.2.5 Factors influencing polyp detection**
Several factors may influence the detection of polyps.  These may relate to the patient, the effectiveness of bowel cleansing, the size and morphology of polyps and the technique employed by the endoscopist.

*1.2.5.1 Patient factors*
Patient factors associated with an increase in the prevalence of polyps include increasing age and male gender.(42, 51) Cigarette smoking also increases the likelihood of adenomas, hyperplastic polyps and CRC(52, 53) but studies examining the relationship between alcohol consumption and colonic polyps and CRC suggest an absent or much weaker relationship(54, 55).

*1.2.5.2  Polyp factors*
The location and morphology of polyps influence their detection. Unsurprisingly large polyps are missed less often than small polyps.  Polyps are also missed more often when they are located behind mucosal folds(49, 56) or have a flat morphology(45).

### 1.2.5.3 Endoscopist related Factors

As already discussed polyp and adenoma detection vary according to the performing colonoscopist.(42) Studies have suggested that variation in adenoma detection may be explained by differences in withdrawal technique.(57, 58)

### 1.2.5.3.1 Withdrawal technique

Rex devised a scale to assess the quality of withdrawal techniques based on four domains: 1) luminal distension 2) colonic cleansing 3) whether the proximal side of colonic folds are examined and 4) adequacy of time spent viewing.(57) This scale was used to compare the withdrawal techniques of two endoscopists, one with a high ADR and the other with a low ADR. Differences in withdrawal technique were felt to explain much of the variation in ADR.

### 1.2.5.3.2 Withdrawal time

It is not surprising that it takes time to adequately examine all the colorectal mucosa during colonoscope withdrawal. In a landmark study, Barclay et al compared endoscopists with a mean colonoscope withdrawal time less than and greater than 6 minutes and reported that those with the longer withdrawal times had a greater detection of adenomas (28.3% vs. 11.8%, P<0.001) and advanced neoplasia (polyps ≥10mm, villous component, HGD or cancer - 6.4% vs. 2.6%, P<0.005).(59) The same group then compared adenoma detection before and after mandating an eight minimum withdrawal time and reported a significant increase in adenoma detection (34.7% vs. 23.5%, P>0.0001) but no significant difference in advanced neoplasia (6.6% vs. 4.5%, P=0.13). (60)

Other studies have also examined the relative importance of withdrawal time and aspects of withdrawal technique in determining adenoma and polyp detection. Lee et al, using the scale devised by Rex, assessed the quality of withdrawals among 11 endoscopists and found poorer technique in endoscopists with lower ADR without there being a significant difference in withdrawal times(58). The influence of withdrawal time on adenoma detection has also been subject to a meta-analysis. This concluded that increasing withdrawal time alone was not an effective intervention to

improve adenoma detection, but a surrogate marker for careful inspection which takes time to perform(61).

Coe et al performed a randomised study to examine whether an endoscopic quality improvement program (EQUIP) improved polyp and adenoma detection. The EQUIP comprised a training session on the methods and techniques proven to increase adenoma detection as well as a session on the recognition of subtle polyps and polyp classification. Following this intervention, ADR significantly improved among the endoscopists randomised to the EQUIP intervention (36% vs. 47%, OR 1.7, p=0.0013) but not in the control group (36% vs. 35%).(62)

*1.2.5.3.3 Patient position*

Adjusting a patient's position redistributes colonic luminal contents due to the influence of gravity such that air rises while liquids and solids sink. It has been suggested that by adjusting patient position such that the colonic segment being examined is uppermost within the abdomen (the right in the left lateral position, the transverse colon in the supine position and the descending colon in the right lateral position), it is possible to improve luminal distension and therefore mucosal visualisation, adenoma and polyp detection. However, studies examining the influence of patient position on luminal distension, adenoma and polyp detection have conflicting outcomes.

East et al compared colonoscope withdrawal using routine position change against withdrawal in the left lateral position in two separate studies.(63, 64) These were both two-way, randomised, cross-over studies, whereby colonic segments were examined in two different positions. Once with the patient in the left lateral position and once with position change. The order in which patients had colonic segments examined was randomised to either position change then left lateral position or vice versa.

A cross over, rather than a parallel study design, significantly reduced the number of patients required to show a difference since each patient acts as their own control. A two-way study design was employed to balance the carry-over effect; since the first withdrawal would have pre alerted the

endoscopist to the findings during the second withdrawal. Without this it would not have been possible to differentiate whether additional polyps were seen due to the change in patient position or repeat examination.

The first study assessed the effect of withdrawal position on luminal distension ratings on a 5-point scale (1 = total collapse, 2 = collapse with view <2 haustral folds into the distance, 3 = some proximal collapse only, with crinkling of folds, 4 = widely distended, distal collapse at limit of vision, 5 = widely distended, no distal collapse to limit of vision) in 14 patient undergoing colonoscopy. The distension ratings were validated by an independent reviewer with whom there was moderate inter-observer agreement, κ = 0.53. Routine position change was reported to significantly improve overall luminal distension ratings in the transverse colon (3.9 vs. 2.9, p=0.02), splenic flexure (4.5 vs. 3.0, p=0.002) and descending colon (4.5 vs. 3.0, p<0.001). The limitation of this study related to the use of an endpoint that has uncertain clinical significance (luminal distension).

The follow up study focussed on improvements in ADR and was powered to detect a 50% increase in the proportion of patients with ≥1 adenoma (130 patients). Examining the transverse colon in the supine position rather than the left lateral position was found to increase adenoma detection but this only reached statistical significance in the transverse colon. (15% vs. 24%, p=0.04). The differences in adenoma detection were attributed to improved luminal distension, as there were a higher proportion of polyps in the segments with adequate distension (16% vs. 7%, p <0.001). Adenoma detection was not significantly different in the other colonic segments. The limitations of this study relate to it being a single centre study and all procedures were performed by a single operator.

Two further studies have examined the benefits of routine position change. Köksal et al performed a two-way crossover study such that patients were randomised to being examined in either the left lateral position followed by position change or vice versa. Unlike the study by East et al position change in the left colon (splenic flexure, descending colon and sigmoid colon) included the supine

position and right lateral position. Furthermore, they compared adenoma detection during a single withdrawal in the left lateral position alone versus the combined detection rate in the left lateral position and the other positions combined. The difference in study design therefore limits the inferences that can be drawn since previous studies have consistently reported that a repeat examination significantly increases polyp detection, regardless of patient position. Therefore, the increase in polyp detection may have occurred due to either the repeat examination or the position change.

Köksal et al reported greater adenoma detection in the transverse colon in the supine and the left lateral position combined compared with the left lateral position alone (11 vs. 16, p=0.05). Unlike East et al, Köksal et al studied withdrawal positions in the sigmoid colon and found that examining the sigmoid in the right lateral, supine and left lateral yielded significantly more polyps and adenomas than in the left lateral position alone, (14 vs. 10, p=0.04 and 9 vs. 5, p=0.04 respectively) although, as noted above, the reason for this increase is open to debate.

Ou et al examined the use of routine position change but unlike the previous studies, compared this against 'usual practice' rather than against a single static position. They also employed a parallel group, rather than a cross-over design and found that routine position change did not significantly increase ADR (37.9% vs. 41.8%, OR = 1.17, p=0.28) or PDR (58.2% vs. 58.0%, OR = 0.99, p=0.93). The major limitation of this study relates to the use of 'usual practice' as the comparator. Comparing position change against usual practice may be considered advantageous as it represents standard clinical care. However, practices differ between colonoscopists with some changing position routinely and others rarely doing so.(65) Further analysis of the data by Ou et al reveals that approximately half of the patients designated to usual practice had their right and transverse colon examined in the left lateral and supine position respectively, such that the comparator was no different to the position change strategy, thereby minimising the benefit associated with position change. Furthermore, it was not stated whether patients were placed in these positions from the

start of the procedure or in response to poor distension. Neither was it clear whether the practices of the study endoscopists were representative of wider practice. This is important as participating endoscopists would presumably be aware of the literature concerning position change. Finally, the study reported overall polyp detection and did not give a breakdown of the benefits in each segment.

A minor limitation of routine position change during colonoscope withdrawal is the perception of inconvenience for both the patient and endoscopist. In this respect, Ou et al reported a statistically significant increase in the mean colonoscope withdrawal time (466 vs. 422 seconds, $p<0.0001$), although the absolute difference has questionable significance.
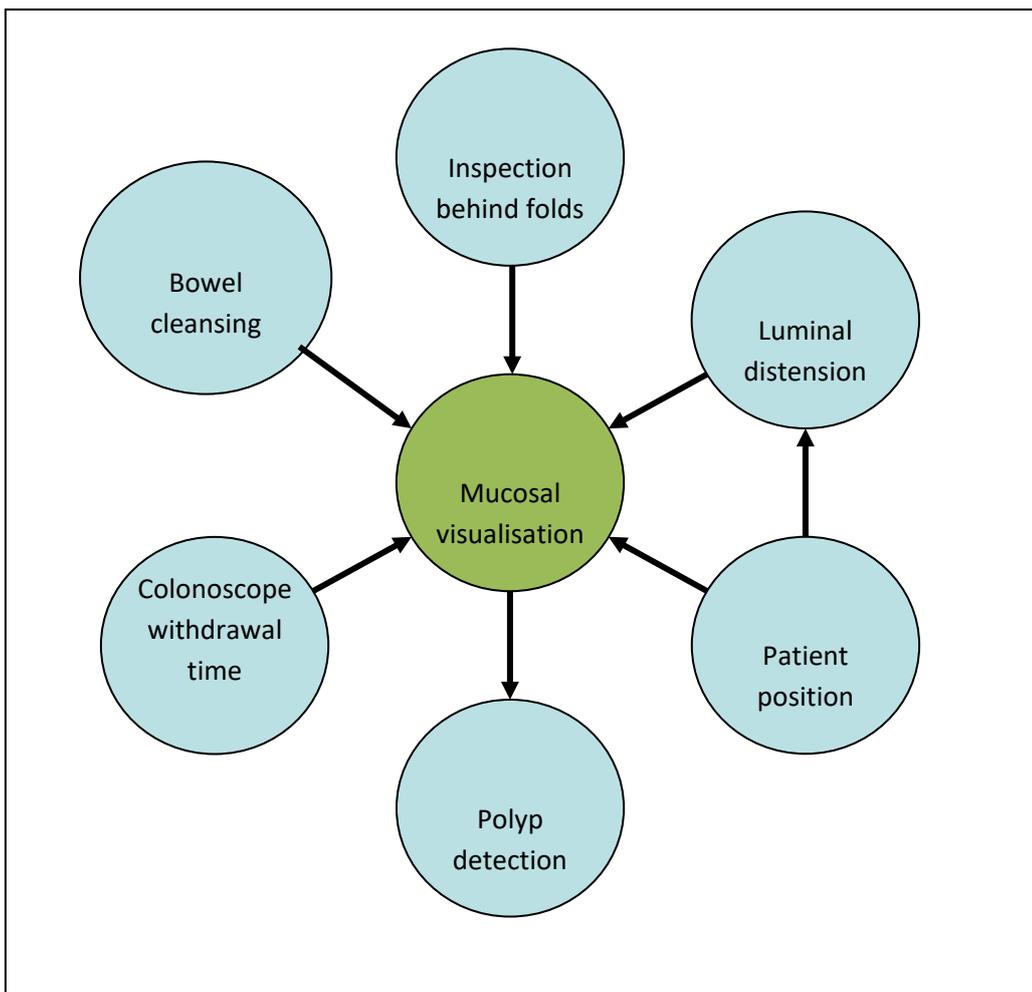


**Figure 1** - **Technique related factors that influence polyp detection**

### 1.2.5.4 Bowel cleansing related factors

Prior to colonoscopy patients consume bowel preparation to remove faecal residue. Residual Faeces may impede mucosal visualisation. Unsurprisingly, poor bowel cleanliness is associated with missed polyps and adenomas.

Several bowel preparations are available but there is no consensus on the optimal agent. The quality of bowel preparation is a major determinant of polyp detection but this is frequently suboptimal or inadequate. A recent English national colonoscopy audit, reported that 11.8% of patients had bowel preparation rated as less than adequate and of those who had incomplete colonoscopies, poor bowel preparation was the cause in almost a quarter.(2)

Large retrospective database analyses have demonstrated that bowel preparation has a significant impact on polyp detection. For example, Froehlich et al performed a multicentre study of 5382 patients and found patients with good quality bowel preparation had higher PDR than those with poor quality preparation (29.4% vs. 23.9%, p = 0.007 for polyps of all sizes, and 6.4% vs. 4.3%, p = 0.016 for polyps >1cm)(66). Similarly Harewood et al analysed 93,004 patient reports from a national endoscopic database and found that PDR were lower in patients with inadequate bowel preparation (19% vs. 21.8%, p = <0.0001). When adjusted for age and sex, only polyps ≤ 9mm were found more frequently in patients with adequate bowel preparation with an odds ratio of 1.23(67).  Finally, Lebwohl et al reviewed the findings of 12,787 patients attending for colonoscopy at a single hospital. Bowel preparation was suboptimal in 24% of patients and 17% underwent a repeat colonoscopy within 3 years with a 42% increase in polyp detection in those who achieved adequate bowel preparation at the time of the repeat examination(68).

### Assessment of bowel cleanliness

The US Multi-society Task Force on Colorectal Cancer suggest bowel cleanliness should be judged as adequate or inadequate according to the likelihood of lesions >5mm being missed(28). However, the assessment of bowel cleanliness is complex. Cleanliness may vary between and within segments and

is dependent on the efforts of the endoscopist to wash and suction residual material. Although scales have been validated to assess bowel preparation, none of these assess the likelihood of missing polyps <5mm(69-71). The choice of scale also depends on whether the user wishes to compare the efficacy of bowel cleansing pre or post cleansing by the endoscopist.

The Boston Bowel Preparation Scale (BBPS) assesses the quality of bowel preparation following optimisation with endoscopic washing and suctioning of residual material(70, 72, 73). The BBPS assesses the quality of bowel preparation in three colonic segments (right colon, transverse colon and left colon) on a four-point scale between 0 and 3 and has good levels of agreement between raters (intra-class correlation coefficient = 0.74). The BBPS is the only scale that has been validated to detect differences in the quality of bowel cleanliness which impact on polyp detection.(70)

The Ottawa scale assesses bowel cleanliness prior to optimisation by the endoscopist. The Ottawa scale also grades the amount of residual fluid. It shows high levels of inter-observer agreement, with an intra-class correlation (ICC) coefficient of 0.94, but validation was limited to only two gastroenterologists.

The Aronchick scale grades the quality of bowel preparation throughout the colon rather than in individual segments. The descriptors include the amount and opacity of residual fluid in addition to the proportion of mucosa visualised(71, 74). The validation of this scale (published in abstract form only) was based on the ratings of five gastroenterologists who viewed recordings of 80 colonoscopies. There was variable inter-observer agreement, with a Kappa ICC between 0.31 and 0.76.

The Ottawa and Aronchick are often used in studies that assess the efficacy of bowel preparation regimens, as they rate bowel cleanliness prior to optimisation as well as grading the efforts required to attain adequate views. It is important to consider the efforts required to optimise bowel cleanliness as it may be possible to optimise most bowels given enough time and effort cleansing the bowel. In contrast, the BBPS rates bowel cleanliness after optimisation and may therefore be best

suited to assess parameters which reflect the adequacy of mucosal visualisation such as polyp detection.

*PEG laxatives*

PEG is a group of polymers of varying lengths that have many applications including use as a laxative. PEG laxatives work primarily by the mechanical effects of large volume lavage.(75) Standard volume (4 litres) PEG preparations contain several electrolytes which are diluted in water to create iso-osmotic solutions to minimises dehydration and electrolyte shifts.

Standard volume PEG preparations are commonly used, but many patients struggle with their consumption due to their volume, side effects (bloating, nausea, abdominal cramps and headaches) and taste. Low volume PEG solutions have been advocated as an alternative to standard volume PEG solutions. Several studies have also assessed the influence of dosing schedule on compliance, patient experience and efficacy.

*Low volume PEG laxatives*

There are several low volume PEG laxatives available(76-81) but further review will be limited to the use of Moviprep which will be the focus of a later chapter. Moviprep contains PEG (Macrogol 3350) in addition to sodium sulphate, a large dose of ascorbic acid and sodium ascorbate with a lemon flavouring. The administration of ascorbic acid in large doses has a significant laxative effect reducing the requirement for the PEG component.

*Efficacy of Moviprep compared with standard volume PEG solutions*

The RCTs comparing Moviprep with standard volume PEG solutions have compared the proportion of patients that achieve 'adequate' or 'successful' bowel cleansing. The extent to which they can be compared however, is limited by variation in the definitions of adequacy and success and the wide range of scales used (table 2) and differences in the dosing of the bowel preparations, inclusion of morning and afternoon examination and how the dose was split (table 3). The standard volume PEG solutions were considered the standard of care and all studies were powered to show that Moviprep

was equivalent(82) or non-inferior(83, 84)  to the standard volume solutions. These were powered to detect a 10-15% difference in the proportion of patients having adequate/successful bowel preparation.

| Study | Definition of adequacy or success | Scale |
|---|---|---|
| Jansen(84) | Bowel preparation was considered to be a success when rated as 'good'. Quality of bowel cleanliness rated in whole colon and recto-sigmoid. | Good - empty colon or the presence of clear liquid in the colon only<br><br>Moderate - the presence of brown liquid or semisolid stool, fully removable with suction<br><br>Bad – the presence of semisolid stool only partially removable with suction or solid stool |
| Ell(83) | Quality of bowel cleanliness rated in 5 segments. Overall rating of A or B defined as successful A = all segments 3 or 4 B = a score of 2 in at least one segment C = a score of 1 in at least one segment D = a score of 0 in at least one segment | 4 -*Very good* - Colon empty and clean.<br><br>3 - *Good* - minor amount of fluid in the colon but easily removed by suction.<br><br>2 - *Moderate* - Fluid or semisolid residual stool, fully removable by suction or displaceable.<br><br>1 - *Bad* - Fluid or semisolid residual stool, only partially removable with risk of incomplete mucosal visualisation<br><br>0 - *Very bad* - colon full of semisolid or solid stool; colonoscopy incomplete or had to be terminated in one of the predefined areas |
| Pontone(85) | Overall cleansing was considered adequate if rated as 1-3 on the Aronchick scale | 1 - *Excellent* - Small volume of clear liquid or greater than 95% of surface seen<br><br>2 - *Good* - Large volume of clear liquid covering 5% to 25% of surface but greater than 90% of surface seen<br><br>3 - *Fair* - Some semi-solid stool that could be suctioned or washed away but greater than 90% of surface seen<br><br>4 - *Poor* - Semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen<br><br>5 - *Inadequate* – Re-preparation needed |
| Corporaal(82) | Quality of bowel cleanliness rated in 3 segments. Overall rating of A or B defined as successful. A - excellent or good score in every B - at least one colon segment with a moderate score C - at least one colon segment with a bad score; D - at least one colon segment with a very bad score. | Excellent - when only a small amount of clear fluid was left in the colon<br><br>Good - when a large amount of clear fluid was left<br><br>Moderate - when a small amount of semi fluid stool was present that could be removed by rinsing or suction;<br><br>Bad - when a significant amount of semisolid stool was present that could not be removed by rinsing or suction<br><br>Very bad - when presence of semisolid or solid stool led to an incomplete colonoscopy |
| Valiante(86) | Cleanliness was considered adequate if rated as 1-3. | Aronchick scale - see above |
| Marmo(87) | Cleanliness was considered adequate if rated as good or excellent (Inverted Ottawa scale) | 4 excellent - colon empty and clean<br><br>3 good - presence of clear liquid in the colon easy to aspirate<br><br>2 fair - presence of brown liquid or small amounts of semisolid residual stool, partially removable by suction to adequately visualize the underlying colonic mucosa<br><br>1 poor - large amounts of fecal residue, not removable, with hampered visualization of the underlying mucosa. |
| Ponchon(88) | Bowel preparation considered successful when grades A or B A - all scores 3 or 4 B ≥1 segments scored 2 C ≥1 segments scored 1 D ≥1 segment scored 0 Harefield cleansing scale | 0: Irremovable, heavy, hard stools<br><br>1: Semi-solid, only partially removable stools<br><br>2: Brown liquid/ fully removable semi solid stool<br><br>3: Clear liquid<br><br>4: Empty and clean |

**Table 2** - Scales used to compare bowel cleanliness in previous Moviprep studies.

| Study | Dosing of bowel preparations | Timing of examination |
|---|---|---|
| Jansen(84) | Kleanprep taken as a 3L:1L split dose with the morning dose at least 1 hour prior to morning colonoscopy.<br><br>Kleanprep taken as a 2L:2L split dose with the morning dose at least 1 hour prior to afternoon colonoscopy.<br><br>Moviprep taken as a 1L:1L split dose prior to the morning colonoscopy<br><br>Moviprep taken as a single dose on the morning prior to an afternoon colonoscopy. | Morning and afternoon<br><br>examinations |
| Ell(83) | Moviprep and Kleanprep both administered as an equal split dose with final dose at least 1 hour prior to colonoscopy. | Examinations prior to 13:00 |
| Pontone(85) | Single dose of Moviprep evening prior to colonoscopy<br><br>4L PEG with simethicone given with a 1 hour break between<br><br>3pm and 8pm on the day prior to colonoscopy | Examinations performed between<br><br>8:30am and 2pm |
| Corporaal(82) | 2l Moviprep on afternoon and evening prior to colonoscopy if scheduled for a morning examination<br><br>Standard volume PEG split as 3L:1L on evening prior to and morning of am examinations.<br><br>Split dose of Moviprep administered on the evening and morning of afternoon examinations<br><br>Standard volume PEG solution split as 2L:2L on evening prior to and morning of pm examinations. | Morning and afternoon examinations |
| Valiante(86) | Single dose of Moviprep evening prior to colonoscopy<br><br>4L PEG with a 1 hour break between 3pm and 8pm on the day prior to colonoscopy | Examinations performed between<br><br>8:30am and 2pm |
| Marmo(87) | Single dose of Moviprep separated by 2 hours administered on the evening prior to morning examinations<br><br>Single dose of standard volume PEG solution on the evening prior to morning colonoscopy<br><br>Split dose of Moviprep administered on the evening prior and morning of afternoon examinations<br><br>Split dose of standard volume PEG solution on the evening prior and morning of afternoon colonoscopy | Morning and afternoon<br><br>examinations |
| Ponchon(88) | Single dose the evening prior to colonoscopy. Moviprep between 6:30 – 10pm and Standard volume PEG between 5pm and 10pm. | Examinations performed between<br><br>8am and 1pm |

**Table 3 -** Dosing schedule and timing of colonoscopy examinations

| Study | Standard 4L PEG | 2L Moviprep | p value |
|---|---|---|---|
| Jansen(84) | 77.5% | 79.3% | ns |
| Ell(83) | 94.8% | 88.9% | ns |
| Pontone(85) | 88% | 91% | ns |
| Corporaal(82) | 96% | 90.6% | 0.13 |
| Valiante(86) | ITT 75.3% | ITT 84.6% | 0.04 |
| | APP 77% | APP 86.2% | 0.2 |
| Marmo(87) | Single dose 44.3 % | Single dose 41.7 % | ns |
| | Split dose73.4 % | Split dose 77% | ns |
| Ponchon(88) | 90.9% | 94.1% | 0.23 |

**Table 4** - Proportion of patients with adequate or successful preparation in reported RCTs of Moviprep.

ns= not significant, ITT = intention to treat, APP = as per protocol.

Six of the seven Moviprep RCTs reported no significant difference in the proportion of patients with adequate or successful bowel preparations (table 4). Valiante et al published the only study to report that more patients randomised to Moviprep had adequate bowel cleanliness. Conversely, a subgroup analysis in the study by Corporaal et al found that patients taking 4 litres PEG were more likely to have bowel cleanliness rated as excellent (79% vs. 52%, p<0.0001).(82)

*Patient experience with Moviprep compared with standard volume PEG solutions*
Low volume PEG solutions were designed with the intention of increasing tolerability and compliance, reducing side effects and maintaining efficacy. Therefore, most of these studies made detailed assessments of patient experience.

Despite differences in the volume of Moviprep and the standard volume PEG solutions, only two studies found significant differences in side effects. Ell et al reported that patients taking Moviprep were less likely to experience nausea and abdominal pain and Ponchon et al reported that abdominal discomfort and bloating were also less common with Moviprep.(83, 88)

Taste was assessed in five of the seven Moviprep RCTs. Most of these reported that patients randomised to Moviprep were more likely to rate the taste of Moviprep as acceptable(83, 84, 87, 88) but a single study found no difference(82). Difference in outcomes between studies may in part be explained by differences in the flavourings added to the standard volume PEG solutions. Furthermore, patients only rated the taste of the allocated bowel preparation and were unaware of the taste of the alternative bowel preparation as a point of reference.

No significant differences in compliance between Moviprep and the standard volume PEG solution were reported in five of the seven studies,(82, 86-88) while the remainder reported either a greater compliance with Moviprep(84) or did not report on this endpoint.(85) It should be noted the two of the studies compared compliance according to the proportion of patients completing at least 75%, rather than the consumption all of the bowel preparation.(83, 88) It should also be noted that differences in compliance were often larger between than within studies. This may suggest that

other factors, such as patient counselling, are more important determinants of compliance than the bowel preparation.(89)

*Dosing schedule of PEG preparations*

The dosing schedule of bowel preparation may be modified in many ways. PEG solutions are generally consumed in two halves with a variable break between. When the break between is short (often an hour) or all taken on a single day (usually the day prior) this is referred to as single dosing. Split dosing refers to taking the first half of the bowel preparation on the day prior to colonoscopy and the second half on the day of colonoscopy.

Most of the RCTs comparing split and single dosing have administered the single dose of bowel preparation on the day prior to colonoscopy other than Matro et al who asked patients to consume the single dose on the morning of colonoscopy. Studies also differed with regards to the interval between completion of bowel preparation and the start of colonoscopy. Most studies report that a split dose schedule is more likely to result in adequate bowel cleanliness (table 5). It is worth noting that the two studies reporting no overall difference in the proportion with adequate bowel preparation found that patients taking a split dosing regimen were more likely to have bowel cleanliness rated as excellent. It should also be noted that the proportion of patients with adequate bowel preparation varied widely between studies, which may relate to differences in the scales used (table 5).

| Study | Proportion of patients with adequate/successful cleansing overall | | | Scale |
| | Single dose PEG | Split dose PEG | P value | |
|---|---|---|---|---|
| Park(90) | 51% | 76% | 0.001 | Aronchick scale |
| Park(91) | n/a | n/a | 0.01** | Ottawa Scale |
| Aoun(92) | 56.2% | 76.5% | 0.011 | Adequate = ratings of excellent or good<br><br>Excellent - No fecal matter or nearly none in the colon; small to moderate amounts of clear liquid<br><br>Good - Small amounts of thin, liquid fecal matter seen and suctioned easily, mainly distal to splenic flexure; all mucosa seen<br><br>Fair - Moderate amounts of thick liquid to semisolid fecal matter seen and suctioned, including proximal to splenic flexure; small lesions may be missed; >90% mucosa seen<br><br>Poor - Large amounts of solid fecal matter found, precluding a satisfactory study; unacceptable preparation; <90% mucosa seen |
| Marmo(87) | 43% | 75.2% | 0.00001 | Inverted Ottawa scale<br><br>See table 2 |
| Manno(93) | 92.8 | 95% | Ns | Adequate = ratings of 3 and 4<br><br>1 = poor (large amounts of faecal residue requiring additional cleansing);<br><br>2 = fair (enough faeces or fluid to prevent a completely reliable exam);<br><br>3 = good (small amounts of faeces or fluid not interfering with the exam);<br><br>4 = excellent (no more than small bits of adherent faeces/fluid). |
| Matro(94) | 91.8% | 94.4% | Ns | Adequate = ratings of 1 or 2<br><br>Excellent (1): greater than 90% of mucosa seen, mostly liquid stool, minimal suction needed for adequate visualization.<br><br>Good (2): greater than 90% of mucosa seen, mostly liquid stool, significant suction needed for adequate visualization.<br><br>Fair (3): greater than 90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed.<br><br>Poor (4): less than 90% of mucosa seen, mixture of semisolid and solid stool, could not be suctioned or washed. |

**Table 5 - Proportion of patients with adequate or successful preparation reported in the RCTs comparing single dose and split dose PEG**

**Park et al assessed the quality of bowel preparation as a continuous variable, rather than a binary outcome, and therefore compared ratings with a *t* test.

*Side effects and compliance with single and split dose PEG*

Three of the six studies found that more patients were willing to repeat split dose bowel preparation (91-93). Most studies suggest side effects are less frequent with the split dosing bowel preparation schedule. Split dose regimens causes less nausea,(91, 93) less bloating(91, 92) and less abdominal pain.(93) In contrast to this, Matro et al found the single dosing rather than split dosing, resulted in less abdominal pain, less interference with daily activities and better sleep quality(94). The opposing outcome of this study may relate to the single dose being administered on the morning of, rather than the evening before colonoscopy as used in the other studies.

Compliance with bowel preparation is important and not surprisingly impacts on Bowel cleanliness.(91) Although none of the studies have reported a significant difference in compliance, two studies reported a trend towards increased compliance with the split dose regimen (92, 94) (84% vs. 72%, p = 0.073 and 90% by 78%, p = 0.062 respectively).

