## *The impact of Endocuff Vision on adenoma detection rates in colonoscopy*

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# The impact of Endocuff Vision on adenoma detection rates in colonoscopy


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**Contents**

## Abstract

### Background

One of the problems with colonoscopy is its imperfection due to variation in operator dependent adenoma detection rates. Low adenoma detection rates are linked to increased interval colorectal cancer rates and reduced cancer survival.

Devices to enhance mucosal visualisation and improve adenoma detection rates such as Endocuff Vision have been developed. The primary aim of this study was to compare adenoma detection rates between Endocuff Vision-assisted colonoscopy and standard colonoscopy.

## Methods

A multicentre, randomised controlled trial in seven hospitals in the United Kingdom was undertaken. Patients aged 18 and above referred for colonoscopy due to symptoms, colonoscopy surveillance, or as part of the Bowel Cancer Screening Programme following a positive screening faecal occult blood test were invited to the study. Patients with a suspicion of bowel obstruction, known colon cancer, polyposis syndromes, known strictures, active colitis, on anticoagulant therapy during the procedure, pregnant, attending for a therapeutic procedure or assessment of a known lesion were excluded.

## Findings

One thousand, seven hundred and seventy-two patients (57% male, mean age 62) were recruited from November 2014 until February 2016. Patient characteristics were comparable between trial arms. Endocuff Vision increased adenoma detection rates by 4.7% (p=0.02). This was largely driven by an increase in adenoma detection rates in screening patients from 50.9% to 61.7% (p<0.001). Endocuff Vision-assisted colonoscopy also detected more mean

adenomas per procedure, left sided adenomas, sessile serrated adenomas, diminutive adenomas, small adenomas and cancers. Cuff removal rate was 4.1%. Median intubation time was one minute quicker with Endocuff Vision- assisted colonoscopy (p=0.001). Anal intubation was rated as more uncomfortable with Endocuff Vision-assisted colonoscopy. There were no significant cuff-related adverse events. Endocuff Vision- assisted colonoscopy was non-inferior to SC in other markers of comfort and procedure time.

## Conclusion

Endocuff Vision significantly improved ADR driven by an improvement in the faecal occult blood test positive screening population. Endocuff Vision-assisted colonoscopy was non-inferior in all aspects other than discomfort on anal intubation.

## Dedications

To my late father, James Ngu Siew Kong and beautiful mother, Jenny Ling Soon Eng for their constant encouragement and for working so hard to provide me with the best quality of education possible – all of my achievements are your achievements.

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## Authorship note

I confirm that no part of the material offered has previously been submitted by me for a degree in this or any other university. Material from work of others has been acknowledged and referenced accordingly.

## List of Tables and Figures

## Glossary of Abbreviations

| | |
|---|---|
| AADR | Advanced Adenoma Detection Rate |
| ADR | Adenoma Detection Rate |
| AE | Adverse Events |

| | |
|---|---|
| AFI | Autofluorescence Imaging |
| BCSP | Bowel Cancer Screening Programme |
| BSS | English Bowel Scope Screening Programme |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CRC | Colorectal Cancer |
| DOPyS | Direct Observational Procedure Assessment Forms For Polypectomy |
| DMC | Data Monitoring Committee |
| EVAC | Endocuff Vision-assisted Colonoscopy |
| ETMI | Endoscopic Trimodal Imaging |
| EWAVE | Extra wide angle view colonoscopy |
| FICE | Fuji Intelligent Colour Enhancement |
| FOBt | Faecal occult blood test |
| FUSE | Full Spectrum Endoscopy |
| JAG | Joint Advisory Group on Gastrointestinal Endoscopy |
| JETS | JAG Endoscopy Training System |
| MACRO | Electronic database for NWORTH Clinical Trials Unit |
| MAP | Mean Adenomas Per Procedure |
| MAP+ | Mean Adenomas Per Positive Procedure |
| NBI | Narrow Band Imaging |

| | |
|---|---|
| NHS | National Health Service |
| NWORTH | North Wales Organisation for Randomised Trials in Health |
| PDR | Polyp Detection Rate |
| RCT | Randomised Controlled Trial |
| SAE | Serious Adverse Events |
| SC | Standard Colonoscopy |
| TER | Third Eye Retroscope |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UK | United Kingdom |

## Introduction

Colorectal cancer is the second most common cause of cancer related death in Europe and North America and is the third most common cancer in the world.

In the United Kingdom, it is the fourth most common cancer with 41,000 cases diagnosed annually. Five decades ago, the link between adenomas and colorectal cancer was established with emerging evidence that the risk of colorectal cancer decreased if some adenomas were removed at the early stages. Adenomas are benign polyps found in up to a third of the Western population over fifty. Adenoma detection rate (ADR) is defined as the percentage of patients in whom at least one adenoma is identified. This can vary per patient or endoscopy group.

Colonoscopy is the accepted state-of-the-art investigation of the colon, as it not only allows for an examination but also removal of polyps and biopsy sampling. However, it is imperfect and only reduces the risk of colorectal cancer by 50% owing to missed adenomas. A standard colonoscope has a forward-facing fibre optic camera at the tip and is used to provide mucosal views of the bowel wall as the instrument is withdrawn. However, adenomas that are small, flat or present in difficult corners between mucosal folds can be missed. There are up to 360,000 colonoscopies performed per year in the United Kingdom and this number is rising. The rate of colonoscopies performed increased from 194 to 329 procedures per 10,000 patients from 2011 to 2012. This rising demand against the backdrop of restricted capacity and National Health Service budget

freeze makes it vital that each procedure is performed to the highest standard possible.

Endoscopy is unique in that it is a procedure that can be carried out by various clinicians including specialist nurses, general practitioners with special interests, gastroenterologists and surgeons. However, standards of colonoscopy and ADR can vary widely between groups of colonoscopists. Despite Bowel Cancer Screening Programme (BCSP) colonoscopists having a high ADR when compared with other groups of colonoscopists, many devices and technological advances created to improve ADR are only being used or tested by BCSP colonoscopists. What is required is an intervention that will improve ADR across all groups of colonoscopists as this will be a more accurate reflection of the general population of colonoscopists and have a larger, more realistic impact on improving ADR in the UK.

The National Bowel Cancer Audit Annual Report, 2013, found that the rate of emergency admissions with colorectal cancer has remained stagnant at 21-22% since 2008 despite Bowel Symptom Awareness and the Bowel Screening Programme. The mortality rate for colorectal cancer has remained at 18 in 100,000 people since 2003. The evidence is that patients who present as emergencies perform poorly when compared with patients undergoing a

planned elective operation. Although many factors can be attributed to this, it could be deduced that interval colorectal cancers from missed adenomas contribute to this percentage.

During my training as a specialist trainee in colorectal surgery, I have experienced first hand how early detection of colorectal cancers can have a substantial improvement on patient outcomes. Early cancers are easier to remove surgically as they are often less bulky, localised and require less radical resection. Patients are more likely to be offered laparoscopic surgery resulting in less postoperative pain, reduced complications and shortened overall hospital stay. One could even argue that 'early cancers' are removed by colonoscopists without the need for any surgical intervention. Early detection of colorectal cancer relies on a chain of events occurring successfully, from patient recognition of signs and symptoms to seeking medical attention to having appropriate investigations. Improving the quality of colonoscopy is only a cog in the wheel of this pathway.

It is timely that numerous devices are now being tested with the aim of increasing ADR. One such device is Endocuff Vision, which is used in this trial. This thesis aimed to address the use of an add-on endoscopic device called Endocuff Vision in improving adenoma detection rate. This will benefit patients

resulting in a more accurate examination with lower rates of missed polyps and ensure that the most accurate endoscopic surveillance programme is selected. It will also benefit NHS and other healthcare providers as there will be a reduced risk due to fewer missed polyps and improved ADR with a potential correlating reduction in interval colorectal cancers. This will be explored in more detail by means of a literature review.

# Chapter 1: A Review of the Literature

## 1.1 Background: Adenomas and colorectal cancer in the United Kingdom

### 1.1.1 Epidemiology

Colorectal cancer (CRC) is the third most common cancer in the world with 1.4 million new cases diagnosed annually [1]. In the United Kingdom (UK), CRC is the fourth most common cancer. In 2014, there were 41,265 new cases with the majority affected being male [2]. There are 72 and 56 new cases of colon cancer for every 100,000 male and female in the UK respectively [2]. A majority (90%) of colorectal cancers are adenocarcinoma that arise from colorectal adenomas. Colorectal adenomas are common and are present in a third of European and American populations [3].

Colorectal cancer is the second most common cause of cancer related death in the UK and accounts for 10% of all cancer deaths [2]. In 2014, there were 15,903 deaths attributed to colorectal cancer: 54% in males and 46% in females [2]. The 2-year overall survival rate of colorectal cancer is 67%. The 2-year survival rate in patients with major resection and associated oncologic therapy is 80% but in those with no major resection this figure falls to 45% [4]. The net colorectal cancer survival rate for both sexes is 76% at one year, 59% at five years and 57% at ten years [5]. Interestingly, the five year net survival ranges from 65% (60-69 year olds) to 43% (80-99 year olds) in males and 66% (60-69 year olds) to 43%

(80-99 year olds) in females [6]. This is probably explained by the availability of bowel cancer screening in the 60-69 year age group.

Colorectal cancer is more common on the left side of the colon with 75% of cancers occurring at or distal to the splenic flexure [2]. In this group, patients often present with abdominal pain, a change in bowel habit or rectal bleeding [7]. On the other hand, cancers proximal to the splenic flexure present with less apparent symptoms.

The diagnosis of CRC is often made when the disease has progressed to a more advanced stage, resulting in poorer clinical outcomes. Patients diagnosed with the earliest stages of the disease (Dukes A) have a 5-year survival rate of 93.2% compared to patients diagnosed with advanced disease (Dukes C) with a 5-year survival rate of 6.6% [8].

### 1.1.2 The adenoma-carcinoma sequence

Cancers are formed through accumulation of mutations in key genes that are responsible for regulating cell growth [9]. This was theorised to happen in three steps – initiation, promotion and progression [10]. Specific to colonic epithelium, there is a disciplined progression of genetic events with corresponding histological abnormalities that lead to colorectal cancer [11].

Most cancers are made up of cells that have pro-tumorigenic mutations which are unable to cause morphological change but do predispose to malignancy [12,13]. Adenomas are a type of colorectal polyp that have the potential to undergo malignant transformation [14]. The adenoma-carcinoma sequence is the pathway by which adenomatous polyps develop into colorectal cancer [15,16]. It is the progression of normal epithelium to dysplastic to malignant based on the accumulation of multiple genetic mutations. Figure 1 illustrates the various stages of the adenoma-carcinoma sequence [17].

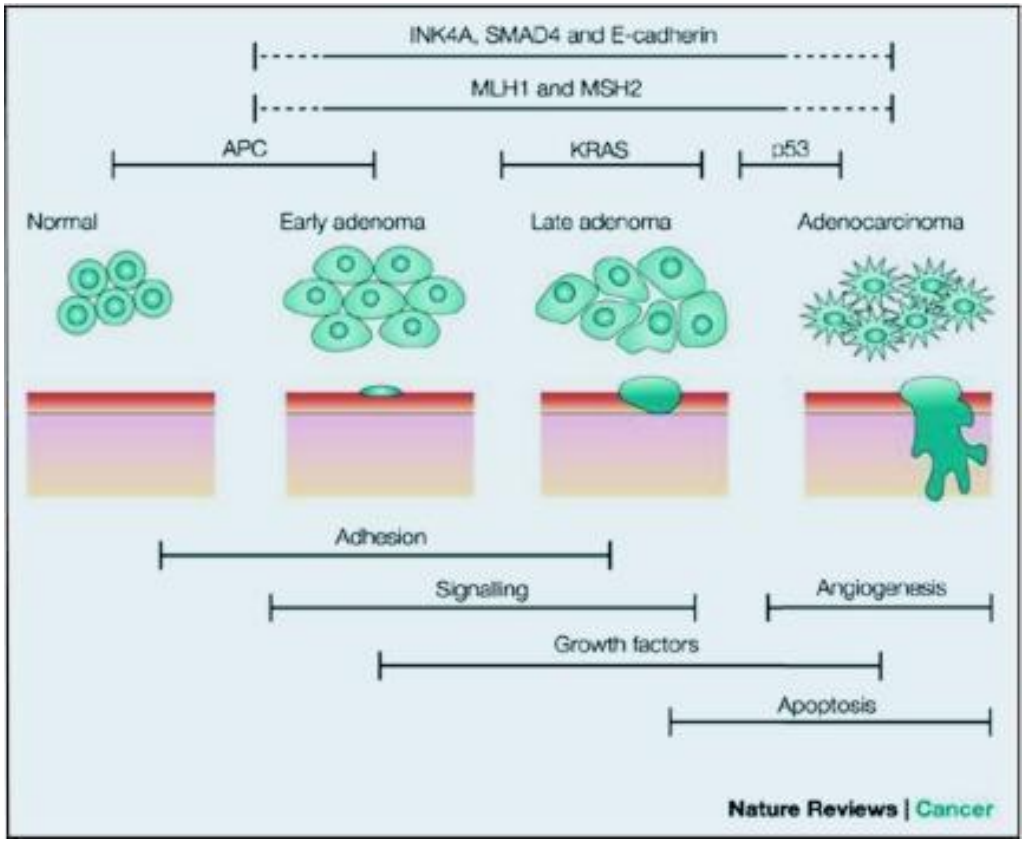

**Figure 1**: Adenoma-carcinoma sequence [17]

Many different factors are responsible for the development of adenomas. These factors can be classified into modifiable and non-modifiable risk groups. Modifiable risk factors include body mass index, alcohol intake, smoking status and diet. Non-modifiable risk factors include gender, age and genetic factors. Other concurrent medical disorders including diabetes, inflammatory bowel disease and obesity also predispose an individual to adenoma formation [18–20]. Good lifestyle advice and modification together with optimisation of medical conditions may reduce the risk of adenomas. However, there is currently not enough evidence to support this.

Thus, another angle of approach is prevention of colorectal cancer by endoscopic removal of precursor lesions such as adenomas. This is a strategy that increasing in popularity as there is evidence that the incidence of CRC in patients with complete colonoscopy and adenoma removal is significantly lower compared with matched cohorts [21].

On the other hand, the correct management of patients with precursor lesions such as adenomas is crucial. Studies have shown that up to 35% of patients who

have had adenomas removed will develop further adenomas in 3-4 years [22,23]. Thus, most guidelines advocate a policy of endoscopic surveillance for patients found to have adenomas. The British Society of Gastroenterology guidelines divide patients into three risk groups based on the number and size of adenomas found to determine colonoscopic surveillance [24]. However, as only a third of the Western population will go on to develop adenomas with only 3% suffering from colorectal cancer; it seems that only a small proportion of adenomas progress to malignancy [15].

There is wealth of literature in favour of the adenoma-carcinoma sequence based on epidemiological, clinicopathological and genetic factors [15]. The prevalence of adenomas and cancer increase with age but adenoma prevalence increases at least 5 years before that of colorectal cancer [16]. Studies have also demonstrated histopathologically that in up to 6% of cases, colorectal adenomas have been found to contain a focus of malignancy [25]. Equally, adenomatous tissue has also been identified in up to 23% of colorectal cancer specimens [16,26] and there is an increased incidence of malignant cells in adenomas of a larger size [27]. In addition, adenomas are encountered more frequently in patients with synchronous primary cancers [28]. Anatomically, the distribution of colorectal adenomas is similar to cancers; both presenting more frequently in the left colon [29,30]. A large randomised controlled trial with a follow up period of 18 years illustrated that faecal occult blood testing

significantly reduced the incidence of colorectal cancer with this being attributed to the fact that adenomatous polyps would have been identified and removed in this group leading to a reduction in overall cancer incidence [31].

### 1.1.3 The role of colonoscopy in detecting colorectal cancer

Colonoscopy has been available since the 1960s when it was first developed by Dr William Wolff and Dr Hiromi Shinya [32]. Prior to this, clinicians were relying on the use of barium enema and sigmoidoscopy to assess the colon but this was quickly superseded by the colonoscope which allowed for direct visualisation of the colon, biopsy sampling and removal of polyps [32]. Colonoscopy is currently the accepted investigation of choice for the detection of colonic pathology. It provides clinicians with the ability to establish a diagnosis, sample colonic tissue and perform therapeutic procedures.

Nevertheless, despite the benefits of a colonoscopy, it remains an invasive procedure that is not without risk. Patients are required to undergo bowel preparation, which involves tolerating a fluid diet and drinking large amounts of laxatives. It is an uncomfortable procedure and in the UK, most patients are offered the choice of mild sedation and analgesia in the form of pethidine, fentanyl, midazolam or an analgesic gas containing 50% nitrous oxide and 50% oxygen (Entonox). In addition, most units subscribe to the use of hyoscine-n-

butylbromide. Most of these prescribed medications have rare side effects that can be life threatening.

There are also associated risk of complications occurring because of the procedure with the most severe being risk of bleeding (1.64/1000) and risk of bowel perforation (0.85/1000) [33]. Post polypectomy complication rates have been quoted at 7 per one thousand tests [34].

Current alternatives to colonoscopy include barium enema, virtual colonoscopy and more recently, colon capsule endoscopy. Barium enema is a radiological x-ray examination that involves the injection of a contrast agent like barium sulphate into the rectum. It carries a risk of radiation exposure and bowel perforation. The sensitivity of barium enema at 83% is lower than the sensitivity of colonoscopy at 95% at detecting colorectal cancer [35]. The polyp detection rate of barium enema is reported to be 38% compared to the polyp detection rate of 80% in patients with colonoscopy [36].

Virtual colonoscopy or Computed Tomography colonography produces a 3-dimensional model of the colon that can digitally detect polyps. It requires no sedation and is none invasive thus avoiding major complications of bleeding and perforation. However, bowel preparation is still required and any polyps detected would still need to be removed by a colonoscopy. There is also a small

risk of radiation exposure which might predispose to more cancers [30]. The sensitivity of virtual colonoscopy in detecting colorectal lesions has been reported at 73% when compared to colonoscopy [37].

In capsule endoscopy, patients are required to swallow a small pill equipped with a camera that travels into the bowel to collect images. It was first used primarily for small bowel imaging in occult bleeding and has been very successful in that aspect. However, advances in capsule technology have allowed for its use in colon imaging with the second generation of colon capsule endoscopy – PillCam Colon 2 being made available. Early studies suggest that it has a role in cases of colonoscopy failure, in patients unwilling to undergo colonoscopy, in cases when colonoscopy is contraindicated and potentially in colorectal cancer screening or surveillance of inflammatory bowel disease patients [38]. Interestingly, Japanese researchers have begun experimenting with a magnetic navigation system which when used together with colon capsule endoscopy aim to provide a less invasive method of potentially investigating the whole gastrointestinal tract. In their small pilot study, they illustrated a completion rate of 97.5% [39]. A recent prospective Japanese trial of 66 patients evaluated the sensitivity of colon capsule endoscopy and found that it had a high sensitivity of 94% in detecting significant colonic lesions when followed by standard colonoscopy [40]. Although this may have been elevated in part because all patients had known colonic

lesions, this study is promising and illustrates that colon capsule endoscopy is safe with a high level of patient acceptability. However, capsule endoscopy does not allow for biopsy, removal of lesions or steering so patients would still be required to have a colonoscopy if any pathology is found.

Colonoscopy remains the superior test in its ability to detect pathology, obtain colonic tissue samples and allow for therapeutic procedures simultaneously. An increase in screening colonoscopy uptake has been linked to a reduction in colorectal cancer and mortality [41,42]. Studies have shown that patients aged 55-64 who undergo single screening flexible sigmoidoscopy and polypectomy, with referral for colonoscopy where high risk features are found, have a reduced incidence of colorectal cancer of 23% and mortality of 31% in intention-to-treat analyses [43].

### 1.1.4 Adenoma detection rate

Adenoma detection rate (ADR) is defined as the proportion of screening colonoscopies in which at least 1 histologically confirmed adenoma is found. As a surrogate marker of thorough mucosal visualisation, it is regarded as the most important indicator of quality in colonoscopy and is the most widely accepted measure [44–47].

Adenoma detection rate is normally utilised as the primary objective of most studies that are set on improving quality of colonoscopy. There is a wide variation in ADR amongst non-screening colonoscopists but mean ADR has been reported as 15.9% [48]. For BCSP colonoscopists, the mean ADR is much higher at 46.5% [44]. This can partially be explained by the increased risk of adenomas in patients with a positive faecal occult blood test, but may also reflect high quality colonoscopy.

There are other methods of measuring adenomas such as mean adenomas per procedure (MAP), mean adenomas per positive procedure (MAP+) and advanced adenoma detection rate(AADR). MAP is defined as the total number of adenomas detected divided by the number of procedure. There are increasing arguments being made for the routine use of MAP and its role in measuring quality as ADR essentially only measures the presence of one adenoma and therefore the removal of one adenoma [44,49]. The identification and removal of every adenoma present is important as this determines the surveillance interval and reduces the risk of interval colorectal cancer [49].

MAP+ is the total number of adenomas detected divided by the number of procedures where one or more adenomas were detected. In the screening population, ADR and MAP correlate positively to each other with 53% of procedures where adenomas are found demonstrating one adenoma [44]. On the

other hand, MAP+ correlated less well with ADR. Polyp detection rate (PDR) has also been studied and correlates well with ADR in colonic segments proximal to the splenic flexure [50]. The application of a conversion factor to the PDR accurately estimates the ADR [51].

AADR measures adenomas more or equal to 10mm in size with or without the presence of villous components or high-grade dysplasia. Advanced adenomas occur less frequently but have a higher malignant potential. An American observational cohort study of 1933 colonoscopies from 14 colonoscopists reported significant variations in ADR and AADR but found no correlation between them [52]. This may be a result of an increase in small non-advanced adenomas that are counted towards ADR, as demonstrated by a German study analysing trends in ADR in a screening programme [53].

### 1.1.5 The relationship between adenoma detection rate, missed lesions and interval colorectal cancers

Although colonoscopy is the gold standard investigation, it remains an imperfect tool for cancer prevention and can be improved upon. Low ADR is implicated as one of the primary reasons for interval colorectal cancers which are colorectal cancers that develop after colonoscopy. Interval colorectal cancers are also often called post colonoscopy colorectal cancers in literature.

A few population-based studies have shown that up to 7.2% of patients newly diagnosed with colorectal cancer underwent a colonoscopy within a few years prior to diagnosis [54,55]. They defined interval colorectal cancers as patients with a diagnosis of cancer 3 years after index colonoscopy [54,55]. A population-based study in the Netherlands of 5107 patients discovered that 2.9% of diagnosed colorectal cancers were interval colorectal cancers. In this group of patients, 57.8% were because of missed lesions. Their definition of interval colorectal cancers were patients who had a cancer diagnosed 5 years after index colonoscopy. Interestingly, they concluded that 86% of interval colorectal cancers were preventable as they were due to factors like missed lesions, inadequate examination or surveillance. Most the lesions that were missed were proximally located, small and had a flat appearance [56]. It is clear that lesions that go on to become cancers in a select group of patients are still being missed. Missed lesions are polyps or adenomas that are missed during index colonoscopy. There are many reasons for missed lesions which include; suboptimal technique; shorter withdrawal time; inadequate bowel preparation; presence of flat, depressed or subtle lesions; and the inability to visualise the proximal side of haustral folds, flexures (blind spots), rectal valves and ileocaecal valve [57–59]. It has been estimated that 10% of the colonic surface remains to be observed under the standard forward-viewing colonoscope even with good bowel preparation [60].

Adenoma miss rate is calculated by dividing the total number of adenomas found on repeat examination by the total number of adenomas found on initial and repeat examination. The miss rate for adenomas have been quoted at up to 24% [59,61]. Small adenomas (<10mm in size) have a significantly higher miss rate compared to larger adenomas (>10mm) [59]. As adenoma miss rate can be difficult to calculate as it requires tandem colonoscopy, most studies use the ADR rate as a measure of quality in identifying and removing adenomas. Missed lesions or a low ADR is implicated as one of the primary reasons for interval colorectal cancers.