Studies comparing split dose and single dose regimens have been the subject of two meta-analyses(95, 96). Both concluded that split dosing of standard volume PEG solutions should be the gold standard to which other bowel preparations should be compared, but also acknowledged that the comparative efficacy of this and Moviprep remained uncertain.

*Split dose post dose interval*
The interval between completion of bowel preparation and colonoscopy also appears to influence bowel cleanliness(97). Seo et al studying split dose bowel preparation found that patients completing bowel preparation 3-4 hours prior to colonoscopy had better bowel preparation scores than patients completing the last dose < 3 hours and >7 hours prior to colonoscopy. Differences in bowel cleanliness were greatest in the right colon.

### 1.3 Pain during colonoscopy

Patient discomfort or the experience of pain is an important also a determinant of the acceptability of colonoscopy and subsequent patient satisfaction.(30) Not surprisingly, it is routinely assessed as a measure of colonoscopy quality.

### 1.3.1 Why does pain occur during colonoscopy?

Pain during colonoscopy is predominantly due to looping of the colonoscope, which causes stretch of the attached colonic mesentery(29), with a lesser contribution from gaseous distension of the colon.

### 1.3.2 How common is pain during colonoscopy?

Pain is a common side effect of colonoscopy but patients' experience of pain are remarkably variable with some having no pain and others having severe pain which limits procedural completion. The duration of pain during colonoscopy is also variable with some patients having brief moments of pain while others have continuous pain.

Measuring pain and discomfort is difficult. Studies have assessed the severity of pain and discomfort using both visual analogue scales(98) and semantic descriptive scales (99). Studies have used varying descriptors and have also varied according to whether they have compared differences on a continuous scale or a binary scale. Comparing the frequency of 'significant discomfort' or 'significant pain' between studies is therefore of limited value. Accepting this limitation, the proportion of patients with significant discomfort during the most recent UK national audit was 9.8%.

### 1.3.3 Pain or discomfort?

Colonoscopic studies have varied as to whether they assess pain, discomfort or both. Physiologically, the spinal pathways modulating pain and discomfort are similar although it has been argued that there may be differences in central processing pathways since patients who describe pain are more likely to have activated brain regions which modulate the unpleasantness associated with an experience.(100) The use of the descriptors pain and discomfort has been studied in patients with irritable bowel syndrome (IBS). Sach et al compared the symptom severity of patients with IBS, who

self categorised their symptoms as either pain or discomfort predominant, and found that patients with pain predominant IBS had higher pain ratings but there were no differences between groups in quality of life or overall GI symptom severity.(101) It has been suggested that patients may preferentially use the term pain when there is a higher threat level. However, are no studies examining whether either of these descriptors more closely associates with patient satisfaction or tolerance of colonoscopy examinations. Anecdotally, patients differ according to whether they describe pain or discomfort during colonoscopy, with many stating that they have discomfort but no pain, and patients seem to tolerate discomfort better than pain.

### 1.3.4 Factors which influence the occurrence of pain

Many factors influence the occurrence of pain during colonoscopy. These can relate to the endoscopic technique, patient related factors and can be modified by the use of medication. Multivariate analysis of factors that influence pain during colonoscopy have suggested that; extremes of age,(102, 103) lower body mass index (BMI)(102), presenting complaint of diarrhoea(102), hysterectomy(102), first time colonoscopy,(102) anxiety,(102, 104) female gender,(104, 105) longer procedure time,(104)  and high anticipated pain level(104) are predictive of a more painful procedure.

### 1.3.5 Why is pain important?

Minimising pain is important for humane reasons but this also influences patient satisfaction(30)and are willingness to undergo a repeat procedure.(106) Pain and/or looping is also reported to be responsible for approximately half of incomplete colonoscopy examinations.(2) Fear of pain has also been cited a barrier to screening colonoscopy uptake.(107-109)

### 1.3.6 Medication

The majority of patients undergoing colonoscopy in the UK receive medications to achieve a state of 'conscious' or moderate sedation. Conscious sedation refers to "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".

Sedatives, such as midazolam, reduce anxiety and calm patients whereas analgesics reduce pain. A recent UK national endoscopy audit found that conscious sedation was used during 88.9% of colonoscopies.(110) The most common analgesics used during colonoscopy were pethidine (56%) and fentanyl (35%) while Entonox® was used in 8.4% of colonoscopies and medication free colonoscopy accounted for only 2.3% of examinations.

### 1.3.7 How does the experience of pain influence recollection of pain

The relationship between experience of pain and recollection of pain is not well understood. Both measures are important as experience of pain may prevent completion of the procedure and recollection of pain influences patient satisfaction(30) and willingness to have a repeat examination.

Two studies have examined the relationship between the experience and recollection of pain/discomfort(104, 111). Elphick et al asked 109 patients to rate discomfort, on a 10 point VA-NRS, at 2 minute intervals and at peaks of discomfort, and assessed their recollection of discomfort immediately after colonoscopy and 2-3 months later. This observational study found patient's recollection of discomfort immediately following colonoscopy is higher than the mean score reported during colonoscopy, while patients' recollection of overall discomfort 2-3 months later was significantly lower than immediately after colonoscopy. Elphick et al observed that mean ratings of discomfort were at their greatest in the first 4-6 minutes during colonoscopy.

Redelmeier et al also examined the relationship between experience and recollection of pain in patients undergoing colonoscopy and lithotripsy, using the Gottman-Levenson method.(111) This method requires patients to use a hand held device to control a marker on a computer screen, which indicates the level of pain. They found that patients' recollection of pain had the greatest correlation with the peak rating and pain levels during the last 3 minutes of colonoscopy.

### 1.3.8 Entonox use during colonoscopy

#### 1.3.8.1 What is Entonox®?

Entonox® comprises a 50:50 mixture of oxygen and nitrous oxide, which has sedative and analgesic properties. Nitrous oxide has low solubility in blood and therefore equilibrates rapidly, giving it a rapid onset and offset of action. The precise mechanism by which nitrous oxide exerts its analgesic effects is uncertain(112). Animal studies have shown that the peri-aquaductal grey matter of the midbrain is an important target for the action of nitrous oxide(113). The analgesic effects of nitrous oxide are partially reversed by the opiate antagonist naloxone,(114) suggesting that some of its effect is mediated via the opiate receptor.

Entonox is administered by inhalation through a demand valve. This minimises issues associated with over sedation.(110) Entonox is often used for the management of acute pain such as during labour and the emergencies managed in accident and emergency departments. More recently it has been used during colonoscopy.

#### 1.3.8.2 Advantages of Entonox® over other agents

Several studies have assessed psychomotor recovery time, pain ratings and side effects with Entonox during colonoscopy against the use of benzodiazepines and opiate analgesics, which are the standard of care in UK colonoscopy practice, as well as propofol and placebo.

Initial studies comparing Entonox with intravenous medications during colonoscopy employed detailed analyses of psychomotor recovery using either a tracking test, multiple choice reaction times, manual dexterity tests, letter cancellation tests(98, 115) or memory testing(116). No differences were apparent between Entonox users and un-sedated patients immediately after and 15 minutes following colonoscopy. Patients receiving sedation performed inferiorly, although not all patients were examined immediately after colonoscopy as they were considered unfit, introducing an obvious selection bias. Lindblom et al similarly reported that patients receiving Entonox performed better in the psychomotor tests prior to discharge, even though patients randomised to Entonox left the department sooner.

A reduction in time to discharge is convenient for the patient and may also improve the efficiency of endoscopy units due to the reduced nursing requirements associated with patient monitoring. The shorter recovery time also allows patients to drive half an hour after use, which is much sooner than the 24 hour period which is recommended for intravenous sedation and analgesia.

### 1.3.8.3 Efficacy of Entonox® during colonoscopy

Studies comparing the efficacy of Entonox® with intravenous analgesics during colonoscopy have reported conflicting results. Maslekar et al randomised patients undergoing colonoscopy to receive either Entonox® or fentanyl plus midazolam and found that patients receiving Entonox® had significantly less pain, shorter recovery times and higher levels of satisfaction. On the other hand, Forbes et al, who randomised patients to either Entonox® or pethidine and midazolam reported that patients receiving Entonox® reported more pain, tolerated colonoscopy less well, were less satisfied and less willing to undergo a repeat colonoscopy under the same circumstances(117).

The conflicting outcomes of the studies examining Entonox use may be due to methodological differences. First of all, the comparator opiate varied although the relevance of this is uncertain; Robertson et al reported that pethidine is more effective than fentanyl(118) while Hayee et al found no significant difference.(119) Second, the equivalent dose of opiate also varied. It is particularly noteworthy that Maslekar et al, used a lower dose of opiate (50mcg fentanyl is equivalent to 25mg pethidine) and midazolam than Forbes et al who reported opposing results. Third, the dosing schedule of the medications varied. (table 6)  Fourth, there were differences between studies as to whether the patients and endoscopists were blinded to the treatment allocation. Fifth, two studies used intravenous saline or inhaled air as placebo,(116, 120) while the remaining studies were of an open study design.(98, 115, 117, 121) Sixth, the scales used to assess pain varied, which may have differed in validity and sensitivity.  Loberg et al, for example, enquired about pain on a four point scale semantic descriptive scale, which are reported to be less sensitive than visual analogue scales(122) as used by Maslekar et al.(98)

| Study | Dosing regimen |
|---|---|
| Lindblom | 2.5 mg ketobemidone and 2.5mg midazolam |
| Saunders | 50mg pethidine and 2.5mg midazolam |
| Trojan | 25-50mg Pethidine and 2.5mg midazolam |
| Maslekar | Midazolam in 1mg increments 0.075-0.1mcg/kg (50-70mcg) fentanyl |
| Forbes | 0.06mg/kg (4mg) midazolam and 0.76mg/kg (50mg) pethidine |
| Notini-gudmarsson | 1mg/kg IM (70mg) pethidine plus 2.5mg midazolam if remained in pain |

**Table 6 - Dosing schedule reported in comparative trials of Entonox and intravenous medications**

* Parentheses denote dose that would have been administered to a 'typical' 70kg patient

Finally, the instructions for Entonox use varied between studies. (table 7) The relevance of this is uncertain, but Westling et al comparing 'continuous' versus 'as required' Entonox use during vaginal delivery and found that continuous use significantly reduced pain and the associated physiological responses.

| Study | Instructions for Entonox use |
|-------|------------------------------|
| Trojan | 'Breathed the gas for 1 minute prior to the procedure and then as required' |
| Saunders | Continuous use through the sigmoid colon and then as required |
| Notini-gudmarsson* | Continuous use with deeper breaths if in pain |
| Lindblom | Not stated |
| Forbes | 'Generally took Entonox until caecal intubation' |
| Maslekar | Continuous use until caecum |
| Loberg et al | As required use |

**Table 7 - Instructions for Entonox use in previous Entonox studies.**

* Denotes Medimix rather than Entonox

### 1.3.8.4 Patient experience with Entonox

Studies have generally reported little difference in side effects. Forbes et al however, found that sedation was more likely to cause drowsiness (72% vs. 11%) and dizziness (43% vs. 20%) than Entonox(117) and a meta-analysis reported that Entonox was less likely to cause nausea.(123)

### 1.3.8.5 Current use of Entonox during colonoscopy

Entonox clearly has advantages over sedation associated with its safety profile and reduced inconvenience particularly the ability of patients to resume driving 30 minutes after use (patients are advised to avoid driving for 24 hours after administration of intravenous sedation and analgesia). Despite this, Entonox was used by only 8.4% of the patients having a colonoscopy during the period of the most recent English national endoscopy audit.(2) The reasons for its low utilisation are uncertain but practice clearly varies between units with it being used by three quarters of the patients undergoing colonoscopy at Sheffield Teaching Hospital.

**Chapter 2 - Aims**

The background reviews the multi-factorial nature of colonoscopy quality. The aims of this thesis were to study key aspects of colonoscopy quality including simple interventions that could readily be introduced into clinical practice. As discussed previously, patient comfort is a key measure of colonoscopy quality. Comfort is influenced by patient factors and endoscopic technique and may also be modified by medication use. However, the relationships between patient comfort and medication use are complex and incompletely understood. It has even been suggested that the colonoscopists who use more medication are more likely to cause discomfort since their colonoscopic technique is inferior. There are also disadvantages to medication use, related to patient safety and potential inconvenience to patients. Furthermore, the medication strategy used during colonoscopy should be dependent on the needs and views of each patient. The BCSP collects standardised data on comfort levels and medication use in patients undergoing screening colonoscopy. The first objective of this thesis was to explore the relationships between significant discomfort and medication use within the BCSP.

Entonox appears an effective analgesic and sedative during colonoscopy and offers advantages with regards to patient convenience. However, it is used in only a small proportion of examinations in the UK and the reasons for its low utilisation are unclear. The second objective of the thesis was to survey current usage and perceptions of Entonox among colonoscopists.

Previous studies of Entonox use as an adjunct to colonoscopy have reported conflicting results. The reasons are unclear but may relate to differences in the method of administration. The third objective was therefore to undertake a randomised controlled trial of 'continuous' and 'as required' use of Entonox during colonoscopy.

Polyp detection is a key measure of colonoscopy quality. Many factors influence polyp detection during colonoscopy including bowel cleanliness and endoscopic technique. Bowel preparations vary in taste, acceptability, ease of consumption and potency. The dosing schedules also influence patient

experience and effectiveness. Studies comparing standard and low volume PEG solutions have reported conflicting outcomes. The fourth objective of this thesis was to compare patient tolerance and bowel cleanliness during a switch over from a standard to a low volume PEG solution in patients attending for screening colonoscopy.

The detection of polyps during colonoscope withdrawal requires time and a good endoscopic technique. Position change has been reported to improve colonic distension and polyp detection but the results are conflicting. The final objective of this thesis was to undertake a randomised controlled trial of adenoma detection comparing a prescribed position change strategy against the supine position during colonoscope withdrawal.

**Chapter 3 - Sedation practice and patient comfort during colonoscopy examinations within the English Bowel Cancer Screening Programme**

## 3.1 Summary

**Background and aims**

Medication may be used to manage discomfort during colonoscopy but practice varies. The relationship between medication use and comfort during colonoscopy was examined in the English Bowel Cancer Screening Programme.

**Patient and methods**

Information relating to BCSP examinations is prospectively entered into a national database. Comfort ratings and medication use were extracted for colonoscopy examinations performed between 01/01/2010 and 31/12/2012 was extracted. The relationships between comfort and analgesic and sedative practice were examined.

**Results**

During the study period 113,316 examinations were performed by 290 endoscopists. 91.1% of colonoscopies were performed without causing significant discomfort but there was considerable variation between individual colonoscopists (range 76.1-99.2%). Significant discomfort was more common in females, patients with diverticulosis and inadequate bowel preparation, incomplete examinations and screening rather than surveillance examinations.

Midazolam was administered during 87.8% and opiate analgesia during 87.3% of procedures. There was wide variation between colonoscopists in the proportion of examinations in which midazolam (range = 4.1%-100%) and opiate analgesia (range = 5.6-100%) were used. Entonox was administered during 7.5% of examinations and 4.7 % of patients underwent medication-free colonoscopy.

There was no significant correlation between the amounts and proportion of sedation and analgesia used by colonoscopists and the proportion of their patients with significant discomfort.

**Conclusion**

In the English Bowel Cancer Screening Programme less than 1 in 10 colonoscopy examinations are associated with significant discomfort. Wide variations exist but colonoscopists' individual medication practice appears unrelated to the occurrence of significant discomfort within the UK screening programme.

Publications arising:

Abstract presented at DDW 2014 and BSG 2014

Ball AJ, Rees C, Corfe BM, Riley SA. Patient comfort and sedation and analgesic practice during colonoscopy in the English Bowel Cancer Screening Programme.

Sedation practice and comfort during colonoscopy: lessons learnt from a national screening programme. Eur J Gastroenterol Hepatol. 2015:27(6);741-6

## 3.2 Background

Colonoscopy is the gold standard investigation for colorectal cancer (CRC) screening.(11) However, some patients report discomfort during colonoscopy and may be deterred from undergoing colonoscopy.(124) Patient comfort is an important outcome measure in the assessment of colonoscopy quality and influences both patient satisfaction(30) and willingness to have a repeat examination.(125)

Discomfort during colonoscopy is mainly due to stretch of the attached colonic mesentery, which is maximal when there is looping in the shaft of the colonoscope.(29) Drug regimens are often used to manage and prevent discomfort during colonoscopy but the optimal regimen is debated.(126)

Worldwide, medication practice to facilitate colonoscopy varies widely. Patients in Scandinavian countries often undergo un-sedated examinations,(127) whereas an increasing proportion of patients in the United States undergo colonoscopy with a general anaesthetic.(128)

Individual sedation strategies clearly differ with respect to cost, efficacy, safety and patient convenience but each has a role depending on the needs and expectations of patients. A survey of American patients reported that most attribute the highest value to being pain-free and unaware during colonoscopy whilst a minority preferred to undergo colonoscopy without sedation.(31)

The English BCSP rollout began in 2006. The target population was initially 60-69 year olds but expanded to age 74 in 2010. Participants are offered faecal occult blood testing (FOBt) biennially and those with a positive FOBt results are invited to be assessed by a Specialist Screening Practitioner (SSP) who explains the significance of the result and offers colonoscopy. Colonoscopy examinations are performed by experienced (>1000 examinations) and specifically accredited colonoscopists whose performance is continually monitored.(129)

Measurement of comfort during colonoscopy is complex since patients' expectations, tolerance and recollection of discomfort differ. Furthermore, the time course and severity of discomfort varies during the procedure, occurring most often during insertion. Prior to the rollout of the English Bowel

Cancer Screening Programme (BCSP) there were no validated comfort scales and no defined standards of care. In their absence, the nurse-rated Modified Gloucester Comfort Scale (MGCS - appendix) was employed.(19)

Data from each examination performed within the English BCSP is collected and entered into a national database in a standardised manner. Comfort is rated on a standardised albeit it an un-validated scale. Furthermore, the BCSP includes a large number of colonoscopists who vary in their medication usage. This allowed an opportunity to perform a detailed examination of the relationship between patient comfort and medication use.

## 3.3 Methods

**Dataset**

Data relating to colonoscopy examinations performed within the BCSP are prospectively entered into a national database, the Bowel Cancer Screening System (BCSS). An SSP attends each examination and rates patient comfort, independent of the colonoscopist, using the MGCS. Previous studies have shown that the BCSS has high levels of completeness and accuracy.(129)

**Data processing**

Data were extracted from the BCSS for all procedures undertaken between 01/01/10 and 31/12/12. The required fields were agreed by panel discussion and included: patient gender and age, procedural indication (screening or surveillance), medication use, patient comfort, insertion and withdrawal times and examination findings. Screening and surveillance examinations were included. Screening refers to examinations prompted by positive FOB testing, whereas surveillance refers to examinations in those previously screened and found to have intermediate or high risk polyps. Data completeness were assessed and data cleaning undertaken. Implausible entries were excluded if they were outside a reasonable range, as determined in a previous analysis of the database (table 8).(129)

|  | Feasible range | Number (%) excluded |
|---|---|---|
| Dose of midazolam | Not administered, 0.5 - 10mg | 373 (0.33) |
| Dose of pethidine | Not administered, 12.5 - 200mg | 246 (0.22) |
| Dose of fentanyl | Not administered, 12.5 - 200mcg | 146 (0.13) |
| Insertion time | 1-60 mins | 1482 (1.3) |
| Withdrawal time | 1-60 mins | 844 (0.7) |

**Table 8 - Data excluded from analysis**

A moderate or severe discomfort rating, on the 5-point MGCS, was defined as 'significant discomfort'. These ratings were considered to indicate a degree of discomfort more likely to be associated with a worse than expected patient experience.(33)

The medication practice of all colonoscopists who performed at least 100 examinations was examined and correlations were sought with patient comfort.

Comfort during each examination is rated by an SSP, independent of the colonoscopist. As there are no direct measures to assess the validity of these ratings, we examined the variation in the comfort ratings of different SSPs who had graded the same colonoscopists. The ratings of SSPs who had rated an individual colonoscopist on at least 50 occasions were compared. This minimised differences due to random variation while remaining inclusive of most colonoscopists.

**Statistical analysis**

Categorical data were compared using the chi-squared test and continuous data were compared with the unpaired *t* test. The correlation between colonoscopists' medication use and comfort, CIR and ADR were assessed using Spearman's Rho ($\rho$). Correlations were interpreted as follows: very high (+/-0.9-1.0), high (+/- 0.7-0.9), moderate (+/- 0.5-0.7), low (+/- 0.3-0.5) and no/negligible (+/-0-0.3).(130)

The study was approved by the BCSP Research Committee. The chair of the local Research Ethics Committee (REC) confirmed this study was a service evaluation and was subject to ethics waiver.

## 3.4 Results

Study population

During the 3-year study period, 113,316 colonoscopy examinations were performed (99,044 screening and 14,272 surveillance examinations). The number of procedures performed increased year on year (from 33,142 in 2010, 39,872 in 2011 and 40,302 in 2012) with an increasing proportion of surveillance examinations (2010 vs. 2012, 7.2% vs. 17.8%, OR 2.8, 95% CI 2.7-3.0).

The mean age of the patients was 66 years (range 59-93 years) and 58.3% were male. Procedures were performed by 290 endoscopists comprising: 213 Physicians, 57 Surgeons, 18 Nurse Endoscopists and 2 General Practitioners. The 262/290 (90%) endoscopists who performed at least 100 examinations performed 99% of the procedures within the study period. The mean (SD, range) caecal intubation rate (CIR) and adenoma detection rate (ADR) of the colonoscopists were 96.6% (1.8, 91.0-99.8%) and 46.7% (6.8, 26.8-61.3%) respectively. The cancer detection rate was 7.5% (screening examinations) and bowel preparation was rated as excellent or adequate in 97.5% of examinations.

**Comfort during colonoscopy**

91.1% of colonoscopy examinations were performed without causing significant discomfort (no=30.3%, minimal=44.1%, mild=16.7%). 7.8% of patients had moderate and 1.1% had severe discomfort. In multivariate binomial regression analysis, the presence of significant discomfort was associated with medication use, diverticulosis, completeness of examinations and female gender (table 9). The proportion of procedures associated with significant discomfort fell over time in both screening (from 10.4% in 2010 to 8.9% in 2011 and 8.0% in 2012, 2010 vs. 2012, OR (95% CI) = 0.7 (0.7-0.8), p<0.0001) and surveillance examinations (from 8.9% in 2010 to 7.8% in 2011 and 6.7% in 2012, 2010 vs. 2012, OR (95% CI) = 0.7 (0.6-0.9), p=0.0004).

| Characteristic | % | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | Odds ratio | 95% CI | p value | Odds ratio | 95% CI | p value |
| Female | 41.7% | 2.24 | 2.15-2.34 | <0.0001 | 2.02 | 1.93-2.11 | <0.0001 |
| Screening examination | 87.3% | 1.24 | 1.16-133 | <0.0001 | 1.05 | 0.98-1.12 | 0.20 |
| Inadequate bowel cleanliness | 2.5% | 1.40 | 1.25-1.57 | <0.0001 | 0.99 | 0.87-1.12 | 0.85 |
| Incomplete examination | 3.1% | 6.80 | 6.37-7.37 | <0.0001 | 6.67 | 6.17-7.25 | <0.0001 |
| Diverticulosis | 33.4% | 1.35 | 1.29-1.41 | <0.0001 | 1.43 | 1.37-1.49 | <0.0001 |
| Entonox use | 7.5% | 3.35 | 3.07-3.43 | <0.0001 | 5.0 | 4.66-5.35 | <0.0001 |
| Midazolam use | 87.8% | 1.38 | 1.29-1.48 | <0.0001 | 1.68 | 1.53-1.86 | <0.0001 |
| Analgesia use | 87.3% | 1.19 | 1.12-1.27 | <0.0001 | 1.59 | 1.45-1.75 | <0.0001 |

**Table 9 - Predictors of significant discomfort during colonoscopy on uni-variate and multivariate binary regression analysis.**

Examinations resulting in significant discomfort were associated with longer colonoscope insertion times (mean (SD) = 20.5 (11) versus 13.0 (8) min, p <0.0001) and longer colonoscope withdrawal times (Mean (SD) = 16.0 (11) min versus 14.6 (9) min, p<0.0001). There was no difference in adenoma detection rate in cases where significant discomfort was reported (41.4% vs. 41.3%, p=0.85).

The proportion of procedures associated with significant discomfort by individual colonoscopist varied considerably ranging from 0.8% to 23.9% (median = 8.1%, IQR 5.0-12.6 - figure2).
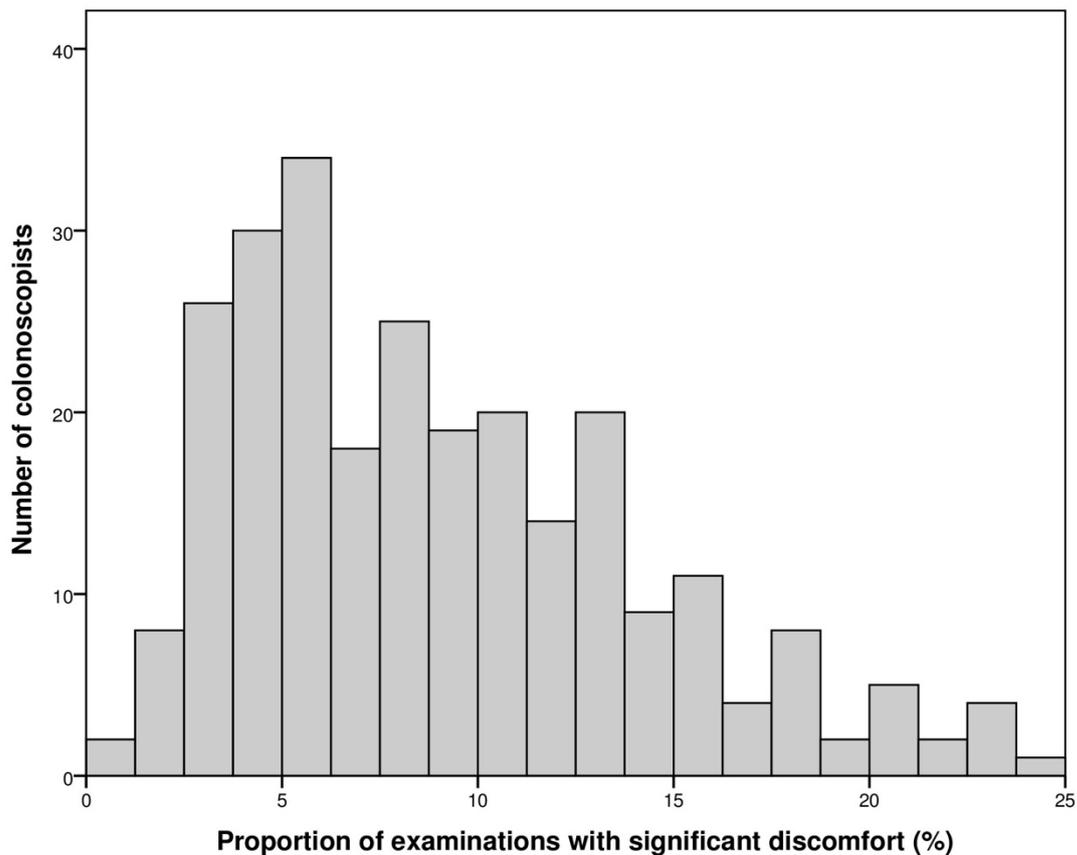
**Figure 2** - **Proportion of examinations associated with significant discomfort among colonoscopists**

**Intravenous sedation and analgesia**

Midazolam was administered during 87.8% of procedures and diazepam in only 0.03%. Opiate

analgesia was given during 87.3% of procedures. Pethidine (49.0 %) and fentanyl (36.5%) were used

most commonly and meptazinol (1.4%) and alfentanyl (0.8 %) used infrequently.

The proportion of procedures associated with midazolam use fell year on year; from 91.0% in 2010

to 88.8% in 2011 and 85.6% in 2012 (2010 vs. 2012, OR (95% CI) = 0.58 (0.56-0.61), *p*<0.0001). The

proportion of patients receiving any form of intravenous analgesia also fell; from 90.3% in 2010 to

84.8% in 2012 (2010 vs. 2012, OR (95% CI) = 0.6 (CI 0.57-0.62), *p*<0.0001).

Most colonoscopists administered sedation during most colonoscopies but practice varied widely with use ranging from 4.1% to 100% (median use = 95.1%, IQR = 81.8-97.8%, range = 4.1%-100%). Similarly, most colonoscopists administered opiates in most of their procedures (median use = 97.3%, IQR = 85.0-99.2%, range = 5.6-100%). The mean doses of midazolam, pethidine and fentanyl given ranged from 0.5-3.7mg (median = 2.2mg), 25-63mg (median = 33mg) and 25-99mg (median = 59mg) respectively. Female patients received slightly higher doses of midazolam (mean (SD) = 2.1(0.7) vs. 2.0(0.6) mg, p<0.0001), fentanyl (mean (SD) = 63.5 (23.5) mcg vs. 59.4 (21.1) mcg, p<0.0001) and pethidine (mean (SD) = 32.5 (11.7) mg vs. 31.1 (11.0) mg, p<0.0001).

A significant minority of patients were given intravenous sedation and analgesia in doses exceeding British Society of Gastroenterology recommendations, particularly in those aged >70 years (table 10).

BSG recommended maximal doses <70 years/≥70 years: midazolam ≤5mg/≤2.5mg, pethidine ≤50mg/≤25mg, fentanyl ≤100mcg/ ≤50mcg.

| Age | Medication | Mean dose administered | Proportion exceeding BSG recommended dose |
|---|---|---|---|
| <70 years | Midazolam | 2.1 mg | 0.03% |
| | Pethidine | 32.4 mg | 0.3% |
| | Fentanyl | 61.6 mg | 0.6% |
| ≥70 years | Midazolam | 2.0 mg | 8.9% |
| | Pethidine | 28.3 mg | 15.2% |
| | Fentanyl | 59.1 mg | 25.1% |

**Table 10 - Medication use exceeding BSG recommendations**

A second bolus of medication was given in 1599 (1.4%) patients. This was most often opiate analgesia (1.2%) whilst additional sedation (0.1%) or a combination of sedation and opiate analgesia (0.1%) were rarely used. Patients with significant discomfort were more likely to receive a second bolus of medication (6.2% vs. 1.0%, OR (95% CI) = 6.3 (5.7-7.0), p<0.0001). A second bolus of medication was given more often in screening examinations (1.5% vs. 1.0%, OR (95% CI) = 1.5 (1.3 - 1.8), *p*<0.0001) female patients (2.0% vs. 1.0%, OR (95% CI) = 2.1, (1.9 - 2.3), *p*<0.0001) and in those with incomplete examinations (3.4% vs. 1.3%, OR (95% CI) = 2.6 (2.2-3.2), *p*<0.0001).

Patients undergoing screening were more likely to receive sedation (88.6%vs. 84.5%, OR (95% CI) = 1.4 (1.35-1.49), p <0.0001) and analgesia (87.7% vs. 84.4%, OR (95% CI) = 1.3 (1.24-1.38), p<0.0001) than patients undergoing surveillance colonoscopy. Female patients were also more likely to receive both sedation (92.9% vs. 84.6%, OR (95% CI) = 2.4 (2.28-2.48), p<0.0001) and analgesia (91.2% vs. 84.4%, OR (95% CI) = 1.9 (1.83-1.98), p <0.0001) than males.

**Entonox®**

Entonox® (50:50 combination of nitrous oxide and oxygen) was administered during 7.5 % of examinations and its use increased year on year, from 4.6 % in 2010 to 7.2% in 2011 and 10.1% in 2012 (2010 vs. 2012, OR (95% CI) 2.3 (2.17-2.45), p <0.0001). The proportion of colonoscopists who used Entonox® also increased (36.4 % in 2010, 49.4 % in 2011 and 56.1 % in 2012), but most colonoscopists who administered Entonox did so in a minority of procedures but with wide variation in practice (median 0.7%, IQR 0-8.2%, range 0-98.9%).

There was little difference in Entonox use between male (7.3%) and female patients (7.9%) but Entonox® was administered more frequently during surveillance than screening colonoscopies. (7.4% vs. 8.1%, OR (95% CI) = 1.1 (1.01-1.18), p=0.003). Entonox® was most commonly administered in isolation (4.0%) but it was also used alongside intravenous sedation and opiate analgesia (table 11).

| Medication strategy | Frequency | No | Minimal | Mild | Significant | | *OR (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|
| | | | | | Moderate | Severe | | |
| Midazolam and analgesia | 81.6% | 31.2% | 44.5% | 16.1% | 7.2% | 1.0% | Reference | n/a |
| Medication-free | 4.7% | 40.0% | 43.5% | 12.5% | 3.6% | 0.3% | 0.46 (0.40-0.53) | <0.0001 |
| Entonox alone | 4.0% | 21.2% | 51.8% | 18.6% | 7.4% | 0.7% | 1.0 (0.9-1.1) | 0.69 |
| Midazolam alone | 3.4% | 29.9% | 42.9% | 17.8% | 8.0% | 1.1% | 1.1 (1.0-1.3) | 0.02 |
| Analgesia alone | 2.7% | 28.2% | 47.4% | 16.8% | 6.7% | 0.8% | 0.9 (0.8-1.1) | 0.4 |
| Entonox, sedation and analgesia | 2.7% | 5.2% | 22.9% | 32.1% | 33.4% | 6.3% | 4.4 (4.1-4.8) | <0.0001 |
| Entonox and sedation | 0.7% | 7.8% | 31.2% | 36.2% | 22.1% | 2.5% | 3.8 (3.2-4.5) | <0.0001 |
| Overall | - | 30.3% | 44.1% | 16.7% | 7.8% | 1.1% | n/a | n/a |

**Table 11 - Medication strategies and patient discomfort during colonoscopy.**

*Odds ratio compares the proportion of patients with significant discomfort against those receiving a combination of intravenous sedation and analgesia

**Medication-free colonoscopy**

Medication-free colonoscopy (no opiate, benzodiazepine or Entonox) was performed in 4.7% of patients and increased year on year (from 3.5% in 2010, to 4.8% in 2011 to 5.4% in 2012, 2010 vs. 2012, OR (95% CI) = 1.6 (1.47-1.71), p<0.0001). 72.5% of colonoscopists performed at least one medication-free colonoscopy during the study period. Most used it in a small minority of examinations with a median usage of 1.9% but practice varied widely with 17.9% of colonoscopists using it in over 10% of examinations (figure 3).
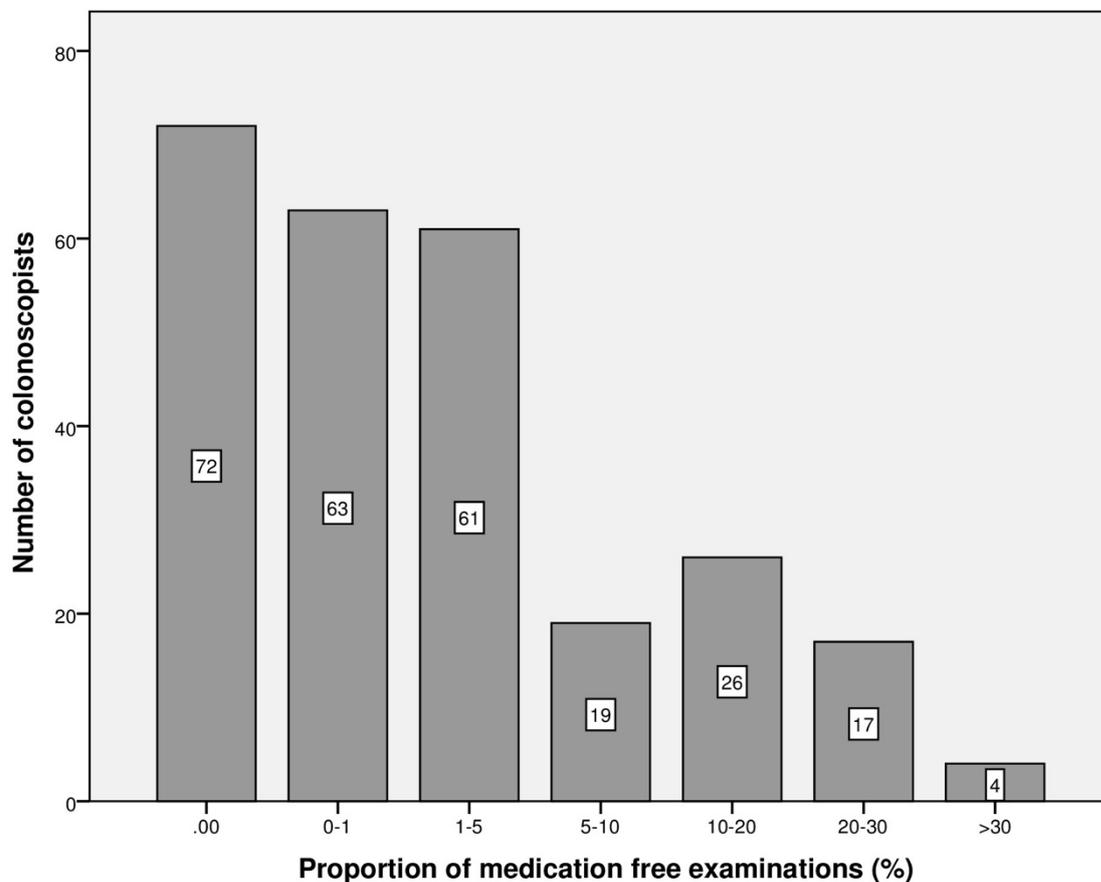


**Figure 3 - Proportion of medication-free examinations performed by colonoscopists**

Male patients were more likely to undergo sedation-free colonoscopy than females (6.6% vs. 1.8 %, OR (95% CI) = 3.9 (3.6-4.2), p<0.0001) as were patients undergoing surveillance rather than screening colonoscopy (7.3% vs. 4.2%, OR (95% CI) = 1.8 (1.66-1.91), p<0.0001).

**Other medication**

Buscopan™ (hyoscine butylbromide) was administered in 43.7% and glucagon during 0.2% of examinations. Some colonoscopists never used Buscopan whereas others used it most of the time (Median = 36.5%, IQR =7.1-77.1%, range = 0-99.5%). Buscopan was given more often in males (45.8% vs. 40.7%, OR (95% CI) = 1.23 (1.20-1.26), p<0.0001) and those with diverticulosis (45.5% vs. 42.7%, OR (95% CI) =1.12 (1.09-1.14), p<0.0001). General anaesthesia (GA) was used infrequently (0.5%). Deep sedation using Propofol was also rarely used in non-GA examinations (<0.1%).

**Adverse events and the use of reversal agents**

Reversal agents were rarely used. 55(0.05%) patients were given flumazenil and 46(0.04%) patients were given naloxone and 8 received both. The dose of midazolam and opiate analgesia associated with flumazenil and naloxone use exceeded BSG recommendations in only one and four patients respectively. Sedation related adverse events were rare. 70 (0.06%) patients had an episode of significant hypotension, 17 (0.015%) had a cardiac arrhythmia and 5 (0.004%) had a respiratory arrest.

**Relationship between comfort and medication use**

The proportion of patients with significant discomfort varied according to the medication strategy used. For the group as a whole significant discomfort was least common amongst patients who used no medication and most common amongst patients using a combination of sedation, opiate analgesia and Entonox (table 11).

When assessing the practice of individual colonoscopists there was no significant correlation between the proportion of procedures in which significant discomfort occurred and the proportion of examinations in which sedation (ρ=-0.17) and analgesia (ρ=-0.08) were used. Furthermore, there was also no significant correlation between comfort and the mean dose of sedation (ρ=0.12), pethidine (ρ=0.02) and fentanyl (ρ=0.18) used. There was also no significant correlation between the

proportion of examinations associated with significant discomfort and CIR ($\rho$=-0.20) and ADR ($\rho$=-0.11).

**Scale reliability**

203/290 (70%) of the colonoscopists had the comfort of their examinations graded by two or more SSPs on at least 50 occasions. The proportion of examinations by each colonoscopist associated with significant discomfort differed according to the rating SSP. The difference between the SSPs who rated significant discomfort most and least often for the same colonoscopist ranged from 0.02 to 34.8% (median =6.9%, IQR =3.6-12.6%).

## 3.5 Discussion

Colonoscopy is the most important tool for the detection and prevention of CRC but has the potential to cause significant discomfort.  In the English bowel cancer screening programme, which predominantly employs a policy of conscious sedation or no sedation, Over 90% of 113,316 examinations were associated with no, minimal or mild discomfort. Previous studies of comfort during colonoscopy report wide ranging results with 2.3-54% being associated with significant pain or discomfort.(125, 131) These studies however, are not directly comparable due to differences in case mix, depth of sedation and the use of different comfort scales.

One of the more striking findings in the present study was the wide variation between colonoscopists in the proportion of examinations associated with significant discomfort (0.8-23.9%). This was not explained by differences in medication practice suggesting that other factors, such as examination technique, may be more important determinants of comfort. Previous studies have shown that peaks of pain usually coincide with looping or straightening of the colonoscope shaft(29) which often relate to increases in the forces applied to the colonoscope. Korman et al found that the magnitude of these forces vary considerably between colonoscopists(132) and that these forces were higher in patients undergoing colonoscopy with deep sedation.(133)

In the present study significant discomfort was more likely to occur in females, those with diverticular disease and those undergoing screening rather than surveillance examinations. Female gender and diverticular disease are well recognised predictors of increased discomfort, but we are unaware of previous studies reporting less discomfort during surveillance examinations. The reduced discomfort in surveillance examinations may reflect a patient selection bias or a favourable effect of the initial screening colonoscopy on tolerance during the follow up surveillance examination.

Previous studies have found an inverse correlation between colonoscopists' comfort ratings and CIR,(33) but the BCSS data do not support such a relationship. This may reflect a difference in the skill-set of the colonoscopists studied, as English BCSP colonoscopists have to pass a stringent

accreditation process and undergo detailed monitoring. Furthermore, we could find no evidence of a relationship between comfort and ADR.

Despite a reduction in the use of analgesia over time, the proportion of examinations associated with significant discomfort fell year on year. Significant discomfort also occurred less often than in the 3 years preceding the start of this study.(129) The reason for the reduction in discomfort over time is uncertain. It may reflect improvements in the quality of colonoscopic technique, as other measures of colonoscopy quality, such as ADR and CIR,(2) also improved.

There are surprisingly few randomised controlled trials comparing the commonly used medication strategies during colonoscopy. Studies comparing agents of the same class generally report minimal differences, and (119) studies assessing the benefit of adding an opiate to intravenous sedation report conflicting outcomes.(134, 135) Furthermore, one study comparing the use of an opiate versus midazolam found that patients given the opiate were less likely to have pain but there was no difference in willingness to undergo a repeat examination.(136) Dosing schedule may also influence the efficacy of medication. Terruzzi et al reported that patients tolerate colonoscopy better with 'routine' as oppose to 'on demand' dosing.(137)

In the present study, medication-free colonoscopy was undertaken in approximately 1 in 20 patents, but a small number of endoscopists used this strategy in over 30% of examinations and its use increased year on year. Medication-free examinations are preferred by some patients as they are associated with less inconvenience than the use of intravenous sedatives and analgesics. However, patient selection seems to be important with previous studies reporting acceptability ratings ranging from 56.2-99% and CIRs ranging between 81.6 - 99.6%.(131, 138)

Entonox was used in 7.5% of colonoscopy examination and its use increased year on year. Studies comparing the use of Entonox versus sedation and opiate analgesia report conflicting outcomes.(98, 117) However, significant discomfort was no more likely in patients using Entonox alone (8.1%) than in those receiving intravenous sedation and analgesia (8.2%). Entonox has advantages associated

with its rapid elimination such that patients are able to drive half an hour after use. Entonox use is

likely to increase further in the UK as access to it is mandated in the national flexible sigmoidoscopy

screening programme.(139) Medication use is influenced by many factors including patient's choice,

endoscopist choice and endoscopy unit policy. Medication is usually used prior to colonoscope

insertion although it may also be used in response to discomfort. Given these potential biases, only

limited comparisons can be made between the groups in such a study. However, patients using no

medication were least likely to have significant discomfort whereas patients receiving a combination

of intravenous sedation, opiate analgesia and Entonox were most likely to have significant

discomfort. This data suggests that the medication needs of patients vary widely, with patients

undergoing medication free colonoscopy being least likely to have significant discomfort whilst

current drug combinations were frequently inadequate for many other patients.

Perhaps the most interesting finding in the present study was the lack of a relationship between

individual colonoscopists' medication practice and the comfort of their patients. There are a number

of possible explanations. It may be that patients can reasonably predict their tolerance of

colonoscopy and request an appropriate strategy. This may be influenced by endoscopists who

recognise well established predictors of increased discomfort such as anxiety, gender or previous

hysterectomy. Alternatively, it may be that medication use is less important than the other factors,

such as insertion technique, in determining comfort during colonoscopy.

Sedation-related adverse events were rare despite the widespread use of medication. Prescribing

practice in the UK is influenced by the British Society of Gastroenterology guidelines on 'Safety and

Sedation during Endoscopic Procedures' which recommend maximal doses for the commonly used

medications.(110)  Within the present study the doses of medications administered to patients

under and over 70 years were similar but it is worth noting that a significant minority of patients

aged over 70 years were given doses of midazolam (8.9%), pethidine (15.2%) and fentanyl (25.1%) in

excess of BSG recommendations. Interestingly, most of the patients requiring reversal agents were

under the age of 70 years, and most of these did not receive medication doses in excess of BSG recommendations.

This is the first report of a national colonoscopy programme to focus on comfort and sedation practice. A major strength of this study is the large number of examinations analysed and the multiple screening centres studied. Data were collected prospectively in a structured format and comfort was rated independently of colonoscopists. Therefore, the results of this study should be generalizable.

A limitation of this, and indeed any study of patient comfort, is the paucity of validated or patient-derived measures of comfort. The correlation of discomfort with factors known to be associated with discomfort using different comfort scales suggests a degree of reliability to the MGCS. Furthermore, the MGCS is similar to the Nurse-Rated Comfort Level (NRCL) scale, which performed well during a limited validation study (appendix 1).(33)

In the absence of a direct measure to validate comfort ratings we assessed the comfort ratings of different SSPs for individual colonoscopists, which were sometimes marked. A quarter of the colonoscopists had over a 12% difference between the lowest and highest rating SSP and in one instance the difference was as high as 34.8%. Some variation would be expected since SSPs were rating different procedures, but marked differences suggest that the nurses' 'frame of reference' is variable. This term refers to their personal viewpoint, determined by their previous experience and training, by which they judge comfort. This study adds weight to the argument for development of well-validated measures of comfort.

Studies examining the agreement between patients' and nurses' rating of comfort have demonstrated some inconsistency.(32, 140) The assessment of comfort may be improved by recording a patient-rated measure of comfort which would internally validate the rating given by the nurse. Patient reported outcome measures(PROM) are gaining a more prominent role in the

assessment of health care quality in the NHS,(141) and we believe that patient derived and validated

measures of comfort and experience should be developed.

## 3.6 Conclusion

Over 90% of the colonoscopic examinations in the English Bowel Cancer Screening Programme are performed without causing significant discomfort. However there is wide variation in comfort levels between colonoscopists and no clear relationship with sedation or analgesic practice. Appropriate patient selection and tailoring medication to achieve comfortable procedures, whilst minimising risk and inconvenience, remains important areas for future research. Improving the tools for assessing patient experience will allow these relationships to be better understood.

**Chaper 4 - Survey assessing the use of and perceptions towards Entonox use during colonoscopy.**

## 4.1 Summary

**Introduction**

Nitrous oxide can improve patient experience during colonoscopy and its rapid elimination minimises after effects and inconvenience. Despite its advantages, nitrous oxide is used infrequently in the UK. We sought to understand the reasons for its low utilisation.

**Methods**

Colonoscopists within the English Bowel Cancer Screening Programme (BCSP) were invited to participate in a web-based survey assessing the availability, current practices and perceptions towards nitrous oxide. Respondents were able to select pre-defined answers or offer written responses. Free text responses were assessed using thematic analysis.

**Results**

The survey was completed by 68% of the English BCSP colonoscopists. Nitrous oxide was available to 73% of respondents but with considerable regional variation. Most colonoscopists rated the properties of nitrous oxide favourably and would use it if they had a colonoscopy themselves. Despite this, nearly half used it in less than 20% of examinations. 80% instruct patients to use nitrous oxide as required and differences in how it was used in combination with intravenous sedation and analgesia were reported. Written responses suggest nitrous oxide is often used in the patients who are expected to have the least discomfort.

**Conclusion**

Most colonoscopists perceive that nitrous oxide is effective and reduces inconvenience and would use it themselves if they required a colonoscopy. Studies to improve patient selection and optimise the use of nitrous oxide would be of value.

Publications arising**:**

Abstract presented at DDW 2014 and BSG 2014

Ball AJ, Campbell JA, Riley SA. Entonox use during colonoscopy: A survey of English Bowel Cancer Screening Programme colonoscopists

Original article published in Frontline Gastroenterology

Ball AJ, Campbell JA, Riley SA. Nitrous oxide use during colonoscopy: a national survey of English screening colonoscopists. Frontline Gastroenterology. 2014;5(4):254-9.

**4.2 Background**

Most patients undergoing colonoscopy in the UK receive medications to minimise distress.(2) Entonox® is a 50:50 combination of nitrous oxide and oxygen which has analgesic and sedative properties. It is administered through a demand valve, which minimises problems associated with over sedation. The precise mechanism by which nitrous oxide exerts its analgesic effects is uncertain,(112) but these can be partially reversed by naloxone(114), suggesting that some of its effects are mediated via the opiate receptor.

The use of nitrous oxide is well established in obstetric and dental practice but has been introduced into colonoscopy relatively recently. Studies assessing the analgesic properties of Entonox® have conflicting outcome but it has advantages with regards to its rapid recovery time. Despite this, it was used in only 8.4% of colonoscopies during the UK national audit. The reasons for its low utilisation were not clear.

This study aims to assess the availability, use and perceptions of Entonox among colonoscopists within the English Bowel Cancer Screening Programme (BCSP).

## 4.3 Methods

The survey was administered to BCSP colonoscopists using *surveymonkey*, a web-based survey programme(142). Colonoscopists within the English BCSP were sent a personalised e-mail to pre-notify them about the purpose of the survey, what would be required and how long this would take. Respondents were informed that they would be sent a copy of the survey results. A week later they were sent an e-mail with a web-link to the survey followed by a reminder e-mail a week prior to its closure.

Respondents were asked their role, experience, the NHS deanery in which they work and whether Entonox was available in their endoscopy unit. Further questions were then asked according to the availability of Entonox. (table 12 and 13) They were able to select from one or more pre-defined answers and offer a written response. Respondents were given the opportunity to make further comments at the end of the survey.

The study was approved by the English BCSP Research Committee.

### Survey development and validation

The aims and objectives were agreed by the study investigators. These were to survey the availability, method of administration, whether and how it is combined with intravenous medications and to survey perceptions regarding its efficacy and barriers to its use.

Many measures were taken during the development of the survey to ensure validity. The survey was developed in several stages by experienced and expert colonoscopists, therefore ensuring content validity. After the objectives were agreed, a draft was written and reviewed to ensure the questions addressed the objectives of the study and there was no ambiguity in the wording. Questions that did not address the objectives of the study were removed to minimise the size of the survey and time for its completion, thereby increasing the likelihood of survey completion.

The framing of questions was carefully considered during the design of the survey as the framing of questions (positive or negative) may be associated with cognitive bias. It has been suggested that this may be reduced by mixing the framing of questions. This may also prevent respondents from answering in a standard and unvarying manner. However, framing questions in a varying manner may also be associated with bias as respondents may fail to notice the variation in framing and incorrectly respond, leading to unintended bias.(143) Taking these potential biases into account, survey questions were all framed in a positive manner.

Respondents were asked their views regarding the usefulness, efficacy, safety, side effects and the influence of Entonox on time to discharge. For this purpose a unipolar scale was used to grade responses, which ranged from 'do not agree' to 'completely agree'. The alternative of a bipolar scale was considered to be less meaningful and open to more variation in interpretation.

The survey was piloted on 10 colonoscopists, including consultant gastroenterologists and colorectal surgeons. Feedback was obtained regarding the wording and clarity of questions, following which no amendments were necessary. This process further ensured face validity.

Non-response bias was also considered in the design of the survey and the Cochrane collaboration recommendations to minimise non-response bias(144) were followed: a personalised invitation; pre notification of respondents; use of a white background; a short survey; stating a deadline for completion; a reminder e-mail and an offer of survey results were used in the design/administration of the survey to maximise response rates.

Although many of the questions had predictable responses, respondents were also given the option of offering free text responses. It was felt that this would further enrich knowledge relating to Entonox use. Free text responses were assessed using thematic analysis, which is a commonly used qualitative research method to identify and report patterns and themes.(145) Thematic analysis includes several steps: familiarisation, generating initial codes, searching for themes, reviewing themes, defining and naming themes and finally producing a report. During each of these stages the

original free text responses were continuously reviewed, to ensure themes were reflective of the original data. The report used extracts to illustrate themes. Thematic analysis was used, as it is easy to perform and does not require the more detailed knowledge required of other techniques, such as conversational analysis and discourse analysis.(145)

BCSP colonoscopists were chosen as the sample population although several alternatives were considered. Advertising the survey on the BSG website was not used since the absence of a personalised invitation may have reduced response rate. Furthermore, this would mainly be seen by gastroenterologists, rather than surgeons or nurse endoscopists, resulting in a selection bias. The Joint Advisory Group on Gastrointestinal Endoscopy (JAG) office was also contacted in an attempt to access the names and e-mail address of all English colonoscopists but the JAG office were unwilling to pass these on, although they did offer to send e-mail invitations on our behalf. This was declined as this would also have precluded personalise invitations and a reminder e-mail, which were considered important in achieving a high response rate.

The option of contacting all endoscopy units to ask for the names and contact details of the endoscopy units was also considered. This option was unfeasible due to the large number of English units and anticipated difficulties in accessing contact details via a telephone consultation.

Sampling BCSP colonoscopists also had advantages. Firstly, it ensured responses represented all regions of England and included Physicians, Surgeons and Nurse Endoscopists. It also allowed access to e-mail addresses, which permitted personalised invitations. Finally, it was felt that BCSP colonoscopists would be more likely to complete a survey in one of their areas of interest, thereby minimising non-response bias.

Ordinal data were compared with the Mann-Whitney U test.

| |
|---|
| Please estimate what proportion of your patients use Entonox? <br><br> 1) 0-19%   2) 20-39%   3) 40-59%   4) 60-79%   5) 80-100% |
| Which of the following best describes how Entonox is most often used in your practice? <br><br> *It is used when patients are in pain despite intravenous sedation and analgesia* <br><br> *Entonox is available from the start of colonoscopy and would be augmented by intravenous sedation/ analgesia where required* <br><br> *Other (please state)* |
| How are your patients usually instructed to use Entonox? <br><br> *Continuously* <br><br> *As required* <br><br> *Other (please state)* |
| Please indicate the extent to which you agree with the following statements: <br><br> *Entonox is useful during colonoscopy* <br><br> *Entonox gives effective analgesia during colonoscopy* <br><br> *Entonox is a safe option during colonoscopy* <br><br> *Entonox has an acceptable frequency of side effects* <br><br> *Patients who use Entonox leave the endoscopy unit sooner* |
| Would you use Entonox if you were to have a colonoscopy? <br><br> *Yes* <br><br> *No* |

Table 12 - Questions asked of colonoscopists for whom Entonox® was available

| Why is Entonox not available in your unit? |
| --- |
| 1) *Practical difficulties introducing Entonox* |
| 2) *Satisfaction with current analgesics and sedation* |
| 3) *Cost* |
| 4) *Entonox has not been considered* |
| 5) *Lack of efficacy* |
| 6) *Side effects*. |
| 7) *Other (please state)* |
| *Would you consider introducing Entonox in your unit?* |
| *Yes* |
| *No* |

Table 13 - Questions asked of colonoscopists for whom Entonox® was not available

## 4.4 Results

The e-mail address of 293/298 (98%) BCSP colonoscopists were obtained and invited to participate. These were e-mailed an invitation to complete. The survey was accessed by 208 (70%) and completed by 204 (68%).

154 physicians, 39 surgeons and 15 nurse endoscopists completed the survey. The length of independent practice varied from: 0-5 years (2.9%), 6-10 years (18.8%), 11-15 years (39.4%), 16 -20 years (23.6%) to 21+ years (15.4%). All English National Health Service (NHS) deaneries were represented. Entonox was available to the majority of respondents (152/204, 74.5%). There was variation in the availability according to the NHS deanery in which respondents were based, with it being available to all in some deaneries and a minority in others (figure 4).
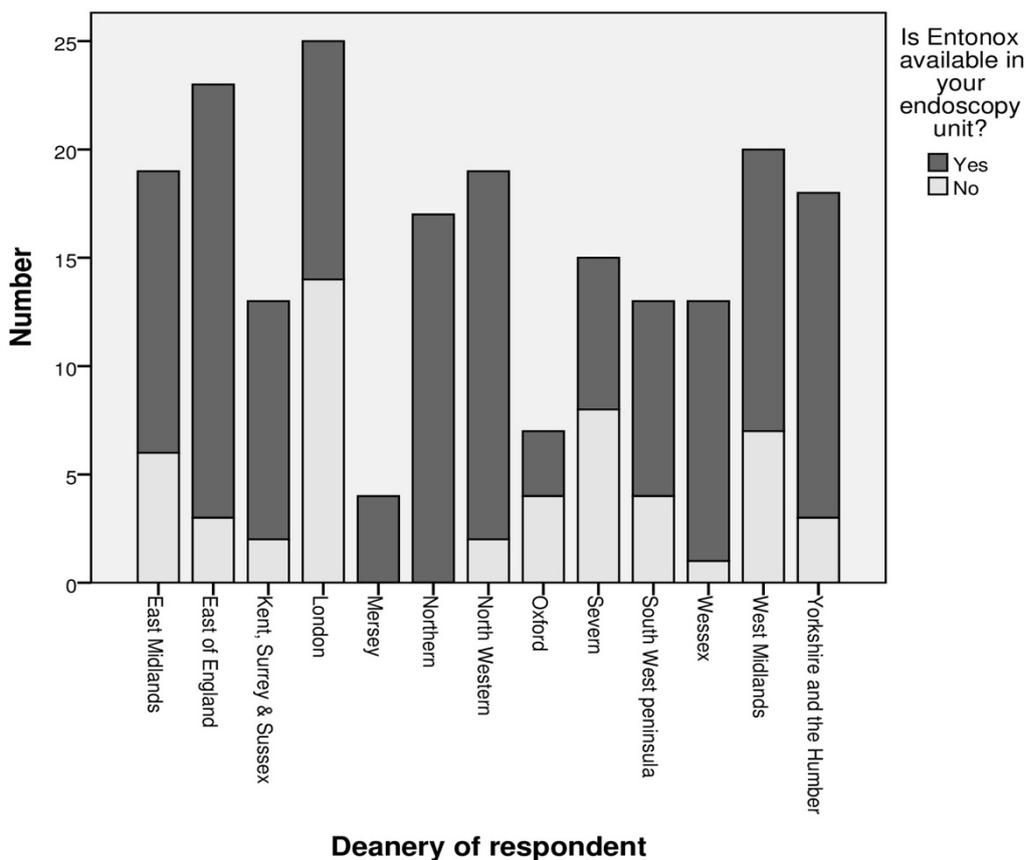


**Figure 4 -** Number of respondents in each NHS deanery

47.3% of respondents used Entonox® during 0- 19% of procedures while 32% used it in 20-39%, 12.7% in 40-59%, 7.3% in 60-79% and 0.6% in 80-100% of examinations. Two did not respond and three indicated that despite Entonox® being available, they had not personally used it.