Two large studies have illustrated the relationship between a low ADR and high interval colorectal cancer rate. A large Polish study evaluated 1866 colonoscopists and 45,026 colorectal screening patients and identified 42 interval colorectal cancers. A low ADR was associated with a greater risk of interval colorectal cancer (P = 0.008.). The hazard ratio for interval colorectal cancers where the colonoscopist had an ADR of less than 20% was ten times that of colonoscopists with an ADR of greater than 20%. This provided a clear correlation that ADR was an independent predictor of the risk of interval colorectal cancer after screening colonoscopy [47]. In contrast, Corley et al studied 300,000 colonoscopies performed by 136 colonoscopists for screening, surveillance or diagnostic purposes and found an inverse relationship between

ADR and the risk of interval colorectal cancer, advanced-stage interval colorectal cancer and fatal interval colorectal cancers. ADR ranged from 7.4 to 52.5% and was inversely related to the risk of developing interval colorectal cancer. A 1% increase in ADR was associated with a 3% reduction in the risk of interval colorectal cancer and a 5% reduction in risk of a fatal interval colorectal cancer [62]. Thus, if we increase ADR, there is evidence that the risk of interval colorectal cancers can be reduced substantially.

### 1.1.6 Factors influencing ADR

Despite a variation in ADR, there has been an improving trend in the United Kingdom over recent years [63–65]. The reasons for these are explored in further detail.

#### 1.1.6.1 Endoscopy training programmes

The Joint Advisory Group on Gastrointestinal Endoscopy (JAG) was established in 1994 with the initial aim of supporting doctors in training. It now oversees quality assurance for endoscopy units and services, sets standards for competencies, regulates accreditation of units and individual endoscopists and is heavily involved in education and training. The National Endoscopy Training Programme was created by JAG and has resulted in an overall improvement in

endoscopy training in the UK. The JAG Endoscopy Training System (JETS) is an e-portfolio system that enables training progress and competencies to be monitored in addition to providing a platform for set training standards. Table 1 illustrates the criteria required for full certification in colonoscopy by JAG.

| Criteria for full criteria | Requirements |
|---|---|
| Colon provisional certification | Granted |
| Caecal intubation rate | ≥ 90% |
| Unassisted (physically) | ≥ 90% |
| Formative DOPyS*(level 2) | ≥ 4 |
| Polypectomy techniques assessed by DOPyS (level 2) – Stalked polyps | ≥ 1 |
| Polypectomy techniques assessed by DOPyS (level 2) – Small sessile lesions/ EMR | ≥ 1 |
| Formative DOPyS scores | ≥ 90% “3”s and “4”s |
| Polyp detection and removal | ≥ 10% |
| Sedation rate for patients aged < 70 | < 5mg midazolam |
| Sedation rate for patients aged > 70 | < 2.5mg midazolam |
| Analgesia rate for patients aged < 70 | < 50mg pethidine, < 100µg fentanyl |
| Analgesia rate for patients aged > 70 | < 25mg pethidine, < 50µg fentanyl |
| Serious complication rate | < 0.5% |
| Number of procedures completed since award of provisional certification | ≥ 100 |
| Recommended lifetime procedure count | ≥ 300 |
| Procedures in previous 3 months | ≥ 25 |

**Table 1** - JAG Criteria for full certification for colonoscopy [66]

* DOPyS are Direct Observational Procedure assessment forms specifically created to assess polypectomy

A study investigating adenoma miss rates in patients undergoing tandem colonoscopy by a trainee followed immediately by an experienced colonoscopist showed that adenoma miss rates improved with experience of the trainee [67]. Along with better training because of JAG, there is also an increased awareness in quality improvement measures that can be utilised to improve adenoma detection rate. This includes measures like using better bowel preparation, longer withdrawal times, using hyoscine-n- butylbromide, performing rectal retroflexion and utilising dynamic patient position changes.

#### 1.1.6.2 National screening programmes

Population screening programmes result in earlier detection of CRC's at a more treatable stage by detecting and removing adenomas that may become malignant over time thus reducing CRC mortality [68]. The introduction of the National Health Service Bowel Cancer Screening Programme (NHS BCSP) in 2006 which utilises faecal occult blood population screening has also resulted in an increase in quality of colonoscopy. The NHS BCSP aims to improve outcomes from colorectal cancer through earlier detection but has inadvertently contributed towards adenoma detection and removal [69].

All BCSP colonoscopists must undergo strict accreditation criteria via the Screening Assessor Accreditation System which is a web-based application

process maintained by JAG. This includes achieving caecal intubation rates of more than 90% and ADR of more than 20% in a total of at least 1000 procedures within a 12-month period prior to being accredited as BCSP colonoscopists. Completion of accreditation examination at an independent unit is then undertaken which consists of multiple choice question examination and performance of two colonoscopies observed by two independent and trained examiners using objective directly observed colonoscopic procedural skills assessment criteria. Following on from this, they are subjected to a rigorous ongoing audit of performance which include carrying out a minimum of 150 screening colonoscopies annually, having a complication rate below the national average, maintaining caecal intubation rate of more than 90% and ADR of more than 35% in patients within the BCSP programme [70].

ADR in the NHS BCSP has been reported at 29% in women and 43% in men [71]. ADR is comparatively higher in BCSP colonoscopist by 30% compared to non-BCSP colonoscopists [44]. This may be explained by an increased risk of adenomas in NHS BCSP patients who attend because of positive faecal occult blood tests but may also reflect higher quality colonoscopy. The quality of BCSP colonoscopy has been reported widely [44].

The English Bowel Scope Screening (BSS) programme began in 2013 and invites adults aged 55 and above for a one off-flexible sigmoidoscopy. The aim of the

BSS programme is to reduce CRC development via the adenoma-carcinoma sequence through the detection and removal of adenomas from the left side of the colon. At present, ADR is not as high as expected in BSS patients compared to the NHS Bowel Cancer Screening Programme with the national ADR reported at 9.2%[72]. However, a large UK study has shown that offering one-off flexible sigmoidoscopy screening to adults aged 55-64 years reduces CRC incidence by 23% and mortality by 31% [43].

#### 1.1.6.3 Quality in colonoscopy

A large study of UK colonoscopy practice carried out in 2004 audited the performance of 68 endoscopy units in the UK. This reported inadequate colonoscopy completion rates of 56.9% and polyp detection rates of 22.5%. In addition, only 17% of colonoscopists had received supervised training for their first 100 colonoscopies and only 39.3% of colonoscopists had attended a training course [64]. These stimulated significant improvements to colonoscopy training and toughened the case for national bowel cancer screening programmes as previously discussed. This combination has resulted in benchmarking of standards and an increased awareness of the need for good quality colonoscopy. High quality colonoscopy is crucial to ensure maximal pathology detection and has been shown to reduce the incidence of colorectal cancer [47]. The aim in a high-quality colonoscopy is perform a complete

procedure in which the caecum is reached, the mucosa inspected thoroughly, patient comfort maintained and any pathology adequately diagnosed and dealt with [73]. In addition, a report of the procedure should be completed with photo-documentation of specific landmarks and abnormalities [46].

Multiple factors are responsible for the variation in ADR which include; suboptimal technique; shorter withdrawal time; inadequate bowel preparation; presence of flat, depressed or subtle lesions; and the inability to visualise the proximal side of haustral folds, flexures (blind spots), rectal valves and ileocaecal valve [57–59]. It has been estimated that 10% of the colonic surface remains to be observed under the standard forward-viewing colonoscope even with good bowel preparation [60]. Therefore, it is unsurprising that other key quality indicators have been proposed for colonoscopy include bowel preparation scores, caecal intubation rate, withdrawal time, completeness of polyp removal and patient safety and satisfaction [58].

Firstly, patients with good bowel preparation scores have a higher ADR. A systematic review and meta-analysis of 11 studies by Clark et al illustrated that ADR was significantly higher in patients with adequate versus inadequate bowel preparation with odds ratio of1.30 (1.10-1.42) and 1.30 (1.02-1.67). There was no significance in patients with intermediate quality versus high quality

bowel preparation which may be because it is often possible to remove small amounts of soft faecal material with saline flushes during colonoscopy [74]. During colonoscopy, the colon is examined predominantly in the withdrawal phase which has been the subject of scrutiny for many studies trying to establish a link between the withdrawal phase and ADR. A study of 31,088 NHS BCSP colonoscopies found that a longer withdrawal time of more or equal to 11 minutes compared to less than 7 minutes improved mean ADR from 42.5% to 47.1% [75]. This is echoed by another large study of 10,955 procedure in the United States which found that colonoscopy withdrawal time of 7 minutes was associated with median PDR [76]. Shorter withdrawal times of less than 6 minutes are associated with lower ADR and an increased risk of interval colorectal cancer [63,77].

In addition, the positioning of patients during colonoscopy and the anatomy of the colon means that not all segments of the colon are distended during the procedure. The use of dynamic position change has been shown allow luminal gas to rise and fluid to drain away from the segment of interest using gravity. A study by East et al demonstrated that carrying out specific and purposeful position changes for different segments of the colon correlated with significantly higher ADR [78].

Bowel spasms and the presence of folds can complicate thorough inspection of colonic mucosa during the withdrawal phase. The administration of antispasmodics such as hyoscine-n-butylbromide have been found to improve ADR in small studies [79,80]. Various endoscopic devices have been invented to improve adenoma detection rate. This will be discussed in further detail in the next section.

## 1.2 Devices in colonoscopy

### 1.2.1 Introduction

Optical imaging innovations and technological developments in the field of colonoscopy have attempted to increase adenoma detection rates with the introduction of high-definition endoscopes, electronic chromo-endoscopy (including narrow band imaging), wide angle colonoscopy and retrograde viewing devices [81,82]. However, lesions located on the proximal sides of colonic folds can still be missed during standard conventional colonoscopy [83]. Although these views may be improved with dynamic patient position changing and routine retroflexion, these manoeuvres may not be effective, particularly in narrower colonic segments, even with the use of a paediatric colonoscope or gastroscope [78,84]. Transparent caps and hoods that attach to the tip of the scope have been created to hold down folds and improve visualisation in the forward

view. However, they can make the tip of the scope more rigid and longer which may impair insertion in an angulated sigmoid colon [85,86].

### 1.2.2 Imaging modalities

#### 1.2.2.1 High definition colonoscopy

High definition colonoscopy is the use of a high definition monitor resulting in more images per second being shown with a higher resolution compared to standard colonoscopy thus improving image quality and potentially identifying more pathology.

Early studies did not report a significant difference in ADR when comparing high definition colonoscopy with standard colonoscopy [87–92]. The earliest positive result was a cohort study where the total number of nonflat, >6mm adenomas was higher in the high definition group compared to standard colonoscopy[87]. A retrospective study of 2430 patients reported a significant increase of 4.5% in ADR in patients with high definition colonoscopy with an up to 3% increase found in adenomas less than 5mm in size. However, confounding factors such as withdrawal time and quality of bowel preparation were not standardised [93].

Two recent studies have reported a significant increase in ADR (8.2% p=0.02, 12.6% p=0.007) with high definition colonoscopy [94,95]. However, these were retrospective cohort studies. A meta-analysis of 4422 patients described marginal differences between high definition colonoscopy and standard colonoscopy for the detection of adenomas with an incremental yield of 3.5% (95% CI 0.9%-6.1%) with a number needed to treat of 28 [96].

In conclusion, high definition colonoscopy appears to improve ADR. However, prospective studies are required to further confirm this.

#### 1.2.2.2 Conventional chromo-endoscopy

Conventional chromo-endoscopy utilises contrast dyes that allow for enhancement of the colonic mucosa, thus improving visualisation and highlighting surface contours (Figure 2b). In conventional pan colonic chromo-endoscopy, dye in the form of indigo carmine or methylene blue is sprayed with a catheter or is applied directly through the working channel of the endoscope in a segmental fashion onto the entire colorectal mucosa.

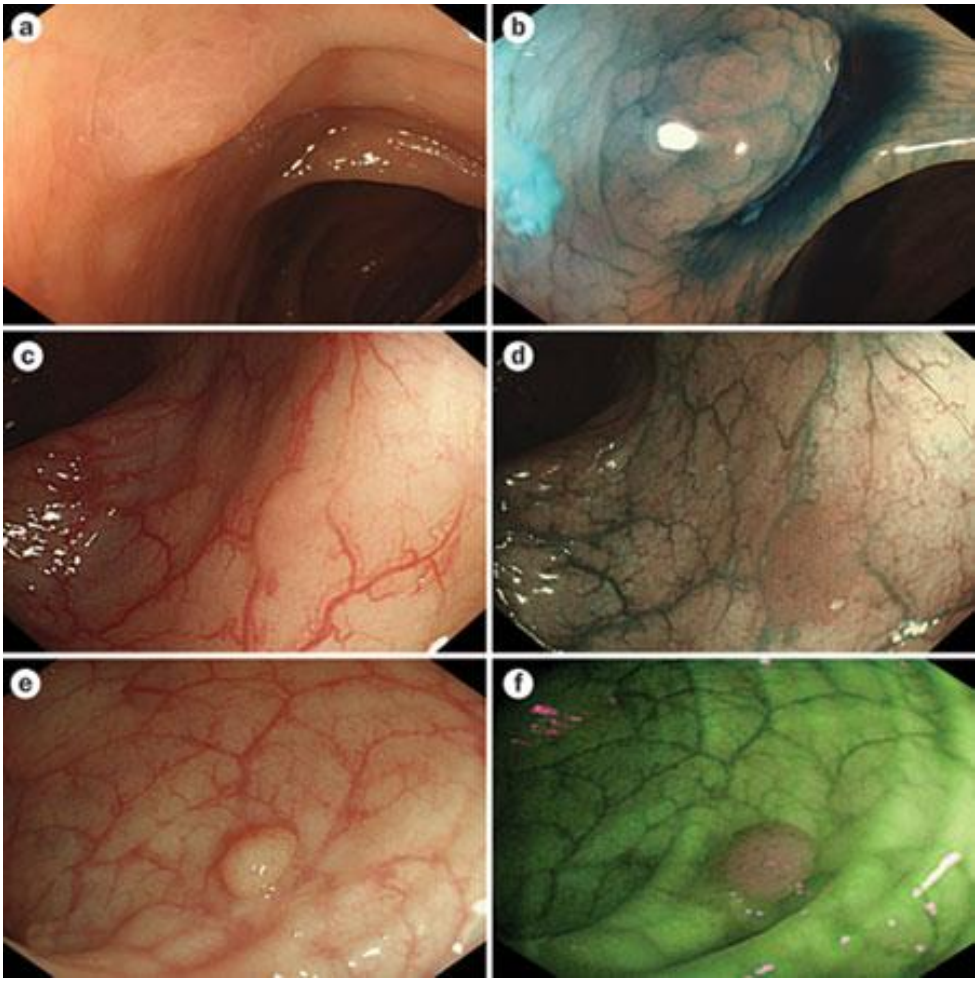


**Figure 2**: (a) High definition endoscopy and (b) conventional chromo-endoscopy, (c) high definition endoscopy and (d) narrow band imaging, (e) high definition endoscopy and (f) autofluorescence imaging[97]

A Cochrane systematic review analysed seven RCTs with a total of 2727 participants and assessed the role of conventional chromo-endoscopy compared to standard colonoscopy in polyp detection and found that chromo-endoscopy generated more participants with at least one neoplastic lesion (OR 1.53, 95% CI 1.31-1.79) and at least one diminutive neoplastic lesion (OR 1.51, 95%

CI 1.19 to 1.92)[98]. They concluded that conventional chromo-endoscopy improved the detection rate of small polyps by 90%[98]. Thus, chromo-endoscopy may have a role in improving ADR.

#### 1.2.2.3 Virtual chromo-endoscopy

Virtual chromo-endoscopy utilises a narrow spectrum of wavelengths with a decreased penetration depth to enhance visualisation of the colon mucosa. These narrow wavelengths increase the vascular contrast of the mucosa and allows for improved visualisation of the colonic mucosal surface. Different manufacturers have developed their own systems of virtual chromo-endoscopy and the use of such modalities has been proposed for characterisation of colonic lesions[99].

##### 1.2.2.3.1 Narrow Band Imaging (NBI)

Narrow band imaging uses narrow band filters placed behind the light source that eliminate red light and increase the exposure of blue and green light. Blue light (415nm) enhances the visualisation of superficial mucosal capillaries while green light (540nm) increases the visibility of submucosal and mucosal vessels (Figure 2d).

A Cochrane review of 11 RCT's and 3673 patients in 2012 found no evidence to suggest that NBI was significantly better than standard colonoscopy at improving detection rates in average risk populations [100]. Six successive RCT's have reflected this and shown no significant increase in ADR with NBI [101–106]. In contrast, a single centre RCT found higher adenoma miss rates in standard colonoscopy compared to high definition colonoscopy utilising NBI (49% versus 27%, p-0.036)[107]. The authors argued that because two different colonoscopes were used in tandem compared to the other previously reported studies – standard colonoscopy followed by another colonoscope with better definition and high contrast, their study was more representative of a true miss rate.

There is evidence that NBI may be of benefit in high risk population groups such as Lynch Syndrome, and hyperplastic polyposis syndrome in ADR [108,109] . In Lynch syndrome, the use of NBI in the proximal colon for surveillance colonoscopies improved ADR by 15%[108] whereas NBI has been reported to significant reduce polyp miss rate by 26% in hyperplastic polyposis syndromes [109].

Current evidence has not demonstrated that NBI significantly improves ADR in normal risk individuals. However, NBI may be of benefit in high risk individuals.

#### 1.2.2.3.2 Fuji Intelligent Colour Enhancement (FICE)

Fuji Intelligent Colour Enhancement is a computed spectral estimation technology system that enhances the visibility of mucosal and vascular details by narrowing the bandwidth of light. FICE offers the endoscopist the choice of different wavelengths for optimal views.

Three tandem RCTs and one none tandem RCT have shown no significant benefit of FICE over standard colonoscopy or NBI [110–113] in improving ADR. However, in the tandem RCT by Chung et al, inadequate bowel preparation in at least 50% of may have impacted on ADR[110]. Yoshida et al also reported that poor visibility was noted with FICE for blood visibility, which may affect detection of more vasculated adenomatous lesions[112]. There is no strong evidence that FICE improves ADR.

#### 1.2.2.3.3 Autofluorescence Imaging (AFI)

Autofluorescence imaging produces real-time pseudo-colour images by a rotating filter that produces short wavelength light. Tissue exposure to this light leads to excitation of endogenous substances and subsequent emission of fluorescent light (Figure 2f).

A tandem prospective study of 88 patients found an ADR rise of 8% with AFI which increased to 30.3% when performed by less experience endoscopists[114]. However, this study only looked at the rectum and sigmoid area. There are no large RCTs available yet for this modality. A recent meta-analysis of six studies with 1199 colonoscopies found no significant differences in ADR or PDR in AFI compared to WLE but reported that AFI did significantly decrease AMR (OR 0.62; 95%CI 0.44–0.86) and PMR (OR 0.64; 95%CI 0.48–0.85) [115].

More evidence is required from RCTs to determine the role of AFI in improving ADR.

#### 1.2.2.3.4 i-SCAN

i-SCAN is another virtual chromo-endoscopy system designed to enhance surface and vascular pattern to improve optical diagnostic performance. It has three modes of image enhancement which are surface enhancement, contrast enhancement and tone enhancement.

Two randomised controlled trials reported conflicting ADR results. One study showed that i-SCAN improved ADR by up to 25% compared to standard colonoscopy [116]. However, this study compared high definition colonoscopy and i-SCAN™ with standard definition colonoscopy. High definition colonoscopy

has been shown to be more sensitive in detecting small flat polyps and therefore this may not be a true representation of i-SCAN [87,90]. Only one study compared standard colonoscopy with standard colonoscopy and i-SCAN which is a better representation of the effectiveness of using i-SCAN in the average-risk population. This study concluded that there was no improvement in ADR but that i-SCAN played a role in real-time histology prediction of polyps [117].

The largest cohort study of 1936 patients reported higher ADR with i-SCAN including higher advanced adenoma detection rates [118]. However, the role of i-SCAN in improving ADR has not yet been proven conclusively and larger RCTs are required.

#### 1.2.2.3.5 Endoscopic Trimodal Imaging (ETMI)

Endoscopic trimodal imaging (ETMI) combines the use of high definition endoscopy, autofluorescence imaging and narrow band imaging during colonoscopy.

The use of ETMI in tandem colonoscopy RCTs has not been found to significantly reduce adenoma miss rates or improve ADR[119–121]. One study utilised non-academic endoscopists whilst the other two RCTs were conducted at expert centres. Two of these RCT's also recruited high risk patients with a

history of previous adenomas, cancer or a positive family history of cancer. Therefore, ETMI has not yet been demonstrated to improve ADR.

### 1.2.3 Devices to attach to scope

#### 1.2.3.1 Cap-assisted colonoscopy

Cap-assisted colonoscopy is the use of transparent caps that attach to the distal tip of the colonoscope to flatten colonic folds to improve mucosal visualisation proximally (Figure 3).

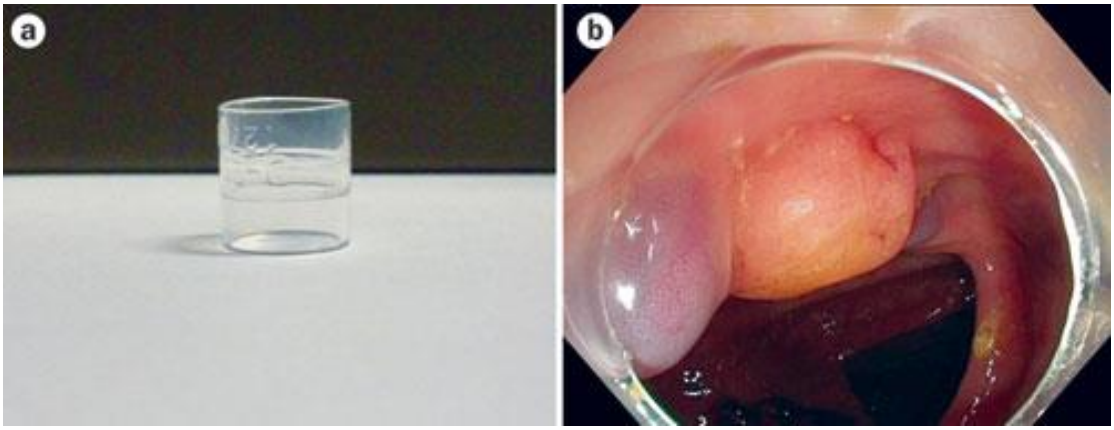


**Figure 3**: (a) A small cap to attach to the tip of the colonoscope, (b) view of mucosal lumen with cap-assisted colonoscopy which improves visualisation behind folds and flexures [97]

There have been mixed results in RCTs evaluating the diagnostic yield of cap-assisted colonoscopy. Initial studies which often included a small sample of endoscopists and had a limited sample size showed no improvement in ADR with cap-assisted colonoscopy [86,122,123].Some studies utilised polyp detection rate instead of ADR as their primary outcome [124]. A Cochrane review also concluded that cap –assisted colonoscopy increased polyp detection rate but there was not enough evidence to suggest it increased ADR as well[125]. A further systematic review concluded that there was an improvement in right sided adenomas with cap-assisted colonoscopy[126].

Other studies have shown equivocal results but they did show that cap-assisted colonoscopy improved patient comfort compared to standard colonoscopy[85,127,128]. The CAP study utilised a two-centre, multi-endoscopist, randomised controlled trial approach to determine the role of cap-assisted colonoscopy in adenoma detection[129]. There was no significant difference found with ADR in both groups. Cap-assisted colonoscopy seemed to be of benefit for some endoscopists who experienced an increase in ADR by 20% whereas in others, there was a 15% decrease. This was not related to endoscopist experience[129].

In conclusion, cap-assisted colonoscopy has not yet been demonstrated to convincingly improve ADR.

### 1.2.3.2 EndoRings

EndoRings is a silicone endoscopic add-on device that consists of a short tube-like core with several layers of flexible circular rings. It is attached to the tip of the scope and during scope withdrawal; the rings centre the scope and straighten colonic folds, thus enhancing mucosal views (Figure 4).


**Figure 4**: EndoRings attachment on a colonoscope [130]

One multicentre, randomised, tandem study has been completed comparing the use of EndoRings with standard colonoscopy and demonstrated a lower adenoma miss rate with EndoRings colonoscopy. There was no significant

difference in caecal intubation or withdrawal times although total procedure time was longer in EndoRings colonoscopy group due to removal of more polyps[131].

The initial study suggests benefits from EndoRings. However, further RCTs are required to validate this.