With regards to how Entonox is used, 24 (21.6%) respondents selected 'It is used when patients are in pain despite intravenous sedation and analgesia' and 87 (78.4%) selected 'Entonox is available from the start of colonoscopy and would be augmented by intravenous sedation/analgesia where required'.

A frequent theme of written responses was the issue of combining Entonox with intravenous sedation and analgesia. Some combine these medications concurrently whereas others stated that they never combine them or do so only after a 5 minute 'washout period' following Entonox use.

Patient selection was also a theme of the free text responses. Some endoscopists mainly use Entonox in patients undergoing flexible sigmoidoscopy or referred for colonoscopy through the BCSP who they anticipate will have less discomfort. Other respondents stated that the patients expected to have significant discomfort are given intravenous sedation and analgesia 'upfront'. High anxiety level was cited as a predictor of increased discomfort.

The majority of respondents indicated that Entonox is used 'when in discomfort or pain' (91.7%) rather than 'continuously' (8.3%). Endoscopists who instructed patients to use Entonox continuously used it in a similar proportion of procedures as those who advised patients to use it as required.

Free text responses were offered by 27 respondents. These revealed further variation in the instructions given to patients, such that some patients who use it as required are familiarised with the effects and technique of Entonox administration prior to colonoscopy. Other patients are asked to use Entonox throughout sigmoid insertion and then switched to as required use depending on their comfort. In addition some endoscopists prompt patients to use Entonox if a painful section is

anticipated. Some respondents indicated that the instructions given are tailored according to how painful they anticipate the examination will be.

Respondents were asked to rate their level of agreement a series of statements about the usefulness, efficacy, safety, acceptability and influence on discharge time of Entonox. 151/152 respondents answered some and 150/152 answered all questions. The majority of respondents mostly or completely agreed with each of the statements. (See table 14)

| | Do not agree (1) | Slightly agree (2) | Somewhat agree (3) | Mostly agree (4) | Completely agree (5) |
|---|---|---|---|---|---|
| *'Entonox is useful during colonoscopy'* | 2 (1.3%) | 10 (6.6%) | 14 (9.3%) | 58 (38.4%) | 67 (44.4%) |
| *'Entonox gives effective analgesia during colonoscopy'* | 2 (1.3%) | 13 (8.6%) | 41 (27.2%) | 62 (41.1%) | 33 (21.9%) |
| *'Entonox is a safe option during colonoscopy'* | 0 (0%) | 2 (1.3%) | 7 (4.6%) | 49 (32.5%) | 93 (61.6%) |
| *'Entonox has an acceptable frequency of side effects'* | 2 (1.3%) | 3 (2.0%) | 4 (2.7%) | 52 (34.7%) | 89 (59.3%) |
| *'Patients who use only Entonox leave the endoscopy unit sooner'* | 13 (8.7%) | 1 (0.7%) | 23 (15.3%) | 43 (28.7%) | 70 (46.7%) |

**Table 14 -** Agreement with statements regarding Entonox®.

Respondents that administered Entonox to more than 20% of patients had higher levels of agreement with statement regarding the usefulness (median(range) = 5(2-5) vs. 4(1-5), p<0.0001), effectiveness (median(range) = 3(1-5) vs. 4(2-5), p=0.002) acceptability of the frequency of side effects (median(range) = 5(1-5) vs. 4(1-5), p=0.009) and its effect on discharge time (median(range) = 5(1-5) vs. 4(1-5), p=0.02) than those who administered it to less than 20% of patients. However,

there was no significant difference between these groups in its perceived safety (median (range) = 5(2-5) vs. 5(3-5) p=0.238).

Most of the endoscopists indicated that they would use Entonox (112/150 (73.7%) vs. 38/152 (25.0%) if they had a colonoscopy themselves. Two did not offer a response. Respondents who used Entonox in more than 20% of procedures were more likely to state that they would use Entonox if they had a colonoscopy (63.4% vs. 83.5%, OR=2.9, 95% CI = 1.4-6.3, *p*=0.006).

The most common reason Entonox wasn't available was '*practical difficulties introducing Entonox'* 20 (48.8%) followed by '*satisfaction with current analgesics and sedation'* 15 (36.6%), '*Cost*' 7 (17.1%), '*Entonox has not been considered' 6* (14.6%), '*lack of efficacy'* 2 (4.9%) and '*side effects' 1* (2.4%).

20 respondents gave free text responses which identified further barriers to the use of Entonox. These included: safety concerns for the staff related to the ventilation requirements in endoscopy rooms. Entonox was in the process of being approved or introduced in several endoscopy units, but there were delays while making a business case or awaiting directorate approval. The implementation of Bowelscope was cited as one of the precipitants for the introduction of Entonox.

Most colonoscopists for whom Entonox wasn't available stated that they would consider introducing it into their unit 49 (94.2%) vs. 3 (5.8%).

Prior to survey completion 43 respondents wrote additional comments about Entonox. Respondents stated further reasons patients choose Entonox. These include wishing to avoid the restrictions caused by intravenous medication such as not being able to drive for 24 hours or not having any home support and wishing to avoid hospital admission. It was also suggested that some patients choose Entonox when they anticipate having little discomfort.

There were conflicting comments about the efficacy of Entonox. Some stated it was useless, unpredictable or not a good as trials suggest whilst others felt it was very useful, effective and what

they preferred patients to use. Furthermore, some felt that Entonox was underused while others had concerns that it was being overly promoted by nursing staff due to the reduced time to discharge.

Difficulties were also identified with regards to the administration of Entonox, with some patients struggling to activate it and some mentioning that its inhalation affects scope handling. Comments were made about confusion regarding the ventilation requirements in endoscopy units and contraindications to its use.

**4.5 Discussion**

Many patients find colonoscopy an unpleasant procedure and a range of medications is available to improve patients' experience. The processes and determinants of drug use during colonoscopy are not well studied, but are likely to include patient choice, endoscopist choice, endoscopy unit policy and patient experience during colonoscopy. The attitudes and priorities of patients towards sedation vary. For some, the priority is being pain free or unaware whereas others want a rapid recovery and discharge or to remain in control and view the examination.(31) The use of medication should therefore be tailored to meet the needs of the individual.

Entonox® has been advocated for use during colonoscopy as it has a quick onset of action, rapid clearance and combined analgesic and sedative properties. This makes it well suited for the management of brief painful episodes, particularly for patients wishing to avoid the inconvenience associated with intravenous sedatives. Despite its favourable characteristics Entonox® is used in only a small proportion of colonoscopy examinations in the UK. We sought to understand the reasons for its low utilisation.

In the present study Entonox® was available to three quarters of respondents. Most of these perceived it to have favourable characteristics and three quarters would use it if they had a colonoscopy themselves. Despite this, nearly half used it in less than 20% of their examinations. The positive perceptions of Entonox® within colonoscopists are at odds with its low usage in clinical practice. The reasons for this are unclear. Potential determinants of Entonox® use may include patient choice, endoscopy unit policy and the preferences of the colonoscopist. The wide variation in Entonox® use suggests the relative contribution of these factors varies between units.

Patient choice was often cited as a factor which influenced the use of Entonox®. It was often used in patients wishing to avoid the inconvenience associated with sedation use. Patients receiving intravenous sedatives and opiates are generally told to avoid driving for 24 hours and to be with a responsible adult for the same period, whereas patients receiving Entonox® only have to refrain

from driving for 30 minutes. This reduced inconvenience makes Entonox® an attractive option for many patients. Several respondents had not introduced Entonox® into their unit as they were satisfied with their current analgesics.

Many respondents preferred to use intravenous medications rather than Entonox® in the patients expected to have most discomfort. This is in keeping with the BSG guidelines which suggest Entonox® may be best used during moderately painful procedures.(110) Although this statement implies that IV medications are more efficacious than Entonox®, a recent Cochrane review reported there were no clear differences between Entonox® and intravenous sedatives with regards to pain relief, but highlighted the need for further high quality studies.(123) However, the potency of Entonox® remains poorly defined,(122) and further studies are clearly indicated.

Most respondents instruct patients to use Entonox® as required. Published studies have employed varied methods of administration. Some recommend continual use until the caecum is reached,(98, 117) or until the sigmoid colon has being traversed.(120) Others recommend its use as required, either with or without pre-loading prior to intubation.(99, 115) There are no comparative studies of different methods of administration in endoscopic practice, although Westling et al found continuous use to be more effective than as required use during vaginal delivery.(146)

The present study found marked variation between colonoscopists in how and whether Entonox® is combined with intravenous sedation and or opiate analgesia. Previous studies examining nitrous oxide use during colonoscopy vary as to whether it was combined with intravenous medications and whether it was used concurrently,(116, 120) or after a washout period.(98, 117) Dental studies report the combination to be safe and reduce the requirement for midazolam, shorten recovery times and improve patient cooperation.(147) Clinical studies to clarify the safety and efficacy of Entonox® as an adjunct to intravenous medication during colonoscopy would be of clinical value.

Prolonged Entonox® exposure can result in serious neurological and haematological side effects,(148) and there have been concerns about effects on fertility.(149) The UK Health and Safety

Executive state the level of occupational exposure should not exceed 100ppm,(150) (time weighted average over 8 hours) but standards differ between countries. The Entonox® Summary of Product Characteristics suggests it should be administered in rooms with 'ventilation and/or exchange systems set to the proper level'. Direct measurement of nitrous oxide concentration is possible, but it is more common to assess its safety by measuring adequacy of ventilation. This can be assessed by measuring air changes per hour (ac/hr). The minimum ac/hr necessary to maintain a concentration of nitrous oxide below 100ppm is not defined as it is dependent on the amount used. Some UK hospital guidelines suggest Entonox® can be safely administered in room having 5-6 ac/hr. This is considerably less than 15 ac/hr which is recommended by the UK Department of Health guidelines,(151) for all endoscopy rooms, regardless of Entonox® use.  Individual units must make an appropriate assessment of risk.

This survey had a number of strengths and some limitations. Surveying rather than observing the practice of colonoscopists allowed this study to sample a large number of colonoscopists who were widely distributed. The survey obtained a good response and represented colonoscopists from all English NHS deaneries. The high response rate is likely to be a consequence of the measures taken to minimise no response bias, which are detailed in the methods.

The survey was piloted on a 10 colonoscopists within Sheffield Teaching Hospitals. Respondents were asked if questions were clear, how long it took to complete and whether they had any difficulties in its completion. They were also asked if there were any topics which the survey did not cover. Following this feedback minor changes were made to the design of the survey.

The method of a surveys administration influence response rate (152). Studies comparing electronic versus postal questionnaires have conflicting outcomes, but suggest electronic versions have advantages over postal versions, in particular ease of completion and return.(153)

We sampled only colonoscopists performing procedures within the English BCSP. Although this may reduce the extent to which the survey results could be generalised, it is likely that the practices

within endoscopy units would be similar and we felt that sampling BCSP colonoscopists would have advantages.

Although perceptions about Entonox are varied most agree that it is useful, has a good safety profile and reduces inconvenience for the patient. Many patients are able to undergo colonoscopy without intravenous medication but appropriate patient selection is important. The relative importance of comfort and convenience is also likely to vary between patients which should be considered when informing patients about the available medications.

Endoscopists' perceptions regarding the properties and usefulness of Entonox, which are generally positive, do not appear to explain the reasons for its low utilisation nationwide. Alternatively, it may relate to either the written or verbal information provided to patients particularly as its utilisation varies nationwide.

## 4.6 Conclusion

Although most BCSP endoscopists rate the properties of Entonox® favourably, its use remains highly selective. The use and availability of Entonox® is likely to increase in the UK due to the rollout of Bowel Scope. Optimising the use of Entonox® and identifying the patients for whom it is of most benefit will help further define its role in colonoscopy.

**Chapter 5 - Randomised controlled trial comparing two methods of Entonox administration during screening colonoscopy.**

## 5.1 Summary

**Background and study aims**

Entonox may be used to manage pain during colonoscopy but the optimal mode of administration is unknown. The aim of this study was to compare two methods of Entonox use.

**Patients and methods**

Patients attending for screening colonoscopy at a single centre were randomized to continuous or as required Entonox use. The primary outcome measure was the patient's overall pain rating at the time of discharge (verbally-administered numerical ratings scale, 0=no pain and 10=extreme pain). Secondary outcome measures included the experience of pain (rated every 2 minutes), side effects and the need for intravenous medications.

**Results**

108 patients were randomised and 100 completed the study (46 continuous, 54 as required). The overall pain scores did not differ between those who used Entonox continuously and as required (mean = 2.4 vs. 3.2, $p$=0.08). There were also no differences in the experience of pain (mean = 1.8 vs. 2.2, $p$=0.28, peak = 4.2 vs. 4.8, $p$=0.26 and area under curve = 23 vs. 30, $p$=0.24). 7/100 patients required rescue intravenous medication. Patients with high anxiety had greater overall pain scores (mean = 3.7 vs. 2.4, $p$=0.03).

Light headedness was the only side effect which occurred more often with continuous Entonox use (48% vs. 21%, p=0.009).

**Conclusion**

In patients attending for screening colonoscopy comfort ratings were similar in those using Entonox continuously and as required but light headedness was more common with continuous use. Further studies to define the efficacy of Entonox during colonoscopy are indicated.

Publications arising:

Abstract presented at UEGW 2014

Ball AJ, Din S, Donnelly MT, Riley SA. Entonox during colonoscopy: how should it be used?

Original article accepted for publication in the European Journal of Gastroenterology and Hepatology.

Ball AJ, Din S, Donnelly M, Riley SA. A randomized controlled trial comparing continuous and as-required nitrous oxide use during screening colonoscopy. Eur J Gastroenterol Hepatol. 2015 Mar;27(3):271-8.

## 5.2 Background

Unfortunately many patients experience pain during colonoscopy. Minimising pain is important for humane reasons and also influences patient satisfaction(30) and willingness to undergo a repeat examination.(154)

Several medications are available to improve patient experience and tolerance of colonoscopy but patients' requirements vary widely. Most Patients in the UK receive a combination of Intravenous sedation and analgesia and a minority use Entonox either alone or in combination with sedation and analgesia.

Studies assessing the efficacy of Entonox during colonoscopy report conflicting outcomes with some finding it provides equivalent analgesia to Propofol,(155) while others report it is no better than placebo.(99) The reasons for these differences are uncertain but the method of administration has varied between published studies, with it being administered either 1) continuously(98, 117) 2) continuously during insertion through the sigmoid colon then as required(120) 3) patients are pre-loaded prior to intubation then use it as required(115) or 4) as required(99). We have also reported that the method of Entonox administration varies in routine practice with over 90% administering it as required.(139) Continuous Entonox use may be expected to increase analgesic efficacy as a consequence of a higher blood nitrous oxide concentration and possibly reduced pain sensitisation; a process whereby pain is experienced more intensely following an initial episode due to modulation of pain pathways.(156) We assessed whether the method of Entonox administration influences its efficacy and therefore some of the variation in outcomes between studies.

Entonox is also given to a high proportion of patients at Sheffield Teaching Hospital, which permitted detailed study of its use with little changes to usual practice.

## 5.3 Methods

**Study design**

We performed an open, parallel design study whereby patients were randomised to receive

Entonox® either as-required or continuously.

**Null hypothesis**

Continuous administration of Entonox® during colonoscopy gives no better analgesia than the as

required method.

**Alternative hypothesis**

Continuous administration of Entonox® during colonoscopy gives better analgesia than the 'as

required' method.

**Study population**

Patients referred for a screening colonoscopy, following a positive faecal occult blood (FOB) within

the South Yorkshire and Bassetlaw hub of the English Bowel Cancer Screening Programme (BCSP),

were invited to participate. Colonoscopy examinations were performed at the Northern General

Hospital, Sheffield, between January 2013 and April 2014. Patients wishing to use Entonox were

considered for inclusion. Patients requesting intravenous sedation or analgesia from the start of the

examination, those with contraindications to Entonox use,(157) previous colonic surgery or a cardiac

pacemaker (as this would preclude the use of a magnetic endoscopic imaging (MEI) device) were

excluded.

**Randomisation**

Patients were randomised in a 1:1 ratio to either 'continuous use' (CU) or 'as required use' (ARU). A

medical secretary, with no other involvement in the study, used the website www.random.org to

generate a randomisation sequence for each colonoscopist. These were stored in opaque sealed

envelopes. After confirmation of consent, envelopes were opened to reveal the method of Entonox use.

**Study protocol**

Entonox was administered via a mouthpiece regulator activated by inhalation. Patients randomised to CU were asked to inhale Entonox with each breath for 1 minute prior to and during colonoscope insertion. Patients allocated to as ARU were asked to inhale Entonox if they experienced discomfort or pain. Endoscopist also prompted use of Entonox if peaks of pain were anticipated.

Colonoscopy examinations were performed by three experienced BCSP accredited colonoscopists using Olympus CF-260 colonoscopes with an MEI device. All patients were given intravenous hyoscine butylbromide immediately prior to colonoscopy. Patients who were in pain, despite the use of Entonox® and endoscopic manoeuvres to reduce pain, were offered alternative analgesia and/or sedation.

The patient's age, gender and body mass index (BMI) were recorded and patients were asked to complete a Hospital Anxiety and Depression Scale prior to colonoscopy (HADS)(158). Patients had their oxygen saturations monitored during colonoscopy but did not receive supplemental oxygen unless given rescue intravenous medications.

**Evaluation of pain severity and development**

The validated tools to assess pain during colonoscopy are endoscopist or nurse rated rather than patient rated. A questionnaire was therefore developed. Visual analogue scales (VAS) are widely used for the assessment of pain and are easy for patients to understand. However, most previous studies had examined the recollection of pain but the present study also examined the experience of pain during colonoscopy. Therefore, a visual analogue scales (VAS) was considered impractical as it would have required the use of a pencil and paper. Instead, a 10-point verbally administered numerical ratings scale (VA-NRS) was employed, which allowed patients to vocalise their rating and

they are reported to correlate highly with VAS in the assessment of acute pain (*r=0.94*).(159) A VA-NRS had been used to assess the experience and recollection of pain during a previous colonoscopy study.

Prior to colonoscopy patients were asked:

*'Between 0 and 10, with 0 being no pain and 10 being extreme pain, what is your current level of pain?'*

*'Between 0 and 10, with 0 being no pain and 10 being extreme pain, how painful do you think the colonoscopy will be?'*

Every 2 minutes during the examination patients were asked:

*'Between 0 and 10, with 0 being no pain and 10 being extreme pain, on average how much pain have you had over the last 2 minutes?'*

Immediately prior to discharge and 1-3 days following colonoscopy patients rated pain, overall satisfaction and willingness to undergo a repeat examination:

*'Between 0 and 10, with 0 being no pain and 10 being extreme pain, on average how much pain did you have during the colonoscopy?'*

*'Overall, between 0 and 10, with 0 being not satisfied at all and 10 being completely satisfied, how satisfied are you with your colonoscopy'*

*'Between 0 and 10, with 0 being not willing at all and 10 being completely willing, how willing would you be to have a repeat procedure?'*

The endoscopist and SSP independently rated the overall level of pain (0 = no pain to 10 = extreme pain) immediately following colonoscopy and the endoscopist also rated the technical difficulty of the examination (0=very easy to 10 = extremely difficult).

The SSP also rated patient comfort on the 5 point Modified Gloucester Comfort Scale (MGCS) which

is used as standard in the English BCSP (Table 15).

The study investigators included expert and experienced colonoscopists, which assured content

validity. To ensure face validity the wording of questions were further reviewed by consultant

gastroenterologists colleagues and specialists screening nurses.

| Comfort grade | Descriptor |
| --- | --- |
| No | resting comfortably throughout |
| Minimal | One or two episodes of mild discomfort, well tolerated |
| Mild | More than two episodes of discomfort, adequately tolerated |
| Moderate | Significant discomfort, experienced several times during the procedure |
| Severe | Extreme discomfort, experienced frequently during the procedure |

**Table 15 – Modified Gloucester comfort scale**

**Assessment of side effects**

Following colonoscopy patients were asked if they experienced: nausea, headache, light headedness

or dizziness, dry mouth or paraesthesia. The clinician rated whether the patient had shown signs of

dysphoria. The severity of side effects was assessed according to whether the patient stopped

Entonox use. Adverse physiological changes, including episodes of oxygen de-saturation (SaO2

<90%), hypotension, (blood pressure <90/50 mmHg) and bradycardia (pulse<50) were noted.

**Study endpoints**

The primary endpoint was the patient's overall pain rating prior to discharge. Secondary outcome

measures included: the mean, peak and sum of all (area under curve) pain ratings during

colonoscopy, patient satisfaction, willingness to undergo a repeat examination, side effects and

need for additional medications. Procedural timings were also noted as well as gender, anxiety level and whether the patient had undergone a previous examination.

**Power calculation and statistical analysis**

With a power (1-β) of 80% and a significance level of 5%, we determined that 198 patients were required to detect a 1 point difference on the 10 point numerical ratings scale, in keeping with the Entonox study by Forbes et al.(117) This assumed a standard deviation of 2.5, as reported in a previous study which assessed comfort during colonoscopy on a NRS.(104) An interim analysis was planned after 100 patients to assess the futility of further recruitment based on whether there were clinically significant differences between the two groups (1 point on a 10-point pain rating scale).

Baseline and procedural characteristics were summarised. Continuous and categorical data were compared using a two-tailed *t* test and chi-squared test respectively. Correlations were assessed using Spearman's correlation coefficient and interpreted as very high (+/-0.9-1.0), high (+/- 0.7-0.9), moderate (+/- 0.5-0.7), low (+/- 0.3-0.5) and no/negligible (+/-0-0.3).(130)  The agreement between observers was assessed using the intra-class correlation coefficient (ICC) and interpreted as poor (0-0.29), fair (0.3-0.49), moderate (0.5-0.69), strong (0.7-0.79) and almost perfect (>0.8). A two-tailed *p* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 20 (IBM Corp).

**Approvals received**

The BCSP Research Committee approved that the study could be conducted within the BCSP in December 2011. The Leeds West Research Ethics Committee (REC), Medicines and Healthcare Products Regulatory Authority (MHRA) and the STH research and Development (R & D) department approval the study.

The study was registered on clinicaltrials.gov (NCT 01865721)

## 5.4 Results

159 patients were screened, 51 were excluded and the outcomes of 100 patients were analysed

(figure 5). The study ceased recruitment after the interim analysis of 100 patients found no clinically

or statistically significant differences in the primary outcome measure.
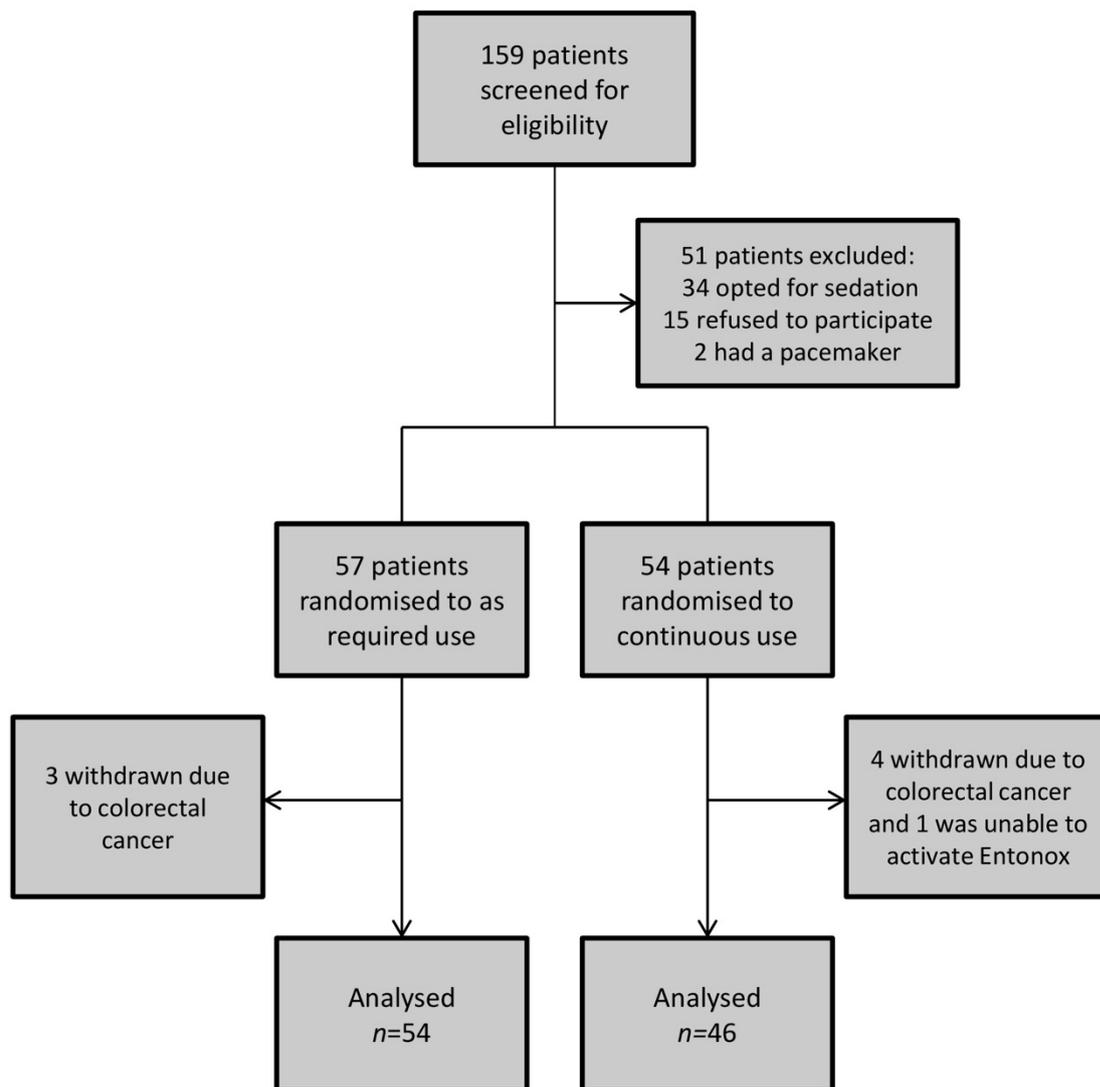


**Figure 5 - Patient flow diagram**

The demographics and endoscopic findings were similar in both groups (table 16). The caecal

intubation rate was 98% with both strategies and the mean (SD) intubation time were also

comparable (CU 12.0 (8.7) min vs. ARU 10.4(6.4) min, p=0.31).