#### 1.2.3.3 Third Eye Panoramic

The Third Eye Panoramic device is a clip that is attached to the tip of a standard colonoscope to provide two additional video cameras. This results in three images which provide a panoramic view and reveals parts of the lumen that may otherwise be hidden with standard colonoscopy (Figure 5). The Third Eye Panoramic is a device that can be cleaned, disinfected and used multiple times prior to disposal.


**Figure 5**: Third Eye Panoramic device[132]

A small prospective observational study of 33 patients illustrated that the Third Eye Panoramic device enhanced colonic views with a caecal intubation rate of 100% and an overall adenoma detection rate of 44%[133].

This seems to be a promising device but RCT's are required to explore the role of this device in colonoscopy.

#### 1.2.3.4 Endocuff and Endocuff Vision

Endocuff is a device made up of polypropylene core and elastomer projections that work to enhance mucosal visualisation of the colon. Endocuff Vision is a newer version of the Endocuff. This will be discussed in further detail in the next section.

### 1.2.4 Different types of colonoscopes

#### 1.2.4.1 Full Spectrum Endoscopy (FUSE)

Full spectrum endoscopy utilises a colonoscope that allows for a high resolution 330 degrees "full spectrum" view of the colonic lumen. It consists of a main control unit and a video colonoscope with three imagers and LED groups located at front and both sides of the flexible tip. The video images transmitted

from the three cameras on the left side, front and right side of the colonoscope are displayed on three continuous monitors. The addition of the two side cameras provides a more comprehensive view of colonic mucosa and visualises blind spots more easily (Figure 6).

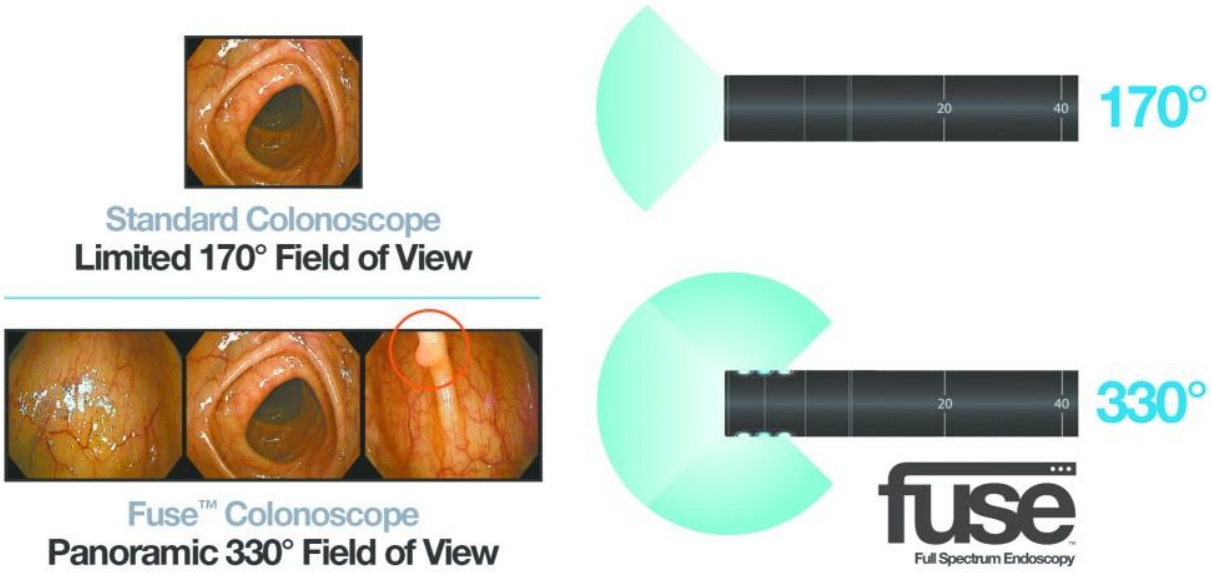


**Figure 6**: Full spectrum endoscopy compared to standard colonoscopy [134]

An initial prospective single centre pilot cohort feasibility study showed that FUSE was feasible, usable and safe [135]. Following on from this, a multicentre, randomised, tandem colonoscopy trial illustrated that the adenoma miss rate was significantly lower in patients in the FUSE group (7% versus 41%, $p<0.0001$)[136]. This result has been mirrored by a Greek tandem study that reported lower miss rates by 23% with FUSE. It is argued that the use of FUSE could lead to an absolute reduction of 145 USD dollars per patient due to a

significantly higher sensitivity associated with FUSE [137]. However, a recent Italian RCT reported no statistifically significant difference in ADR and AADR between FUSE and standard colonoscopy in screening programme patients [138].

Therefore, there is inconclusive evidence for the use of FUSE in reducing adenoma miss rates. In addition, more studies are required to determine the learning curve of looking at three monitors at the same time and the efficacy of FUSE in day to day endoscopy practice.

#### 1.2.4.2 Third Eye Retroscope (TER)

Third Eye Retroscope was invented to enhance the visualization of proximal colonic folds. It is a device that consists of a video processor, a single-use polarizing filter cap for colonoscope light source and a 3.5mm flexible single-use catheter with a camera and diode light source at the tip. The TER is retroflexed at 180 degrees after being inserted through the working channel of the colonoscope and provides a 135-degree retrograde view of the colon (Figure 7).


**Figure 7**: Third Eye Retroscope [132]

The TERRACE study which was the only randomised back-to-back study of TER found a net additional detection rate of 30% for polyps and 23% for adenomas [139]. The disadvantages of TER are that it needs to be removed from the working channel if an accessory device is required. The insertion of TER reduces the suctioning capacity by 50% and it is also expensive as a single use, disposable device. More RCTs are required to assess the role of TER in ADR improvement.

#### 1.2.4.3 NaviAid G-EYE Balloon Colonoscope

The NaviAid G-EYE colonoscope is made up of a standard colonoscope with a permanently integrated, reusable balloon at the distal end of the colonoscope.

It allows for the colonoscope to be withdrawn with the balloon partially inflated, thus allowing for straightening of haustral folds and improving mucosal views. In addition, the balloon can be inflated to help anchor and stabilise the colonoscope when required (Figure 8).

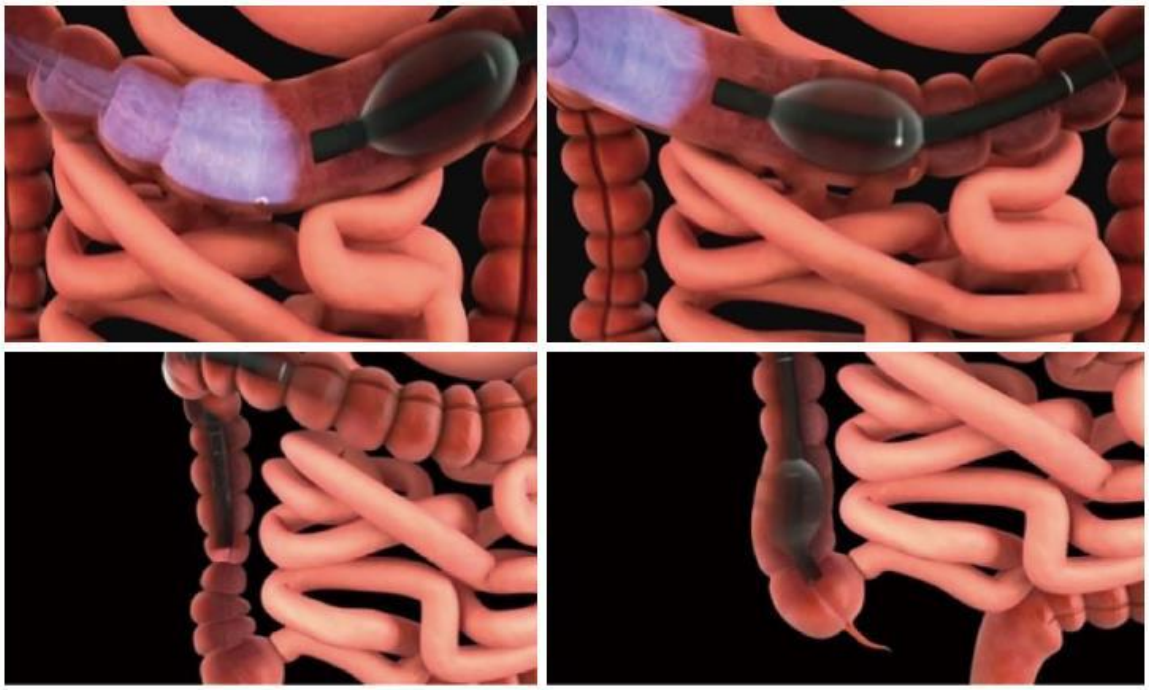

**Figure 8**: NaviAid G-EYE colonoscopy [140]

A prospective cohort study of 50 patients identified an ADR of 45% with no major complications[141]. A recent tandem randomised controlled trial found that the adenoma miss rate of NaviAid G-EYE colonoscopy was significantly lower 7.5% vs 44.7%, P=0.0002) compared to standard colonoscopy[142]. This was a

relatively small trial of 106 patients and the same colonoscopist performed both tandem procedures and was not blinded to the technology used.

In conclusion, large RCT's are required to further investigate the role of NaviAid G-EYE Balloon Colonoscope in ADR improvement.

#### 1.2.4.4 Aer-O-Scope colonoscope

The Aer-O-Scope consists of a disposable scanner which is the colonoscope component and a work station. The disposable scanner is made up of a soft multi-lumen tube with a unique pneumatic self-propulsion system that utilises balloons and low-pressure carbon dioxide gas. This system maximises the views of the entire colonic mucosa, including behind haustral folds. The lens head enables 360 degrees panoramic, omni-directional visualisation on a single screen (Figure 9).

**Figure 9**: Aer-O-Scope [143]

A pilot study of 12 patients found a promising caecal intubation rate of 83% with no complications observed[144] but there are no RCTs comparing the use of Aer-O-Scope against standard colonoscopy. Thus, larger studies are required to assess the safety and accessibility of Aer-O-Scope before considering its role in ADR improvement.

### 1.2.4.5 Extra wide angle view colonoscopy (EWAVE)

The extra wide angle view colonoscope has a 147-235 degree angle lateral and backward view lens and a standard 140 degree angle forward view lens and is able to combine views from both lenses to display a single image (Figure 10).

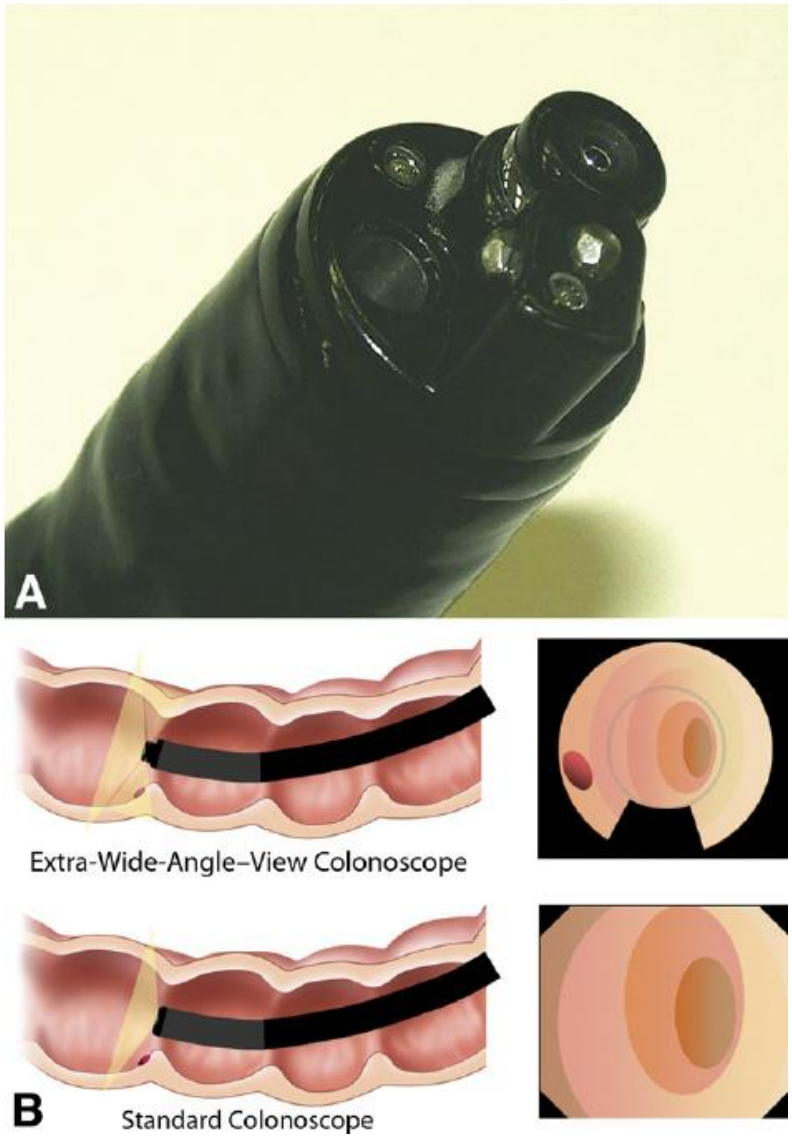


**Figure 10 :** Extra Wide Angle View Colonoscope[145]

The only published study so far is a small study of 47 patients where 57.1% of polyps were detected with the lateral-backward view. This study concluded that E-WAVE was safe and feasible with potential to improve ADR[146].

More studies are required to determine the role of E-WAVE in colonoscopy.

### 1.2.5 Others

#### 1.2.5.1 Water immersion and water exchange colonoscopy

Water immersion colonoscopy is the infusion of water during the insertion of the colonoscope with air insufflation. This method allows water to flow in the direction of the lumen which assists in locating the correct direction for intubation. Water immersion has been shown to reduce pain scores, reduce the need for sedation and improve tolerability of the procedure (102). Early studies reported no differences in ADR when comparing water immersion with air insufflated colonoscopy [147].

Water exchange colonoscopy is the infusion of water during the insertion of the colonoscope without air insufflation. It is a technique where water containing faeces is removed and exchanged for clean water in the absence of air insufflation. Early RCTs reported no improvement in ADR [148,149].

A Cochrane review of 16 RCTS and 2933 patients found the main benefit of water immersion and water exchange colonoscopy to be reduction in pain scores[150]. There was also a small improvement in ADR (RR 1.16, 95%CI 1.04 to 1.30, P=0.007)[150]. A recent RCT of 1200 patients reported that water exchange colonoscopy achieved higher ADR (adenomas < 10mm) in the right colon of 5% in compared to water immersion and 4.7% compared to air insufflation colonoscopy[151]. The results are promising but further evidence for the benefit of water aided colonoscopy from RCTs is required.

## 1.3 The birth of Endocuff and Endocuff Vision

To understand how the Endocuff was invented, it is important to consider the background of its inventors. Professor Anthony Axon is a retired Consultant Gastroenterologist who qualified in medicine with Distinction from Bart's and The London University in 1965. He was appointed as a Consultant Gastroenterologist at The General Infirmary at Leeds in 1975 and was awarded the honorary title of Professor of Gastroenterology by the University of Leeds in 1995. He retired from clinical practice in 2012 but is still currently active in the medico-legal field, medical research and medical education. He has three children – Patrick who trained in surgery, Anthony who became a barrister and Antonia who qualified as a General Practitioner. The Endocuff project became a family affair but Patrick Axon has become the main driving force behind the

device. In his spare time, he works as a Consultant Otologist, Hearing Implant and Skull Base Surgeon who works at Addenbrooke's Hospital within the Cambridge University Hospitals NHS Foundation Trust.

The notion of Endocuff came about as Professor Axon was devising devices that would allow for more stability in the caecum during colonoscopy. Together with input from the rest of the family they formed ARC Medical Design Limited in 2008 and sourced the help of a design company – Design Edge to form the first prototype of the Endocuff. The main objective of the Endocuff at that point was for its finger-like projections to grapple onto the colonic folds thus propelling the colonoscope further towards the caecum. However, they quickly discovered during experimental stages that the Endocuff seemed be more of use in holding back colonic folds during withdrawal of the colonoscope.

The Endocuff is a new disposable device that is made up of a polypropylene core and thermoplastic elastomer 'finger like' projections. It was first CE marked in August 2011. The first version of Endocuff comprised backwards pointing flexible 'finger like' 12mm projections at intervals around the device circumference (Figure 11). It is mounted at the tip of the scope and held on by friction with a minimum pull-off force of 10 Newton's. It anchors the scope tip against the bowel wall to provide a stable platform of access. The soft, elastic projections are pushed back and recoil towards the scope shaft during insertion

but evert during withdrawal to hold colon folds away from the field of view allowing for excellent visualisation of the colonic lumen. The distal end of the Endocuff does not extend beyond the tip of the colonoscope and therefore does not get in the way of the suction, flushing or working channels. Endocuff is available in four different sizes (length of 23.8mm x diameters of 16.1/16.7/17.2/18.5mm with the finger like projections folded back and 32.6/33.1/33.6/34.8mm with finger like projections opened out) and therefore compatible with most colonoscopes.

**Figure 11**: Endocuff (personal photograph by author)

The use of Endocuff is contraindicated in patients with known colonic strictures or active inflammatory disorders such as acute infective colitis, colonic Crohn's disease, ulcerative colitis and acute diverticulitis. Endocuff has won multiple industry awards namely the 'Industrial Product Design of the

Year category of the Plastics Industry Awards 2013' that is dedicated to rewarding innovation and exceptional performance to the best designers within the polymer field. It has also won the' Red Dot Award' in 2012 and a Silver Award in the 'A Designs Awards 2013'.

There have been a few studies looking at the role of Endocuff during colonoscopy with promising results. The first study performed was a case series of 12 patients, which looked at complex sigmoid polyp resection and scar assessment in the sigmoid colon. A complete colonoscopy was not performed. The authors concluded that Endocuff-assisted colonoscopy (EAC) was a safe and easily used device. However, they reported minor mucosal 'scratches' observed in 25% of patients [152]. Following on from this in 2013, German researches carried out a study of 50 EAC procedures with caecal intubation rate of 98%, ileal intubation rate of 76% and ADR of 34%. In 30% of patients, small, superficial, "scratch-like" mucosal lesions were observed, especially in the ileocaecal region [153].

In the United States, a case series of 93 EAC and 143 standard colonoscopy (SC) procedures was reported with EAC resulting in a higher PDR (78.5% vs 57.3%, $p<0.001$, higher ADR (44.1% vs 27.3% $p=0.01$), flat polyp detection rate (23.8% vs 12.3% $p=0.04$) and sessile serrated adenoma detection rate (10.8% vs 4.2%,

p=0.06). The mean number of polyps per procedure was higher in the Endocuff group (2.99 vs 1.60, p=<0.001). Polyp detection was not improved with the use of the Endocuff in the average risk screening population [154]. Subsequently, a Swiss pilot study of 104 screening colonoscopies utilising Endocuff demonstrated an ADR of 47% with no adverse events noted [155].

Initially, the most promising results were from two large multicentre trials from Germany and the United States. In Germany, a four-centre prospective trial randomised 500 patients to EAC or SC with the primary outcome measure being ADR. There was an increase from 21% to 35% in ADR (p=0.0001) with an absolute increase of 14% and a relative improvement of 74%. The total number of adenomas detected increased from 88 to 144 with a relative improvement of 64%. There was no difference in procedural and withdrawal times and caecal and ileal intubation rates were unchanged. Interestingly, there were no reports of mucosal lacerations or adverse events in this larger trial [156].

In the United States, a multicentre study retrospectively compared 165 patients with EAC and 153 patients with SC. The average number of polyps detected per patient in the Endocuff group was 1.31 vs. 0.82 (p=<0.001) and the average number of adenomas 0.8 vs 0.38 (p=<0.001) which is an increase of 110%. The ADR was also higher amongst patients where the Endocuff was used compared

with standard colonoscopy (46.6% vs. 30.0%, p=0.002) a difference of 16.6%, which is 55% more than the original ADR. The Endocuff was also significantly superior in right sided adenoma detection (32.1% vs 18.3%; p=0.004). These results suggest that EAC may result in higher overall ADR and be more effective in detecting right sided adenomas by enabling better inspection of proximal colonic folds [157].

An Italian single centre RCT enrolled 288 patients and reported that Endocuff-assisted colonoscopy increased ADR by 3.3% (p<0.01). In addition, they also described mucosal erosions in 2.5% of patients with 1 patient requiring mucosal adrenaline injections [158].

The largest multicentre study to date is a recent prospective Dutch study that compared the use of Endocuff-assisted colonoscopy with standard colonoscopy in 1063 procedures. Interestingly, there was no difference in ADR found between both groups (p=0.92). There was a much higher ADR in the control group for this study compared to the previous studies from Germany and America which may account for this in part. However, MAP was found to be higher in the EAC group. In addition, detection of diminutive adenomas (<6mm) and flat adenomas was significantly higher in the EAC group. Caecal intubation rates were similar in both groups but caecal intubation time (7 vs 8.3

minutes, p=0.25) and withdrawal time (median 7 vs 8 minutes, p=0.02) was significantly shorter in the EAC group [159]. Therefore, it seems that Endocuff may still have a role to play in improving colonoscopy quality.

Despite the promising results of Endocuff in improving ADR, the Axon family felt that they could improve the Endocuff and aimed to create a new generation of the device that would prevent the small, superficial, "scratch-like" mucosal lesions that were associated with the earlier studies. This gave birth to the Endocuff Vision that consists of a single row of 15mm projections that gently evert and flatten folds even in the ascending colon to provide clearer views (Figure 12). Endocuff Vision was CE marked in August 2016. These changes deliver yet more tip control without compromising ease of intubation or loop management. Each arm is at least 3mm longer than the original Endocuff. In addition, it was felt that just having one row of arms instead of two would eliminate the risk of trauma to mucosal surfaces as observed with the first version.

**Figure 12**: Endocuff Vision (personal photograph by author)

**Figure 13**: Endocuff Vision mounted on the tip of a colonoscope (personal photograph by author)

St Marks Hospital in London have performed a small pilot study of 3 experienced colonoscopists in using the new Endocuff Vision attachment in their Bowel Cancer Screening Programme by comparing ADR before and after using Endocuff Vision. The mean adenoma detection rate rose from 52% to 76%

with a caecal intubation rate of over 98% [160]. In addition, they compared the cumulative ADR of 4 screening colonoscopists before and after the use of Endocuff Vision and found that this rose from 48.71% to 65.5%. No adverse events have been reported so far in these early small studies [161].

A similar randomised controlled trial that completed recruitment recently is the E-CAP (Endocuff-assisted colonoscopy versus standard colonoscopy in the faecal occult blood test-based UK Bowel Cancer Screening Programme) trial based in Portsmouth. The authors recruited 534 patients and reported no significant difference in adenoma detection rate, advanced adenoma detection rate or cancer detection rate.

Mean withdrawal time was significantly shorter in Endocuff-assisted colonoscopy (16.9 minutes versus 19.5 minutes, $p<0.005$). However, this study was only a single centre study comparing the use of Endocuff-assisted colonoscopy versus standard colonoscopy in the screening population [162] .

The ADENOMA (Accuracy of Detection using ENdocuff Optimisation of Mucosal Abnormalities) study is the first large multicentre prospective trial powered to comparing ADR in Endocuff Vision- assisted colonoscopy versus standard colonoscopy in the diagnostic, screening and surveillance population.

## 1.4 Synopsis of the literature to date

Several devices and imaging modalities have been made available. Of these, the most promising imaging modalities are high definition colonoscopy and conventional chromo-endoscopy. With regards to devices, cap-assisted colonoscopy has been studied the most but the results have not yet been demonstrated to convincingly improve ADR. Larger randomised control trials are still needed to investigate the use of Endocuff Vision, EndoRings, FUSE, TER, NaviAid G-EYE and Aer-O-Scope in improving ADR. This study will contribute towards determining the efficacy of Endocuff Vision in improving ADR.

# Chapter 2: Aims and Objectives

The intention of this trial was to investigate the use of Endocuff Vision in patients attending for a colonoscopy.

Endocuff Vision is designed to improve fold retraction during the withdrawal to provide a wider field of view and assist in improving scope tip stabilisation thus possibly improving ADR. Endocuff Vision is designed to have a positive effect on scope insertion time, caecal or terminal ileal intubation, patient comfort and satisfaction.

## 2.1 Primary objective

The primary objective was to ascertain if there was a difference in adenoma detection rate between Endocuff Vision– Assisted colonoscopy (EVAC) and standard colonoscopy (SC) patient groups and to quantify this by measuring the adenoma detection rate (ADR).

Adenoma detection rate is defined as the proportion of colonoscopies in which at least 1 histologically confirmed adenoma is found. It is calculated by taking the number of colonoscopies in which there is at least 1 histologically confirmed adenoma found divided by the total number of colonoscopies

performed in the same time. It is a surrogate marker of mucosal visualisation and is regarded as the most important indicator of quality in colonoscopy [163].

## 2.2 Secondary objectives

The secondary objectives were:

1. To compare mean adenomas detected per procedure (MAP) between EVAC and SC.
2. To demonstrate non-inferiority of caecal intubation rates and insertion time to caecum between EVAC and SC.
3. To demonstrate non-inferiority in complete withdrawal time in procedures where no polyps are detected between EVAC and SC.
4. To demonstrate non-inferiority of patient satisfaction with EVAC and SC groups.
5. To ascertain the distribution of polyps in the colon in EVAC and SC groups by location.
6. To establish the rate of cuff exchange (that is, how often the cuff has to be removed)

In addition, we planned to analyse the data to check for any difference in future colonoscopic workload produced by increased ADR in terms of number of potential follow up procedures based on British Society of Gastroenterology

adenoma surveillance guidelines [164] between the EVAC and SC groups. Furthermore, we also compared the ADR of NHS Bowel Cancer Screening Programme (BCSP) and non-BCSP colonoscopists, compared the ADR of the first 20% of patients scoped by each colonoscopist with the last 20% of patients in each arm to identify any changes in ADR and lastly, compared the baseline ADR of each colonoscopist prior to trial recruitment with their individual ADR in patients where Endocuff Vision was not used. These outcomes were analysed on an intention to treat basis.

# Chapter 3: Methodology

## 3.1 Study design

This clinical, randomised, multicentre study was conducted in subjects referred and scheduled for screening or surveillance colonoscopy via the Bowel Cancer Screening Programme (BCSP), diagnostic or surveillance colonoscopy through the symptomatic National Health Service (NHS), and compared Endocuff Vision-assisted colonoscopy (EVAC) with standard colonoscopy (SC). Patients were recruited from 6 participating hospital sites within the Northern Region Endoscopy Group and St Mark's Hospital, London. Initial recruitment began at South Tyneside Hospital, North Tees Hospital and St Mark's Hospital as part of an "internal pilot" for 1 month, which allowed for testing of the protocol and data collection processes. Any protocol amendments afterwards were disseminated to all participating sites. Study data was collected and analysed by the principal investigators.

The aim was to recruit 1772 patients. All patients were referred for a colonoscopy at each participating site. All potential participants were given a patient information leaflet about the study when their colonoscopy paperwork was sent to them, allowing adequate time to read the information leaflet (at least 24 hours) before consenting to the study. On attending the endoscopy

unit for their procedure, they were approached by a member of the research team, and given the opportunity to discuss the study. If they were willing to proceed with the study, they completed written consent forms, and baseline data was collected. Patients were then randomised to either EVAC group or SC group using a computer-generated randomisation tool. Following on from this, colonoscopy was performed and intra-procedural data collected by a member of the research team and transcribed onto a case report form. Any polyps that were detected and removed were followed up at the 21-day review date and histological diagnosis recorded post procedure by the research team. All colonoscopes were calibrated and serviced as per local guidelines.

Patients remained in the study for 21 days to allow collection of standard post colonoscopy complication data through review of medical notes, electronic hospital systems or via a phone call to the patient after the 21-day period elapsed. Serious Adverse Events (SAEs) were recorded for all patients from the day of colonoscopy to 21 days' post procedure. No additional follow-up visits from the patient were required. The timing of routine outpatient appointments and results was not affected by the study. All data was collated and analysed by the research team. All adverse events were collected and classified by the research team with input from the Data Monitoring Committee.

Data collected before colonoscopy:

1. Patient demographics (age, gender)
2. Indication for colonoscopy
3. Past abdominal surgical history

Data collected during colonoscopy procedure:

1. Polyps detected (total number, plus for each polyp seen; location; size; morphology; removed (Yes/No); removal method)
2. Extent of examination
3. Insertion time to caecum
4. Insertion time to terminal ileum (if applicable)
5. Withdrawal time
6. Position change
7. Use of bowel preparation
8. Use of carbon dioxide insufflation
9. Patient satisfaction and comfort scores
10. Immediate complications

Data collected post procedure:

1. Polyp histology
2. Complications up to 21 days
3. Adverse events

## 3.2 Inclusion Criteria

All patients attending for screening, surveillance or diagnostic colonoscopy were invited to participate in the study. All patients were aged 18 and over and could give informed consent.

## 3.3 Exclusion Criteria

1. Patients with absolute contraindications to colonoscopy
2. Patients with established or suspicion of large bowel obstruction or pseudo-obstruction
3. Patients with known colon cancer or polyposis syndromes
4. Patients with known colonic strictures
5. Patients with a known severe diverticular segment (that was likely to impede colonoscope passage)
6. Patients with active colitis (Ulcerative Colitis, Crohn's colitis, diverticulitis, infective colitis)
7. Patients lacking capacity to give informed consent
8. Patients on clopidogrel, warfarin, or other new generation anticoagulants who have not stopped this for the procedure
9. Patients who were attending for a therapeutic procedure or assessment of a known lesion

10. Pregnancy

## 3.4 Withdrawal criteria

During colonoscopy, Endocuff Vision was withdrawn in situations where:

1. There was an acute angulation in a fixed sigmoid colon rendering scope insertion not feasible with the Endocuff Vision mounted
2. There was a new diagnosis of polyposis syndrome
3. There was a new diagnosis of active colitis (where the colonoscopist is concerned regarding the risk of mucosal damage)
4. There was identification of a new colonic stricture
5. There was a new cancer diagnosis and progression of the colonoscope with the Endocuff Vision attached was not possible.

## 3.5 Setting/ Participating centres

Seven NHS hospital sites participated and enrolled patients into the trial. Six participating sites within the Northern Region Endoscopy Group included one tertiary referral centre (North Tees and Hartlepool Hospitals NHS Foundation Trust) and five district general hospitals (South Tyneside NHS Foundation Trust, , Northumbria Healthcare NHS Foundation Trust, County Durham and Darlington NHS Foundation Trust, City Hospitals Sunderland NHS Foundation

Trust, South Tees Hospitals NHS Foundation Trust) whilst St Mark's Hospital (London North West Healthcare NHS Trust) was a tertiary referral centre for endoscopy.

## 3.6 Randomisation

Patients underwent stratified randomisation into EVAC or SC groups based on age, gender, hospital site and BCSP status. This was done by means of a computer-generated system using a dynamic adaptive algorithm in collaboration with North Wales Organisation for Randomised Trials in Health (NWORTH) Clinical Trials Unit.

## 3.7 Participating colonoscopists and training with Endocuff Vision

There was a maximum of 10 colonoscopists per site and colonoscopists were chosen to reflect the range of experience. At each site, a limited number (maximum 4) of BCSP colonoscopists were selected. All colonoscopists at participating units underwent theoretical and practical sessions of training (using online/DVD tutorials) with Endocuff Vision and had a lifetime experience of at least 20 cases with using the device prior to study commencement. A retrospective review of colonoscopists using Endocuff identified that a learning curve of 4 procedures seemed to be adequate with the

ability to improve ADR from 20% to 54.5% (p=0.03) when looking at 4 operators [165]. At least one colonoscopist from each site attended the training day where the study was discussed, use of the Endocuff Vision demonstrated and online/DVD tutorials provided for training of other colonoscopists.

## 3.8 Central training

I organised a central training day which was held on 8th December 2014 and attended by all lead colonoscopists and principal research nurses from participating sites. As part of my preparations for the training day, I selected the venue which was the Endoscopy Unit at North Tees and Hartlepool NHS Hospital, distributed and prepared all training material including training DVD's and PowerPoint presentations. Professor Colin Rees led the training day which included live endoscopy case demonstrations of the use of Endocuff Vision. Mrs Debbie Skelhorn (Quality Assurance and Compliance Lead) and Mr David Hunnisett (Information Technology Manager) from NWORTH Clinical Trials Unit provided training on the use of randomisation system and data entry onto the MACRO database.

This meeting generated multiple valuable ideas that resulted in substantial and none-substantial protocol amendments. A substantial protocol amendment was made to allow research nurses to have the option of making a phone call to

patients that did not live within the geographical reach of their local hospital to ensure that they had not encountered any complications because of their colonoscopy procedure at the 21-day review. This was necessary as some hospitals were tertiary referral centres.

A virtual training package was provided to lead colonoscopists at each site to distribute in their respective hospitals as training aids. This consisted of a training DVD, which contained copies of all PowerPoint presentations, delivered during the training day, a training video on the use of Endocuff Vision and all site file documents.

### 3.9 Local training

I visited individual sites with Mrs Gayle Clifford (Principal research nurse at South Tyneside Hospital) to provide further training and carry out site initiations.

The principal research nurse and lead colonoscopist for each site including all participating trial colonoscopists and research nurses for each unit attended this meeting. These visits were pre-arranged with sites in advance, with each visit taking an hour and a half. During the visits, the training video was shown and I went through the paper Case Report Forms with all attendees. All sites

were required to have signed training logs for each trial member confirming that training had taken place.

St Marks Hospital in London was the only site that did not receive a site initiation visit as they already had sufficient training in the use of Endocuff Vision. All participating colonoscopists at St Marks had already used the Endocuff Vision more than 20 times prior to involvement in the trial and published a small case series on the use of Endocuff Vision in improving ADR [161].

I also delivered an extra additional local training session to the bowel cancer screening specialist nurses at the Durham and Darlington NHS Hospital site as they had expressed their interest in participating in the study to the lead colonoscopist and wanted to assist in recruiting patients.

### 3.10 Data collection and data entry

Research nurses and occasionally bowel cancer screening nurses performed data collection and captured data in real time onto the paper Case Report Form. This method allowed for more accurate documentation especially as the research nurses were often supernumerary and did not have to carry out any

other duties in the endoscopy room, allowing for the completion of the Case Report Forms in a timely and accurate manner.

Research nurses were also responsible for data transfer from the paper Case Report Form onto the electronic MACRO database. All research nurses had undergone training on the use of Case Report Forms and MACRO database. Any missing data points were flagged up by MACRO, identified by NWORTH and passed on to myself to investigate and discuss with respective sites. We were unable to arrange for all data entry transfer from paper Case Report Form to MACRO to be double-checked and verified. However, Mrs Debbie Skelhorn from NWORTH carried out regular monitoring visits, which included choosing patients at random and comparing patient endoscopy reports and details in the medical case notes with the paper Case Report Forms and the electronic MACRO database system to check for accuracy. These monitoring visits occurred on the week of 8th June 2015 for South Tyneside NHS Foundation Trust and North Tees and Hartlepool Hospitals NHS Foundation Trust, week of 13th July for Northumbria Healthcare NHS Foundation Trust and City Hospitals Sunderland NHS Foundation Trust, week of 3rd August for St Mark's Hospital (London North West Healthcare NHS Trust) and week of 24th September for County Durham and Darlington NHS Foundation Trust and South Tees Hospitals NHS Foundation Trust.

### 3.11 Adverse events

The risks of adverse events for EVAC were believed to be equivalent to SC, including bleeding and perforation risks. There were also adverse events related to sedation such as cardio-respiratory compromise that were similar in both EVAC and SC procedures.

We measured Adverse Events (AEs), which were recorded in patients' medical notes and on case report forms. AEs were recorded for the 21-day period from the day of colonoscopy, or until withdrawal from study. Adverse events were defined as any new medical occurrence, or worsening of a pre-existing medical condition in a patient. There were no known complications or adverse events from Endocuff Vision. All AEs were graded as mild, moderate or severe, and was assessed by an Investigator to define the relationship to the Endocuff Vision.

Serious adverse events (SAEs) were treated clinically as appropriate and reported to the trial team within 24 hours of the research team becoming aware of the event, using the study specific SAE Form. The main NHS research ethics committee were informed of any related and unexpected SAEs within 15 days of the trial team becoming aware of the event, using the National Research Ethics Service SAE form.

An event was serious if it:

1. Resulted in death
2. Was life threatening
3. Resulted in hospitalisation or prolongation of existing hospitalisation (Exceptions to this were routine planned admissions, including admission for colonoscopy procedures as part of the study)
4. Lead to persistent significant disability or incapacity
5. Was otherwise considered to be medically significant by the Investigator

SAEs were recorded and reported from the time of colonoscopy until 21 days following the colonoscopy or until the time of withdrawal. SAEs were assessed for expectedness, severity and relatedness to the Endocuff Vision device. SAEs were followed until resolution, death, or until resolution with sequelae. In addition, all SAEs were recorded in the Case Report Form on the Adverse Events section. SAEs were reported even if they were expected events or unrelated events by the Investigator.

### 3.12 Assessment and follow up

Clinical follow up was performed as per routine clinical practice for each respective unit. Colonoscopy related complications were recorded up to 21 days' post procedure. All patients had their post colonoscopy surveillance interval (as per British Society of Gastroenterology or Bowel Cancer Screening Programme guidelines) recorded in the Case Report Form, where appropriate. In cases of incomplete colonoscopy, the reason for this was recorded. Eligible, consented patients remained in the study for 21 days following colonoscopy. SAEs were reported for the 21-day period post colonoscopy for all patients in the study. Complication data and adverse events at 21 days were reviewed by the most appropriate method for the population at each local site. This consisted of either a phone call to the patient or review of medical notes and hospital databases. If a patient was found to have presented to a different hospital post procedure to the hospital where the colonoscopy was performed, we contacted their General Practitioner to obtain information regarding the event. All units were given a 14-day allowance after the end of the 21-day follow up period to perform their 21-day review, but only data within the 21-day window was included. No additional visits were required for patients who entered the study. All follow up appointments post colonoscopy were arranged as per routine care for the respective unit if required. The timescale for the outpatient appointments and subsequent care was unaltered by participation in the study.

### 3.13 Sample size

The study was powered to detect a difference in the ADR between two groups. In calculating the sample size, we took into consideration that there were 2 subgroups of participants – those undergoing colonoscopy via the BCSP, and those with symptoms or being followed up in the general, non-screening, NHS service. ADR varied between these two groups; in the BCSP screening population ADR was 46.5%, and in the non-screening population it was 15.9% [44,48]. A difference in ADR of 5-10% would be of clinical importance (5% in the non-screening cohort, and 10% in the screening cohort). Preliminary work on BCSP participants at one of the Chief Investigators' sites suggested that such a rise in ADR for EVAC procedures was possible. The proportion of screening to non-screening participants was anticipated to be approximately 20:80. Mean ADR for the whole group was therefore likely to be 21.8%, and a 6% increase in ADR to 27.8% was deemed to be clinically significant. Therefore, to demonstrate a 6% increase in ADR with a 5% significance level and 90% power using a one-sided test it was calculated that 886 patients per group were required for the study resulting in 1772 patients in total.

## 3.14 Data analyses

The primary outcome was adenoma detection rate. A chi-square test was used to compare this outcome between groups. A secondary outcome was the number of adenomas detected per procedure. This was likely to have a positively skewed distribution, and so the Mann-Whitney test was used to compare between groups. An additional secondary outcome was the proportion of patients who required a follow up procedure (based on British Society of Gastroenterology adenoma surveillance guidelines), which was be compared between groups using the chi-square test. Other secondary outcomes were examined on a non-inferiority basis, namely caecal intubation rate, insertion time to caecum, withdrawal time in procedures where no polyps were found and patient satisfaction. The margin of non-inferiority was set for all outcomes which were:

- Caecal intubation rate – 5%
- Withdrawal time – 1 minute
- Insertion time – 1 minute
- Patient satisfaction (nurse assessment of comfort) – 1 point (on 0-9 scale)
- Patient satisfaction (Patient experience questionnaire: Binary variables Q12, Q15, Q16, Q17, Q18) – 10%

- Patient satisfaction (Patient experience questionnaire: Ordinal variables Q13, Q14) – 10% in percentage answering 'agree' or 'strongly agree'
- Patient satisfaction (next day questionnaire) - 1 point (on 0-11 scale)

For the continuous outcomes, one-sided 97.5% confidence interval for the mean difference between groups was calculated. For the binary outcomes, a one-sided 97.5% confidence interval for the difference in proportions was calculated. Non-inferiority was assumed if the bound of the confidence interval did not cross the point of non-inferiority. The rate of cuff exchange was calculated in the EVAC group, along with a corresponding confidence interval. Data analyses were performed on an intention to treat basis. Data and all appropriate documentation were stored for a minimum of 15 years after the completion of the study, including the follow-up period. Data cleaning was performed on a 5% sample of participants randomly selected by the clinical trials unit using excel random number generations from each of the seven sites.

### 3.15 Data Monitoring Committee

The trial was supervised by the Data Monitoring Committee, which consisted of an independent chair, with 2 independent clinicians and an independent statistician. The aim of the Data Monitoring Committee was to safeguard the interests of trial participants, assess the safety and viability of the intervention during the trial and monitor the overall conduct of the clinical trial. The Data Monitoring Committee met every 4 months.

### 3.16 Trial Management Group

The Chief Investigator had overall responsibility for the study and oversaw all study management. The Trial Management Group was responsible for the day to day running of the trial. The Trial Management Group was supported by and reported to an independent Trial Steering Committee. The Trial Management Group met every 2 months.

### 3.17 Trial Steering Committee

The trial was supervised by the Trial Steering Committee, which consisted of an independent chair, independent clinician, patient and public involvement representative and an independent statistician. The role of the Trial Steering

Committee was to supervise the trial to ensure that the trial was conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the principles of Good Clinical Practice. The Trial Steering Committee met every 6 months.

### 3.18 Ethical considerations

Ethical approval was awarded by the North East – York Research Ethics Committee prior to the study starting (REC reference 14/NE/1111). There were no known additional risks to patients associated with the use of the Endocuff Vision device. The addition of Endocuff Vision did not add significantly to the duration of the procedure, although if adenoma detection rate increased significantly, the procedure would take longer due to increased polypectomy numbers. Patients were informed of the risks associated with standard colonoscopy and consented for the procedures as per standard clinical practice in each centre. In addition, patients completed a study specific consent form after discussion with the research team.

The study was conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The ADENOMA Study was supported by the British Society of Gastroenterology Endoscopy Research Committee and had been identified as a research priority. The protocol for

ADENOMA study was reviewed and endorsed by the Bowel Cancer Screening Research Committee.

### 3.19 Sponsorship and funding

South Tyneside NHS Foundation Trust was the study sponsor. The ADENOMA Study was conducted on existing NHS and BCSP lists, at no extra cost to the NHS. Funding was provided by ARC Medical Design Ltd to cover Endocuff Vision devices, clinical trial unit costs, and results analysis. ARC Medical Design Ltd is a company formed by Mr Patrick Axon that designed and invented Endocuff Vision. The two chief investigators of the ADENOMA study were full-time dedicated clinical researchers. Principal investigators at each site had a research team (of fellows and/or nurses) who recruited participants and collected data. No additional NHS resources were required for this study.

### 3.20 My role and responsibilities in this study

I developed the protocol with Professor Colin Rees prior to the start of the trial. This involved refining the protocol after performing a basic literature review and going through the practicalities of the patient recruitment process with our research nurses which allowed for identification of appropriate inclusion, exclusion and withdrawal criteria. Data points were chosen based on established quality indicators including bowel preparation and withdrawal times. I discussed and worked with our trial statistician to identify the sample size required and ensured that we had a robust statistical analysis plan in place prior to patient recruitment. Any issues identified were corrected with amendments sent to relevant ethical and research authorities. I worked closely with NWORTH ensuring that the trial protocol and any additional documents were accurate and compatible with their electronic systems. This included safeguarding clear randomisation procedures, data monitoring and reporting systems. I prepared all the standard operating procedure documents for the study including pre-attendance to endoscopy, day of procedure and 21-day review and adverse events.

I arranged for one-to-one training sessions with all colonoscopists at each site in the use of Endocuff Vision and led the training of research nurses in study protocol and data collection. This included organising a training day event for

all principal investigators and lead research nurses with live demonstrations of Endocuff Vision. I ensured that all investigators were trained in Good Clinical Practice. In addition, I organised site initiation visits, ensured adequate distribution of Endocuff Vision supplies and acted as the first point of contact for any queries from participating sites.

During the running of the trial, I recruited patients and collected data at the South Tyneside Hospital site with help from the research nurses. In addition, I oversaw the recruitment of patients at the other sites, allowing me to identify any issues during recruitment. Any adverse events were identified, escalated and investigated appropriately. During the trial, I prepared seven none substantial amendments and two substantial amendments which were approved by the local ethics committee. I sat on the the Trial Management Group and was an observer in the Trial Steering Committee and Data Management Committee.

On completion of the trial, I analysed the data with our trial statistician based on the statistical analysis plan. We identified trends in the data which led to further subgroup analyses. Once all the results were finalised, I presented the findings of this study at local, regional and international meetings. Lastly, I also prepared a manuscript for publication in the GUT journal which has been accepted and is currently in press.

### 3.21 The role of the Clinical Trials Unit

This trial was supported by the North Wales Organisation for Randomised Trials in Health (NWORTH) clinical trials unit. NWORTH provided:

- Electronic database that enabled sites to upload information on recruitment data, withdrawals and adverse events reporting. This database was called MACRO.
- Online randomisation system
- Monitoring visits at the start of the study to ensure compliance with Good Clinical Practice principles and trial protocol requirements
- Site closure visits

### 3.22 A description of the practical process

All patients referred for colonoscopy at each participating site were sent a patient information leaflet for the ADENOMA study at least 24 hours before they attended for the procedure. In most sites, this information was sent out together with their bowel preparation and instructions for the procedure. The information leaflet also contained contact details in case patients had any queries before their procedure.

On the day of the procedure, patients were approached by the research nurse who checked that they had received and read the patient information leaflet. After this was confirmed, the research nurse discussed the trial with patients, including going through eligibility criteria. Following on from this, patients were given the opportunity to read and sign the consent form. A copy of the consent form was given to the patient, a copy retained in the patient's medical notes and a copy kept in the trial file.

Subsequently, patients were transported to the endoscopy procedure room where the research nurse entered the patient's details (including age, gender and bowel cancer screening programme status) onto the randomisation website which determined if the patient was in the 'control' group or the 'intervention' group. This result was relayed to the colonoscopist. The colonoscopy procedure proceeded as routine if the patient was in the control group. If the patient was in the intervention group, Endocuff Vision was placed onto the tip of the colonoscope before proceeding. The research nurses stayed for the duration of the procedure in the endoscopy room and recorded use of sedation, position change, start and finish times of procedure, procedural findings and patient comfort scores onto a paper Case Report Form (CRF) (Appendix 1).

On procedure completion, the research nurse completed the nurse assessment comfort score questionnaire (Appendix 1) and the patient assessment of comfort questionnaire (see Appendix 1). This was done in either the endoscopy room or the endoscopy day ward depending on the level of sedation that the patient had received. On discharge from the endoscopy unit, patients were given the next day questionnaire (see Appendix 2) together with a pre-paid addressed envelope to be completed at home once they have recovered from the procedure.

Case Report Forms were filed by research nurses into the trial folder. On the 21-day review date, the research nurse looked at medical notes and electronic IT hospital systems or rang patients to check if they had any complications or emergency hospital admissions within that time. We also checked histology results for any polyps that were removed. If the patient lived locally, the research nurses only looked at medical notes and electronic IT systems. However, as some sites were tertiary referral centres, the research nurses rang patients that did not live locally to and enquired about any admissions or complications to other hospitals. This was documented on the 21-day review form (see Appendix 3).

Once the 21-day review form was completed, all data were uploaded by the research nurse onto MACRO which was an electronic database established by NWORTH. The MACRO electronic database was created based on the paper CRF and contained all the data points of the paper CRF. All site had a grace period of 14 days from the 21-day review date to complete the review and a further 28 days' grace period for data entry onto MACRO. Lastly, any next day questionnaires that were returned were also uploaded onto MACRO. Figure 14 illustrates a flow chart of the recruitment process.