15/54(27.7%) patients in the ARU group did not use Entonox at all while 4/46(8.7%) patients in the

CU group reverted to ARU due to side effects.

| | Continuous | As required | p value |
|---|---|---|---|
| Age - mean(SD) | 66.7 (4.1) | 66.5 (4.6) | 0.86 |
| BMI - mean (SD) | 27.8 (5.2) | 29.0 (6.1) | 0.32 |
| HADS - mean (SD) | 5.8 (4.5) | 4.5 (3.8) | 0.18 |
| Anticipated pain - mean (SD) | 4.5 (2.3) | 4.3 (2.0) | 0.57 |
| Difficulty of examination - mean (SD)* | 5.2 (2.1) | 4.8 (2.1) | 0.38 |
| Previous colonoscopy - n (%) | 12 (26.1) | 12 (22.2) | 0.65 |
| Diverticulosis – n (%) | 18 (39.1) | 25 (46.3) | 0.59 |
| $CO_2$ use | 5 (10.8) | 12 (22.2) | 0.13 |

**Table 16 – Demographic and procedural characteristics.**

* (0= Very easy and 10= extremely difficult)

**Pain ratings**

There was a trend towards lower overall pain ratings at the time of discharge in the patients

randomised to continuous Entonox use, (2.4 vs 3.2(2.1), p=0.09) although this fell short of both

clinical and statistical significance. There were also no significant differences in the mean, peak or

area under curve of the pain ratings during colonoscopy (table 17). At most time points during

colonoscope insertion the pain ratings were lower with continuous use although this only reached

significance between 10- 12 minutes (figure 6).

|  | Method of Entonox use | | p value |
|  |---|---|---|
|  | As required use - mean (SD) | Continuous use - mean (SD) | |
| Patients' pain ratings | | | |
|    Mean | 2.2 (1.9) | 1.8 (1.8) | 0.28 |
|    Peak | 4.8 (2.8) | 4.2 (2.9) | 0.26 |
|    Area under curve | 29.6 (27) | 22.8 (29) | 0.24 |
|    Prior to discharge | 3.2 (2.1) | 2.4 (2.2) | 0.08 |
|    1-3 days later* | 3.0 (2.0) | 2.4 (2.3) | 0.18 |
| Endoscopists' ratings | 2.9 (2.0) | 3.0 (1.8) | 0.78 |
| SSPs' ratings | 2.7 (2.0) | 2.7 (1.9) | 0.90 |

**Table 17 - Pain ratings with each treatment strategy**

*79 of 100 patients were contactable 1-3 days later
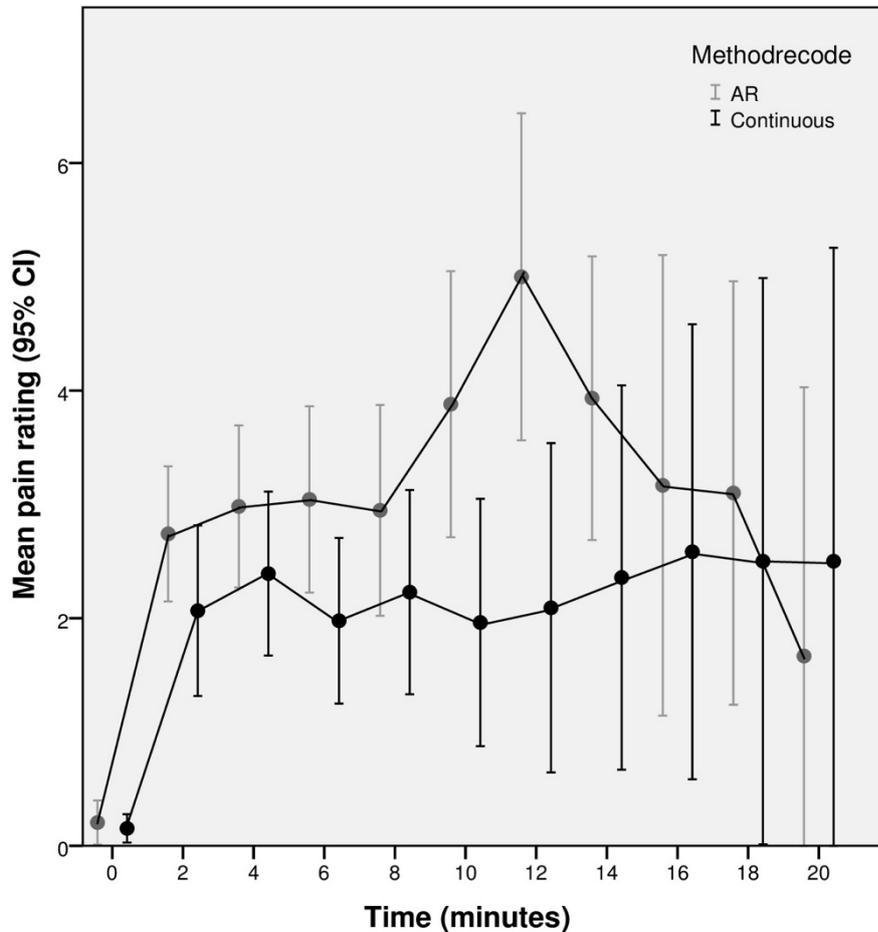
**Figure 6 - Mean (95% CI) pain ratings every 2 minutes during colonoscope insertion**

Patients with a HADS score ≥8 anticipated higher levels of pain (mean (SD) = 5.4 vs. 3.8, p=0.02).

Patients with a HADS score of ≥8 reported higher pain ratings than those with a score <8 during

colonoscopy (mean score (SD) = 2.8 (2.2) vs. 1.6 (1.7), p=0.03, peak score = 5.9 (2.5) vs. 4.1 (2.9),

p=0.02), and at the time of discharge (mean score (SD) = 3.7 (2.3) vs 2.4 (2.1), p=0.03). Patients with

a HADS score ≥8 were also rated as having more pain by the endoscopists (mean (SD) 3.9 (2.1) vs 2.6

(1.8), p=0.01) and the SSP (mean (SD) = 3.8 (2.4) vs 2.3 (1.7), p=0.007).

Patients with a HADS score <8 who were randomised to CU rather than ARU reported lower overall

pain ratings (mean (SD) 1.7 (1.9) vs. 2.9 (2.2), p=0.03) but this was not the case in those with a HADS

score ≥8 (Mean (SD) = 4.0 (2.5) vs. 3.3 (2.0), p=0.54 - figure 7). Patients with a HADS <8 who were

randomised to ARU were less likely to use Entonox although this fell short of statistical significance (64% vs. 100%, p=0.06).

The overall pain score was similar in males and females at the time of discharge (Mean (SD) = 2.6 (2.1) vs. 3.4 (2.3), p=0.11) and during colonoscopy (mean (SD) =1.9 (1.7) vs. 2.3 (2.1), p=0.36) although there was a trend towards higher peak pain ratings in females (mean (SD) = 5.4 (2.9) vs. 4.2 (2.8), p=0.07). Overall pain scores were similar in patients with and without diverticulosis and in those who had a previous colonoscopy examination and those who had not.

**Correlations**

There was a very high correlation between the patients overall pain rating prior to discharge and their rating 1-3 days later (r=0.96). There was also a high correlation between the patients overall pain rating prior to discharge and their mean rating (r=0.90), peak rating (r=0.86) and the AUC (r=0.83) while there was a moderate correlation with the pain rating during retroversion (r=0.54).

There was no correlation between the patients overall pain rating prior to discharge and the patients anticipated level of pain (r=0.12) or their baseline level of pain (r=0.19). There was also no
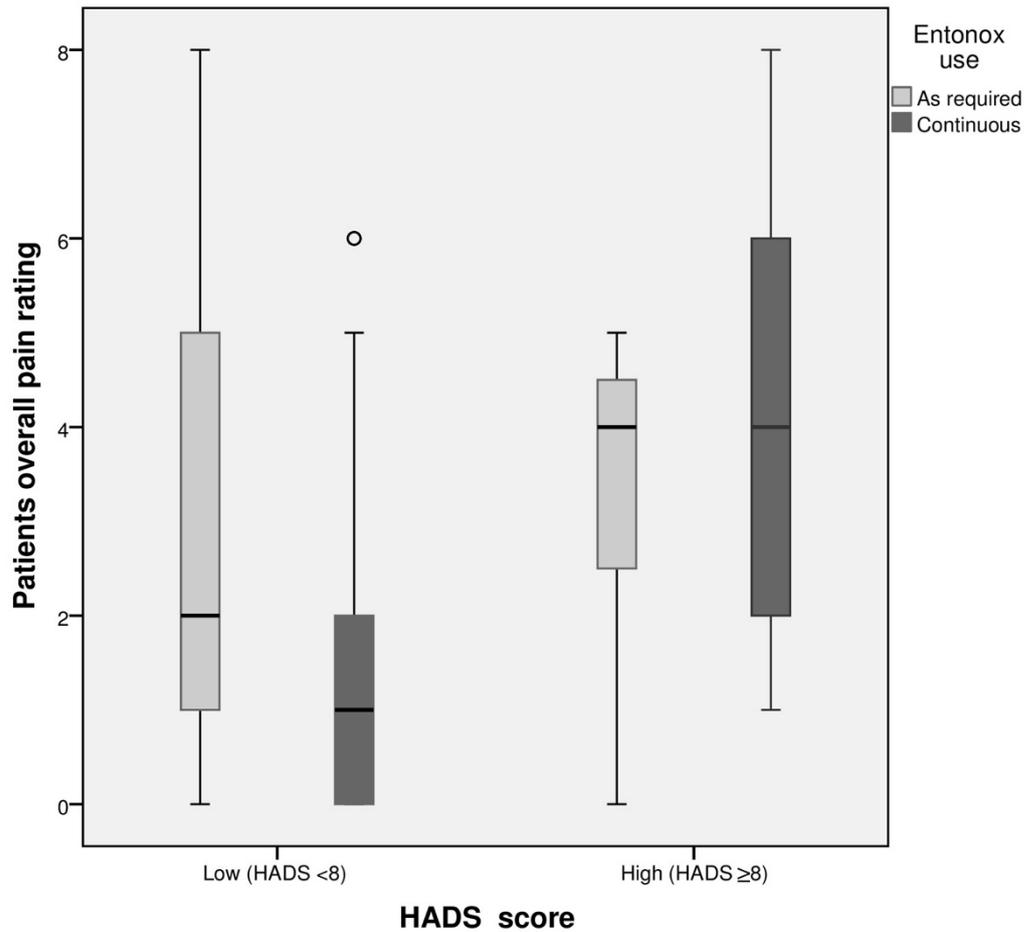
**Figure 7- Pain ratings in patients with low and high anxiety scores**

correlation between patients overall pain rating and their satisfaction (r=0.28) but there was a low

correlation with their willingness to undergo a repeat examination (r=0.40).

The technical difficulty of colonoscopy did not correlate with the patients overall pain ratings

(r=0.27) or that of the SSPs (r=0.28). However, there was an association between the endoscopists

rating of technical difficulty and the endoscopists overall pain rating (r=0.38).

Using the VA-NRS there was almost perfect agreement between the patients and the SSPs and

endoscopists overall pain, with ICCs of 0.86 (95% CI 0.79-0.91, *p*<0.0001) and 0.88 (95% CI 0.82-0.92,

p<0.0001) respectively. There were lower levels of agreement between the comfort ratings using the

MGCS and the nurses (ICC=0.69, 95% CI 0.53-0.79, $p<0.0001$), endoscopists (ICC=0.66, 95% CI 0.50-0.77, $p<0.0001$) and patients (ICC=0.58, 95% CI 0.38-0.72, $p<0.0001$) overall pain rating on the VA-NRS.

The proportion of patients given rescue intravenous medication did not differ between treatment strategies (CU 4/46 vs. ARU 3/54, p=0.54).  Light headedness occurred more frequently in the as required group but there were no significant differences in other side effects (table 18).

| Side effect | Continuous | As required* | OR (95% CI) | p Value |
|---|---|---|---|---|
| Nausea (%) | 3/46 (6.5) | 3/39 (7.7) | 1.2 (0.2-6.2) | 0.83 |
| Headache (%) | 0/46 (0) | 0/39 (0) | n/a | 1.0 |
| Dysphoria (%) | 3/46 (6.5) | 0/39 (0) | n/a | 0.1 |
| Light-headedness (%) | 22/46 (47.8) | 8/39 (20.5) | 3.5 (1.3-9.4) | 0.009 |
| Dry mouth (%) | 39/46 (84.7) | 34/39 (87.2) | 1.1 (0.3-4.3) | 0.75 |
| Paraesthesia (%) | 3/46 (6.5) | 1/39 (2.6) | 2.7 (0.3-26.6) | 0.39 |

**Table 18: Frequency of side effects with each method of Entonox use**

* Only 39 of 51 patients allocated to the as required group used any Entonox.

4 of 46 patients who were randomised to CU reverted to ARU due to side effects. 3 stopped due to light headedness and 1 due to dysphoria. 3 of 54 patients in the ARU group also stopped Entonox use due to side effects; 2 due to light headedness and 1 because of a dry mouth.

2 patients who used Entonox continuously transiently dropped their blood oxygen saturations below 90%. 1 patient who used Entonox as required had a transient episode of hypotension (systolic <90mmhg). There was no difference in the mean (SD) time to discharge between CU and ARU (41(17) min vs. 40(15) min, p=0.9).

Overall patient satisfaction was high with both CU and ARU (mean (SD) = 9.9 (0.4) vs. 9.7 (0.9), p=0.23) as was willingness to undergo a repeat examination (mean (SD) = 9.2 (2.1) vs. 9.7 (1.0), p=0.09).

## 5.5 Discussion

Entonox is one of a range of medications that may be used to manage pain during colonoscopy. It has advantages compared to intravenous medications associated with its rapid elimination, such that patients are fit for discharge sooner and able to drive 30 minutes after use. The efficacy of Entonox, however, is not well defined and there are conflicting outcomes between studies.(99, 155) The reason for this is unclear but the method of Entonox administration has varied between studies. Some have instructed patients to use it continuously and others as required. Use in routine practice is also variable but it is most often used as required.(139) Obstetric studies have reported an advantage to continuous Entonox use, but there have been no equivalent studies during colonoscopy. The dosing schedule of intravenous agents during colonoscopy has also been reported to influence their efficacy, with 'routine' rather than 'on demand' dosing being more effective.(137)

In the present study we found that the method of Entonox administration made no difference to the overall pain ratings. However, continuous use was associated with a trend towards lower pain ratings at many time points during colonoscope insertion. These differences may reflect a better analgesic effect of continuous use, although it should be noted that significant differences were only present for brief periods in those with prolonged insertion times. Given that differences were only identified on subgroup analysis, which are inherently susceptible to bias,(160) it is perhaps unsurprising that there were no differences in the overall pain ratings. The lack of an overall difference may reflect the endoscopists giving appropriate prompts for as required use, since peaks of pain are often predictable and usually coincide with the formation and resolution of colonoscope loops.(29) Alternatively, the act of inhaling Entonox, which is common to both groups, may distract patients, adding to the placebo effect and minimising differences between the groups.(161)

Patients with higher anxiety levels reported higher pain levels regardless of the mode of administration of Entonox. Many previous studies have also reported that patients with an increased anxiety level experience more pain during colonoscopy.(102, 104) Identifying patients who are most

likely to report significant amounts of pain, with simple tools such as the HADS scale, would allow more potent medications to be targeted on those who need it most.

Continuous Entonox use was also found to be superior in the patients with low anxiety ratings (mean score 1.6 vs. 2.7, p=0.03). The reason why a difference was limited to patients with low anxiety levels is not clear. It may be that the higher pain ratings in those with high anxiety levels prompted proportionately more Entonox use which reduced any potential difference between continuous use and as required use. Conversely, the lower pain ratings seen in patients with low anxiety levels may not have been of sufficient magnitude to trigger Entonox use, even though it may have been of value.

It is worth noting that over a quarter of the patients randomised to ARU did not use any Entonox and many of the patients who were randomised to as required use only used a small amount of Entonox although the amounts used were not formally measured. In addition, only 7% required rescue intravenous medication, and this did not differ between groups (CU=4 and ARU =3). Previous studies report that 0-26.8% of patients are given intravenous medication after commencing with Entonox alone.(98, 99, 117, 120, 155) The reason for the variation between studies is unclear but may relate to differences in case-mix, endoscopic technique or the threshold at which medication is administered. It should be noted that only a minority of the patients screened were excluded due to a preference for intravenous sedation use and therefore our results should remain applicable to a wider screening population.

Entonox is widely considered to be safe but transient side effects are well described. The frequency of side effects observed in the present study was broadly similar to previous reports of Entonox use.(162) Not surprisingly patients using Entonox continuously were more likely to feel light-headed (48% vs. 21%) and only occasionally converted to 'as required' use as a consequence. Dysphoria occurred in 3(6.5%) patients who used Entonox continuously but not at all in those randomised to ARU but this difference did not reach statistical significance. There were no significant differences in

the other side effects. Over 80% of patients had a dry mouth with both methods of administration, which is perhaps unsurprising as it also occurs in association with the bowel preparation and the administration of hyoscine butylbromide. Hypoxemia occurred in 2 patients, which may appear counterintuitive in a formulation which includes 50% oxygen but this is well recognised, rapidly reversible and commonly attributed to the process of diffusion hypoxia.(163)

Patient satisfaction and willingness to undergo a repeat examination were high in both groups and perhaps surprisingly showed no association with pain ratings. This may be a consequence of factors unrelated to the technical performance of colonoscopy such as good communication, explanation and short waiting times, which are known to influence these outcomes.(164)

The experience of pain is enormously subjective and the global measurement of pain during colonoscopy is difficult due to the large variation in severity over time. The present study however, found a high correlation between patients' experience and recollection of pain as well as strong agreement between observers. We believe this may be a consequence of repeatedly assessing pain during colonoscopy which may have calibrated the patients overall rating. Although this process may have biased the clinicians' ratings it is usual practice for colonoscopists to continually monitor and be aware of patient comfort.

This study has a number has a number of limitations. The patients were asymptomatic and the demographics were limited as recruitment was from the Bowel Cancer Screening Programme. Furthermore, examinations were performed by accredited screening colonoscopists who are expected to be proficient in scope handling and effectively manage colonoscope loops. A limited cohort was studied to minimise confounding co-variables and therefore make treatment differences more apparent although this may limit the extent to which the study results can be generalised. It was also not feasible to blind the patient or study investigators to the method of Entonox administration. Finally, the amount of Entonox used during colonoscopy was not quantified but the instructions for Entonox use were representative of routine practice.(139)  This study suggests that

differences in the method of Entonox administration in previous studies are unlikely to be a

significant factor in explaining conflicting outcomes. Further studies to clarify the relative

effectiveness of Entonox against the other commonly used medications are indicated.

## 5.6 Conclusion

Patients attending for screening colonoscopy had similar comfort ratings whether Entonox was used

continuously or as required but light headedness was more common with continuous use. Further

studies to define the relative efficacy of Entonox and the intravenous medications used during

colonoscopy are clearly indicated.

**Chapter 6 - A comparison of a low and standard volume polyethylene glycol solution as bowel cleansing prior to screening colonoscopy**

## 6.1 Summary

**Background & aims**

Moviprep®, a low volume polyethylene glycol (PEG) solution plus ascorbic acid, and standard volume PEG solutions are commonly used as bowel preparation prior to colonoscopy. The study aimed to compare the real life outcomes of these two solutions prior to screening colonoscopy.

**Methods**

150 consecutive patients attending for a screening colonoscopy were asked to rate acceptability, side effects and willingness to repeat their bowel preparation. This occurred during a switch over from a standard volume PEG solution to Moviprep®. Bowel cleanliness was rated using the Ottawa scale.

**Results**

Patients taking Moviprep® were more adherent (73/75 vs. 65/75, p=0.02) and judged taste as unacceptable less often (22/75 vs. 37/75, p=0.01). However, patients taking the standard volume preparation who were scheduled to have a morning colonoscopy were more likely to have cleanliness of the right colon rated as good or excellent (9/60 vs. 19/60 p=0.04). Patients scheduled for an afternoon, rather than morning examination, were more likely to have bowel cleanliness rated as good or excellent with both solutions.

**Conclusion**

Moviprep® was better tolerated but resulted in less effective bowel cleansing during colonoscopies scheduled in the morning.

Publications arising

Abstract presented at DDW 2014, Chicago

Ball AJ, Riley SA. A comparison of a standard volume polyethylene glycol solution and low volume polyethylene glycol plus ascorbic acid as bowel preparation prior to screening colonoscopy

## 6.2 Background

Colonoscopy is the gold standard investigation for patients with colonic symptoms and is an effective method in screening for colorectal cancer. However, the benefits of colonoscopy are reduced in the presence of poor bowel cleanliness. Unfortunately, suboptimal bowel preparation is common. A recent UK national audit reported poor bowel preparation was present in 11.8% of patients and was responsible for 22% of incomplete colonoscopy examinations.(2)

PEG based solutions are widely used to cleanse the bowel prior to colonoscopy and work primarily by the mechanical effects of lavage. These solutions are combined with electrolytes and diluted in water and considered to be safe. However, many patients struggle with the taste and volume of the standard 4 litre PEG preparations due to which low volume PEG solutions have evolved. Moviprep® (Norgine Pharmaceuticals) was developed as a lower volume PEG solution that contains ascorbic acid which acts as an osmotic laxative and also modifies the taste.

Since the roll out of the National Bowel Cancer Screening Programme (BCSP), the South Yorkshire and Bassetlaw (SYB) consortium have employed Kleanprep® (Norgine Pharmaceuticals) for bowel cleansing. However, many patients cite difficulty with the consumption of the preparation as the most troublesome aspect of colonoscopy. In response, bowel preparation was switched from Kleanprep® to Moviprep® for a trial period during which patient experience, adherence and bowel cleanliness were assessed.

## 6.3 Methods

**Study approval**

The study and associated documents were registered and approved as a Service Evaluation by the Sheffield Teaching Hospitals Clinical Effectiveness Unit (project number 4741).

**Study population**

Patients found to have a positive faecal occult blood (FOB) test referred for colonoscopy within the SYB BCSP between 7th October 2012 and 14th December 2012.

**Study procedures**

Consecutive patients listed for outpatient colonoscopy from four hospital sites were asked to participate in a service evaluation. Patient experience, adherence and efficacy of bowel preparation were assessed during a trial change-over in bowel preparation from the Kleanprep® to Moviprep®. Prior to colonoscopy the BCSP Specialist Screening Practitioner (SSP) stressed the importance of adherence to bowel preparations with an explanation that incomplete consumption may result in missed lesions or necessitate a repeat examination.

All patients were asked to consume a 'low residue' diet in the 2 days prior to colonoscopy and this was supplemented by an information sheet. Patients were also asked to stop taking iron preparations and opiates where possible.

Both bowel preparations were given according to the manufacturer's instructions (see appendix 1). All patient scheduled for a morning colonoscopy were asked to take their bowel preparation on the day prior to colonoscopy, whereas patients scheduled for an afternoon colonoscopy were asked to take their bowel preparation over two days with the first half being consumed on the evening prior and the second half on the morning of colonoscopy, referred to as 'split dosing'. Colonoscopies were performed by seven BCSP colonoscopists, all with experience of over 2000 colonoscopies.

**Outcome measures and survey development**

Bowel cleanliness was rated using the Ottawa scale, (appendix 2) which is a previously validated and extensively used bowel preparation scale.(69) This assesses the adequacy of bowel cleanliness in three bowel segments and quantifies the amount of cleansing required to make views adequate. Other available scales, such as the Boston Bowel preparation scale, assess bowel cleanliness after cleansing by the endoscopist and do not take account of the efforts required to achieve this. Endoscopists and SSPs were familiarised with and used the Ottawa scale over a two-week period prior to commencement of the study. The endoscopist and attending SSP agreed a rating after each procedure. Colonoscopy examinations were digitally recorded. A random cohort of 15 examinations was later viewed and the bowel preparation was graded to assess the reliability and validity of the scale.

Comparisons were made according to the proportion of patients with bowel cleanliness ratings of good or better. This was chosen in preference to comparing the distribution of bowel cleanliness ratings, as it has greater clinical relevance. This is also in keeping with previous bowel preparation studies.

The survey to assess patients' experience with each bowel preparation was developed by the study investigators, which included experienced and expert endoscopists. This ensured content validity. There are no validated scales to assess patient experience with bowel preparations, but previous studies had assessed the acceptability of taste, volume, side effects, effect on planned activities and overall experience. A 5-point Likert scale, ranging from completely unacceptable to completely acceptable, was used to assess these domains. A Likert scale was used as these are easy to complete and widely used to survey opinions. A potential disadvantage of Likert scales is central tendency bias whereby respondents avoid extreme responses. On the other hand, the option of a neutral response means that respondents are not forced into offering a positive or negative response when they feel indifferent.

To provide face validity feedback was sought from a group of SSPs who reviewed the survey. Following this, minor changes were made to the wording of questions.

Patients rated the severity of side effects including: bloating, abdominal cramps, nausea, vomiting, abdominal pain, sleep disturbance and headache. These domains are also commonly assessed in bowel preparation studies. A unipolar scale was considered most appropriate for this purpose and the descriptors; absent, mild, moderate or severe were employed.

Patients also rated their willingness to repeat the same bowel preparation by stating their agreement with: 'I would be willing to repeat the same bowel preparation if I required a colonoscopy in the future' on a 5-point Likert scale, ranging from completely agree to completely disagree.

The interval between completion of bowel preparation and the start of the colonoscopy, examination during a morning or afternoon list, age, body mass index (BMI), the consumption of constipating medications and the amount of bowel preparation consumed were also noted.

**Statistical methods**

Categorical data were compared using the Fishers exact test and ordinal data were compared using the Mann-Whitney U test. The reliability of bowel cleanliness ratings was assessed by two study investigators (AJB and SAR) who viewed and rated 15 recordings, from which intra-class correlation (ICC) coefficients were calculated. Statistical analyses were performed using SPSS version 20.

## 6.4 Results

During the study period 194 patients were referred for screening colonoscopy. 44 were excluded from the analysis: 2 did not wish to take part in the evaluation, 26 failed to return the questionnaire, 6 had an incomplete colonoscopy (none due to inadequate bowel cleanliness), 4 had undergone colonic surgery, 1 required inpatient preparation and 2 were identified as requiring augmented preparation prior to colonoscopy. A similar number of these patients were excluded in the Moviprep® and Kleanprep® groups. A further 3 patients were excluded as they were unable to consume the bowel preparation. Of these, 2 patients were unable to consume Kleanprep® and 1 patient followed the instructions for Moviprep® incorrectly (consumed a day early).

The demographics and procedural times were similar in each group (table 19). The interval between completion of bowel preparation and colonoscopy was longer in morning than afternoon lists (mean (SD) = 13.2 (1.7) vs. 6.4 (2.9) hours, P<0.0001). The interval between completion of preparation and colonoscopy in patients scheduled to have a morning colonoscopy was shorter in those who took Moviprep (mean (SD) =12.7 (1.2) vs. 13.7 (1.9) hours, $p$=0.002). But there was no difference in the time intervals between preparations in the patients scheduled to have an afternoon colonoscopy.

**Bowel cleanliness**

Five patients had inadequate bowel cleanliness, four of whom had taken Moviprep®. All were booked for further investigation.

Patients who had taken Kleanprep® had bowel cleanliness rated as good or excellent more often in the right colon (29/75 (39%) vs. 18/75 (24%), odds ratio (OR)=2.0, 95% confidence interval (CI)=0.98 - 4.0, p=0.053), mid colon (37/75 (49%) vs. 31/75 (41%), OR=1.4, 95% CI=0.73 - 2.63, p=0.33) and recto-sigmoid (40/75 (53%) vs. 31/75 (41%), OR=1.6, 95% CI=0.85 - 3.1, p=0.14) but this failed to reach conventional statistical significance (figure 8). There were no significant differences in the proportion of patients achieving bowel cleanliness rated as fair or better in the right colon (54/75 (72%) vs. 48/75 (64%), OR=1.4, 95% CI=0.73 - 2.88, p=0.29) mid colon (62/75 (83%) vs. 61/75 (81%),

OR=1.1, 95% CI=0.48 - 2.52, p=0.83) or recto-sigmoid (65/75 (87%) vs. 67/75 (89%), OR=0.78, 95% CI=0.29 - 2.1,  p=0.62). Sub-group analysis however, revealed that patients taking Kleanprep® were more likely to have bowel cleanliness of the right colon rated as good or excellent during colonoscopy scheduled in the morning (19/60 (31.6%) vs. 9/60 (15%), OR=2.62, 95% CI=1.07 - 6.41, p=0.04).

| Descriptor | Moviprep® | Kleanprep® | *P* value |
|---|---|---|---|
| Age (mean and range) | 68.1 (60-74) | 67.8 (60-74) | 0.75 |
| Gender | 46 male<br><br>29 female | 43 male<br><br>32 female | 0.74 |
| BMI (kg/m$^2$) (mean and range) | 28.8 (18-41) | 29.6 (20-49) | 0.39 |
| Previous colonoscopy | 9/75 (12%) | 7/75 (9%) | 0.79 |
| Morning list | 60 patients | 60 patients | 1 |
| Afternoon list | 15 patients | 15 patients | 1 |
| Constipating medications | 15 patients | 22 patients | 0.18 |

**Table 19 - Demographic details of patients receiving Moviprep® and Kleanprep®.**

The proportion of patients with bowel cleanliness rated as good or excellent was greater in patients scheduled for an afternoon colonoscopy than those scheduled for a morning colonoscopy in all colonic segments irrespective of the bowel preparation taken (see table 20). However, when comparisons were made between the proportions of patients with bowel cleanliness rated as fair or better this difference disappeared.

There was moderate agreement between the bowel cleanliness ratings given at the time of the colonoscopy and the study investigators and between the study investigators following colonoscopy (ICC = 0.68 and 0.63).
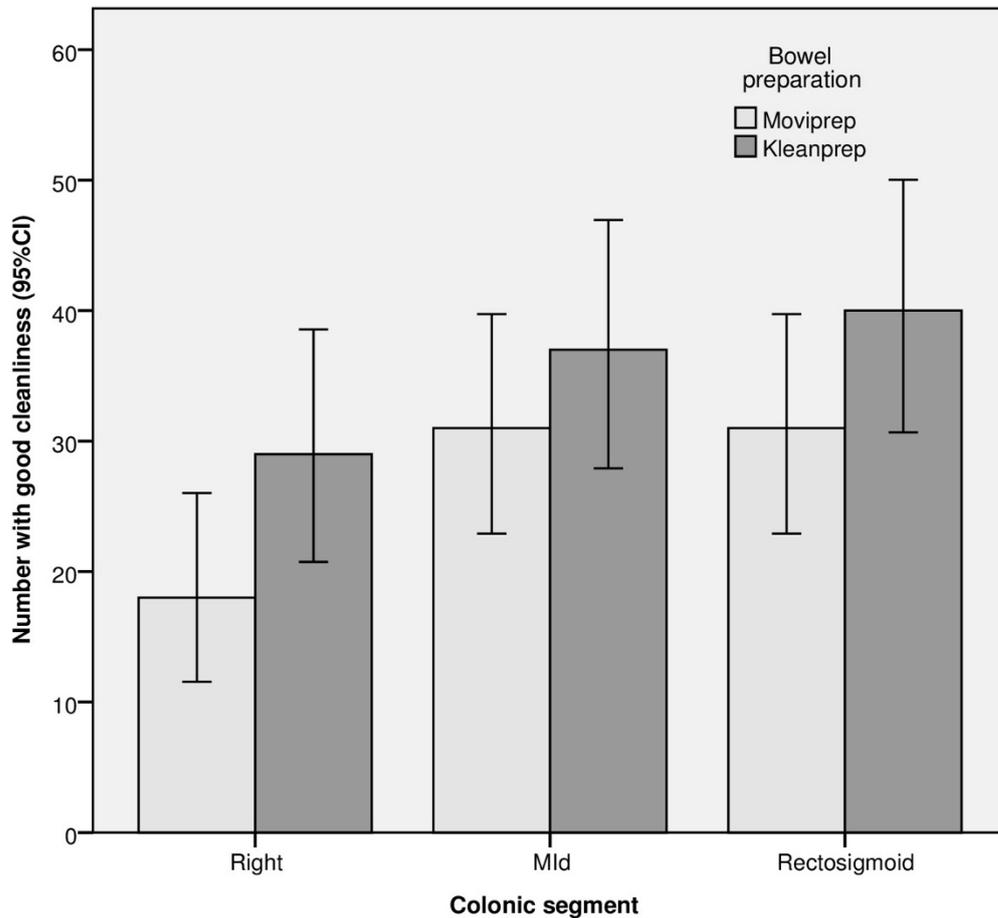


**Figure 8- Frequency of good bowel cleanliness in each colonic segment**

**Adherence and patient experience.**

All 150 patients consumed >75% of the prescribed preparation but a higher proportion of the patients taking Moviprep® consumed all the preparation (73/75 (97%) vs. 65/75 (87%), OR=5.6, 95% CI=1.18 - 16.2, p=0.02).

There were no significant differences in the proportion of patients rating each domain of patient experience as unacceptable apart from taste (table 21). There was also no significant difference in the frequency of significant side effects between the two preparations (table 22).

| Bowel Preparation | Bowel segment | Morning list | Afternoon list | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| Kleanprep® | Right colon | 19/60 (32%) | 10/15 (67%) | 4.3 (1.3 - 14.4) | 0.01 |
| | Mid colon | 25/60 (42%) | 12/15 (80%) | 5.6 (1.4 - 21.9) | 0.01 |
| | Recto-sigmoid | 28/60 (47%) | 12/15 (80%) | 4.6 (1.2 - 17.9) | 0.02 |
| Moviprep® | Right colon | 9/60 (15%) | 9/15 (60%) | 8.5 (2.4 -29.8) | <0.001 |
| | Mid colon | 21/60 (35%) | 10/15 (67%) | 3.7 (1.1 - 12.3) | 0.03 |
| | Recto-sigmoid | 20/60 (33%) | 11/15 (73%) | 5.5 (1.6 - 19.5) | 0.005 |

**Table 20 - Number of patients with bowel cleanliness rated as good or better. Comparisons were made with Fishers exact test.**

| Domain | Moviprep® | Kleanprep® | *P* value |
|---|---|---|---|
| | Median (range) | Median (range) | |
| Taste | 2 (1-5) | 3 (1-5) | 0.01 |
| Volume | 3 (1-5) | 3 (1-5) | 0.23 |
| Side effects | 3 (1-5) | 3 (1-5) | 0.88 |
| Effect on planned activities | 3 (1-5) | 3 (1-5) | 0.65 |
| Overall experience | 3 (1-5) | 3 (1-5) | 0.27 |

**Table 21 – Patients' acceptability ratings (1= completely acceptable, 5 = completely unacceptable) with each bowel preparation. Comparisons made with Mann-Whitney U test.**

| Side effect | Moviprep® (%) | Kleanprep® (%) | Odds Ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Bloating | 5/75 (6.6) | 4/75 (5.3) | 0.79 (0.2 - 3.1) | 1.0 |
| Abdominal cramps | 3/75 (4) | 6/75 (8) | 2.09 (0.5 - 8.6) | 0.3 |
| Nausea | 8/75 (10.7) | 8/75 (10.7) | 1 (0.4 - 2.9) | 1.0 |
| Vomiting | 1/75 (1.3) | 6/75 (8) | 6.4 (0.8 - 54.8) | 0.053 |
| Abdominal pain | 4/75 (5.3) | 6/75 (8) | 1.5 (0.4 - 5.7) | 0.5 |
| Sleep | 5/75 (6.6) | 12/75 (16) | 2.7 (0.9 - 8.0) | 0.07 |
| Headache | 6/75 (8) | 8/75 (10.7) | 1.4 (0.5 – 4.2) | 0.5 |

**Table 22 - Number of patients rating the severity of side effects as moderate or severe, with each bowel preparation.**

There was no difference in patients' willingness to repeat bowel preparation between PEG solutions (median (range) = 3 (1-5) vs. 3 (1-5), p = 0.95).

## 6.5 Discussion

The importance of bowel cleanliness to effective colonoscopy is self-evident. Large multicentre studies have found polyp detection rates are higher in patients with good bowel cleanliness(66, 67) and poor bowel preparation is responsible for many incomplete colonoscopies.(2) The importance of bowel cleanliness is recognised in the National Health Service BCSP Quality Assurance Guidelines(19) and the European Society of Gastrointestinal Endoscopy quality in screening colonoscopy position statement(21), both of which have set the standard that 90% of colonoscopies should have bowel cleanliness rated as adequate or better. Although adequate in this context refers to the examination not needing to be repeated, the threshold for this is likely to vary between endoscopists. The U.S. Multi-society Task Force on Colorectal Cancer are somewhat more precise in their definition of adequacy, stating that 'an adequate examination is one that allows confidence that mass lesions other than small (≤5 mm) polyps were generally not obscured by the preparation'(165).

With respect to bowel cleanliness, patients taking Kleanprep® in the present study were more likely than patients taking Moviprep® to have cleanliness rated as good or excellent. However, this only reached statistical significance in the right colon during examinations scheduled in the morning (9/60 vs. 19/60, p=0.04). Previous comparisons of efficacy between Moviprep® and standard volume PEG solutions have reported conflicting results. Corporaal et al also found that patients taking Kleanprep® were more likely to have bowel cleanliness rated as good(82) and that the differences were most apparent in the right colon during morning colonoscopies. Valiante et al, on the other hand, found Moviprep® resulted in adequate bowel cleanliness more often than a standard volume PEG solution (75% vs. 85%, p=0.04).

Perhaps the most striking finding in the present study was that patients scheduled for an afternoon colonoscopy had better bowel cleanliness than those scheduled for a morning colonoscopy. This difference was apparent in all colonic segments and is likely to be due to variation in the dosing schedule. Taking bowel preparation over two days, referred to as a split dosing, shortens the interval between completion of bowel preparation and colonoscopy as compared to evening before dosing.

Many studies suggest this interval is an important determinant of bowel cleanliness. Marmo et al, for example, compared Moviprep® with a standard volume PEG solution during morning and afternoon colonoscopies and found that both sets of patients were more likely to have better bowel cleanliness when the preparation was administered as a split dose prior to an afternoon colonoscopy. Seo et al reported an observational study which found that an interval of 3-5 hours between completion of PEG bowel preparations and colonoscopy resulted in the best quality bowel cleanliness, with the right colon being most sensitive to time differences(97). The present study also found that the influence of dosing schedule was most marked in the right colon, particularly in patients taking Moviprep®. Cleanliness of the right colon is believed to deteriorate when there is a prolonged interval between preparation and colonoscopy due to ongoing small bowel and biliary secretions. This is important given that many right sided polyps are flat and can be subtle in appearance(45).

In the present study patients attending for morning colonoscopy took their bowel preparation on the evening before colonoscopy, which is common practice in the UK. However, there is growing awareness about the detrimental effect of a prolonged time between the consumption of bowel preparation and the performance of the colonoscopy(166). It has been suggested that reducing this interval, by waking early to take bowel preparation prior to a morning colonoscopy may improve bowel cleanliness. A recent US survey reported that 85% of patients would be willing to wake early to take their bowel preparation(167), but, early morning dosing is not commonly practised in the UK and its acceptability is uncertain. It has also been proposed that administering loperamide, after consumption of bowel preparation, could prevent the deterioration of bowel cleanliness in the right colon associated with a prolonged interval between its consumption and colonoscopy (168). These strategies are worthy of further study.

In the present study, patients found the taste of Kleanprep® less acceptable than the taste of Moviprep®. Surprisingly, there were no differences in how patients rated the acceptability of volume

with each preparation, although such differences may be more apparent in a cross-over study. Some previous studies have reported that taste (83, 84, 87) and overall experience (83, 86) are more acceptable with Moviprep®, whilst others have found no differences.(82)

Dosing schedule also influences the acceptability of bowel preparation, such that patients taking Kleanprep® were more likely to rate the volume of the preparation as unacceptable when scheduled for a morning colonoscopy. A recent meta-analysis of studies comparing single and split dose PEG schedules also found that dosing schedule influenced patient experience, with patients given a split dose regimen being more likely to have greater adherence and suffer less nausea(95).

Only a small proportion of patients reported significant side effects following the two bowel preparations. Previous studies have also found that side effects are infrequent with PEG preparations, although Ell et al reported that patients taking a standard volume PEG solution were more likely than patients taking Moviprep® to suffer nausea and abdominal pain (83).

Adherence to both bowel preparation regimens was generally good, but complete adherence was higher with Moviprep® than Kleanprep® (97% vs. 87%). Previous studies have reported that between 87% - 97.2% and 80.8% - 98.6% of patients had full adherence to Moviprep® and standard volume PEG solutions respectively (82-87), with most of the studies finding better adherence to Moviprep®. We found no difference in willingness to repeat bowel preparations between PEG solutions, although previous studies have reported a higher willingness among patients using Moviprep (83, 85, 86).

The relationship between patient experience and adherence is complex and variable, particularly as some of the difficulty in consuming any bowel preparation can be overcome through appropriate counselling (89, 169). Our current results suggest that patient experience is better with Moviprep® and this translates into better adherence.

This study has a number of limitations. The study design is open and observational such that the results are susceptible to investigator bias. However, this was a multi-operator, multi-site study assessing consecutive patients during screening colonoscopy. Furthermore this study observed 'real-life practice' and the results should therefore be generalisable to other screening centres. Whether these results are applicable to a symptomatic population is uncertain. In addition, the scale used to assess patient experience with bowel preparation is un-validated, although it does have face validity and the findings are in keeping with the results of previous studies (83, 84, 87). Finally, this study could be criticised for not being formally powered since it was undertaken as a service evaluation and for simplicity we used a 1-month period for each bowel preparation (date assessed in clinic).

We used the Ottawa scale to assess bowel cleanliness as this includes an assessment of the amount of cleansing required to make the views adequate. We also presented the proportion of patients with bowel cleanliness rated as good or better and fair or better and it should be noted that the only significant difference was found on subgroup analysis of patients achieving cleanliness of good or better. The clinical relevance of having an increased proportion with good rather than fair bowel cleanliness may be debated. However, a recent study of adenoma detection and screening intervals performed within 3 years of an initial colonoscopy where cleanliness was rated as fair reported an adenoma detection rate of 28% during the follow up colonoscopy.(170) In addition, when bowel cleanliness was rated as fair, surveillance colonoscopies were frequently performed earlier than guidelines recommend. Given the high prevalence of polyps in a FOB positive screening population(129), and growing awareness of the importance of flat and subtle lesions(171), we believe that high quality bowel cleanliness should always be the goal. Furthermore, improved bowel cleanliness increases the efficiency of colonoscopy as less time spent remedying imperfect bowel preparation allows more time for mucosal visualisation.

**6.6 Conclusion**

There appears to be a trade-off between bowel cleanliness and patients experience when choosing between standard and low volume PEG solutions. A split dosing schedule was more likely to result in

good bowel cleanliness than a single dosing schedule with both standard and low volume PEG

solutions. Differences in the efficacy of standard and low volume PEG solutions were limited to the

right colon in patients undergoing morning examinations.

Appendix 1

Patients receiving Kleanprep® who were scheduled for colonoscopy in the morning were asked to stop eating at 2 pm on the day before colonoscopy and were instructed to take the first 2 litres of bowel preparation from 4pm at a rate of 250ml every 15 minutes, followed by the second 2 litres from 7pm. Patients receiving Kleanprep® scheduled for colonoscopy in the afternoon were asked to stop eating from 4 pm the day before colonoscopy. They were instructed to take the first 2 litres of bowel preparation from 6pm at a rate of 250ml every 15 minutes, followed by the second 2 litres from 8am on the morning of colonoscopy.

Patients receiving Moviprep® scheduled for a colonoscopy in the morning were asked to stop eating at 9am on the day before colonoscopy. Patients were instructed to take the first litre of Moviprep® at 5pm, over 1-2 hours and the second litre at 8-9pm. Patients were also asked to consume a further 500ml of clear fluid for every litre of litre of Moviprep® taken. Patients receiving Moviprep® scheduled for a colonoscopy in the afternoon were asked to stop eating from 1pm on the day before colonoscopy and were instructed to take the first litre of Moviprep® from 7pm over 1-2 hours followed by the second litre of Moviprep® from 6am on the day of colonoscopy. Patients were also asked to consume an additional 500ml of clear fluid with every litre of Moviprep® consumed.

Appendix 2

The Ottawa scale is a validated scale which assesses bowel cleanliness in the right colon, mid colon and recto-sigmoid on a 5 point scale according to the following descriptors: Excellent (0) (*mucosal detail clearly visible. If fluid is present it is clear. Almost no stool residue)*, Good (1) (*Some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary*), Fair (2) *(Turbid fluid or residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary)*, Poor (3) *(Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained)*, or Inadequate (4) (*Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning).* In addition a global rating is given for the amount of residual fluid as either: small, moderate or large.

**Chapter 7 - A randomised control study comparing two patient positioning strategies during colonoscope withdrawal.**

## 7.1 Summary

**Background**

It has been suggested that changing patient position during colonoscope withdrawal increases adenoma detection. The results of previous studies have been conflicting. This study evaluated whether routine position change, during colonoscope withdrawal, improves polyp detection.

**Methods**

130 patients attending for diagnostic colonoscopy had colonic segments examined twice. Patients were randomised in a 1:1 ratio to having their right, transverse and left (splenic and descending) colon examined in the supine position followed by position change (right colon in the left lateral position, the transverse colon in the supine position and the left colon in the right lateral position) or vice versa . The primary outcome measure was the proportion of patients with ≥1 polyp in each colonic segment. Secondary outcome measures included the number and proportion of patients with ≥1 adenoma in each segment and adequacy of luminal distension (1= total collapse and 5= no collapse).

**Results**

Examination of the right colon in the left lateral position significantly improved polyp detection (26.2% vs. 17.7%, p=0.01) and luminal distension (mean = 4.0 vs.3.5, p<0.0001). Position change did not improve polyp detection in the left colon (5.4% vs. 4.6%, p=0.99) There was no significant correlation between luminal distension and polyp detection in the right colon (r=0.03).

**Conclusion**

Examining the right colon in the left lateral position increased polyp detection compared to the supine position. Polyp detection in the left colon was similar in the right lateral and supine positions.

Publications arising

Ball AJ, Johal SS, Riley SA. Position change during colonoscope withdrawal increases polyp and adenoma detection in the right but not in the left side of the colon: results of a randomized controlled trial. Gastrointest Endosc. 2015; 82(3):488-94

## 7.2 Background

CRC associated mortality is significantly reduced by the colonoscopic removal of polyps.(39, 172) However, not all polyps are identified during colonoscopy and miss rates of 17-28% have been reported.(45, 46, 173, 174) This is important since the risk of interval CRC following colonoscopy is inversely associated with the adenoma detection rate (ADR) of the colonoscopist.(26, 27)

The factors that determine polyp detection are complex but colonoscope withdrawal time, inspection behind colonic folds, adequate luminal distension and cleaning of residual debris have been highlighted as important determinants.(57, 58) In addition, it has been suggested that changing the position of the patient during colonoscope withdrawal may improve polyp detection.

Traditionally, following insertion of the colonoscope, the instrument was most often withdrawn and the colon examined with patients in a single position (usually left lateral or supine). However, positioning patients such that the colonic segment being examined is uppermost in the abdomen (right colon in the left lateral position, the transverse whilst supine and the splenic flexure and descending colon in the right lateral position) improves luminal distension and may increase polyp detection. The merits of this strategy have been assessed in several recent studies but the results are conflicting. (63, 64, 175, 176)

East et al were the first to report that position change improved polyp detection but the benefit was only apparent in the transverse colon.(64) Similar results were reported by Köksal et al,(175) but the largest and most recent study has reported negative results.(176) Given these conflicting results the benefits of position change during colonoscope withdrawal were re-examined.

## 7.3 Methods

Patients eligible for this study were those attending the Northern General Hospital for diagnostic colonoscopies on lists performed by four experienced endoscopists. Patients were given a participant information sheet (PIS), either at the time of booking their colonoscopy or through the post.

Exclusion criteria were patients age <40 or >80, patients with a known polyposis syndrome, colitis and patients who feel their mobility would limit their ability to turn. The age exclusion was used to avoid recruiting young patients with too few polyps (177, 178) and elderly patients in whom small polyps are less important. Patients with a polyposis syndrome were excluded as these patients are likely to have polyps in all positions regardless of views while patients with UC were excluded as many of these patients are examined with chromoendoscopy.

Patients were excluded if caecal intubation took longer than 20 minutes on the presumption that each repeat intubation would be more uncomfortable and take an unacceptably long period of time.

**Study procedure**

Each of the four colon segments: right colon, transverse colon, descending colon and sigmoid colon, were examined and then re-examined with the patient in the alternative position. Therefore, it was necessary to standardise the place where each segment starts and ends.

During colonoscope insertion the sigmoid-descending junction, splenic flexure and hepatic flexure were marked with a double pinch biopsy based on their endoscopic and Scopeguide appearances (figure 9). The positions of these flexures are usually obvious during colonoscope insertion, due to the formation of acute angles in the colonoscope, which are less prominent during colonoscope withdrawal. Standardising the start and end positions of each colon segment avoids researcher bias when deciding which segment polyps arise from, particularly if they are close to flexures. It is uncertain whether this method is better than using standard measurements. A Scopeguide was used for each examination as it improves assessment of tip location(179).
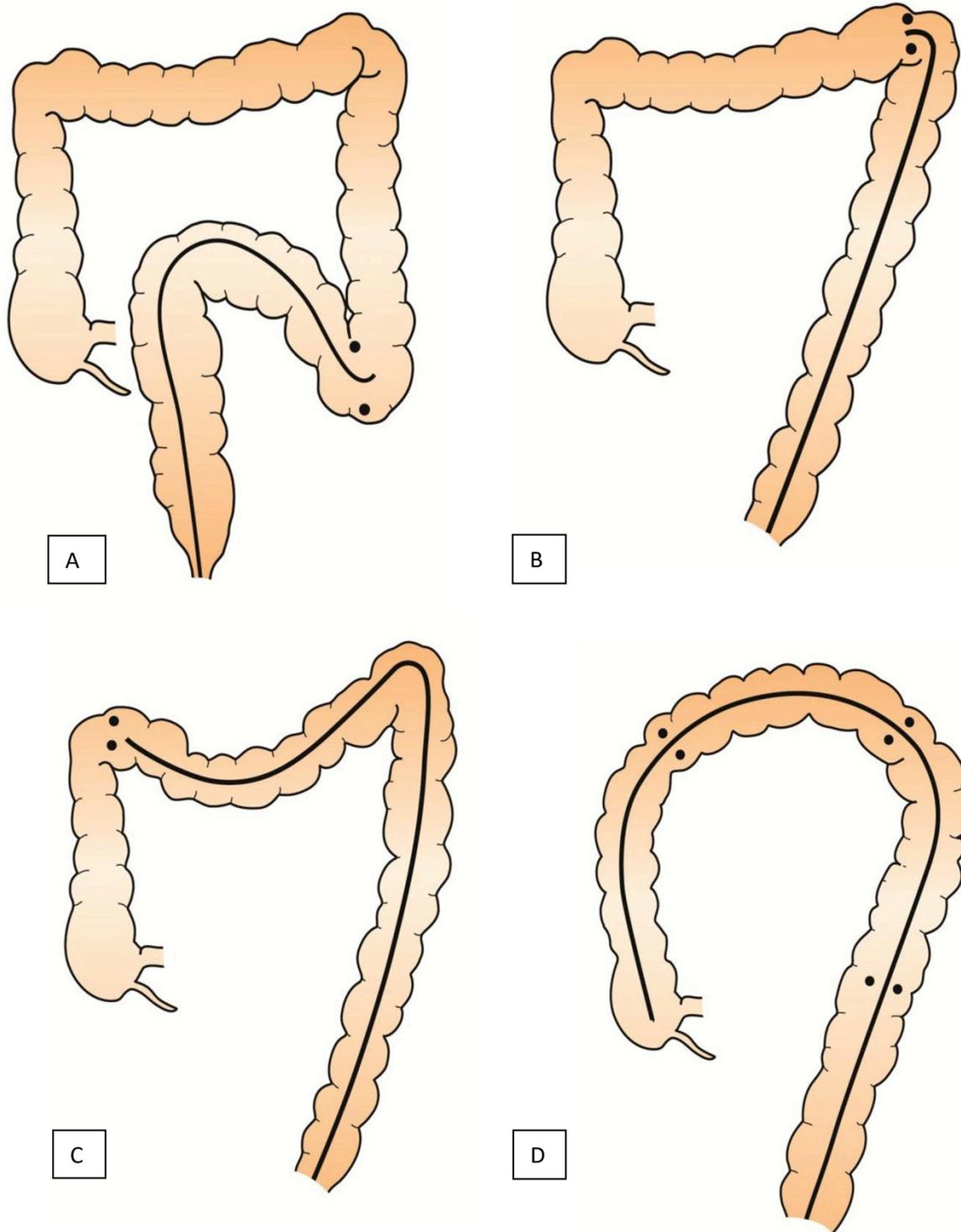
**Figure 9 -** Characteristic configurations of the Scopeguide image (solid line) during insertion (images A, B and C) facilitated the placement of pairs of mucosal pinch biopsies to define colonic segments during colonoscope withdrawal (image D)

Polyps seen during colonoscope insertion were marked or removed in keeping with BSG guidelines.(180) This minimises the risk of missed polyps during colonoscope withdrawal.

Colonoscope insertion was performed in the endoscopists usual manner, such that the patient's position was changed, Buscopan administered, abdominal pressure applied and the scope stiffness was adjusted as required.

When caecal intubation was achieved in less than 20 minutes a sealed opaque envelope was opened to reveal the randomisation strategy: Supine then Dynamic or Dynamic the supine.

Patients were given 20 milligrams of hyoscine butylbromide after caecal intubation was confirmed. Further doses were given at the discretion of the endoscopist.

**Recording Equipment**

The images from each colonoscopy were recorded, via an analogue to digital converter, onto a Mac computer using I Video™. All images were anonymised such that they only included the participants study number. Images were recorded in order to further validate the scale assessing distension ratings for each withdrawal strategy

**Examination of colonic segments**

Caecal intubation was confirmed though identification of at least two of the three caecal landmarks; Ileocaecal valve, appendiceal orifice or triradiate fold. The colon was examined in four segments (right colon - caecum to hepatic flexure, transverse colon, left colon - splenic flexure and descending colon and sigmoid colon) The randomisation sequence informed the endoscopist whether to perform the initial withdrawal in each segment in either the supine or dynamic positions. The same segment was then re-intubated in order that a second withdrawal could be performed in the alternative position i.e. dynamic then supine or supine then dynamic. Dynamic positions were as follows; left lateral when examining caecum to hepatic flexure, supine when examining the

transverse colon, right lateral when examining the splenic flexure to sigmoid-descending junction and prone when examining the sigmoid-descending junction to rectum.

No previous study has compared withdrawal strategies in the sigmoid colon. Since sigmoid re-intubation may cause patient discomfort. Therefore, the endoscopist monitored patient discomfort and offered additional analgesia and the option to withdraw from the study if significant discomfort were caused (as was the case for all segments). The alternative position in the sigmoid colon was prone. Examining in a diametrically opposed position is most likely to determine if there is a difference between these withdrawal strategies.

During withdrawal the endoscopist inflated each section of colon with $CO_2$/air. This was standardised by insufflating air until further insufflation no longer improved luminal distension or caused discomfort.

Each endoscopist was asked to take a minimum of 120 seconds to examine each of the 4 segments to help ensure that a thorough examination had been performed.

Polyps identified during insertion were categorised separately from polyps seen during withdrawal. Polyps seen during withdrawal were removed only after performing the second withdrawal in order that the withdrawal positions could be directly compared.

**Primary outcome measures**

The primary outcome measure for this study was the presence or absence of polyps in each colonic segment. Withdrawal strategies were compared by assessing the proportion of patients with polyps in each segment.

**Secondary outcome measures**

Luminal distension was scored using a validated 5 point scale as previously described by East(63). Scores for luminal distension were based on average luminal distension. We rated average rather than peak distension as this was believed this was most reflective of overall mucosal visualisation.

Patient and procedural characteristics were compared between groups including: bowel cleanliness, age, gender, indication for procedure, intravenous sedation, analgesia received and caecal intubation time. Bowel preparation was rated following the procedure with the Boston Bowel Preparation Scale (BBPS) (70, 72).

**Power calculation**

It was determined that 130 patients were required to detect a 50% increase in the proportion of patients with polyps assuming a baseline of 10% detection in each colonic segment at a power of 80% and a 2 sided for a significance level of 5%. This study used the same assumptions as used by East et al(64).

**Statistical analysis**

The proportion of patients with ≥1 polyps, in each colonic segment, with each withdrawal strategy was compared using the Prescott test. The Prescott test takes account of the period effect resulting from it being a cross over study.

Luminal distension ratings and the total number of polyps were compared with the Wilcoxson signed rank test.

**Study reviews and approvals**

This study underwent independent scientific review in December 2011. The South Yorkshire Research Ethics Committee (REC) and the STH R & D department approved the study in February 2012.

STH code: STH16220

The study was registered on clinicaltrials.gov (NCT01554098)

A non-substantive amendment was made in March 2012, which allowed the Participant Information Sheet (PIS) to be sent though the post. This was done in response to slow recruitment as a consequence of patients not receiving PIS.

**7.4 Results**

198 patients were screened for study inclusion. 67 were excluded, most commonly due to patient preference and insertion time over 20 minutes. One patient was withdrawn due to difficulty reinserting in the right colon leaving 130 patients for analysis (figure 10). The procedural characteristics and medication use did not significantly differ between the study groups, although more males and fewer patients referred for investigation of anaemia were randomized to an initial examination with position change (table 23).

During insertion of the colonoscope polyps were found in 23 of 130 (17.7%) patients and 18 (13.8%) had adenomas. The mean (SD, range) size of these polyps was 7mm (8, 2-45mm). These polyps were excluded from the subsequent analysis.

The overall number of patients with ≥1 polyp in the right, transverse and left colon was higher during colonoscope withdrawal with position change than in the supine position (47/130 (36.2%) vs. 38/130 (29.2%), odds ratio (OR) = 1.4, p=0.04). However, the difference in adenoma detection was not significant (39/130 (30%) vs. 33/130 (25.4%), OR = 1.3, p=0.11). The number of polyps per patient was also greater with position changes (mean (SD) = 0.54 (0.8) vs. 0.45 (0.8), $p$=0.02) as was the number of adenomas but the latter did not reach statistical significance (mean (SD) = 0.44 (0.8) vs. 0.38 (0.7), $p$=0.11).

Examining the right colon in the left lateral rather than supine position significantly increased the proportion of patients with ≥1 polyp and ≥1 adenoma (34/130(26.2%) vs. 23/130(17.7%), OR = 1.6, p=0.009 and 30/130(23.1%) vs. 21/130(16.2%), OR=1.6, p=0.025 respectively). The number of polyps and adenomas per patient in the right colon was also greater during withdrawal in the left lateral position (mean (SD) = 0.24 (0.6) vs. 0.32 (0.6), $p$=0.008 and 0.22 (0.6) vs. 0.29 (0.6), $p$=0.02 respectively).

Examining the left colon in the right lateral position did not significantly increase the proportion of patients with ≥1 polyp(s) and ≥1 adenoma(s) compared with the supine position (7/130(5.4%) vs.

6/130(4.6%), OR=1.2, p=0.99 and 4/130 (3.1) vs. 4/130 (3.1), OR= 1.0, p=0.66 respectively).