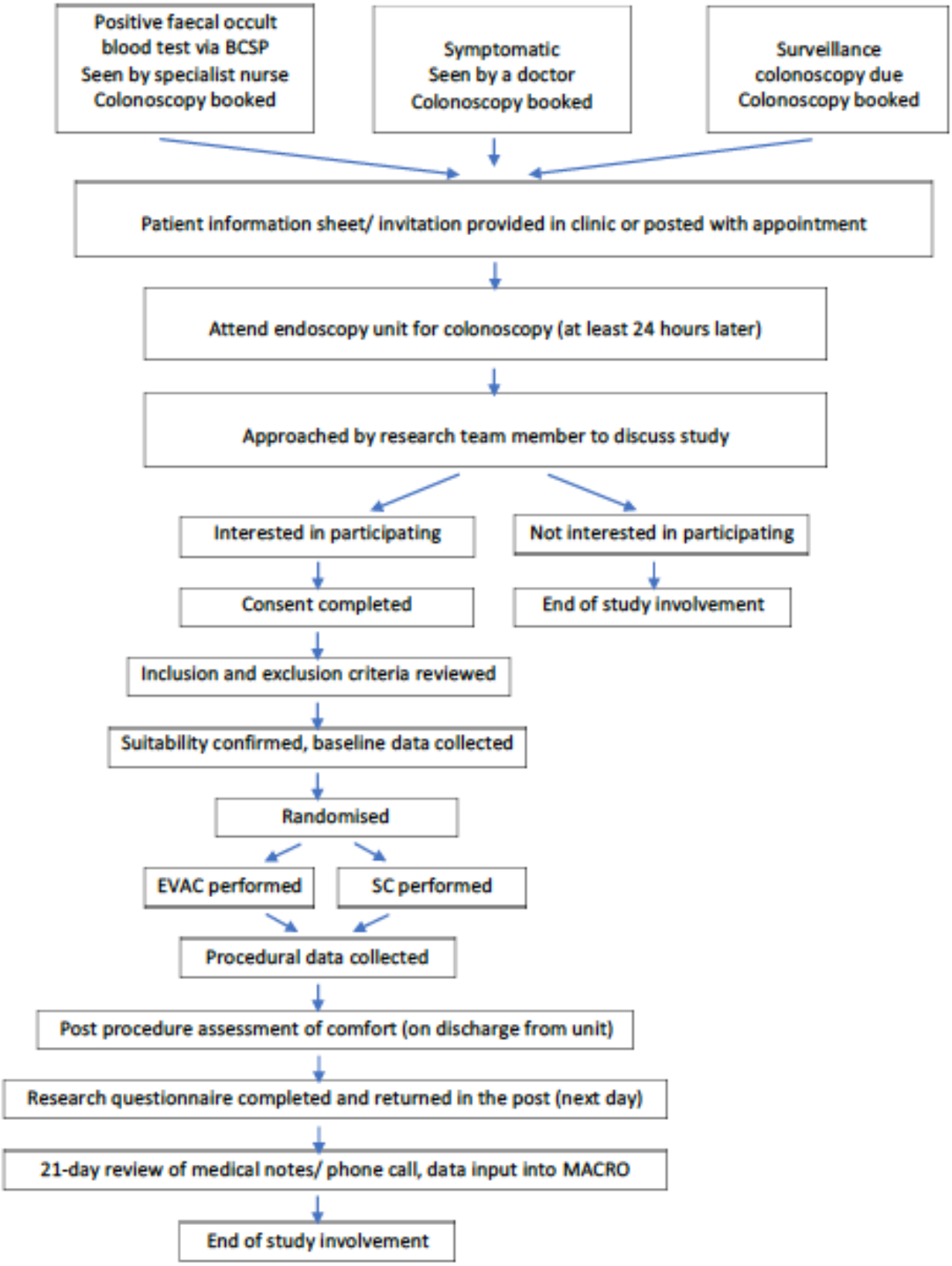


**Figure 14:** Flow chart of the recruitment process

# Chapter 4: Results

## 4.1 Descriptive data

Patients were assessed for eligibility prior to recruitment into the study based on the specific inclusion and exclusion criteria as described in Table 2.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Age 18 years and over<br>2. Referral for screening, surveillance, or diagnostic colonoscopy<br>3. Ability to give informed consent | 1. Absolute contraindications to colonoscopy<br>2. Established or suspicion of large bowel obstruction or pseudo-obstruction<br>3. Known colon cancer or polyposis syndromes<br>4. Known colonic strictures<br>5. Known severe diverticular segment (that is likely to impede colonoscope passage)<br>6. Patients with active colitis (ulcerative colitis, Crohn's colitis, diverticulitis, infective colitis)<br>7. Patients lacking capacity to give informed consent<br>8. Patients who are on clopidogrel, warfarin, or other new generation anticoagulants who have not stopped this for the procedure.<br>9. Patients who are attending for a therapeutic procedure or assessment of a known lesion.<br>10. Pregnancy |

**Table 2**: Inclusion and exclusion criteria

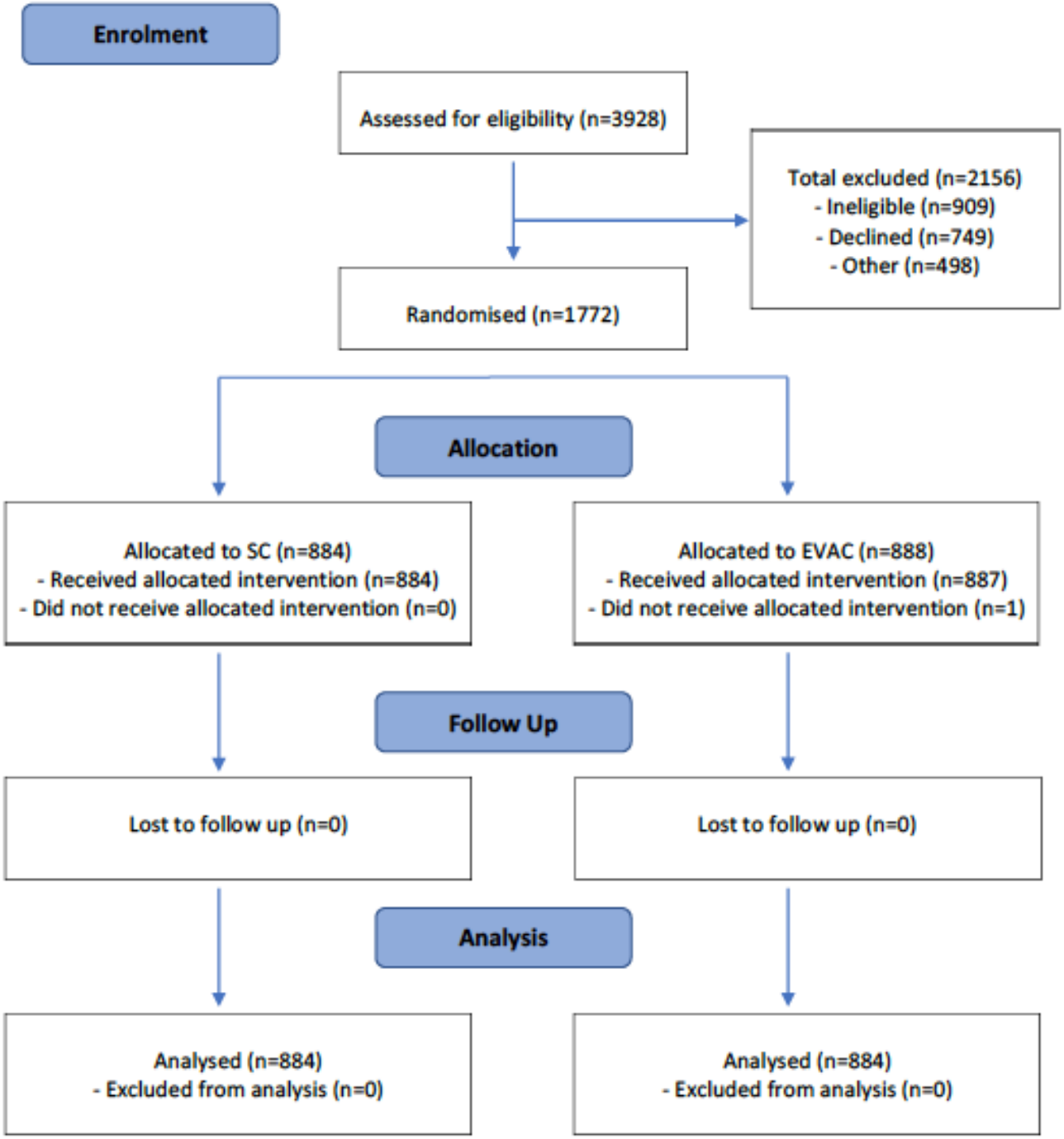


**Figure 15**: CONSORT trial flow diagram

| Reasons | Number of patients | Gender | | Age |
|---|---|---|---|---|
| | | M | F | |
| Not eligible | 909 | 499 (55%) | 410 (45%) | 62 (Range 17-98) |
| Declined to participate | 749 | 347 (46%) | 402 (54%) | 63 (Range 17-94) |
| Research team unavailable | 253 | 124 (49%) | 129 (51%) | 61 (Range 22-88) |
| Procedure cancelled | 139 | 78 (56%) | 61 (44%) | 62 (Range 18-88) |
| Did not attend | 100 | 60 (60%) | 40 (40%) | 56 (Range 22-85) |
| Randomisation system maintenance | 6 | 4 (67%) | 2 (33%) | 67 (Range 60-72) |

**Table 3**: Patients excluded from the study

| Factor | Both groups (n=1772) | SC (n=884) | EVAC (n=888) |
|---|---|---|---|
| Male | 1009 (56.9%) | 502 (56.8%) | 507 (57.1%) |
| Female | 763 (43.1%) | 382 (43.2%) | 381 (42.9%) |
| Mean age (SD) | 61.9 (11.4) | 62.1 (11.1) | 61.7 (11.7) |
| Age < 60 | 546 (30.8%) | 273 (30.9%) | 273 (30.7%) |
| 60-73 | 1029 (58.1%) | 515 (58.3%) | 514 (57.9%) |
| 74+ | 197 (11.1%) | 96 (10.9%) | 101 (11.4%) |
| Previous abdominal surgery | | | |
| No | 1089 (61.5%) | 542 (61.3%) | 547 (61.6%) |
| Yes | 683 (38.4%) | 342 (38.7%) | 341 (38.4%) |
| Recruitment | | | |
| Non-BCSP | 975 (55.0%) | 481 (54.4%) | 494 (55.6%) |
| BCSP | 797 (45.0%) | 403 (45.6%) | 394 (44.4%) |
| Indication for colonoscopy | | | |
| Cancer screening | 557 (31.4%) | 283 (32.0%) | 274 (30.9%) |
| Cancer surveillance follow up | 177 (10.0%) | 88 (10.0%) | 89 (10.0%) |
| Colonoscopy conversion | 63 (3.4%) | 32 (3.6%) | 31 (3.5%) |
| Symptomatic diagnostic | 703 (39.7%) | 346 (39.1%) | 357 (40.2%) |
| Symptomatic surveillance | 272 (15.4%) | 135 (15.3%) | 137 (15.4%) |

**Table 4**: Patient demographics for all patients randomised into study

| Factor | Both groups (n=975) | SC (n=481) | EVAC (n=494) |
|---|---|---|---|
| Male | 468 (48.0%) | 228 (47.4%) | 240 (48.6%) |
| Female | 507 (52.0%)) | 253 (52.6%) | 254 (51.4%) |
| Mean age (SD) | 59.1 (13.9) | 59.4 (13.6) | 58.7 (14.2) |
| Age < 60 | 464 (47.6%) | 228 (47.4%) | 236 (47.8%) |
| 60-73 | 362 (37.1%) | 180 (37.4%) | 182 (36.8%) |
| 74+ | 149 (15.3%) | 73 (15.2%) | 76 (15.4%) |
| Previous abdominal surgery | | | |
| No | 564 (57.8%) | 276 (57.4%) | 288 (58.3%) |
| Yes | 411 (42.2%) | 205 (42.6%) | 206 (41.7%) |
| Indication for colonoscopy | | | |
| Symptomatic diagnostic | 703 (72.1%) | 346 (71.9%) | 357 (72.3%) |
| Symptomatic surveillance | 272 (27.9%) | 135 (28.1%) | 137 (27.7%) |

**Table 5**: Patient demographics in non-BCSP subgroup

| Factor | Both groups (n=797) | SC (n=403) | EVAC (n=394) |
|---|---|---|---|
| Male | 541 (67.9%) | 274 (68.0%) | 267 (67.8%) |
| Female | 256 (32.1%) | 129 (32.0%) | 127 (32.2%) |
| Mean age (SD) | 65.4 (5.5) | 65.3 (5.5) | 65.5 (5.5) |
| Age < 60 | 82 (10.3%) | 45 (11.2%) | 37 (9.4%) |
| 60-73 | 667 (83.7%) | 335 (83.1%) | 332 (84.3%) |
| 74+ | 48 (6.0%) | 23 (5.7%) | 25 (6.4%) |
| Previous abdominal surgery | | | |
| No | 525 (65.9%) | 266 (66.0%) | 259 (65.7%) |
| Yes | 272 (34.1%) | 137 (34.0%) | 135 (34.3%) |
| Indication for colonoscopy | | | |
| Cancer screening | 557 (69.9%) | 283 (70.2%) | 274 (69.5%) |
| Cancer surveillance follow up | 177 (22.2%) | 88 (21.8%) | 89 (22.6%) |
| Colonoscopy conversion | 63 (7.9%) | 32 (7.9%) | 31 (7.9%) |

**Table 6**: Patient demographics in BCSP subgroup

Figure 15 is a flow diagram of the trial recruitment process. A total of 3928 patients were assessed for eligibility. However, 2156 were excluded with 909 patients being ineligible and 749 patients declining to participate (Table 3). Four hundred and ninety eight patients fell into the 'other' category. Of these, 253 patients had their colonoscopies performed in a list where there was no member of the research team available, 139 patients cancelled their procedures or had their procedures cancelled by clinicians, 100 did not attend their appointment and six had their colonoscopies performed when the randomisation online system was undergoing maintenance. However, when analysed by gender and mean age, the excluded group of patients were comparable to patients recruited into the study,

Table 4 illustrates the patient demographics. Most patients were male with a mean age of 62. Most patients did not have previous abdominal surgery. For BCSP and non-BCSP subgroups and indications for colonoscopy, patients were well matched in both SC and EVAC subgroups (Table 5 and Table 6).

Olympus colonoscopes were used in 1760 patients and Fuji colonoscopes in 12 patients. However, the use of these two types of colonoscopes were similar in both subgroups. A total of 48 colonoscopists participated in the trial, 17 of which were BCSP colonoscopists.

| Outcome | SC (n=884) | EVAC (n=888) | One-sided P-value |
|---|---|---|---|
| Hyoscine-n-butylbromide use | 568 (64.3%) | 627 (70.6%) | 0.002 |
| Carbon dioxide gas use | 678 (76.7%) | 672 (75.7%) | 0.69 |
| Position change | 772 (87.5%) | 718 (81.3%) | 1.00 |
| Rectal retroflexion | 785 (88.8%) | 723 (81.4%) | 1.00 |

**Table 7**: Use of hyoscine-n-butylbromide, carbon dioxide gas, position change and rectal retroflexion in all patients

| Outcome | SC (n=481) | EVAC (n=494) | One-sided P-value |
|---|---|---|---|
| Hyoscine-n-butylbromide use | 259 (53.9%) | 327 (66.2%) | <0.001 |
| Carbon dioxide gas use | 311 (64.7%) | 315 (63.8%) | 0.61 |
| Position change | 413 (86.0%) | 392 (79.8%) | 0.99 |
| Rectal retroflexion | 422 (87.7%) | 401 (81.2%) | 1.00 |

**Table 8**: Use of hyoscine-n-butylbromide, carbon dioxide gas, position change and rectal retroflexion in non-BCSP subgroup

| Outcome | SC (n=403) | EVAC (n=394) | One-sided P-value |
|---|---|---|---|
| Hyoscine-n-butylbromide use | 309 (76.7%) | 300 (76.1%) | 0.57 |
| Carbon dioxide gas use | 367 (91.0%) | 357 (90.6%) | 0.59 |
| Position change | 359 (89.3%) | 326 (83.2%) | 0.99 |
| Rectal retroflexion | 363 (90.1%) | 322 (81.7%) | 1.00 |

**Table 9**: Use of hyoscine-n-butylbromide, carbon dioxide gas, position change and rectal retroflexion in BCSP subgroup

The use of hyoscine-n-butylbromide and carbon dioxide was compared in both groups. The use of hyoscine-n-butylbromide was significantly higher in the EVAC arm when all patients were analysed together. Hyoscine-n-butylbromide was used in 70.6% of patients in the EVAC arm, compared to only 64.3% in the SC arm. A similar significant difference was observed in the non-BCSP patients, but no difference between arms was found for the BCSP subgroup. No difference between the two study groups was found with carbon dioxide gas use in all patients, or in the two main subgroups. There was no evidence that position changes or rectal retroflexion was higher in the EVAC group. These outcomes were assessed on a one-sided basis, specifically examining superiority

in the EVAC group. The data suggested lower occurrences of both outcomes in the EVAC group.

| **Variables** | **n/ N** | **% (95% CI)** |
|---|---|---|
| Endocuff Vision removal | 36 / 887 | 4.1% (2.9%, 5.6%) |
| **Reasons for removal** | **N** | **% removals** |
| Angulation in fixed sigmoid colon | 19 | 52.8% |
| New diagnosis of polyposis syndrome | 0 | 0.0% |
| New diagnosis of active colitis | 1 | 2.8% |
| Identification of colonic stricture | 6 | 16.7% |
| New cancer diagnosis | 7 | 19.4% |

**Table 10**: Endocuff Vision removal in all patients

| **Variable** | **n/ N** | **% (95% CI)** |
|---|---|---|
| Endocuff Vision removal | 21 / 494 | 4.3% (2.7%, 6.4%) |
| **Reasons for removal** | **N** | **% removals** |
| Angulation in fixed sigmoid colon | 13 | 61.9% |
| New diagnosis of polyposis syndrome | 0 | 0.0% |
| New diagnosis of active colitis | 1 | 4.8% |
| Identification of colonic stricture | 3 | 14.3% |
| New cancer diagnosis | 2 | 9.5% |

**Table 11**: Endocuff Vision removal in non-BCSP subgroup

| Variable | n/ N | % (95% CI) |
|---|---|---|
| Endocuff Vision removal | 15 / 393 | 3.8% (2.2%, 6.2%) |
| **Reasons for removal** | **N** | **% removals** |
| Angulation in fixed sigmoid colon | 6 | 40.0% |
| New diagnosis of polyposis syndrome | 0 | 0.0% |
| New diagnosis of active colitis | 0 | 0.0% |
| Identification of colonic stricture | 3 | 20.0% |
| New cancer diagnosis | 5 | 33.3% |

**Table 12**: Endocuff Vision removal in BCSP subgroup

Endocuff Vision was fitted in 887 patients but was subsequently removed in 36 patients (4.1% of those receiving it). The most common reason for removal was angulation in the fixed sigmoid colon, which accounted for just over half (53%) of removals. Other reasons for removal included new cancer diagnosis (19% of removals) and the identification of colonic stricture (17% of removals). Endocuff Vision removal was similar in non-BCSP patients (4.3%) and BCSP patients (3.8%).

| Outcome | SC<br>Mean (SD) | EVAC<br>Mean (SD) | Difference<br>(1-sided 97.5% CI) | Non-inferiority margin |
|---|---|---|---|---|
| Nurse assessment comfort (0-9 scale) (*) | 2.6 (2.2) | 2.6 (2.2) | 0.1 (-°, 0.3) | 1 unit |
| Next day questionnaire (0-11 scale) (*) | 3.4 (2.5) | 3.6 (2.3) | 0.2 (-°, 0.4) | 1 unit |
| ➢ Given sedation | 353 (67.9%) | 370 (68.4%) | 0.5% (-∞, 6.1%) | 10% |
| ➢ More uncomfortable than expected | 115 (21.8%) | 107 (19.7%) | -2.1% (-∞, 2.7%) | 10% |
| ➢ Camera insertion uncomfortable | 79 (15.0%) | 128 (23.6%) | 8.6% (-∞, 13.3%) | 10% |
| ➢ Colonoscopy stopped | 23 (4.4%) | 23 (4.3%) | -0.1% (-∞, 2.3%) | 10% |
| ➢ … satisfied response | 21 (91.3%) | 23 (100.0%) | 8.7% (-2.8%, ∞) | 10% |
| ➢ Bottom/stomach pain | 87 (16.5%) | 114 (21.0%) | 4.6% (-∞, 9.2%) | 10% |
| ➢ Bleeding from bottom | 40 (7.6%) | 50 (9.2%) | 1.6% (-∞, 4.9%) | 10% |

(*) Higher score indicates a lower level of satisfaction

**Table 13**: Patient scores non-inferiority outcomes – all patients

| Outcome | SC<br>Mean (SD) | EVAC<br>Mean (SD) | Difference<br>(1-sided 97.5% CI) | Non-inferiority margin |
|---|---|---|---|---|
| Nurse assessment comfort (0-9 scale) (*) | 3.1 (2.2) | 3.1 (2.2) | 0.1 (∞, 0.3) | 1 unit |
| Next day questionnaire (0-11 scale) (*) | 4.1 (2.5) | 4.1 (2.3) | 0.1 (∞, 0.4) | 1 unit |
| ➢ Given sedation | 195 (75.3%) | 209 (74.9%) | -0.3% (-∞, 6.9%) | 10% |
| ➢ More uncomfortable than expected | 71 (27.0%) | 73 (26.1%) | -0.9% (-∞, 6.6%) | 10% |
| ➢ Camera insertion uncomfortable | 49 (18.7%) | 81 (29.1%) | 10.4% (-∞, 17.6%) | 10% |
| ➢ Colonoscopy stopped | 12 (4.6%) | 16 (5.8%) | 1.2% (-∞, 4.9%) | 10% |
| ➢ … satisfied response | 11 (91.7%) | 16 (100.0%) | 8.3% (-7.3%, ∞) | 10% |
| ➢ Bottom/stomach pain | 65 (24.7%) | 83 (29.8%) | 5.0% (-∞, 12.5%) | 10% |
| ➢ Bleeding from bottom | 27 (10.3%) | 29 (10.3%) | 0.0% (-∞, 5.1%) | 10% |

(*) Higher score indicates a lower level of satisfaction

**Table 14**: Patient scores non-inferiority outcomes – non-BCSP subgroup

| Outcome | SC<br>Mean (SD) | EVAC<br>Mean (SD) | Difference<br>(1-sided 97.5% CI) | Non-inferiority margin |
|---|---|---|---|---|
| Nurse assessment comfort (0-9 scale) (*) | 1.9 (2.1) | 2.0 (2.0) | 0.1 (∞, 0.4) | 1 unit |
| Next day questionnaire (0-11 scale) (*) | 2.7 (2.3) | 3.0 (2.2) | 0.3 (∞, 0.6) | 1 unit |
| ➢ Given sedation | 158 (60.5%) | 161 (61.5%) | 0.9% (-∞, 9.3%) | 10% |
| ➢ More uncomfortable than expected | 44 (16.6%) | 34 (12.9%) | -3.7% (-∞, 2.3%) | 10% |
| ➢ Camera insertion uncomfortable | 30 (11.4%) | 47 (17.8%) | 6.4% (-∞, 12.4%) | 10% |
| ➢ Colonoscopy stopped | 11 (4.2%) | 7 (2.7%) | -1.5% (-∞, 1.6%) | 10% |
| ➢ … satisfied response | 10 (90.9%) | 7 (100.0%) | 9.1% (-7.9%, ∞) | 10% |
| ➢ Bottom/stomach pain | 22 (8.3%) | 31 (11.8%) | 3.5% (-∞, 8.6%) | 10% |
| ➢ Bleeding from bottom | 13 (4.9%) | 21 (8.0%) | 3.1% (-∞, 7.3%) | 10% |

(*) Higher score indicates a lower level of satisfaction

**Table 15**: Patient scores non-inferiority outcomes – BCSP subgroup

Nurse assessment of the patient comfort and the patients' satisfaction on the next day questionnaire was also evaluated on a non-inferiority basis, with the results for all patients summarised in Table 13. Both measures were found to be non-inferior in the EVAC arm relative to the SC, with the upper bound of the confidence intervals not crossing the margin of non-inferiority. The EVAC group was also found to be non-inferior on these measures in both the non-BCSP patients (Table 14) and BCSP patients (Table 15).