Furthermore, there was no significant increase in the number of polyps and adenomas per patient in

the descending colon (mean (SD) = 0.05 (0.3) vs. 0.05 (0.2), $p=0$.65 and 0.03 (0.2) vs. 0.03 (0.2),

p=1.00 respectively).
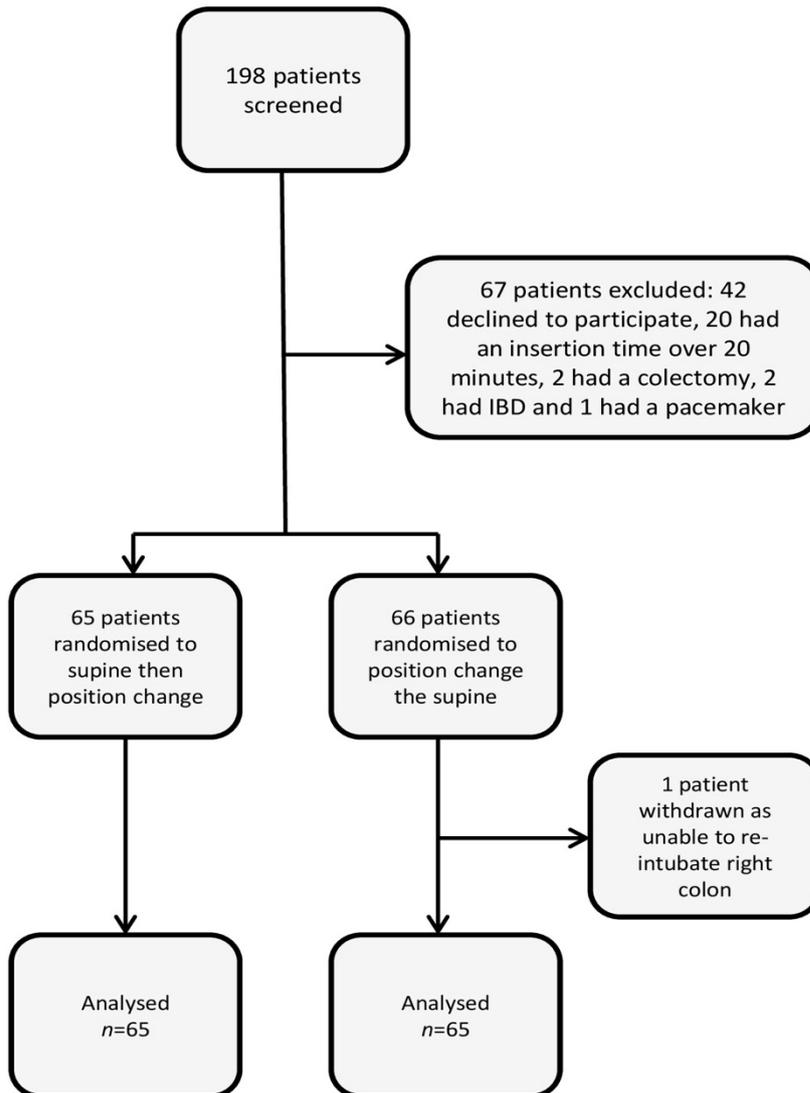


**Figure 10 - Patient flow diagram**

|  | Withdrawal order | | *p* value |
| --- | --- | --- | --- |
|  | Position change then supine | Supine then position change |  |
| Polyps identified during colonoscope insertion, n (%) | 11 (16.9) | 12 (18.4) | 0.81 |
| Caecal intubation time, minutes<br><br>mean ±SD | 11.5 (3.5) | 11.7 (4.1) | 0.72 |
| Hyoscine butylbromide used<br><br>n (%) | 64 (98.4) | 65 (100) | 1.0 |
| Bowel cleanliness rating<br><br>mean ±SD | 5.6 ±1.1 | 5.8 ±1.1 | 0.42 |
| Intravenous sedation or analgesia used<br><br>n (%) | 15 (23.1) | 12 (18.5) | 0.51 |
| Entonox used<br><br>n (%) | 50 (77.9) | 51 (78.4) | 0.83 |
| Procedural indication, n (%) |  |  |  |
| Change in bowel habit | 34 (52.3) | 32 (49.2) | 0.86 |
| Anaemia | 7 (10.8) | 18 (27.7) | 0.02 |
| Polyp surveillance | 10 (15.4) | 6 (9.2) | 0.42 |
| Rectal bleeding | 9(13.8) | 6 (9.2) | 0.58 |
| Family history | 2 (3.1) | 3 (4.6) | 1.0 |
| Abdominal pain | 3(4.6) | 0 (0) | 0.24 |

**Table 23 - Patient and procedural characteristics and medication use**

There were no significant differences in the proportion of patients with ≥1 polyp or ≥1 adenoma during the first and second withdrawal through the transverse colon in the supine position (14(10.8%) vs. 16(12.3%), OR = 1.2, p=0.69 and 12(9.2) vs. 14(10.8), OR = 1.2, p=0.69) or the number of polyps and adenomas per patient (mean (SD) 0.12 (0.4) vs. 0.15 (0.4), *p*=0.21 and 0.11 (0.4) vs. 0.12 (0.4), *p*=0.79 respectively).

The mean (range) size of polyps found during colonoscope withdrawal was 3mm (1-8mm). There was one polyp over 5mm that was found in the ascending colon in the left lateral but not in the supine position (8mm). Polyps were predominantly sessile (Is) morphology (81%) with the remainder being Paris IIa (18%) and Isp (1%).

An increase in luminal distension was seen in the right colon in the left lateral position and in the left colon in the right lateral position. (Table 24) Luminal distension was more likely to be rated as adequate (ratings of 4 and 5) using the position change strategy in the right (76% vs. 46%, p<0.0001) and left colon (92% vs. 58%, p<0.0001). Fewer patients had luminal distension rated as inadequate (ratings of 1 and 2) during colonoscope withdrawal in the right lateral position in the left colon (6% vs. 0%, p=0.007) and there was a similar trend in the left lateral position in right colon (5% vs. 1%, p=0.06).There was substantial agreement between the luminal distension ratings of the colonoscopists (weighted kappa = 0.70).(181)

There were no significant correlations between luminal distension and the number of polyps in the right colon (r=0.03, p=0.69), the transverse colon (r=-0.05, p=0.47) or the left colon (r=-0.05, p=0.54).

Using the position change strategy rather the supine withdrawal position would have resulted in a change to the recommended surveillance interval in 10 patients. In four patients who wouldn't have undergone a further examination, a 5-year surveillance examination would have been recommended. In three patients earlier surveillance examinations would have been recommended (2 patients having a 3 rather than 5 year surveillance examination and 1 patient having a 1 rather than 3 year surveillance examination). Two patients would be having a later examination (5 years

instead of 3 years) and surveillance would not have been indicated in one patient for whom a 5 year surveillance examination was recommended.

| Colonic segment | Mean (±SD) luminal distension scores with each withdrawal strategy | | $p$ value |
|---|---|---|---|
| Right colon | Supine | Left lateral | <0.0001 |
| | 3.5 (±0.8) | 4.0 (±0.7) | |
| Transverse colon | 1st withdrawal | 2nd withdrawal | 0.06 |
| | 4.0 (±0.8) | 4.1 (±0.7) | |
| Left colon | Supine | Right lateral | <0.0001 |
| | 3.6 (±0.8) | 4.4 (±0.6) | |

**Table 24 - Luminal distension in the right, transverse and left colon (1 = collapsed, 5 = maximal distension).**

**7.5 Discussion**

Modifying a patient's position is accompanied by the intra-abdominal movement of the colon and the intraluminal movement of fluid and gas. Radiologists have used these changes to optimise views during barium examinations for decades and it has been suggested that adjusting the patient position, to bring colonic segments uppermost within the abdomen, improves luminal distension and therefore lesion detection during colonoscope withdrawal.

However, practice among endoscopists varies with some colonoscopists examining the colon with the patient in one fixed position (often left lateral or supine) whereas others use position change routinely during colonoscope withdrawal.(65) These differences may relate to the inconvenience associated with moving patients or uncertainty regarding its benefit. However, studies have repeatedly found that examining the transverse colon in the supine position increases polyp detection.(64, 175) We therefore chose to compare withdrawal through the right colon in the left lateral position, through the transverse colon in the supine position and the left colon in the right lateral position with withdrawal through the whole colon in the supine position.

In the present study, examining the right colon in the left lateral position increased polyp and adenoma detection. Data regarding the optimal position to examine the right colon was hitherto lacking. Strategies to improve polyp detection in the right colon may be of particular value given that colonoscopy is reported to offer less protection against right-sided CRC.(39, 182) There was no significant correlation between luminal distension and polyp detection, which is perhaps unsurprising, since improved visualisation does not guarantee identification of additional polyps and many polyps are visible regardless of luminal distension. It should also be stressed that although East et al reported a positive correlation between luminal distension and polyp detection, the strength of this correlation may be considered negligible ($r=0.11$, $p<0.01$). Despite the lack of correlations between luminal distension and polyp detection we still feel that adequate luminal distension aids in the detection of polyps and should be a goal of colonoscope withdrawal. Furthermore, despite the benefits associated with the use of the left lateral position in the right colon, alternative positions

should be considered whenever views remain suboptimal. The caecum, for example, may be situated medially and in such patients the right lateral position may be advantageous.

In the present study a second examination of the transverse colon did not significantly increase the detection of adenomas or polyps. This may suggest that there is little benefit to a second examination in the same patient position, particularly when there are adequate views during the initial examination.

We found no increase in polyp or adenoma detection by examining the left colon (splenic flexure and descending colon) in the right lateral rather than the supine position. East et al reported that examining patients in the right lateral rather than left lateral position increased polyp (16% vs. 25%, p=0.05) but not adenoma detection (12% vs. 15%, p=0.64) whereas Köksal et al found no differences in adenoma and polyp detection. The lack of difference in polyp detection in the left colon may well relate to the low prevalence of polyps within this colonic segment.

The methodology used in the present study was quite different to that employed by Köksal et al and Ou et al, and this limits the extent to which these studies may be directly compared. Köksal et al also employed a two-way cross over design whereby colonic segments were initially examined in the left lateral position followed by position change or vice versa. Unlike the present study however, the position change strategy in the left colon included both the supine and right lateral positions. Furthermore, the study compared adenoma detection during withdrawal in the left lateral position alone versus adenoma detection in the left lateral position and position change combined. This is an important methodological difference since studies of back-to-back colonoscopies have consistently reported that a repeat examination, regardless of patient position, leads to an increase in polyp detection.(45, 46, 173, 174) It is therefore uncertain whether the additional polyps detected by Köksal et al occurred as a consequence of the repeat examination(s) or the change in patient position. Furthermore, they failed to take account of the 'period effect' whereby the findings of the

first withdrawal may pre-alert endoscopists to the same findings during the second examination.

(183)

Ou et al, on the other hand, employed a parallel group design that compared prescribed position change against 'usual practice', and reported no overall differences in adenoma (40.7% vs. 37.9%, p=0.28) or polyp detection (58.2% vs. 56.5%, p = 0.93). It should be noted, however, that approximately half of the patients randomized to 'usual practice' had their right colon examined in the left lateral position and around half the patients had their transverse colon examined in the supine position, thereby minimising the possible benefit of position change.

In the present study, luminal distension in the supine position was rated adequate in approximately half of the withdrawals in the right and left colon. On the assumption that the increase in polyp detection was a consequence of improved luminal distension, this would suggest that the supine position is frequently an adequate strategy. Furthermore, although position change increases the probability of adequate distension, ratings were less than adequate in 24%. This may be a consequence of the colonic muscle tone, which is not always overcome by hyoscine butylbromide administration, or variations in colonic anatomy. In these circumstances colonoscopists should take additional time and care to maximise mucosal visualisation.

It should be noted that the additional polyps and adenomas detected following position change were mostly diminutive and therefore of debatable clinical significance. Regardless of size, however, ADR is a well-established measure of colonoscopy quality since it inversely associates with post colonoscopy cancer risk. Furthermore, the increase in adenoma detection would have translated into a change in management with regards to the number and timing of surveillance examinations. The small size of the additional polyps detected may simply reflect the typical size distribution of colonic polyps and it is likely that a larger study would be required to determine whether position change also increases detection of larger polyps during colonoscope withdrawal.

As with most studies of colonoscopy technique, an open study design was employed, which is susceptible to unintentional researcher bias. This study may also be criticised for excluding the polyps found during colonoscope insertion, although we believe this makes for a fairer and more appropriate comparison of an intervention performed during colonoscope withdrawal. We also believe that polyps seen during colonoscope insertion are more likely to be larger and in 'easy to see places' and therefore easily detectable with either withdrawal strategy. A further limitation relates to patient positioning during colonoscope insertion, which was not standardised. Colonoscopists used position change as required to facilitate colonoscope insertion, which may have caused bias, although the numbers of polyps found during insertion was similar with each strategy.

The study was undertaken by four operators and performed on patients undergoing colonoscopy for assessment of symptoms and those attending for polyp surveillance. The study did not include patients attending for bowel cancer screening. Despite this selection bias, we feel the results remain generalizable, since the size and location of polyps were reflective of the wider population. A further strength of the present study related to the use of marker biopsies to define the start and end point of each examination, which avoided researcher bias with regards to designating the position of polyps, particularly those near flexures.

Although we initially planned to compare polyp detection in different patient positions whilst withdrawing through the sigmoid colon, some patients had discomfort during re-intubation and were therefore not examined twice. In addition, some polyps were identified in areas of the sigmoid colon that were considered easy to miss during a second examination and consequently removed during the first withdrawal.  Data regarding the sigmoid colon were therefore not appropriate for analysis due to the biases introduced. The only study to compare withdrawal positions in the sigmoid colon was performed by Köksal et al, who reported that examination of the sigmoid colon in the supine, right lateral and left lateral position increased polyp detection compared to the left lateral position. As noted above it is not possible to state whether this increase was due to the

repeat examination or the change in position. The variation in sigmoid colon anatomy is such that

the ideal position may vary between patients and at present, we would suggest colonoscopists

should use position change in the sigmoid colon if luminal distension is poor and views are

suboptimal.

**7.6 Conclusion**

Examining the right colon in the left lateral position during colonoscope withdrawal is associated with increased luminal distension and greater polyp and adenoma detection. This is complementary to previous studies, which report that the optimal position to examine the transverse colon is the supine position. Position change appears to be less critical in the left colon but is recommended when views are suboptimal. Position change during colonoscope withdrawal should be routine in endoscopic practice.

**Chapter 8 Summary of key findings, recommendations for future research and conclusions**

**8.1 Summary of key findings**

- Medication use and patient comfort during screening colonoscopy

    o Significant discomfort occurred during 8.9% of examinations

    o There was wide variation in the occurrence of significant discomfort between colonoscopists. (0.8-23.9%)

    o Medication practice varied widely between colonoscopists.

    o There was no apparent relationship between screening colonoscopists' medication practice and patient comfort.

    o The use of the comfort scale appears to differ between SSPs.

- National survey assessing the Entonox use among screening colonoscopists

    o Entonox was available to three-quarters of English screening colonoscopists.

    o Most colonoscopists have positive perceptions regarding the usefulness and efficacy of Entonox but views vary widely.

    o Most colonoscopists advise patients to use Entonox as required

    o The use of Entonox in combination with intravenous medications varies widely.

    o Few colonoscopists use Entonox on a regular basis.

- Continuous versus as required Entonox use during screening colonoscopy: results of a randomised controlled trial

    o There was no significant difference the efficacy of 'continuous' and 'as required' administration of Entonox.

- Continuous Entonox administration was associated with more side effects but these were usually minor.

- Patients with high anxiety levels (HADS ≥8) anticipated and experienced more pain during colonoscopy

- A comparison of a low and standard volume PEG solution during screening colonoscopy: results of a service evaluation

  - Standard volume PEG solution was more likely to result in good bowel cleanliness in the right colon but this was significant only during morning examinations.

  - The use of a split rather than a single dosing bowel preparation regimen was associated with improved bowel cleanliness.

  - There was greater adherence to the low volume PEG solution

- Position change during colonoscope withdrawal: results of a randomised cross over trial.

  - Routinely examining the right colon in the left lateral position, rather than supine position, significantly increased polyp and adenoma detection.

Colonoscopy is widely used for the assessment of colonic symptoms and screening for CRC. The quality of colonoscopy is dependent on many factors and seems to vary between colonoscopists. This thesis has examined important measures of colonoscopy quality and assessed simple methods for its improvement.

Patient comfort was found to vary widely between colonoscopists within the English BCSP but there was no apparent relationship with medication use. This adds weight to the argument that other factors, such as endoscopic technique, are more important determinants of patient comfort than medication use. This study also suggested that the measurement of patient comfort during colonoscopy is unreliable and highlights a need for the introduction of validated comfort rating scales. With such a tool, it would be possible to compare the performance of colonoscopists and set a standard of care.

The reasons for the low usage of Entonox during colonoscopy were uncertain. Perceptions towards Entonox use among BCSP colonoscopists were generally positive although opinion varied widely. Entonox was often perceived to be less efficacious than the intravenous alternatives and used in patients expected to have minimal discomfort. Therefore, its low utilisation may relate to perceptions regarding its limited efficacy. Differences in how patients were instructed to use Entonox were found between colonoscopists but most use it 'as required'. This data may have prompted endoscopists to reflect on the role of Entonox in their own practice, including how it is selected and its method of use, but the reasons for its low utilisation remain unclear.

The method of Entonox use differed between previous studies and in clinical practice. The relevance of this was examined by comparing 'continuous' and 'as required' Entonox administration during screening colonoscopy. The method of administration made no significant difference to efficacy, although continuous use was more likely to associate with light-headedness. The outcomes from this study may prompt the colonoscopists who advise continuous Entonox use to revise their practice. A significant proportion of patients randomised to 'as required' use did not require any medication

and most patients had low pain ratings. This would suggest that medication-free and Entonox only colonoscopy may be a feasible strategy for many patients.

Effective bowel cleansing facilitates good mucosal visualisation but the optimal bowel cleansing agent is uncertain. A low and standard volume PEG solution were compared. Major differences in the bowel cleanliness of standard volume and low volume PEG solutions were found between patients scheduled for morning and afternoon examinations. Dosing schedule is a well recognised determinant of bowel cleansing efficacy but previous studies have not examined the low volume PEG solutions. The standard volume PEG solution was more likely to result in good or excellent bowel cleanliness, but only in an individual segment in patients attending for a morning examination. In keeping with previous studies, we found that patient experience and compliance were better with the low volume PEG solution. The major limitation of this study was its open study design and the lack of randomisation, which limits the extent to which the finding can be generalised.

The left lateral position, rather than the supine position, was found to significantly increase polyp and adenoma detection in the right colon. The data from this study augments the previous literature concerning position change during colonoscope withdrawal. Position change is a simple, cost neutral, intervention that could be employed by all endoscopists. This data may help convince those colonoscopists who are sceptical of its value to increase their use of position change, particularly when luminal distension is suboptimal.

The extent to which the studies presented within this thesis will change clinical practice remains uncertain. However, improvements in the quality of colonoscopy occurred during the period between the two English national endoscopy audits.(2, 18) The factors that brought about the improvements are uncertain but may relate to the £8.2 million government investment and the creation of National and Regional Endoscopy Training Centres.(184) These centres delivered endoscopy courses designed to give hands on experience, teach good techniques and safe practice,

suggesting that colonoscopy practice is amenable to change. Improvements may also have been due to increased awareness of deficiencies in the quality of colonoscopy and the setting of minimum standards of care and regular audit. Setting standards and comparing personal performance with that of colleagues is a well recognised motivator for change.(185) Regardless, the endoscopic community appear willing and capable of improving practice, particularly when there is an evidence base to support change.

## 8.2 Recommendations for future research

The studies presented within this thesis add to the current body of literature on colonoscopy quality but like most research pose many further research questions. The following areas are particularly worthy of further study.

It is clear from the work presented here that most colonoscopists in the English BCSP administer a combination of intravenous sedation and analgesia during most colonoscopy examinations. However, the wide variation in practice would suggest that the determinants of medication use vary between colonoscopists. Few studies have examined patients' and endoscopists' priorities with regards to medication use and comfort. Whilst significant minorities of patients manage well without medication or with only Entonox, unfortunately about 1 in 10 patients undergoing screening colonoscopy experience significant discomfort. Most of these patients received intravenous sedation and analgesia suggesting that the commonly used regimens do not adequately manage comfort in a significant minority of patients. How these patients should be identified and managed is an important area for future research.

Colonoscopists' views regarding Entonox use were generally positive and Entonox appears widely available. Therefore, the reasons for the low utilisation of Entonox remain unclear. Areas worthy of further research would therefore include the assessment of patients' perceptions towards the use of medication during colonoscopy and explore the relative importance of comfort versus convenience. Continuous, rather than as required, administration of Entonox did not significantly increase its analgesic effect but did increase the likelihood of side effects. The pain scores of most patients were low and very few required rescue intravenous medication although those with high anxiety levels reported higher pain scores. Further avenues for research would be the development of tools to identify the patients in whom Entonox would be appropriate.

Patients undergoing afternoon examinations had superior bowel cleanliness, which appeared most likely to relate to differences in dosing schedule. However, there is little data on the use of split dose PEG bowel preparations in patients undergoing morning examinations or the use of split dose

Moviprep. Strategies to improve bowel cleanliness in patients attending for morning examinations would be of clinical value. A split dose regimen may be an option but its feasibility and acceptability is uncertain.

Routinely examining the right colon in the left lateral rather than supine position increases both polyp and adenoma detection. This augments the results of previous studies, which have reported benefit in other bowel segments. However, there remain several uncertainties regarding the optimal colonoscope withdrawal strategy. It is unclear whether prescribed position change is of value when luminal distension and mucosal visualisation is judged adequate and whether endoscopists reliably judge adequate distension. The optimal withdrawal position in the sigmoid colon, which is a common site of neoplasia, also remains unclear.  Due to anatomical variation, a 'double pass' may be of value. Further studies to assess this may be of clinical value.

## 8.3 Conclusion

Colonoscopy is an important diagnostic and therapeutic tool that is increasingly being utilised for the

assessment of colonic symptoms and CRC screening. It is important to continually examine quality

and I hope that the presented studies add to the body of literature and translate into clinical benefit.

**Summary of publications arising**

**Chapter 1**

Letters to editor relating to polyp detection and patient comfort.

Ball AJ, Campbell JA, Riley SA. Position change during colonoscope withdrawal: Is it worth the effort? Gastrointest Endosc. 2014;80(5):914-5.

Ball AJ, Riley SA, Assessment of comfort during colonoscopy: a nurse- or patient-rated scale? Gastrointes Endosc. 2013;78(4): 668

**Chapter 3**

An abstract presented at DDW 2014 and BSG 2014

Ball AJ, Rees C, Corfe BM, Riley SA. Patient comfort and sedation and analgesic practice during colonoscopy in the English Bowel Cancer Screening Programme.

Original article published in the European Journal of Gastroenterology and Hepatology

Sedation practice and comfort during colonoscopy: lessons learnt from a national screening programme. Eur J Gastroenterol Hepatol. 2015; 27(6):741-6

**Chapter 4**

Abstract presented at DDW 2014 and BSG 2014

Ball AJ, Campbell JA, Riley SA. Entonox use during colonoscopy: A survey of English Bowel Cancer Screening Programme colonoscopists

Original article published in Frontline Gastroenterology

Ball AJ, Campbell JA, Riley SA. Nitrous oxide use during colonoscopy: a national survey of English screening colonoscopists. Frontline Gastroenterology. 2014; 5(4):254-9.

**Chapter 5**

Abstract presented at UEGW 2014

Ball AJ, Din S, Donnelly MT, Riley SA. Entonox during colonoscopy: how should it be used?

Original article published in the European Journal of Gastroenterology and Hepatology.

Ball AJ, Din S, Donnelly M, Riley SA. A randomized controlled trial comparing continuous and as-required nitrous oxide use during screening colonoscopy. Eur J Gastroenterol Hepatol. 2015 Mar;27(3):271-8.

**Chapter 6**

Abstract presented at DDW 2014

Ball AJ, Riley SA. A comparison of a standard volume polyethylene glycol solution and low volume polyethylene glycol plus ascorbic acid as bowel preparation prior to screening colonoscopy

**Chapter 7**

Original article published in Gastrointestinal Endoscopy

Ball AJ, Johal SS, Riley SA. Position change during colonoscope withdrawal increases polyp and adenoma detection in the right but not in the left side of the colon: results of a randomized controlled trial. Gastrointest Endosc. 2015; 82(3):488-94

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182.     Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst. 2010;102(2):89-95.

183.     Prescott J. The comparison of success rates in cross-over trials in the presence of an order effect. Journal of the Royal Statistical Society1981. p. 9-15.

184.     Palmer K, Morris AI. A snapshot of colonoscopy practice in England: stimulus for improvement. Gut. 2004;53(2):163-5.

185.     Kiefe CI, Allison JJ, Williams OD, Person SD, Weaver MT, Weissman NW. Improving quality improvement using achievable benchmarks for physician feedback: a randomized controlled trial. JAMA. 2001;285(22):2871-9.

**Appendix**

**Approvals and case report forms for studies within this thesis**

**From:** Sharrack, Basil (Neurology)
**Sent:** 16 January 2013 22:43
**To:** Ball, Alex (Gastroenterology)
**Cc:** b.sharrack@sheffield.ac.uk
**Subject:** RE: Letter regarding need for REC review

Dear Alex

Many thanks for your email.

Reading through your project, it looks as though you are planning to analyse a set of anonymised data which had been collected to part of a standard clinical care. You will not have access to any patients' identifiable data. As such you do not need a REC approval.
Hope this is helpful.
Regards
Basil Sharrack

Professor B Sharrack
Chair
Sheffield REC

**From:** Ball, Alex (Gastroenterology)
**Sent:** 16 January 2013 14:18
**To:** Sharrack, Basil (Neurology)
**Subject:** Letter regarding need for REC review

Dear Dr Sharrack

I attach a letter which asks about the need for REC review.

I am a research fellow working with Dr Riley (Gastroenterology). We have been given permission to access and audit data within the Bowel Cancer Screening Programme. As we plan to publish this data on completion of analysis, and journals often require ethics review or confirmation this is not required, we would like your confirmation of whether this will need REC review prior to analysis.

Thank you for your help with this

Yours sincerely

Alex Ball

Clinical Research Fellow
Northern General Hospital

Appendix 1 - Confirmation from chair of local REC that study in chapter 3 did not require REC review

**NHS**

**Bowel Cancer Screening Programme**
**Research Committee**

**John Scholefield**
Chair

C/o NHS Cancer Screening Programmes
Fulwood House
Old Fulwood Road
Sheffield
S10 3TH

Tel: 0114 2711060

alex_ball81@yahoo.co.uk

Ginny.Fieldsend@cancerscreening.nhs.uk

11th January 2013

Dear Alex

The Bowel Cancer Screening Programme (BCSP) Research Committee met on 12th December 2012 to discuss your audit project: Study to assess the variation in sedation practice within the BCSP.

**The Committee gave their support to the project**.
The Committee noted that the project would need to consider the facilities in place and how the data will be cleaned and analysed.

As a condition of support, the BCSP Research Committee requires you to keep them informed of developments with the project, including any changes of status, any significant adverse events, when completed, and when written up.

The BCSP Research Committee requires you to notify them promptly of any incidents that would be recorded on the National Research Ethics Service (NRES) Breaches Register. Undertaking research within the Screening Programme following receipt of this letter of support assumes your agreement to fulfil this obligation. NRES has the potential to share information with the BCSP Research Committee regarding any breaches of ethics related to projects involving the BCSP.

The Committee wishes you well with your research.

Yours sincerely

Ginny Fieldsend
On behalf of the NHS BCSP Research Committee.

Appendix 2 - BCSP Research Committee approval for study in Chapter 3

# Bowel Cancer Screening Programme
# Research Committee

**John Scholefield**
Chair

C/o NHS Cancer Screening Programmes
Fulwood House
Old Fulwood Road
Sheffield
S10 3TH

Tel: 0114 2711060

Ginny.Fieldsend@PHE.gov.uk

Stuart.riley@sth.nhs.uk
alex_ball81@yahoo.co.uk

28ᵗʰ June 2013

Dear Alex

The Bowel Cancer Screening Programme (BCSP) Research Committee met on the 18ᵗʰ June 2013 to discuss your service evaluation project: *Entonox use amongst screening colonoscopists: A survey of practice and attitudes.*

**The Committee gave their support to the project.**
The Committee agreed to support this service evaluation but noted that colonoscopists receive numerous questionnaires and questioned how you would endorse your questionnaire to maximise the response rate.

As a condition of support, the BCSP Research Committee requires you to keep them informed of developments with the project, including any changes of status, any significant adverse events, when completed, and when written up.

The BCSP Research Committee requires you to notify them promptly of any incidents that would be recorded on the National Research Ethics Service (NRES) Breaches Register. Undertaking research within the Screening Programme following receipt of this letter of support assumes your agreement to fulfil this obligation. NRES has the potential to share information with the BCSP Research Committee regarding any breaches of ethics related to projects involving the BCSP.

The Committee wishes you well with your research.

Yours sincerely

Ginny Fieldsend
On behalf of the NHS BCSP Research Committee.

Appendix 3 - BCSP Research Committee approval for study in chapter 4

**From:** Cafferty, Christine (Clinical Effectiveness Unit)
**Sent:** 10 April 2013 11:53
**To:** 'alex ball'
**Cc:** Riley, Stuart (Gastroenterology); Basu, Kumar (Gastroenterology); Donnelly, Mark (Gastroenterology); Ball, Alex (Gastroenterology)
**Subject:** 5212- Entonox registration

Dear Alex,

Project 5212 Survey assessing the use of Entonox during colonoscopy has been approved as service evaluation subject to the clarification of the following;

- You have ticked- academic project- please could you inform me which course? And will your email to practitioners make it clear that it is an academic project?
- Please ensure that all references to research are removed from the correspondence to others
- Please could I have a copy of the email that you will be sending?
- What information will be given in the telephone call?
- Whose licence will be used to carry out this survey monkey?
- How will this study be used to benefit the patients at STHFT?
- Will this reported information be presented locally and nationally?
- You will provide a report in the Trust CEU format?

It has been be included on the Directorate's Clinical Audit and Effectiveness Programme to ensure that the project's progress can be monitored throughout all the stages of the cycle. It is placed on the programme as locally managed priority 4 project. Any project that is progressing as planned with be issued a green colour status, any with a minor problem – hoping to resolve - is issued an amber status and any which has a significant problem will be issued a red status. Please remember to keep me informed of your project status at all times. The progress of projects is reported regularly to the Trust Clinical Audit and Effectiveness Committee (CEC) and Directorate meetings. If you let me know of any problems, I will try to resolve them in a timely fashion to prevent any escalation procedures.

It was expected that on completion of the project you will submit a final written report in the STHFT CEU format. I have attached a partially populated report for you to amend once you have the results. The same headings should be used when you prepare a presentation. This is not only built into the terms and conditions of the Clinical Audit Policy but the report is also used as evidence of compliance for the NHS Litigation Authority Level 2 assessment. The report is used as evidence for:
. Care Quality Commission (CQC) Essential Standards for Quality and Safety
. CQC Engagement in Clinical Audit Performance Indicator
. NHSLA and Information Governance Standards
. Department of Health Quality Accounts
. Providing assurances to the Trust Board
. NHS Sheffield Commissioner contractual obligations
. Meeting NICE guidance (all types)
. NCAPOP programme

If you need to discuss this email further with me then I am available Monday to Thursday.

Kind regards,

Christine

## Appendix 4 - Approval for study in chapter 4 as a service evaluation

**John Scholefield**
Chair

C/o NHS Cancer Screening Programmes
Fulwood House
Old Fulwood Road
Sheffield
S10 3TH

Tel: 0114 2711060

Stuart.riley@sth.nhs.uk

tj.day@cancerscreening.nhs.uk

alex_ball81@yahoo.co.uk

11 January 2012

Dear Dr Riley,

The Bowel Cancer Screening Programme (BCSP) Research Committee met on 14 December 2011 to discuss your research plans: *Optimising the use of nitrous oxide during screening colonoscopy*.

**The Committee gave their support to the project.**

As a condition of support, the BCSP Research Committee requires you to keep them informed of developments with the project, including any changes of status, any significant adverse events, when completed, and when written up.

The BCSP Research Committee requires you to notify them promptly of any incidents that would be recorded on the National Research Ethics Service (NRES) Breaches Register. Undertaking research within the Screening Programme following receipt of this letter of support assumes your agreement to fulfil this obligation. NRES has the potential to share information with the BCSP Research Committee regarding any breaches of ethics related to projects involving the BCSP.

The Committee wishes you well with your research.

Yours sincerely

TJ Day MSc MA
On behalf of the NHS BCSP Research Committee.

Appendix 5 - BCSP research committee approval for study in chapter 5

**NRES Committee Yorkshire & The Humber - Leeds West**

First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Telephone: 0113 3050122
Facsimile: 0113 8556191

26 September 2012

Dr Stuart Riley
Clinical Research Fellow
Sheffield Teaching Hospitals
Herries Road
Sheffield
Sheffield
S5 7AU

Dear Dr Riley

| | |
|---|---|
| **Study title:** | **Optimising the use of Entonox during screening colonoscopy: an open randomised controlled trial** |
| **REC reference:** | **12/YH/0407** |
| **Protocol number:** | **STH16359** |
| **EudraCT number:** | **2012-003342-33** |

Thank you for your letter of 24 September, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by Dr Elliott.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Ethical review of research sites**

[Omit this sub-section if no NHS sites will be taking part in the study, e.g. Phase 1 trials in healthy volunteers]

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Appendix 6 - NHS REC committee approval for study in chapter 5

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

**Conditions of the favourable opinion**

*The favourable opinion is subject to the following conditions being met prior to the start of the study.*

*Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.*

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| Document | Version | Date |
|---|---|---|
| GP/Consultant Information Sheets | 3.0 | 06 August 2012 |
| Investigator CV | | |
| Investigator's Brochure | | |
| Letter from Statistician | | 31 January 2012 |
| Other: CV for Dr Ball | | |
| Other: CV for Dr Corfe | | |
| Other: Case report form | 1 | 06 August 2012 |
| Participant Consent Form | 3.0 | 06 August 2012 |
| Participant Information Sheet | 4.0 | 24 September 2012 |

A Research Ethics Committee established by the Health Research Authority

Appendix 6 - NHS REC committee approval for study in chapter 5 (page 2)

| Protocol | 3.0 | 30 July 2012 |
|---|---|---|
| Questionnaire: HADS | | |
| REC application | | 15 August 2012 |
| Referees or other scientific critique report | | |
| Response to Request for Further Information | | |

**Statement of compliance**

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

| 12/YH/0407 | Please quote this number on all correspondence |
|---|---|

With the Committee's best wishes for the success of this project

Yours sincerely

**Dr Rhona Bratt**
**Chair**

Appendix 6 - NHS REC committee approval for study in chapter 5 (page 3)

Safeguarding public health

**MHRA**

Mr J Lithgow
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
1ST FLOOR, 11 BROOMFIELD ROAD
SHEFFIELD
S10 2SE
UNITED KINGDOM

RECEIVED
2 7 SEP 2012
JKL

24/09/2012

Dear Mr J Lithgow

**THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031 (as amended)(the 'Regulations')**

Our Reference:        21304/0244/001-0001
Eudract Number:    2012-003342-33
Product:                  ENTONOX MEDICINAL GAS
Protocol number:     STH16359

**ACKNOWLEDGEMENT OF NOTIFICATION**

I am writing to confirm receipt of your notification of a clinical trial received on 21/09/2012.

For the purposes of regulation 18(2)(c) or 20(2)(a) and (5) of the Regulations (as appropriate), this letter is notice of authorisation of the trial referenced above with effect from 5/10/2012 (the 'effective date') subject to the following condition:

- that no further correspondence is received from the Licensing Authority before the effective date requiring full assessment of your request for authorisation.

You are reminded that your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed.

Yours sincerely,

**Clinical Trials Unit**
**MHRA**

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000  www.mhra.gov.uk

An executive agency of the Department of Health

Appendix 7 - MHRA approval for study in chapter 5

# Sheffield Teaching Hospitals NHS
## NHS Foundation Trust

Ref: STH16359/JB/JKL

10th October 2012

Dr Stuart Riley
Consultant Gastroenterologist
Northern General Hospital
Herries Rd
Sheffield, S5 7AU

Dear Dr Riley,

## Project Authorisation
## NHS Permission for Research to commence

| | |
|---|---|
| STH ref: | STH16359 |
| NIHR CSP ref: | n/a |
| REC ref: | 12/YH/0407 |
| MHRA ref: | CTA no.: 21304/0244/001-0001    EudraCT no.: 2012-003342-33 |
| Study title: | Optimising the use of Entonox during screening colonoscopy |
| Chief Investigator: | Dr Stuart Riley |
| Principal Investigator: | Dr Stuart Riley |
| Sponsor: | Sheffield Teaching Hospitals NHS Foundation Trust |
| Funder: | Sheffield Colonoscopy Research and Education Fund (S Riley) |
| URMS ref: | n/a |

The Research Department has received the required documentation as listed below:

| | | |
|---|---|---|
| 1. | Sponsorship Agreement | n/a |
| | Clinical Trial Agreement | n/a |
| | Material Transfer Agreement | n/a |
| | Funding Award Letter | Letter of funding, S Riley, 17/8/12 |
| 2. | Monitoring Arrangements | STH Study Management and Monitoring Plan, signed S Riley 8/10/12 |
| 3. | STH registration document | NHS R&D Form signed S Riley and D Patel 3/10/12 |
| 4. | Evidence of favourable scientific review | STH ISR approval 28/06/2012 |

Appendix 8 - NHS R + D department approval for study in chapter 5

5.  Protocol – final version                         V4, 9/8/12

6.  Participant Information sheet                     V4, 24/9/12

7.  Consent form                                      V3, 6/8/12

8.  Letter of indemnity arrangements                 NHS Indemnity
    Insurance Certificate                            n/a

9.  ARSAC certificate / IRMER assessment             n/a

10. Ethical review- Letter of approval from          NRES Yorkshire & Humber – Leeds West, initial
    NHS REC/ UREC                                     approval 26/9/12

                                                     Minor Amendment 1 26/9/12

11. Site Specific Assessment                         SSI Form signed S Riley, 3/10/12
                                                     STH R&D, 10/10/12

12. Clinical Trial Authorisation from MHRA           Notice of authorisation effective from 5/10/12

13. Evidence of hosting approvals                    STH Finance Form

    -   STH Principal Investigator                   S Riley, 8/10/12
    -   Clinical Director                            M Donnelly, 4/10/12
    -   Research Finance                             E Fraser, 5/10/12
    -   Data Protection Officer                      P Wilson, 9/10/12

    -   CRF                                          n/a
    -   Pharmacy                                     n/a
    -   MIMP/Academic Radiology                      n/a
    -   Laboratory Medicine                          n/a
    -   Diagnostic Cardiology                        n/a
    -   Respiratory Function Unit                    n/a

14. Honorary Contract/Letter of Access              n/a

15. Associated documents
    -All REC approved documents                      GP Letter v3, 6/8/12
                                                     HADS questionnaire not versioned nor dated

                                                     Entonox Gas Summary of Product
    -IB/SmPC                                         Characteristics, 2011

                                                     Case Report Form, August 2012
    -Any other documents


**This project has been reviewed by the Research Department. NHS permission for the above
research to commence has been granted on the basis described in the application form,
protocol and supporting documentation** on the understanding that the study is conducted in
accordance with the Research Governance Framework, GCP and Sheffield Teaching Hospitals
policies and procedures (see attached appendix).

**Additional conditions:**
STH Sponsored CTIMP
You must notify your Research Co-ordinator [jennifer.boston@sth.nhs.uk], as soon as the first
participant is consented into the study so that appropriate monitoring arrangements can be made.

2

Appendix 8 - NHS R + D department approval for study in chapter 5 (page 2)

**From:** Cafferty, Christine (Clinical Effectiveness Unit)
**Sent:** 12 September 2012 08:27
**To:** Ball, Alex (Gastroenterology); Riley, Stuart (Gastroenterology)
**Cc:** Basu, Kumar (Gastroenterology); Pickford, Sadie (Gastroenterology); Smith, Karen (Emergency Care Group); Donnelly, Mark (Gastroenterology); Vickers, Hannah (Emergency Care Group); Hill, Carol (Gastroenterology); Hill, Anna (Emergency Care Group); Webster, Maxine (Emergency Care Group)
**Subject:** 4741- To compare the effectiveness of klean prep verus moviprep for endoscopic procedures for patients -approved as audit and SE

Dear Project Team,

I have submitted the registration form to the CEU project panel and they have informed me that they have approved the project as audit and service evaluation.. Please use project number 4741 when corresponding with me.

Please ensure that any documents with PID are securely stored and transferred.

It has been be included on the Directorate's Clinical Audit and Effectiveness Programme to ensure that the project's progress can be monitored throughout all the stages of the cycle. The project is now on the programme as a priority 4 performance managed project. Any project that is progressing as planned with be issued a green colour status, any with a minor problem – hoping to resolve - is issued an amber status and any which has a significant problem will be issued a red status. Please remember to keep me informed of your project status at all times. The progress of projects is reported regularly to the Trust Clinical Audit and Effectiveness Committee (CEC) and Directorate meetings. If you let me know of any problems, I will try to resolve them in a timely fashion to prevent any escalation procedures.

It was expected that on completion of the project you will submit a final written report in the STHFT CEU format. Please find attached the draft partially populated report. The same headings should be used when you prepare a presentation. This is not only built into the terms and conditions of the Clinical Audit Policy but the report is also used as evidence of compliance for the NHS Litigation Authority Level 2 assessment. The report is used as evidence for:
. Care Quality Commission (CQC) Essential Standards for Quality and Safety
. CQC Engagement in Clinical Audit Performance Indicator
. NHSLA and Information Governance Standards
. Department of Health Quality Accounts
. Providing assurances to the Trust Board
. NHS Sheffield Commissioner contractual obligations
. Meeting NICE guidance (all types)
. NCAPOP programme

The Trust actively encourages that all project findings are disseminated within your Directorate/Speciality groups, along with stakeholders, to agree and monitor action plans following any recommendations for change. All audits require this formal report (a presentation is not appropriate since it does not outline all the relevant points in the report such as the action plan). An audit cannot be closed on the programme unless the action plan has been implemented.

If you need to discuss this email further with me then I am available Monday to Thursday.

Kind regards,

Christine

Appendix 9 - Approval for study in chapter 6 as a service evaluation

Ref: STH16220/JB

# Sheffield Teaching Hospitals **NHS**

NHS Foundation Trust

22nd February 2012

Dr Alex Ball
Clinical Research Fellow
Sheffield Teaching Hospitals NHS Foundation Trust
Department of Gastroenterology
Northern General Hospital
Sheffield
S5 7AU

Dear Dr Riley,

## Authorisation of Project

**STH ref:**     STH16220
**Study title:**   A comparison of two colonoscopic withdrawal techniques on colonic
                polyp detection: an open randomised cross over trial

**Chief Investigator:**     Dr Alex Ball, Sheffield Teaching Hospitals NHS Foundation Trust
**Principal Investigator:** Dr Stuart Riley, Sheffield Teaching Hospitals NHS Foundation Trust

**Sponsor:**   Sheffield Teaching Hospitals NHS Foundation Trust
**Funder:**    Unfunded

The Research Department has received the required documentation for the study as
listed below:

| | | |
|---|---|---|
| 1. | Sponsorship IMP studies (non-commercial) | Not applicable |
| | Sponsorship responsibilities between institutions | Not applicable |
| | Responsibilities of investigators | Not applicable |
| | Monitoring Arrangements | Not applicable |
| 2. | STH registration document: completed and signed | REC application form: Version 3.4 A Ball, 11 Jan 12 |
| | | STH Finance Form: S Riley, 09 Feb 12 |
| 3. | Evidence of favourable scientific review | STH NHS FT: 16 Dec 11 |
| 4. | Protocol – final version | Version 3, 03 Feb 12 |
| 5. | Participant Information sheet – final version | Version 2.0, 03 Feb 12 |
| 6. | Consent form – final version | Version 1.0, 01 Dec 11 |
| 7. | Signed letters of indemnity | NHS Indemnity |
| 8. | ARSAC / IRMER certificate | Not applicable |
| 9. | Evidence of hosting approval from STH directorate | STH Finance Form: M Donnelly, 13 Feb 12 |
| 10. | Evidence of approval from STH Data Protection Officer | STH Finance Form: P Wilson, 17 Feb 12 |

Chairman: David Stone OBE • Chief Executive: Andrew Cash OBE

smoke-free
hospitals

Appendix 10 - NHS R + D department approval for study in chapter 7

Ref: STH16220/JB

| | | |
|---|---|---|
| 11. | Letter of approval from REC | Yorkshire & The Humber – South Yorkshire 12/YH/0032 06 Feb 12 |
| 12. | Proof of locality approval | SSA by STH R&D: 22 Feb 12 |
| 13. | Clinical Trial Authorisation from MHRA | Not applicable |
| 14. | Honorary Contract | Not applicable |
| 15. | Associated documents GP Information Sheets | Version 1.0, 11 Jan 12 |
| 16. | Signed financial agreement/contract | STH Finance Form: L Fraser, 09 Feb 12

STH Finance Form: J Broscomb, 16 Feb 12 |

The project has been reviewed by the Research Department and authorised by the Director of R&D on behalf of STH NHS Foundation Trust to begin.

Yours sincerely

Professor S Heller
Director of R&D, Sheffield Teaching Hospitals NHS Foundation Trust
Telephone +44 (0) 114 2265934
Fax +44 (0) 114 2265937

2

Appendix 10 - NHS R + D department approval for study in chapter 7 (page 2)

**NHS**

**Health Research Authority**

**NRES Committee Yorkshire & The Humber - South Yorkshire**

Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 30 50128
Facsimile: 0113 85 56191

06 February 2012

Dr Alex Ball
76 Brooklands Crescent
Fulwood
Sheffield
S10 4GG

Dear Dr Ball

| | |
|---|---|
| Study title: | A comparison of two colonoscopic withdrawal techniques on colonic polyp detection: an open randomised cross over trial |
| REC reference: | 12/YH/0032 |
| Protocol number: | STH16220 |

Thank you for your letter of 03 February 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

*Conditions of the favourable opinion*

Appendix 11- NHS REC Committee approval for study in chapter 7

*The favourable opinion is subject to the following conditions being met prior to the start of the study.*

*Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.*

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

*Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.*

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| Document | Version | Date |
|---|---|---|
| Covering Letter | | 03 February 2012 |
| Investigator CV | | |
| Letter from Statistician | | 22 November 2011 |
| Other: Letter for GPs | 1 | 11 January 2012 |
| Other: Academic Supervisor CV | | |
| Participant Consent Form | 1 | 01 December 2011 |
| Participant Information Sheet | 2 | 03 February 2012 |
| Protocol | 3 | 03 February 2012 |
| REC application | | 11 January 2012 |
| Referees or other scientific critique report | | |
| Response to Request for Further Information | | 03 February 2012 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Appendix 11 - NHS REC Committee approval for study in chapter 7 (page 2)

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

| 12/YH/0032 | Please quote this number on all correspondence |
| --- | --- |

With the Committee's best wishes for the success of this project

Yours sincerely

Ms Jo Abbott
Chair

Email: sinead.audsley@nhs.net

*Enclosures:*     "After ethical review – guidance for researchers"

Copy to:      *Mrs Jennifer   Boston, Sheffield Teaching Hospitals NHS Foundation Trus*

Appendix 11- NHS REC Committee approval for study in chapter 7 (page 3)

**Sheffield Teaching Hospitals** **NHS**

NHS Foundation Trust

# Case Report Form

Patients study number..............................................Date of examination...............................................

Patients Initials.......................................................................................................................................

D.O.B.......................................Age....................................Gender...................................................................

Inclusion and exclusion criteria form completed.................................................................................

Indication for colonoscopy.....................................................................................................................

Height……………………Weight…………………………..BMI…………………………...

Previous colonoscopy (Yes/No)..............................................................................................................

Patient information sheet given (tick) ☐          Consent form signed ☐

Withdrawal of consent and reason.........................................................................................................

HADS ........................................................................................................................................................

**Randomised to;**          **continuous** ☐          **as required** ☐ **(please tick)**

Time at start of test..................................................................................................

**Endoscopist** (circle)  SAR ☐          MTD ☐          KS ☐

**Pain scores**

**Prior**

'Between 0 and 10, with 0 being no pain and 10 being extreme pain, what is your current level of pain?'

**Anticipated**

'Between 0 and 10, with 0 being no pain and 10 being extreme pain, how painful do you think the colonoscopy will be?'

*Note – Administer Entonox prior to starting colonoscopy*

**During –** *Ask every 2 minutes*

'Between 0 and 10, with 0 being no pain and 10 being extreme pain, on average how much pain have you had over the last 2 minutes?'

Appendix 12 - Case report form for study in chapter 5

|  | Prior | Anticipated | 2min | 4min | 6min | 8min | 10min | 12min | 14min | 16min |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain score |  |  |  |  |  |  |  |  |  |  |

|  | 18min | 20min | 22min | 24min | 26min | 28min | 30min | 32min | 34min |
|---|---|---|---|---|---|---|---|---|---|
| Pain score |  |  |  |  |  |  |  |  |  |

|  | 36min | 38min | 40min | 42min | 44min | 46min | 48min | 50min | Retroflexion |
|---|---|---|---|---|---|---|---|---|---|
| Pain score |  |  |  |  |  |  |  |  |  |

**Scope retroflexion**

'Between 0 and 10, how painful did you find the last part of the test?' (enter score into box above)

Time to sigmoid descending...............................................

Time to splenic flexure...........................................................

Time to hepatic flexure...........................................................

Time to Caecal pole.................................................................

Time for withdrawal.................................................................

Time at completion of test....................................................

**Overall** pain scores (To be asked immediately after colonoscopy)

'Between 0 and 10, with 0 being no pain and 10 being extreme pain, on average how much pain have you had during the colonosopy?'

.............................................................................................

**Overall side effects - Ask at end of procedure**

|  | Side effects present? | | Reason for discontinuation? | |
|---|---|---|---|---|
|  | **Yes** | **No** | **Yes** | **No** |
| **Nausea** |  |  |  |  |
| **Light headedness** |  |  |  |  |
| **Headache** |  |  |  |  |
| **Dysphoria (BCSP rating)** |  |  |  |  |
| **Dry Mouth** |  |  |  |  |
| **Tingling/ numbness** |  |  |  |  |

Appendix 12 - Case report form for study in chapter 5 (page 2)

Number of polyps found.................................................

Additional analgesia used/dose and reason (side effects or not tolerating pain)

.................................................................................................

Did patient have to stop using Entonox?   Yes ☐        No ☐

State reason...............................................................................................

Additional Buscopan administered        Yes/ No        Time.....................................

**Bowel preparation** (BCSP rating scale)

Excellent (no or minimal solid stool and only clear fluid requiring suction)
Adequate (collections of semi-solid debris that are cleared with washing/suction)
Inadequate (solid or semi-solid debris that cannot be cleared effectively).

|  | Right | Transverse | Left |
|---|---|---|---|
| Score |  |  |  |

**Complications (state value and no of events)**

Hypotension (<90/50)...........................................................................

Bradycardia (<50bpm)..........................................................................

Desaturation (<90%)............................................................................

**Gas insufflated**        Air ☐                Co2 ☐

**Degree of difficulty of colonoscopy (endoscopist assessment)**

0-10 (0 = Very easy, 10 = Very Diffucult).........................................................................

**Degree of pain (endoscopist assessment)**

0-10..................................................................................................

**Degree of pain (Nurse assessment)**

0-10..................................................................................................

**Time at discharge**

.................................................................................................

Appendix 12 - Case report form for study in chapter 5 (page 3)

**Questions to be asked prior to discharge from endoscopy unit**

**Overall** pain scores

'Between 0 and 10, with 0 being no pain and 10 being extreme pain, on average how much pain have you had during the colonosopy?'

...............................................................................................

**Overall patient satisfaction**

'Overall, between 0 and 10, with 0 being not satisfied at all and 10 being completely satisfied, how satisfied are you with your colonoscopy'

...............................................................................................

**Willingness to have a repeat procedure?**

'Between 0 and 10, with 0 being not willing at all and 10 being completely willing, how willing would you be to have a repeat colonoscopy?'

...............................................................................................

Appendix 12 - Case report form for study in chapter 5 (page 4)

**Questions to be asked 1-3 days following colonoscopy**

**Overall** pain scores

'Between 0 and 10, with 0 being no pain and 10 being extreme pain, on average how much pain have you had during the colonosopy?'

.................................................................................

**Overall patient satisfaction**

'Overall, between 0 and 10, with 0 being not satisfied at all and 10 being completely satisfied, how satisfied are you with your colonoscopy'

.................................................................................

**Willingness to have a repeat procedure?**

'Between 0 and 10, with 0 being not willing at all and 10 being completely willing, how willing would you be to have a repeat colonoscopy?'

.................................................................................

Appendix 12 - Case report form for study in chapter 5 (page 5)

## Sheffield Teaching Hospitals NHS

NHS Foundation Trust

## <u>Audit form</u>

Patients audit number.............................................Date of examination...........................................

Patients Initials......................................................................................................................................

D.O.B......................................Age...................................Gender...........................................................

Height ..........................Weight............................................BMI.....................................................

Previous colonoscopy    Yes ☐          No ☐

**What is the patients usual stool frequency?**

More than 3 times/day ☐       Between 3 times/day - every 3$^{rd}$ day ☐       Less than every 3 days ☐

Timing of list       Am list ☐

Pm list ☐

Time at start of colonoscopy.............................

Time from completing last dose of prep to start of test (to nearest hour).......................................

Time to caecum (minutes).............................................................................................................

Withdrawal time (minutes)...........................................................................................................

**Bowel preparation**   Klean Prep ☐      amount taken to nearest 0.5 Litres.................... All ☐

Moviprep ☐      amount taken to nearest 0.5 Litres.................... All ☐

**Number of polyps, location, size and morphology**

|  | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Size(mm) | | | | | | | |
| Location (left/trans/right) | | | | | | | |
| Morphology (flat/sess/ped) | | | | | | | |

Endoscopist....................       SSP.............................        Hospital...............................

Appendix 13 - Case report form for study in chapter 6

**Does the Patient take any of the following medications?**

Opiates (codeine/fentanyl/tramadol etc)    Yes ☐    No ☐    Name/dose.............................................

Tricyclic antidepressants (amitriptyline)    Yes ☐    No ☐    Name/dose.............................................

Calcium channel blockers (amlodipine)    Yes ☐    No ☐    Name/dose.............................................

**Quality of bowel preparation – Ottawa scale**

| Bowel Segment | Score |
|---|---|
| Right colon | |
| Transverse | |
| Left colon | |
| Residual fluid | |

0 = Excellent    -    *mucosal detail clearly visible. If fluid is present it is clear. Almost no stool residue.*

1 = Good    -    *Some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary*

2 = Fair    -    *Turbid fluid or residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary.*

3 = Poor    -    *Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained.*

4 = Inadequate    -    *Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning*

Fluid in whole colon.    Small(0)    Moderate(1)  Large (2)

Appendix 13 - Case report form for study in chapter 6 (page 2)

**Patient questionnaire**

Please answer ALL the following questions.

1) With regards your bowel preparation, how acceptable were each of the following (please tick the appropriate boxes)

|  | Completely acceptable | Slightly acceptable | Neutral | Slightly unacceptable | Completely unacceptable |
|---|---|---|---|---|---|
| Taste of bowel preparation |  |  |  |  |  |
| Amount of bowel preparation |  |  |  |  |  |
| Side effects (Nausea,bloating etc) |  |  |  |  |  |
| Effect on planned activities (work, hobbies etc) |  |  |  |  |  |
| Overall experience |  |  |  |  |  |

2) Please rate the severity of the following side effects due to taking bowel preparation.

|  | Absent | Mild | Moderate | Severe |
|---|---|---|---|---|
| Bloating |  |  |  |  |
| Cramping |  |  |  |  |
| Nausea |  |  |  |  |
| Vomiting |  |  |  |  |
| Abdominal pain |  |  |  |  |
| Sleep disturbance |  |  |  |  |
| Headache |  |  |  |  |

Appendix 13 - Case report form for study in chapter 6 (page 3)

3) Please indicate the extent to which you agree with the following statement:

*I would be willing to repeat the same bowel preparation if I required a colonoscopy in the future*

| Strongly agree | Agree | Neither agree or disagree | Disagree | Strongly disagree |
|---|---|---|---|---|
|  |  |  |  |  |

4) Do you have any further comments about your experience taking bowel preparation.

………………………………………………………………………………………………………………………………………………………………

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Appendix 13 - Case report form for study in chapter 6 (page 4)

**Sheffield Teaching Hospitals** **NHS**

NHS Foundation Trust

# Case Report Form

Patients study number............................................Date of examination............................................

Patients Initials..................................................................................................................................

D.O.B.....................................Age...................................Gender......................................................

Inclusion and exclusion criteria form completed...............................................................................

Indication for colonoscopy.................................................................................................................

Patient information sheet given.................................Consent form signed......................................

Withdrawal of consent and reason.....................................................................................................

Randomisation strategy: Supine then dynamic ☐          Endoscopist:  SSJ      ☐

Dynamic then supine ☐                                                  SAR     ☐

AJB     ☐

**Polyps found on insertion**

| Polyp number | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Endoscopic polyp size (mm) | | | | | | |
| Polyp size (histology) | | | | | | |
| Polyp location (right/transverse/ left/ sigmoid) | | | | | | |

**Polyps found on 1st withdrawal**

| Polyp number | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Endoscopic polyp size (mm) | | | | | | |
| Polyp size (histology) | | | | | | |
| Polyp location (right/transverse/ left/ sigmoid) | | | | | | |

Appendix 14 - Case report form for study in chapter 7

**Polyps found on 2nd withdrawal**

| Polyp number | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Endoscopic polyp size (mm) | | | | | | |
| Polyp size (histology) | | | | | | |
| Polyp location (right/transverse/ left/ sigmoid) | | | | | | |

**Times**

Caecal intubation time (mins)..................................Withdrawal to sigmoid time...........................................

**Sedation used**

Midazolam(mg)..............................Fentanyl(Mcg).....................................Entonox.......................................

Buscopan administered       Yes/ No          Time....................................

Additional dose administered    Yes/No          Time....................................

**Boston bowel preparation scale**

| | Right colon | Transverse | Left | Sigmoid/rectum |
|---|---|---|---|---|
| AJB | | | | |
| SSJ | | | | |
| SAR | | | | |

**Luminal distension score**

| | Right colon | Transverse | Left | Sigmoid/rectum |
|---|---|---|---|---|
| AJB | | | | |
| SSJ | | | | |
| SAR | | | | |

**Pathology of Polyp 1**

Low grade...........................................High grade.................................................

Size(mm)...................................................................................................................

Tubular............................Villous.........................Tubulovillous.........................

**Pathology of Polyp 2**

Low grade...........................................High grade.................................................

Size(mm)...................................................................................................................

Tubular............................Villous.........................Tubulovillous.........................

Appendix 14 - Case report form for study in chapter 7 (page 2)

**Pathology of Polyp 3**

Low grade.........................................High grade.................................................

Size(mm)..............................................................................................................

Tubular.............................Villous.........................Tubulovillous.........................

Appendix 14 - Case report form for study in chapter 7 (page 3)