Questions from the Research questionnaire also, asking about patient satisfaction, were evaluated on a non-inferiority basis. The results for all patients are summarised in Table 13. When all patients were analysed together the EVAC was found to be non-inferior on most of the measures assessed. The exception was for the question "inserting the camera through the anus was uncomfortable". Here 15.0% of the SC group agreed or strongly agreed with this statement, which rose to 23.6% in the EVAC group. The upper bound for a confidence interval for the difference between groups was 13.3% which crossed the bound of non-inferiority, which was set at 10%. The EVAC group was also not found to be non-inferior on this measure in the non-BCSP subgroup (Table 14), and the BCSP subgroup (Table 15).

Aside from camera comfort, in the non-BCSP group, there non-inferiority was also not achieved for the question "after going home I suffered pain in my

bottom and/or stomach". The percentage of patients answering yes to this question was 5% higher in the EVAC group, and the confidence interval for the difference crossed the 10% non-inferiority margins. All other parameters met the criteria for non-inferiority in this subgroup. Aside from the camera comfort, already discussed, in the BCSP subgroup all the other measures of patient satisfaction were non-inferior in the EVAC group to the SC group.

## 4.2 Primary outcome – adenoma detection rate

| Analysis | Adenoma detection | SC N (%) | EVAC N (%) | One-sided P-value |
|---|---|---|---|---|
| ITT | No adenoma | 564 (63.8%) | 525 (59.1%) | 0.02 |
| | 1+ adenomas | 320 (36.2%) | 363 (40.9%) | |
| Per Protocol 1 (*) | No adenoma | 564 (63.8%) | 525 (59.2%) | 0.02 |
| | 1+ adenomas | 320 (36.2%) | 362 (40.8%) | |
| Per Protocol 2 (**) | No adenoma | 564 (63.8%) | 498 (58.5%) | 0.01 |
| | 1+ adenomas | 320 (36.2%) | 353 (41.5%) | |

(*) Omitting patients with where Endocuff was not used
(**) Omitting patients with where Endocuff was not used and where Endocuff was removed

**Table 16**: Primary outcome, adenoma detection rate – all patients

| Adjustments | Odds Ratio (1 sided 95% CI) | One-sided P-value |
|---|---|---|
| Unadjusted (primary analysis) | 1.22 (1.04, ∞) | 0.02 |
| Site (FE), recruitment, age | 1.27 (1.07, ∞) | 0.01 |
| Endoscopist (RE), recruitment, age | 1.27 (1.07, ∞) | 0.01 |

Key: FE = fixed effects; RE = random effects

**Table 17**: Primary outcome, model based sensitivity analyses – all patients

| Subgroup | SC | | EVAC | | 1-sided |
|---|---|---|---|---|---|
| | N | % ADR | N | % ADR | P-value |
| BCSP patients | 403 | 50.9% | 394 | 61.7% | 0.001 |
| Non-BCSP patients | | | | | |
| All | 481 | 23.9% | 494 | 24.3% | 0.44 |
| Non-BCSP colonoscopists | 411 | 24.1% | 425 | 23.8% | 0.54 |
| BCSP colonoscopists | 70 | 22.9% | 69 | 27.5% | 0.26 |

**Table 18**: Primary outcome – subgroups

The primary outcome was adenoma detection rate (ADR) which is the detection of one or more adenoma per patient. When all patients were analysed using the primary analysis population (ITT population), there was a significantly superior ADR in the EVAC group (p=0.02 using a one-sided test). The results suggested that 36.2% of patients had an adenoma detected in the SC group, compared to 40.9% in the EVAC group. The full details are shown in Table 16. The odds of adenoma detection were found to be 22% higher in the EVAC group than in the SC group. A significant difference between study groups was also observed when the data was analysed on a per protocol basis.

Table 17 shows several model-based sensitivity analyses using the primary analysis population. These also suggested a statistically significant benefit of EVAC over SC in terms of ADR, with a similar size of difference between groups as the primary analysis.

The difference between study arms was also examined in patient subjects, with the results summarised in Table 18. There was a significant benefit of EVAC over SC in patients recruited through the BCSP. In this subgroup, adenomas were detected in 61.7% of patients in the EVAC group, compared to only 50.9% of patients in the SC group. However, there were no differences between study groups for patients not recruited through the BCSP. This was the case for all non-BCSP patients, and when this group was further split into non-BCSP and BCSP colonoscopists.

## 4.3 Secondary outcomes

| Analysis | SC | | EVAC | | 1-sided |
|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | P-value |
| ITT analysis | 884 | 0.75 (1.40) | 888 | 0.95 (1.89) | 0.02 |
| PP analysis 1 (*) | 884 | 0.75 (1.40) | 887 | 0.94 (1.89) | 0.03 |
| PP analysis 2 (**) | 884 | 0.75 (1.40) | 851 | 0.96 (1.91) | 0.01 |
| BCSP patients | 403 | 1.20 (1.77) | 394 | 1.59 (2.32) | 0.004 |
| Non-BCSP patients | | | | | |
| All | 481 | 0.37 (0.80) | 494 | 0.44 (1.24) | 0.42 |
| Non-BCSP colonoscopists | 411 | 0.37 (0.80) | 425 | 0.44 (1.28) | 0.51 |
| BCSP colonoscopists | 70 | 0.37 (0.80) | 69 | 0.45 (0.96) | 0.28 |

(*) Omitting patients with where Endocuff was not used

(**) Omitting patients with where Endocuff was not used and where Endocuff was removed

**Table 19**: Mean adenomas per patient – all patients

The main secondary outcome was mean adenomas detected per procedure (MAP) which calculates the mean of all adenomas detected per patient. The analysis results for this outcome are shown in Table 19. When all patients were included in the analysis there was a significant difference between the two study arms (p=0.02) when using the primary analysis population. A higher number of adenomas was detected in the EVAC group (mean 0.95 per patient) than in the SC group (mean 0.75 per patient). Similar results were obtained from the per protocol analyses. A statistically significant difference in MAP between the study groups was observed when the analysis was restricted to BCSP patients. MAP was higher in the EVAC arm (mean 1.59 per patient) compared to the SC arm (mean 1.20 per patient). No significant difference was found between study arms for the non-BCSP patients, either all together, or separately for those treated by non-BCSP and BCSP colonoscopists.

| Outcome | SC (n=884) | EVAC (n=888) | One-sided P-value |
|---|---|---|---|
| Polyp detection | 424 (48.0%) | 480 (54.1%) | 0.005 |
| Sessile serrated adenoma | 10 (1.1%) | 20 (2.3%) | 0.03 |
| Cancer - all | 20 (2.3%) | 36 (4.1%) | 0.02 |
| Cancer - endoscopic | 19 (2.2%) | 32 (3.6%) | 0.03 |
| Cancer - histology | 1 (0.1%) | 4 (0.5%) | 0.09 |
| Adenoma in left colon | 196 (22.2%) | 232 (26.1%) | 0.03 |
| Adenoma in right colon | 219 (24.8%) | 244 (27.5%) | 0.10 |
| Adenoma 10+ mm | 61 (6.9%) | 70 (7.9%) | 0.21 |
| Adenoma 6-9 mm | 68 (7.7%) | 94 (10.6%) | 0.02 |
| Adenoma ≤5 mm | 272 (30.8%) | 307 (34.6%) | 0.04 |
| Non-polypoid adenoma | 206 (23.3%) | 226 (25.5%) | 0.15 |
| Polypoid adenoma | 87 (9.8%) | 100 (11.3%) | 0.17 |

**Table 20:** Polyp detection (yes/no) – all patients

| Outcome | SC (n=481) | EVAC (n=494) | One-sided P-value |
|---|---|---|---|
| Polyp detection | 169 (35.1%) | 189 (38.3%) | 0.16 |
| Sessile serrated adenoma | 5 (1.0%) | 12 (2.4%) | 0.05 |
| Cancer - all | 5 (1.0%) | 10 (2.0%) | 0.11 |
| Cancer - endoscopic | 4 (0.8%) | 9 (1.8%) | 0.09 |
| Cancer - histology | 1 (0.2%) | 1 (0.2%) | 0.51 |
| Adenoma in left colon | 64 (13.3%) | 71 (14.4%) | 0.31 |
| Adenoma in right colon | 66 (13.7%) | 74 (15.0%) | 0.29 |
| Adenoma 10+ mm | 11 (2.3%) | 16 (3.2%) | 0.18 |
| Adenoma 6-9 mm | 25 (5.2%) | 19 (3.9%) | 0.85 |
| Adenoma ≤5 mm | 92 (19.1%) | 102 (20.7%) | 0.28 |
| Non-polypoid adenoma | 57 (11.9%) | 63 (12.8%) | 0.33 |
| Polypoid adenoma | 28 (5.8%) | 34 (6.9%) | 0.25 |

**Table 21:** Polyp detection (yes/no) – non-BCSP subgroup

| Outcome | SC (n=403) | EVAC (n=394) | One-sided P-value |
|---|---|---|---|
| Polyp detection | 255 (63.3%) | 291 (73.9%) | <0.001 |
| Sessile serrated adenoma | 5 (1.2%) | 8 (2.0%) | 0.19 |
| Cancer - all | 15 (3.7%) | 26 (6.6%) | 0.03 |
| Cancer - endoscopic | 15 (3.7%) | 23 (5.8%) | 0.08 |
| Cancer - histology | 0 (0.0%) | 3 (0.8%) | 0.04 |
| Adenoma in left colon | 132 (32.8%) | 161 (40.9%) | 0.009 |
| Adenoma in right colon | 153 (38.0%) | 170 (43.2%) | 0.07 |
| Adenoma 10+ mm | 50 (12.4%) | 54 (13.7%) | 0.29 |
| Adenoma 6-9 mm | 43 (10.7%) | 75 (19.0%) | <0.001 |
| Adenoma ≤5 mm | 180 (44.7%) | 205 (52.0%) | 0.02 |
| Non-polypoid adenoma | 149 (37.0%) | 163 (41.4%) | 0.10 |
| Polypoid adenoma | 59 (14.6%) | 66 (16.8%) | 0.21 |

**Table 22**: Polyp detection (yes/no) – BCSP subgroup

| Outcome | SC (n=884)<br><br>Mean (SD) | EVAC (n=888)<br><br>Mean (SD) | One-sided<br><br>P-value |
|---|---|---|---|
| Polyp detection | 1.16 (1.87) | 1.49 (2.43) | 0.004 |
| Sessile serrated adenoma | 0.017 (0.174) | 0.024 (0.159) | 0.03 |
| Cancer - all | 0.02 (0.15) | 0.04 (0.20) | 0.02 |
| Cancer - endoscopic | 0.02 (0.15) | 0.04 (0.19) | 0.03 |
| Cancer - histology | 0.001 (0.03) | 0.005 (0.07) | 0.09 |
| Adenoma in left colon | 0.33 (0.77) | 0.40 (0.90) | 0.02 |
| Adenoma in right colon | 0.42 (0.92) | 0.54 (1.38) | 0.08 |
| Adenoma 10+ mm | 0.08 (0.32) | 0.08 (0.31) | 0.22 |
| Adenoma 6-9 mm | 0.10 (0.43) | 0.14 (0.49) | 0.02 |
| Adenoma ≤5 mm | 0.06 (1.12) | 0.72 (1.55) | 0.03 |
| Non-polypoid adenoma | 0.39 (0.90) | 0.45 (1.08) | 0.15 |
| Polypoid adenoma | 0.12 (0.40) | 0.14 (0.47) | 0.16 |

**Table 23:** Polyp detection (number of polyps) – all patients

| Outcome | SC (n=481)<br><br>Mean (SD) | EVAC (n=494)<br><br>Mean (SD) | One-sided<br><br>P-value |
|---|---|---|---|
| Polyp detection | 0.66 (1.20) | 0.82 (1.74) | 0.14 |
| Sessile serrated adenoma | 0.015 (0.151) | 0.024 (0.154) | 0.05 |
| Cancer - all | 0.01 (0.10) | 0.02 (0.14) | 0.11 |
| Cancer - endoscopic | 0.01 (0.09) | 0.02 (0.13) | 0.09 |
| Cancer - histology | 0.002 (0.05) | 0.002 (0.04) | 0.51 |
| Adenoma in left colon | 0.16 (0.46) | 0.18 (0.51) | 0.30 |
| Adenoma in right colon | 0.20 (0.61) | 0.26 (1.01) | 0.30 |
| Adenoma 10+ mm | 0.02 (0.15) | 0.03 (0.19) | 0.18 |
| Adenoma 6-9 mm | 0.06 (0.26) | 0.04 (0.20) | 0.85 |
| Adenoma ≤5 mm | 0.29 (0.71) | 0.36 (1.11) | 0.26 |
| Non-polypoid adenoma | 0.17 (0.57) | 0.19 (0.63) | 0.35 |
| Polypoid adenoma | 0.06 (0.27) | 0.07 (0.28) | 0.25 |

**Table 24**: Polyp detection (number of polyps) – non-BCSP subgroup

| Outcome | SC (n=403) Mean (SD) | EVAC (n=394) Mean (SD) | One-sided P-value |
|---|---|---|---|
| Polyp detection | 1.77 (2.30) | 2.32 (2.87) | 0.001 |
| Sessile serrated adenoma | 0.020 (0.199) | 0.023 (0.166) | 0.20 |
| Cancer - all | 0.04 (0.19) | 0.07 (0.25) | 0.03 |
| Cancer - endoscopic | 0.04 (0.19) | 0.06 (0.23) | 0.08 |
| Cancer - histology | 0.000 (0.000) | 0.008 (0.09) | 0.04 |
| Adenoma in left colon | 0.53 (0.98) | 0.68 (1.17) | 0.01 |
| Adenoma in right colon | 0.70 (1.15) | 0.90 (1.66) | 0.05 |
| Adenoma 10+ mm | 0.15 (0.44) | 0.15 (0.41) | 0.32 |
| Adenoma 6-9 mm | 0.16 (0.56) | 0.26 (0.67) | <0.001 |
| Adenoma ≤5 mm | 0.89 (1.40) | 1.17 (1.88) | 0.01 |
| Non-polypoid adenoma | 0.65 (1.13) | 0.78 (1.39) | 0.10 |
| Polypoid adenoma | 0.18 (0.51) | 0.23 (0.62) | 0.18 |

**Table 25**: Polyp detection (number of polyps) – BCSP subgroup

In addition to adenoma detection, the overall polyp detection and detection of different adenoma types was compared between groups.

The results when all patients were analysed together are summarised in Table 20. There were significant differences between arms in terms of overall polyp detection. This was higher in the EVAC arm (54.1% of patients) than in the SC arm (48.0%) of patients. Occurrence of sessile serrated adenomas and all cancers and endoscopic cancers were also significantly higher in the EVAC arm. Cancers were found in 4.1% of patients in the EVAC arm, but in 2.3% in the SC arm.

The two groups were found to significantly differ in terms of the presence of adenomas in the left colon, although there was no difference in adenomas in the right colon. Left colon was defined as transverse colon, splenic flexure, descending colon, sigmoid and rectum. Right colon was defined as caecum, ascending colon and hepatic flexure. Left colon adenomas were significantly higher in the EVAC arm (26.1% of patients, compared to 22.2% in the SC group). There was no difference between groups for large adenomas (10+mm), but there were significantly more patients with an adenoma of 6-9mm and of ≤5mm in the EVAC. 10.6% of patients in the EVAC group had an adenoma of 6-9mm, compared to 7.7% in the SC group. The presence of non-polypoid and polypoid adenomas was not found to significantly differ between groups.

The results for the for the number of polyps/adenomas for all patients combined is shown in Table 20. The results mirrored those for the presence of different types of polyps. The overall number of polyps, the number of sessile serrated adenomas, the number of all cancers and the number of endoscopic cancers were all significantly higher in the EVAC group. The number of adenomas in the left colon was significantly higher in the EVAC arm, whilst the difference in the right colon did not reach statistical significance. There were more medium sized (6-9mm) and small (≤5mm) adenomas in the EVAC group, but the groups did not significantly vary in terms of the number of large polyps.

In Table 21 and 24, analyses were repeated for non-BCSP patients. The results suggested no strong evidence that any of the variables varied between the two study groups. There was slight evidence that the presence and number of sessile serrated adenomas was higher in the EVAC arm. However, these results were of borderline statistical significance.

In Table 22 and 25, analyses were performed for BCSP patients. The proportion of patients with a polyp detected was higher in the EVAC arm, as was the number of polyps. There was a mean of 2.9 polyps detected in the EVAC arm, compared to 2.3 polyp in the SC arm. The number of cancers overall, and proportion of patients with a cancer, was also significantly higher in the EVAC arm. Cancers were detected in 3.7% of patients in the SC arm, whilst they were

detected in 6.6% of patients in the EVAC arm. Additionally, the presence and number of cancers detected through histology was high in the EVAC arm, but the difference in endoscopic cancers was not quite statistically significant. The number and presence of sessile serrated adenomas did not vary between study arms in this subgroup.

As with the analysis of all patients, the presence of adenomas in the left colon, medium sized adenomas and small adenomas were all significantly more common in the EVAC arm. The number of these types of adenomas were also significantly higher. 40.9% of patients had an adenoma in the left colon in the EVAC group, compared to 32.8% of patients in the SC group. Additionally, there was slight evidence that the presence and number of adenomas in the right colon was higher in the EVAC arm, but this difference did not quite reach statistical significance.

| Outcome | SC | EVAC | Difference (1-sided 97.5% CI) | Non-inferiority margin |
|---|---|---|---|---|
| Reached caecum | 852 (96.4%) | 858 (96.7%) | 0.4% (-1.3%, ∞) | 5% |
| Insertion | 9 (6, 15) | 8 (5, 12) | -1 (-∞, 0) | 1 minute |
| Insertion (all) (*) | 9 (6, 16) | 8 (6, 13) | -1 (-∞, 0) | 1 minute |
| Withdrawal (+) | 8 (6, 11) | 8 (6, 10) | 0 (-∞, 0) | 1 minute |
| Entonox | 291 (32.9%) | 283 (31.9%) | -1.0% (-∞, 3.3%) | 10% |
| IV sedation | 591 (66.9%) | 586 (66.1%) | -0.8% (-∞, 3.6%) | 10% |
| IV analgesia | 582 (65.8%) | 588 (66.3%) | 0.5% (-∞, 4.9%) | 10% |

Figures are median (IQR) and median difference, or N (%) and % difference
(*) Including patients not reaching the caecum
(+) Figures for patients where no polyps were found

**Table 26**: Insertion and sedation non-inferiority outcomes – all patients

| Outcome | SC | EVAC | Difference (1-sided 97.5% CI) | Non-inferiority margin |
|---|---|---|---|---|
| Reached caecum | 458 (95.2%) | 474 (96.0%) | 0.7% (-1.8%, ∞) | 5% |
| Insertion | 12 (8, 17) | 10 (7, 14) | -2 (-∞, -1) | 1 minute |
| Insertion (all) (*) | 12 (8, 18) | 10 (7, 15) | -2 (-∞, -1) | 1 minute |
| Withdrawal (+) | 7 (5, 10) | 7 (5, 10) | 0 (-∞, 1) | 1 minute |
| Entonox | 209 (43.5%) | 180 (36.4%) | -7.0% (-∞, -0.9%) | 10% |
| IV sedation | 349 (72.6%) | 357 (72.3%) | -0.3% (-∞, 5.3%) | 10% |
| IV analgesia | 342 (71.1%) | 360 (72.9%) | 1.8% (-∞, 7.4%) | 10% |

Figures are median (IQR) and median difference, or N (%) and % difference
(*) Including patients not reaching the caecum
(+) Figures for patients where no polyps were found

**Table 27**: Insertion and sedation non-inferiority outcomes – non-BCSP subgroup

| Outcome | SC | EVAC | Difference (1-sided 97.5% CI) | Non-inferiority margin |
|---|---|---|---|---|
| Reached caecum | 394 (97.8%) | 384 (97.7%) | -0.1% (-2.1%, ∞) | 5% |
| Insertion | 6 (4, 11) | 7 (4, 10) | 0 (-∞, 1) | 1 minute |
| Insertion (all) (*) | 7 (4, 11) | 7 (5, 10) | 0 (-∞, 1) | 1 minute |
| Withdrawal (+) | 9 (7, 12) | 8 (6, 10) | -1 (-∞, 0) | 1 minute |
| Entonox | 82 (20.4%) | 103 (26.2%) | 5.9% (-∞, 11.7%) | 10% |
| IV sedation | 242 (60.1%) | 229 (58.3%) | -1.8% (-∞, 5.0%) | 10% |
| IV analgesia | 240 (59.6%) | 228 (58.0%) | -1.5% (-∞, -5.3%) | 10% |

Figures are median (IQR) and median difference, or N (%) and % difference
(*) Including patients not reaching the caecum
(+) Figures for patients where no polyps were found

**Table 28**: Insertion and sedation non-inferiority outcomes – BCSP subgroup

The results for reaching the caecum, insertion, withdrawal times along with the use of analgesia/sedation are shown for all patients in Table 26. The results suggested than the EVAC met the criteria for non-inferiority relative to the SC group, based on the pre-defined non-inferiority margins, for these outcomes. Additionally, EVAC was non-inferior to SC for all these outcomes in the non-BCSP subgroup (Table 27) and most outcomes for the BCSP subgroup (Table 28). The exception for the BCSP subgroup was for use of Entonox, where the use of Entonox was not non-inferior in the EVAC group.

| Bowel preparation | SC | EVAC |
|---|---|---|
| Excellent preparation | 143 (16.2%) | 146 (16.4%) |
| Good preparation | 444 (50.2%) | 453 (51.0%) |
| Adequate preparation | 195 (22.1%) | 214 (24.1%) |
| Poor preparation | 102 (11.5%) | 75 (8.5%) |

**Table 29**: Bowel preparation scores in both groups

The Bowel Cancer Screening Programme four-point scale was used to assess quality of bowel preparation in this study[70]. Bowel preparation was found to be of an equivalent standard in both groups as illustrated in Table 29.

| Patient group | Study arm | ADR - First 20% n/N (%) | ADR – Last 20% n/N (%) | P-value |
|---|---|---|---|---|
| All | SC | 66/165 (40.0%) | 65/177 (36.7%) | 0.53 |
| | EVAC | 72/184 (39.1%) | 68/170 (40.0%) | 0.87 |
| Non-BCSP patients | SC | 21/91 (23.1%) | 25/95 (26.3%) | 0.61 |
| | EVAC | 22/106 (20.8%) | 23/89 (25.8%) | 0.40 |
| BCSP patients | SC | 45/74 (60.8%) | 40/82 (48.8%) | 0.13 |
| | EVAC | 50/78 (64.1%) | 45/81 (55.6%) | 0.27 |

**Table 30**: Comparison of ADR in first and last 20% of cases

An additional analysis defined in the SAP was to compare the ADR between the first 20% and last 20% of cases for each endoscopist. The analysis results are summarised in Table 30. This shows no statistically significant difference in ADR between the first and last 20% of cases for either study arm. This result was found for all patients combined, and when split by route of recruitment.

| Endoscopist | ADR Pre-trial n/N (%) | ADR SC n/N (%) | Change % (95% CI) | P-value |
|---|---|---|---|---|
| 1 | 34/85 (40.0%) | 19/40 (47.5%) | 7.5% (-11.2%, 26.2%) | 0.43 |
| 2 | 59/139 (42.5%) | 11/26 (42.3%) | -0.1% (-20.8%, 20.6%) | 0.99 |
| 3 | 71/243 (29.2%) | 6/22 (27.3%) | -1.9% (-21.4%, 17.5%) | 0.85 |
| 4 | 119/375 (31.7%) | 29/82 (35.4%) | 3.6% (-7.7%, 15.0%) | 0.52 |
| 5 | 94/205 (45.9%) | 18/33 (54.6%) | 8.7% (-9.6%, 27.0%) | 0.35 |
| 6 | 142/231 (61.5%) | 24/38 (63.2%) | 1.7% (-14.9%, 18.3%) | 0.84 |
| 7 | 112/213 (52.6%) | 16/24 (66.7%) | 14.1% (-5.9%, 34.1%) | 0.19 |
| 8 | 67/165 (40.6%) | 23/36 (63.9%) | 23.3% (5.9%, 40.6%) | 0.01 |
| 9 | 25/194 (12.9%) | 3/15 (15%) | 2.1% (-14.2%, 18.5%) | 0.79 |
| 10 | 50/89 (56.2%) | 29/60 (48.3%) | -7.8 (-24.2%, 8.5%) | 0.35 |
| 11 | 21/118 (17.8%) | 7/36 (19.4%) | 1.6% (-13.0%, 16.3%) | 0.82 |
| 12 | 23/59 (39.0%) | 26/75 (34.7%) | -4.3% (-20.8%, 12.1%) | 0.61 |
| 13 | 9/53 (17.0%) | 6/26 (23.1%) | 6.1% (-13.0%, 25.2%) | 0.52 |
| 14 | 21/104 (20.2%) | 6/23 (26.1%) | 5.9% (-13.6%, 25.4%) | 0.53 |

**Table 31**: Comparison of ADR in the 6 months pre-trial to ADR in the SC arm

Table 31 illustrates the ADR of each endoscopist 6 months before the trial period and compared this with their ADR when scoping patients undergoing

standard colonoscopy as part of the trial. This was done to assess for the Hawthorne effect. We were only able to obtain pre-trial ADR for 14 endoscopists but only found a significant increase in ADR for one endoscopist by 23.3%.

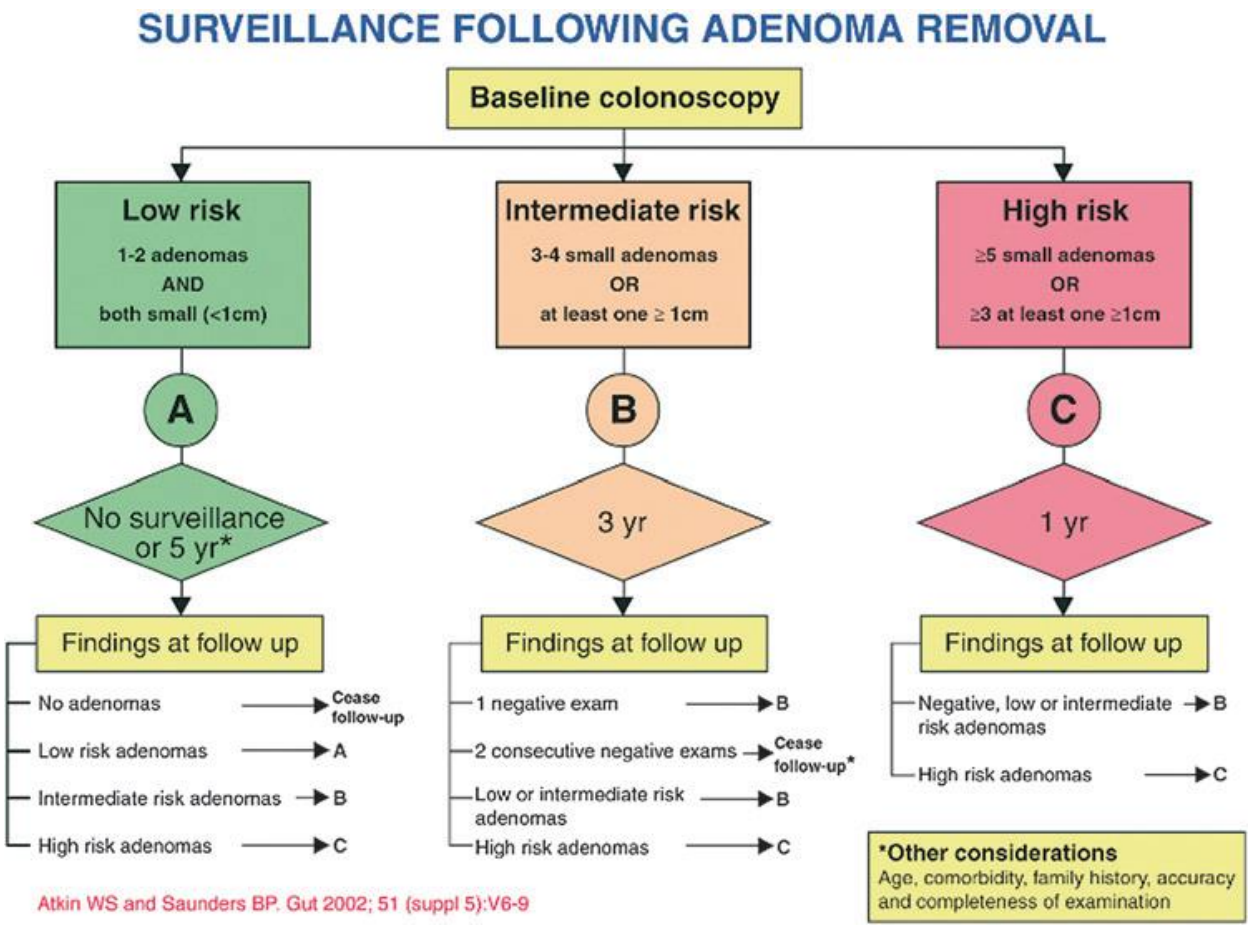


**Figure 16**: Surveillance guidelines after adenoma removal[164]

| Patient group | Risk | SC<br>N (%) | EVAC<br>N (%) | 2-sided<br>P-value |
|---|---|---|---|---|
| All patients | No adenoma | 564 (63.8%) | 525 (59.1%) | 0.03 |
| | Low | 205 (23.2%) | 225 (25.3%) | |
| | Intermediate | 87 (9.8%) | 95 (10.7%) | |
| | High | 28 (3.2%) | 43 (4.8%) | |
| Non-BCSP | No adenoma | 366 (76.1%) | 374 (75.7%) | 0.78 |
| | Low | 93 (19.3%) | 89 (18.0%) | |
| | Intermediate | 18 (3.7%) | 25 (5.1%) | |
| | High | 4 (0.8%) | 6 (1.2%) | |
| BCSP | No adenoma | 198 (49.1%) | 151 (38.3%) | 0.004 |
| | Low | 112 (27.8%) | 136 (34.5%) | |
| | Intermediate | 69 (17.1%) | 70 (17.8%) | |
| | High | 24 (6.0%) | 37 (9.4%) | |

**Table 32**: Patient risk group according to British Society of Gastroenterology surveillance guidelines[164]

In Table 32, patients were grouped into risk groups based on British Society of Gastroenterology surveillance guidelines (Figure 16). In the BCSP subgroup, EVAC significantly increased the number of patients in the high risk group by 3.4% which would increase the colonoscopy workload as these patients have to undergo repeat colonoscopy at 1 year.

## 4.4 Adverse events and serious adverse events

Adverse events were defined as any new medical occurrence, or worsening of a pre-existing medical condition in a patient and were graded as mild, moderate or severe. An event was a serious adverse event when it:

- Resulted in death
- Was life threatening
- Resulted in hospitalisation or prolongation of existing hospitalisation (exceptions to this were routine planned admissions, including admission for colonoscopy as part of this study)
- Led to persistent significant disability or incapacity
- Was otherwise considered to be medically significant by the trial team

All adverse and serious adverse events were reported from the time of colonoscopy until 21 days following the colonoscopy or until time of withdrawal from the trial. All adverse events and serious adverse events were reported to the trial team and assessed for expectedness, severity and relatedness to Endocuff Vision. Serious adverse events were followed until resolution, death or until resolution with sequelae. In addition, all adverse and serious adverse events were reported to the chair of the Data Monitoring Committee who in

turn discussed these events with 2 independent clinicians who assessed the relationship of these events to Endocuff Vision.

There were 6 serious adverse events (Table 33) and 17 adverse events (Table 34) reported during the trial. These were all reported promptly to the principle and chief investigators and were independently reviewed by the chair of the Data Monitoring Committee and two independent clinicians and felt unlikely to be related to Endocuff Vision.

There was an equal distribution of serious adverse events in both the intervention and control group. In the intervention group, none of the serious adverse events were attributed to Endocuff Vision.

In the adverse events group, there were marginally more events reported in the control group compared to the intervention group. No obvious trends were seen in both groups.

| Serious Adverse Events: Intervention Group | | | |
|---|---|---|---|
| 1 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101051<br>: 23/02/2015<br>: 26/02/2015 | Seen in clinic routinely 26/02/15 with lower abdominal pain, vomiting, weight loss and dehydration and was admitted to the ward. Chest and abdominal computed tomography scan found a left breast lesion. Patient was also treated for urinary tract infection and discharged 6/3/15 |
| 2 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101323<br>: 14/09/2015<br>: 05/10/2015 | Admitted with sudden onset chest pain on 5/10/15 and was admitted to the medical ward. Patient had history of previous myocardial infarction in 2014. Chest x-ray, electrocardiogram and troponin blood test was all normal. Patient was discharged 8/10/15 with cardiology follow up. |
| 3 | Patient ID<br>Date of colonoscopy<br>Date of event | : 671412<br>: 19/01/2016<br>: 07/02/2016 | Admitted to hospital 7/2/16 after presenting with epigastric abdominal pain and chest pain. Patient was diagnosed with acute gallstone cholangitis and given antibiotics. Patient was discharged 17/2/16 from hospital and was arranged for endoscopic retrograde cholangio-pancreatography on the 9/3/16. |
| **Serious Adverse Events: Control Group** | | | |
| 1 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101032<br>: 22/01/2015<br>: 22/01/2015 | Patient was discharged from unit following endoscopic mucousal resection, attended 1 hour later with abdominal pain, admitted overnight for analgesia and antibiotics, abdominal computed tomography scan was normal. Patient was diagnosed with post polypectomy syndrome and discharged the next day. |
| 2 | Patient ID<br>Date of colonoscopy<br>Date of event | : 785014<br>: 13/05/2015<br>: 27/05/2015 | Admitted to hospital with rectal bleeding, abdominal pain and diarrhoea. Had bloods, stool sample, abdominal ultrasound and a repeat colonoscopy on 1/6/15 which reported campylobacter colitis. Discharged 5/6/15. |
| 3 | Patient ID<br>Date of colonoscopy<br>Date of event | : 558025<br>: 04/11/2015<br>: 15/11/2015 | Patient presented to A&E, found to have low haemoglobin of 56. Had upper gastrointestinal endoscopy on 16/11/15 which found an ulcerated lesion adjacent to gastric fundus which was treated with argon plasma therapy. This was confirmed on histology later to be high grade neuroendocrine tumour. Patient was discharged on 18/11/15 with plans for palliative chemotherapy. |

**Table 33**: Serious Adverse Events

| Adverse Events: Intervention Group | | | |
|---|---|---|---|
| 1 | Patient ID<br>Date of colonoscopy<br>Date of event | : 671005<br>: 19/01/2015<br>: 19/01/2015 | Had abdominal pain for 11 days after procedure, saw GP, reassured and pain settled. |
| 2 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101051<br>: 23/02/2015<br>: 11/03/2015 | Attended A&E with slurred speech, reduced mobility, bloods and electrocardiogram normal, discharged same day |
| 3 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101163<br>: 21/05/2015<br>: 24/05/2015 | Attended A&E with a possible seizure, bloods and X-rays normal, patient admitted alcohol excess, discharged same day with referral to seizure clinic |
| 4 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101163<br>: 21/05/2015<br>: 05/06/2015 | Attended GP for lethargy, had bloods, found to have thyrotoxicosis, given carbimazole and beta blocker, referred to endocrinologist |
| 5 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101487<br>: 31/12/2015<br>: 07/01/2016 | Went to A&E with back pain after putting up fence, examination normal, discharged with analgesia. |
| 6 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101494<br>: 04/01/2016<br>: 07/01/2016 | Attended A&E with abdominal pain, has a known healing enterocutaneous fistula from previous laparotomy, reassured fistula looked fine and was drying up, discharged |
| 7 | Patient ID<br>Date of colonoscopy<br>Date of event | : 671409<br>: 11/01/2016<br>: 13/01/2016 | Had abdominal pain and wind 2 days post colonoscopy, went to A&E, had CXR normal, bloods normal, given peppermint solution and discharged home the same day |
| 8 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101525<br>: 22/01/2016<br>: 31/01/2016 | Went to A&E with right knee pain, no trauma history, diagnosed with soft tissue injury, given analgesia and discharged same day |
| **Adverse Events: Control Group** | | | |
| 1 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101012<br>: 16/12/2014<br>: 17/12/2014 | Attended A&E with abdominal pain, bloods and X-rays normal, discharged same day |
| 2 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101073<br>: 16/03/2015<br>: 31/03/2015 | Attended A&E with chest pain, bloods and X-rays normal, discharged same day |
| 3 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101085<br>: 19/03/2015<br>: 13/04/2015 | Attended A&E with shortness of breath, chest and back pain, bloods and electrocardiogram normal, discharged same day |

| | | | |
|---|---|---|---|
| 4 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101204<br>: 15/06/2015<br>: 06/07/2015 | Attended A&E with abdominal pain, bloods normal, discharged same day with outpatient abdominal ultrasound arranged which was normal |
| 5 | Patient ID<br>Date of colonoscopy<br>Date of event | : 558011<br>: 10/08/2015<br>: 13/08/2015 | Presented to GP with muscular pains down both legs from buttocks to mid-calf. GP performed bloods, urine tests and physical examination, diagnosed muscular pain and prescribed analgesia. |
| 6 | Patient ID<br>Date of colonoscopy<br>Date of event | : 671338<br>: 13/10/2015<br>: 16/10/2015 | Patient reported spotting of blood on wiping bottom. This had happened on several episodes prior to his colonoscopy as he was undergoing treatment for prostate cancer. He saw the GP who confirmed that the spotting of blood was likely to be due to prostate treatment. |
| 7 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101429<br>: 17/11/2015<br>: 01/12/2015 | Went to A&E with shortness of breath, tight chest, productive cough. Had bloods, treated as pneumonia, discharged same day with antibiotics and steroids |
| 8 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101537<br>: 01/02/2016<br>: 19/02/2016 | Went to A&E having fainted with abdominal pain (has a background of longstanding intermittent abdominal pain). Bloods and observations normal, patient reassured and discharged same day |
| 9 | Patient ID<br>Date of colonoscopy<br>Date of event | : 101543<br>: 02/02/2016<br>: 02/02/2016 | Went to A&E with fever, chills and abdominal pain. Patient had a cold before colonoscopy was performed. CXR normal. Discharged same day with antibiotics |

**Table 34**: Adverse events

## 4.5 Trend analysis

Patients who underwent Endocuff Vision-assisted colonoscopy (EVAC) had a significantly higher adenoma detection rate by 4.7% when analysed on an intention to treat basis. A significant improvement in ADR in the EVAC group was also observed when analysed on a per protocol basis. When analysed on a model based sensitivity analysis adjusted by site, endoscopist, indication for procedure or age, there was statistically significant difference with EVAC over standard colonoscopy (SC). When divided into subgroups, it is clear that a significant improvement in ADR was only seen in BSCP patients. There was no significant improvement in ADR in the non-BCSP subgroup even when these patients were scoped by BCSP colonoscopists. This pattern was repeated for mean adenomas per patient (MAP), polyp detection, sessile serrated adenomas, cancers, left colon adenomas and small and diminutive adenomas. Each of these demonstrated a significant improvement in the EVAC arm but when analyses were repeated for subgroups, the results were only statistically significant in BCSP patients.

The use of hyoscine-n-butylbromide was significantly higher in the EVAC arm and was used in 70.6% procedures. There was no significant difference in the use of carbon dioxide insufflation, position change or rectal retroflexion. In

addition, there was no statistically significant difference in endoscopist ADR between the first and last 20% of cases for either study arm. We also analysed the ADR of each endoscopist 6 months before the trial period and compared this with their ADR when scoping patients undergoing standard colonoscopy to assess for the Hawthorne effect. There was only a significant increase in ADR for one endoscopist by 23.3%.

# Chapter 5: Discussion and Conclusions

## 5.1 Main findings and outcomes

This study demonstrated that Endocuff Vision (EV) significantly improved adenoma detection rate (ADR). The difference in ADR in the EVAC arm was predominantly seen in BCSP patients who were scoped by BCSP colonoscopists. This group of patients have undergone faecal occult blood testing (FOBt) and found to be positive. Consequently, they may have higher rates of pathology compared to patients who undergo colonoscopy for various reasons unrelated to screening. These results suggest that EV improves visualisation and detection of adenomas in a population where they are commonly found.

Adenoma detection also relies heavily on individual colonoscopists being vigilant in spotting adenomas, understanding and recognising relevant pathology and being rigorous in removing small lesions. All these factors are characteristic of BCSP colonoscopists but perhaps less so for non-BCSP colonoscopists. Interestingly, in this study we found that in the non-BCSP population, there was no significant difference in ADR when patients were scoped by BCSP colonoscopists so it may be that Endocuff Vision improves ADR in the right patient population instead of being skill dependant. ADR in

both subgroups was higher than predicted but similar to current national averages. This most likely reflects the ongoing improving practice in UK colonoscopy but may also represent improved performance in a trial setting.

Currently ADR is the main marker of colonoscopy quality and a 1% increase in ADR is associated with a 3% reduction in interval colorectal cancer and 5% reduction in risk of fatal interval colorectal cancer [62]. If applied to this study, EV could potentially reduce the risk of interval colorectal cancer by 14%. It is not possible currently to quantify the effect of an 11% rise in ADR in FOBt positive BCSP patients as no data exist on long term outcomes.

The benefits of improving ADR on reduced interval colorectal cancer rates have all been demonstrated in populations directly screened by colonoscopy. In addition, the ceiling at which further improvements in ADR confer no additional patient benefit has not yet been established nor is a 'device assisted' ADR known. A rise of 11% in ADR in an RCT is, however, highly significant and is likely to be associated with significant clinical benefit.

EV differs from the original Endocuff with the removal of the second row of projections and lengthening the remaining row of projections by 2mm resulting in a more streamlined device that improves manoeuvrability and allows

improved visualisation on withdrawal. These improvements may explain why this study illustrated an improvement in ADR with EV use which was not reported with the Dutch RCT of the original Endocuff [159].

## 5.2 Secondary outcomes and findings

Mean adenomas detected per procedure (MAP) was also found to be higher with EVAC. ADR is the most widely used marker of quality but the importance of MAP is growing as high quality colonoscopy should find all adenomas in a patient. MAP measures this, unlike ADR where finding a single adenoma positively affects this key performance indicator. Improvement in both ADR and MAP in this study suggest genuine clinical benefit associated with EV use. EV is the upgraded, second generation model of the original Endocuff. It works by flattening haustral fold and the increased detection of adenomas with EV was in the left colon, the area where colonic folds are most prominent. EV did not confer additional detection in the right colon. EV improved detection of small and diminutive polyps but perhaps unsurprisingly not larger polyps. The improvement in cancer detection with EV is surprising and in contrast to this. EV might be expected to hold back folds and find smaller lesions but appears to have also improved detection of larger lesions.

Previous studies have demonstrated that whilst the greatest miss rates are for small lesions, miss rates for large lesions are still significant [59], therefore the improved cancer detection may be a true effect. EV also increased detection of sessile serrated adenomas, however this was a small change and the clinical significance of this should not be over interpreted.

It is important that devices attached to colonoscopes do not cause harm by hindering the procedure, increasing discomfort or causing adverse events. In addition, it is important that the devices do not require frequent removal. The EV cuff removal rate of 4.1% is at an acceptably low level. EV did not hinder colonic intubation and intubation time was quicker.

It is likely that the EV flattened haustral folds which allowed for quicker and easier mucosal inspection, without the need for position change. Use of hyoscine-n-butylbromide was higher in the EVAC arm. Colonic spasm may hinder insertion during any colonoscopy and this may be more of a hindrance when EV is in use. Hyoscine-n-butylbromide is used widely in BCSP and this is likely to explain the increased use in this group. EV use was safe and did not cause any adverse events in this trial.

EVAC was non-inferior in almost all measures of patient experience. Overall patients reported no difference in experience scores between SC and EVAC.

When directly asked regarding anal insertion, EVAC anal intubation was reported to be slightly more uncomfortable. Where colonoscopy is undertaken under deep sedation this is less likely to be an issue but where light or no sedation is used, attention should be given to cuff lubrication and gentle insertion technique to minimise discomfort.

## 5.3 Implications of this research

The ADENOMA study was the first multicentre, randomised controlled trial comparing Endocuff Vision-assisted colonoscopy with standard colonoscopy in patients attending for symptomatic, surveillance and Bowel Cancer Screening Programme colonoscopy. It is the first study to demonstrate improved ADR with Endocuff Vision. As ADR is the most important contemporaneous marker of colonoscopy quality and low ADR is strongly linked to higher interval colorectal cancer rates, this is a significant finding with major potential clinical impact [47]. In a Polish screening study, the hazard ratio for interval colorectal cancer where the colonoscopist had an ADR of less than 20% was ten times that of colonoscopists with an ADR of greater than 20% [47]. A large USA study found an inverse relationship between ADR and the risk of interval colorectal cancer, advanced-stage interval colorectal cancer and fatal interval colorectal cancer. A 1% increase in ADR was associated with a 3% reduction in interval colorectal cancer and a 5% reduction in risk of a fatal interval colorectal cancer [62]. If

results of the current trial mirrored this study, EV could potentially reduce the risk of interval colorectal cancer by 14% and fatal interval colorectal cancer by 24%.

The ADENOMA study was designed to check the efficacy of Endocuff Vision in ADR rather than cost effectiveness and therefore a formal economic analysis was not included. However, at a cost of £15 per device in the United Kingdom, it may provide a method of improving ADR which is simple, safe and well tolerated.

## 5.4 Study limitations

There are limitations to this study. Whilst the study was a randomised controlled trial, it could not be performed with operator blinding as the cuff was visible on insertion and the projections can be clearly seen holding back folds. Tandem studies have previously been used to compare devices in colonoscopy to identify missed lesions. However, a randomised controlled trial comparing ADR in two equivalent arms allowing for confounders is the optimal way to study this intervention. As this study compared ADR in both arms and both arms involved a single colonoscopy, missed adenomas are unlikely to have a significant impact on results. Although not stratified for or standardised, other interventions known to improve ADR were similar in the two groups.

Many studies purporting to demonstrate benefit of new technologies are conducted in expert (often single) centres. This study was undertaken in a mixture of academic and community settings and therefore results should be generalisable to standard clinical practice. Other studies have reported adenoma miss rate or other markers of quality but ADR is the most widely used and has been shown to correlate strongly with interval colorectal cancer rates and therefore has been chosen here as the primary outcome measure.

## 5.5 A critique of thesis

The aim of the study was to ascertain if there was a difference in adenoma detection rate between Endocuff Vision– Assisted Colonoscopy (EVAC) and Standard Colonoscopy (SC) patient groups and to quantify this by measuring ADR. Adenoma detection rate only identifies the percentage of procedures in which at least one adenoma is detected. Perhaps the more useful measure would have been to look at mean adenomas per procedure (MAP) which identifies the total number of adenomas detected divided by the number of procedures as it is more important to find and remove every adenoma present to reduce the risk of interval colorectal cancer and determine surveillance interval [47,49].

In the recent Dutch RCT investigating the relationship between Endocuff-assisted colonoscopy and ADR, they found no difference between ADR in both groups but a significantly higher MAP in the Endocuff-assisted colonoscopy group [159]. However, ADR is still currently the main marker of quality and used in most studies assessing quality in colonoscopy. In addition, ADR and MAP have been positively correlated in screening studies [44]. In hindsight, there is a potential paradox in the way the outcome measures have been measured as in theory it is possible for one arm of the study to be inferior in ADR but superior in MAP. However, by evaluating both these indices, both arms of the study can be compared.

The ADENOMA study was designed as a multicentre prospective randomised controlled trial which compared the performance of Endocuff Vision against standard colonoscopy in improving adenoma detection rate. It was conducted at multiple sites to reflect tertiary and secondary centres. Although a large-scale trial, it had a simple patient recruitment process. In addition, use of the Endocuff Vision did not unnecessarily lengthen colonoscopy time and no additional NHS resources were required. The ADENOMA study is a good example of collaboration between sites and illustrates that it is easy to recruit patients from BCSP. In addition, this study is less likely to have any known or unknown confounders as recruitment was completed very quickly.

The minimum of 20 training cases required for completion by each trial colonoscopists ensured that all colonoscopists had a minimum standard from which to progress from. However, it also contributed to a delay in initial patient recruitment. Particularly at the South Tees NHS Hospital site, the lead colonoscopist staggered the training of each participating colonoscopist, which resulted in low recruitment numbers in the initial months of the trial. This happened unbeknownst to the trial team and was only identified when I performed monitoring checks and enquired about the low recruitment numbers. Fortunately, this was swiftly corrected and all participating colonoscopists encouraged to start training immediately.

The ADENOMA study was not a tandem study and therefore there is a possibility that some adenomas were missed. However, as this study compared adenoma detection rate in both arms and both arms of the study involve a single colonoscopy, missed adenomas are unlikely to have a significant impact on results.

The study methods did not require standardisation of known quality improvement measures in colonoscopy. Colonoscopic withdrawal time of more than 6 minutes improves adenoma detection rate [63,166]. In addition, the use of hyoscine-n-butylbromide [60,80], position change during colonoscopy [78] and rectal retroflexion [167] have been advocated to improve adenoma detection. This was

considered but it was felt that it would result in a study of a group of colonoscopists in a controlled environment and would not necessarily reflect real-life general practice of colonoscopists on a daily basis.

One limitation of this study was that colonoscopists were not blinded to EVAC or SC groups. Therefore, this may have influenced colonoscopist behaviour through the Hawthorne effect. In addition, the presence of a research nurse in the room whilst the procedure was performed by the colonoscopist may also have resulted in more careful inspection of colonic mucosa and contributed to an elevated ADR. To combat this, alternatives were discussed which included having a different colonoscopist perform initial anal intubation or to video record each colonoscopy to be double read by a different colonoscopist after the procedure. However, this was felt to be impractical as the 'finger-like' projections of the Endocuff Vision occasionally came into luminal view during colonoscopy.

In addition, it would have been useful to know what colonoscopists thought both objectively and subjectively about the use of Endocuff Vision. Therefore, we have arranged to conduct a further study by sending out questionnaires to colonoscopists to ask how they felt about the use of Endocuff Vision in their patients which will be in the next phase of the study.

In the ADENOMA study, the highest recruiting site was South Tyneside with 538 patients followed by North Tees with 413 patients. This could reflect that these sites were more motivated to recruit patients and therefore potentially more sensitive to finding adenomas and increasing ADR. However, in South Tyneside, 147 number of participants were recruited by surgeons with lower than average ADRs.

Another source of bias in this study is the experience of each colonoscopist. This was not standardised in the study and we did not ask information regarding years of experience or previous number of colonoscopies performed. With hindsight, this should have standardized this as colonoscopist related factors can affect ADR and quality of colonoscopy. On the other hand, by taking 'all comers', this may be a better reflection of the general population.

Whilst this study stratified for the BCSP subgroup in both arms, the proportion of patients overall recruited as BCSP and non-BCSP was not mandated. Thus, the recruitment of BCSP and non-BCSP patients differed from the anticipated 80/20 ratio. Over-recruitment in the BCSP population occurred due to the optimal research environment in BCSP with research interested clinicians and nurses.

Lastly, the ADENOMA study was designed to check the efficacy of Endocuff Vision in ADR rather than cost effectiveness and therefore a formal economic analysis was not included. However, at a cost of £15 per device in the United Kingdom, it may provide a method of improving ADR which is simple, safe and well tolerated.

## 5.6 Issues with recruitment

All patients were recruited consecutively and were only excluded from the study if they fulfilled the exclusion criteria or if they did not consent to study participation.

However, on 26 May 2015 as part of a statistical periodic review of the randomisation system, NWORTH observed that several changes were made to the randomisation system. NWORTH IT were instructed to not make any further changes to the system until the change had been discussed and agreed with the trial management team. I carried out an internal investigation and found that in 9 instances there was a removal of randomisation. The details of each removal of randomisation are illustrated in Table 35.

| Site | Patient ID | Reasons |
|---|---|---|
| South Tyneside | 101167 | Patient was on anticoagulation and this was only discovered when patient was in endoscopy room before procedure was performed. |
| | 101076 | This patient ID number had been used twice in error |
| | 101180 | This patient was not eligible to participate in the study due to being age 17. |
| North Tees | 616840 | The wrong patient ID number was entered. This was meant to be 671139. |
| St Marks | 215008 | Patient randomised twice in error. |
| | 215076 | Wrong birth date entered. |
| South Tees | 443014 | Patient found to be on warfarin so not eligible. |
| | 443019 | Patient was too unwell for colonoscopy so procedure was rearranged. This patient should have been included in the study instead of being removed and this was treated as a protocol deviation. |
| | 443020 | Patient had a poor result from bowel preparation so procedure was rearranged. This patient should have been included in the study instead of being removed and this was treated as a protocol deviation. |

**Table 35**: Issues with recruitment

Table 35 illustrated that in two cases – patient 443019 and 443020, there was a protocol deviation from the study. The research nurses at South Tees Hospital were informed immediately about the error and underwent further training to ensure this did not happen again.

In addition, all research nurses and principal investigators were informed of these events during the Gastrointestinal Clinical Research Network meeting on 4th June 2015 and reminded that such patients should be included on a 'intention to treat' basis. All sites were advised to only randomise patients in the endoscopy room to avoid any last-minute changes. In addition, any further requests for removal of randomisations from NWORTH were monitored and discussed with me to prevent any further similar violations. The randomisation algorithm was also corrected to disallow patients under the age of 18 from being recruited.

## 5.7 Reflections from undertaking thesis

The experience of starting and then completing this thesis has been an informative and interesting journey to say the least. I have learnt and picked up many skills along the way and continue to do so. I have found this journey challenging at times but having an interesting and relevant research topic

coupled with a wonderful research unit has made my out of programme research experience fulfilling and enjoyable.

In completing the literature review for this thesis, I have developed my ability to review and critically appraise medical literature. I have also gained a clearer understanding of basic research principles and I am more confident with research methodology and basic statistics. Due to the nature of this thesis, I have a much greater knowledge and understanding of the importance of detecting and removing colorectal adenomas and the various methods and devices available to me to achieve this. This will stand me in good stead in my career as a colorectal surgeon.

I am confident that the results of the ADENOMA study will make a significant contribution towards improving quality in colonoscopy and provide the groundwork for other studies. I hope that, in time, the results of this study will contribute towards reducing morbidity and mortality from colorectal cancer.

Lastly, I have found setting up and running a multicentre RCT extremely rewarding and plan to continue to be active in academia and research.

## 5.8 Suggestions for further work

This study has shown that Endocuff Vision significantly improves the detection of left colon adenomas by 3.9%. In particular, there were significant improvements in the detection of 6-9mm and ≤5mm adenomas with EVAC. This suggests that Endocuff Vision may have a role to play in the NHS Bowel Scope screening (BSS) programme. The BSS programme began in 2013 and offers all men and women in England a one-off flexible sigmoidoscopy. The aim of the BSS programme is to reduce colorectal cancer development via the adenoma-carcinoma sequence through the detection and removal of adenomas from the left side of the colon. However, ADR is not as high as expected in BSS patients compared to the NHS BCSP with national BSS ADR reported at 9.2% [72]. In addition, there seems to be a significant ADR variation of 7-12% between BSS endoscopists [72] . The reasons for variation can be extrapolated from colonoscopy data and include poor technique, shorter withdrawal time, inadequate bowel preparation, the presence of flat or subtle lesions, the inability to visualise the proximal side of haustral folds, blind spots in flexures, and rectal or ileocaecal valves [57,58]. However, in the BSS population, it is difficult to implement measures such as better bowel preparation, using anti-spasmodics or lengthen withdrawal time without increasing patient risk or discomfort.

Interventions to improve ADR such as the utilisation of adjuncts like Endocuff Vision may offer a safe way of improving ADR. Attachment of Endocuff Vision can slightly increase anal irritation on anal intubation but emphasis on adequate lubrication and careful insertion will ensure that discomfort is kept to a minimum. As a result of the findings in the ADENOMA study, a multicentre randomised controlled trial into the use of Endocuff Vision in NHS Bowel Scope participants is currently underway. This study has been called the B-ADENOMA (BowelScope: Accuracy of Detection using Endocuff Optimisation of Mucosal Abnormalities) study.

In addition, a head-to-head comparison of Endocuff Vision with other devices such as cap-assisted colonoscopy or EndoRings will be beneficial in assessing the best and safest device to improve ADR. Lastly, it may be appropriate that large multicentre RCT's utilise MAP as their primary study outcome instead of ADR as it is becoming clearer that it is more important to detect and remove all adenomas.

**Appendix 1:** Case Report Form

# Accuracy of Detection using ENdocuff™ Optimisation of Mucosal Abnormalities

ADENOMA

**Chief Investigator:** Professor Colin Rees

| | |
|---|---|
| Patient Forename | |
| Patient Surname | |
| Patient Hospital Number | |
| Hospital Site | |
| Site Principal Investigator | |
| Patient Study Number | |

**Please note – If requested by NWORTH, CRF pages 2 onwards are to be photocopied and sent to NWORTH. The Covering Sheet (Page 1) should not leave the hospital site.**

Study ID: _____

**Source Data: Data collected as part of the ADENOMA Study**
***TO BE FILED IN PATIENT'S MEDICAL NOTES ONCE COMPLETED***

| Details of information | Information |
|---|---|
| **Informed Consent** | |
| 1. Date of written consent (dd/mm/yyyy) | __ / __ / ____ |
| 2. Has patient read and understood the current ethically approved patient information sheet (record version number and date)? | YES☐ NO☐ Version _._ Date __/__ /____ |
| 3. Is the patient able to provide written consent? | YES☐ NO☐ |
| 4. Name of person taking consent | |
| **Eligibility Check** | |
| 5. Is the patient aged 18 years or over? | YES☐ NO☐ |
| 6. Is the patient attending for routine screening, surveillance, or diagnostic colonoscopy (all non-emergency colonoscopies)? | YES☐ NO☐ |
| 7. Does the patient have capacity to give informed consent? | YES☐ NO☐ |
| *If answers 2,3,5,6 and 7 are YES, proceed to Question 8. If answers 2,3,5, 6 or 7 are NO, patient is not eligible for study.* | |
| 8. Is there suspicion of large bowel obstruction or pseudo-obstruction? | YES☐ NO☐ |
| 9. Is the patient known to have colon cancer or a polyposis syndrome? | YES☐ NO☐ |
| 10. Is the patient known to have a colonic stricture? | YES☐ NO☐ |
| 11. Does the patient have active colitis (UC, Crohn's, diverticulitis, infective colitis)? | YES☐ NO☐ |
| 12. Is the patient known to have severe diverticular disease? (not including uncomplicated diverticulosis) | YES☐ NO☐ |
| 13. Is the patient taking clopidogrel, warfarin, or other new generation anticoagulants and has not stopped this for the procedure? | YES☐ NO☐ |
| 14. Is the patient attending for a therapeutic procedure / assessment of a known lesion? | YES☐ NO☐ |
| 15. Does the patient report that they are pregnant (self-reported)? | YES☐ NO☐ N/A ☐ |

Name: _____ Signature: _____
Date: _____

**Study ID:** _____

*If answers 8-15 are NO, proceed with CRF completion. If any answers for 8-15 are YES, patient is not eligible for study. Please input patient's details into screening log*

| **Demographics** | | | |
|---|---|---|---|
| Gender: Male ☐ Female ☐ | | Age (years): | |
| Indications for colonoscopy : | | | |
| Bowel cancer screening | ☐ | Bowel cancer surveillance follow up | ☐ |
| Colonoscopy conversion from Bowelscope | ☐ | Symptomatic NHS diagnostic | ☐ |
| Symptomatic NHS surveillance | ☐ | | |
| Has patient had any abdominal surgery : | YES ☐ | NO | ☐ |

| **Study Number Generation and Randomisation** | |
|---|---|
| *Log on to study website and follow instructions to complete randomisation process.* | |
| Study number | |
| Randomisation outcome | Endocuff ☐ No Endocuff ☐ |

| **Colonoscopy** | |
|---|---|
| Endoscopist name: | |

**Medications**: Midazolam YES( __ mg) / NO Pethidine YES( __ mg) / NO

Fentanyl YES( __ mcg) / NO Entonox YES / NO Other (list/dose)_____

Buscopan YES / NO - If YES, was this given during (tick answer and fill in dose):

INTUBATION ☐ / _____(mg)

EXTUBATION (including administration at caecum) ☐ / _____(mg)

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

| |
|---|
| **Videoprocessor**: OLYMPUS / PENTAX / FUJI **Cuff colour**: BLUE / GREEN / PURPLE / N/A |
| Start time of colonoscopy **(hh:mm )** _ _ : _ _ |
| Time caecum reached **(hh:mm)** _ _:_ _ Time terminal ileum intubated **(hh:mm) or N/A** _ _:_ _<br>Complete colonoscopy? (ie caecum/ileum reached) YES☐ NO☐ |
| If INCOMPLETE colonoscopy, please tick reasons below. If COMPLETE colonoscopy, please proceed to next question<br>☐ Obstructing lesion<br>☐ Poor bowel preparation<br>☐ Technical difficulties (ie excessive looping)<br>☐ Patient discomfort<br>☐ Withdrawal of consent<br>☐ Others (please list) : _____ |
| Was colonoscopy completed by same endoscopist? YES☐ NO☐ Retroflexion? YES☐ NO☐ |
| End time of colonoscopy **(hh:mm)** _ _ : _ _ |

| | |
|---|---|
| Quality of bowel preparation | EXCELLENT ☐ GOOD ☐<br>ADEQUATE ☐ POOR ☐ |
| Was carbon dioxide (CO2) insufflation used? | YES☐ NO☐ |
| Was position change used during intubation? | YES☐ NO☐<br>If YES, No of times _____ |

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

| | |
|---|---|
| Was position change used during extubation? | YES☐ NO☐<br>If YES, No of times _____ |
| Did the patient experience any adverse events during the colonoscopy? If yes, details on additional page: | YES☐ NO☐ |
| Was the Endocuff removed? | YES☐ NO☐ NOT APPLICABLE ☐ |
| If YES, please tick reasons for removal below. If NO, please proceed to next question.<br>☐ Patients with an acute angulation in a fixed sigmoid colon rendering scope insertion not feasible with Endocuff mounted<br>☐ Patients with a new diagnosis of polyposis syndrome<br>☐ Patients with a new diagnosis of active colitis<br>☐ Patients where there is identification of a colonic stricture<br>☐ Patients with a new cancer diagnosis (if progression of colonoscope with the Endocuff attached is not possible | |
| Was there any endoscopic cancer detected ? | YES☐ NO☐ |
| If YES, was Endocuff in situ during detection | YES☐ NO☐ NOT APPLICABLE ☐ |
| Polyps detected? (if YES, proceed to polyp section of CRF) | YES☐ NO☐ |
| Total number of polyps detected | |
| | |

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

**Polyps detected – Sheet __ of __ (add extra sheets as required)**

**(*see attached sheet (Page 9) for polyp morphology)**

Polyp number: _____ Endocuff on: YES☐ NO☐ N/A ☐Detected on: insertion ☐ withdrawal ☐

Location: caecum☐ ascending☐ hepatic flexure☐ transverse☐ splenic flexure☐

descending☐ sigmoid☐ rectum☐ Size: _____mm

Morphology*: Ip ☐ Ips ☐ Is ☐ 0-IIa ☐ 0-IIa/c ☐ 0-IIb ☐ 0-IIc ☐ 0 -IIc/IIa☐

Removed: YES☐ NO☐ Specimen pot ID: _____

Removal method: cold biopsy ☐ hot biopsy ☐ cold snare ☐ hot snare ☐ hot EMR ☐

cold EMR ☐ not removed☐

Histology result (*Please circle most appropriate option*)

Adenoma / Cancer / Sessile serrated adenoma / Normal (including hyperplastic)

Other: _____

Polyp number: _____ Endocuff on: YES☐ NO☐ N/A ☐Detected on: insertion ☐ withdrawal ☐

Location: caecum☐ ascending☐ hepatic flexure☐ transverse☐ splenic flexure☐

descending☐ sigmoid☐ rectum☐ Size: _____mm

Morphology*: Ip ☐ Ips ☐ Is ☐ 0-IIa ☐ 0-IIa/c ☐ 0-IIb ☐ 0-IIc ☐ 0 -IIc/IIa☐

Removed: YES☐ NO☐ Specimen pot ID: _____

Removal method: cold biopsy ☐ hot biopsy ☐ cold snare ☐ hot snare ☐ hot EMR ☐

cold EMR ☐ not removed☐

Histology result (*Please circle most appropriate option*)

Adenoma / Cancer / Sessile serrated adenoma / Normal (including hyperplastic)

Other: _____

**Name:** _____ **Signature:** _____

**Date:** _____

| **Nurse assessment of comfort (during procedure)** | | | | | | |
|---|---|---|---|---|---|---|
| Domain | Item | 0 | 1 | 2 | 3 | Score (0-3) |
| Pain | 1 – Intensity | None or minimal | Mild | Moderate | Severe | |
| | 2 – Frequency | None | Few (1 or 2 episodes) | Several times (3-4 episodes) | Frequent (>4 episodes) | |
| | 3 – Duration | None | Short duration (<30 seconds) | Moderate duration (30-60 seconds) | Long duration (>1 minute) | |
| | Total pain score out of 9 (intensity + frequency + duration) | | | | | |
| Sedation | Level of consciousness* | Alert | Sleepy but initiates conversation | Responds only when asked or stimulated | Unresponsive or only responds with pronounced stimulation | |
| Global | Tolerability* | Very well tolerated | Reasonably well tolerated | Just tolerated | Poorly tolerated | |

*Note: Level of consciousness and tolerability are not used in overall score.

Nurse assessed patient comfort score (NAPCOMS) –
Rostom, A., et al., Development and validation of a nurse-assessed patient comfort score for colonoscopy. Gastrointest Endosc, 2013. 77: p. 255-61

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

**Patient assessment of experience (to be completed when ready for discharge from endoscopy unit):**

***Did you experience any discomfort during the procedure? (tick the box that applies)***

| | | | |
|---|---|---|---|
| None or minimal | ☐0 | Mild | ☐1 |
| Moderate | ☐2 | Severe | ☐3 |

***How many times did you have discomfort? (tick the box that applies)***

| | | | |
|---|---|---|---|
| I had no discomfort | ☐0 | Few (1 or 2 times) | ☐1 |
| Several times (3-4 times) | ☐2 | Frequent (more than 4 times) | ☐3 |

***How long did each episode of discomfort last? (tick the box that applies)***

| | | | |
|---|---|---|---|
| I had no discomfort | ☐0 | Short time (less than 30 seconds) | ☐1 |
| Moderate time (30-60 seconds) | ☐2 | Long time (more than 1 minute) | ☐3 |

***Was there any discomfort when the camera was passed through the anus? (tick the box that applies)***

| | | | |
|---|---|---|---|
| I had no discomfort | ☐0 | There was a lot of discomfort | ☐1 |
| There was some discomfort but it was OK | ☐2 | | |

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

Any other information :

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

Polyp morphology :

| Endoscopic appearance | Paris class | | Description |
|---|---|---|---|
| Protruded lesions | Ip |  | Pedunculated polyps |
| | Ips |  | Subpedunculated polyps |
| | Is |  | Sessile polyps |
| Flat elevated lesions | 0–IIa |  | Flat elevation of mucosa |
| | 0–IIa/c |  | Flat elevation with central depression |
| Flat lesions | 0–IIb |  | Flat mucosal change |
| | 0–IIc |  | Mucosal depression |
| | 0–IIc/IIa |  | Mucosal depression with raised edge |

**Name:** _____ **Signature:** _____
**Date:** _____

**Study ID:** _____

| Day of colonoscopy - Adverse event report | |
|---|---|
| Details of adverse event | Bleeding ☐ Perforation ☐<br>Abdominal pain ☐ Other ☐<br>Details: |
| Onset (dd/mm/yyyy) | __/__/____ |
| Severity | Mild ☐ Moderate ☐ Severe ☐ |
| Relationship to Endocuff | Not related ☐ Unlikely ☐ Possibly ☐<br>Probably ☐ Definitely ☐ |
| Expectedness | Expected ☐ Unexpected ☐ |
| AE outcome | Resolved ☐ Resolved with sequaelae ☐<br>Persisting ☐ Death ☐ Unknown ☐ |
| Resolution date (dd/mm/yyyy) | __/__/____ |
| Reported as serious? | YES ☐ NO ☐ |
| Comments: | |

**Name:** _____ **Signature:** _____
**Date:** _____

**Appendix 2:** Next Day Questionnaire

**Study ID:** _____

# Research questionnaire

This questionnaire is given to everyone who has had a colonoscopy as part of the ADENOMA study.

We would be grateful if you would complete and return it.

Please read each statement carefully. For each statement, tick the box by the response that most closely matches your opinion.

## A. Your views on the invitation materials

| | Strongly disagree | Disagree | Neither agree nor disagree | Agree | Strongly agree |
|---|---|---|---|---|---|
| 1. The invitation letter to the study was helpful | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. The patient information sheet was helpful | ☐ | ☐ | ☐ | ☐ | ☐ |

3. I contacted the research team to discuss the study. Yes ☐ No ☐

*If 'yes' to question 3 above*

| | Strongly disagree | Disagree | Neither agree nor disagree | Agree | Strongly agree |
|---|---|---|---|---|---|
| 4. The research team were able to answer my questions | ☐ | ☐ | ☐ | ☐ | ☐ |

## B. Meeting with the Research Nurse/Doctor

| | Strongly disagree | Disagree | Neither agree nor disagree | Agree | Strongly agree |
|---|---|---|---|---|---|
| 5. I found the appointment with the research nurse/doctor helpful. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. I felt I had enough time with the research nurse/doctor. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Any questions I had were answered by the research nurse/doctor. | ☐ | ☐ | ☐ | ☐ | ☐ |

**Study ID:** _____

| | Strongly disagree | Disagree | Neither agree nor disagree | Agree | Strongly agree |
|---|---|---|---|---|---|
| 8. I felt pressured by the research nurse/doctor to take part in the study. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. I felt I had an understanding of the risks of taking part in the study. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. I felt I had an understanding of the possible benefits of taking part. | ☐ | ☐ | ☐ | ☐ | ☐ |

## C. Your Colonoscopy

| | Yes | No | Don't remember |
|---|---|---|---|
| 11. I signed the consent form before going into the colonoscopy room. | ☐ | ☐ | ☐ |
| 12. I was given sedation for my colonoscopy (sedation is a drug to make you feel relaxed). | ☐ | ☐ | ☐ |

| | Strongly disagree | Disagree | Neither agree nor disagree | Agree | Strongly agree |
|---|---|---|---|---|---|
| 13. The colonoscopy was more uncomfortable than I expected. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. Inserting the camera through the anus was uncomfortable. | ☐ | ☐ | ☐ | ☐ | ☐ |

15. During the colonoscopy, I asked for it to be stopped or paused. Yes ☐ No ☐

*If 'yes' to question 15:*
16. I was satisfied with the response to my request. Yes ☐ No ☐

## D. After your Colonoscopy (At home)

17. After going home I suffered from pain in my bottom and /or stomach.

Yes ☐ No ☐

18. After going home, I had bleeding from my bottom.

Yes ☐ No ☐

**Study ID:** _____

## E. Additional comments

If you would like to comment about anything not already covered in this questionnaire, please use the space below.

Thank you for taking the time to complete this questionnaire. Please return it in the pre-paid envelope provided.

All replies remain part of your confidential record.

We appreciate all returned questionnaires and comments made, as they help us to improve our service.

**Appendix 3:** 21-day review form

**Study ID:** _____

| 21 day review | |
|---|---|
| Date of review | __ / __ / ____ |
| Period under review | __ / __ / ____ - __ / __ / ____ |
| **Items reviewed** | |
| Medical notes | YES ☐ NO ☐ |
| PCS/electronic appointments system | YES ☐ NO ☐ |
| Histology results | YES ☐ NO ☐ |
| Endoscopy reports | YES ☐ NO ☐ |
| Telephone call to patient | YES ☐ NO ☐ |
| **Polyp data** | |
| Number of polyps detected | |
| - Number of adenomas | |
| - Number of cancers | |
| - Number of sessile serrated adenomas | |
| - Number of normal (including hyperplastic) polyps | |
| - Number of 'Other' polyps (please document what 'Other' is) | |
| **Adverse events** | |
| Any adverse events reported?<br>If yes: details below (use extra sheets as required) Adverse event report sheet to be completed by medical staff | YES ☐ NO ☐ |

Name: _____ Signature: _____ Date: _____

ADENOMA Study – 21 day review form Version 5.0 03.03.2015

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