

# **BowelScope – Accuracy of Detection using ENdocuff Optimisation of Mucosal Abnormalities (The B- ADENOMA Study): A multicentre, randomised controlled flexible sigmoidoscopy trial**

Authors:

Professor Colin J Rees <sup>1</sup>  
Dr Andrew Brand <sup>2</sup>  
Ms Wee Sing Ngu<sup>3</sup>  
Mr Clive Stokes <sup>4</sup>  
Dr Zoe Hoare <sup>2</sup>  
Ms Nicola Totton <sup>2</sup>  
Professor Pradeep Bhandari <sup>5</sup>  
Professor Linda Sharp <sup>1</sup>  
Ms Alexandra Bastable <sup>2</sup>  
Professor Matthew Rutter <sup>6</sup>  
Dr Ajay M Verma <sup>6</sup>  
Dr Tom Lee <sup>6</sup>  
Mr Martin Walls<sup>3</sup>

1. Population Health Sciences Institute, Newcastle University Centre for Cancer, Newcastle University, Newcastle Upon Tyne, United Kingdom
2. North Wales Organisation for Randomised Trials in Health (NORTH), University of Bangor, Wales, United Kingdom.
3. Department of Gastroenterology, South Tyneside NHS Foundation Trust, South Shields, United Kingdom.
4. Gloucestershire Hospitals NHS Foundation Trust, Gloucester, United Kingdom.
5. Department of Gastroenterology, Portsmouth Hospitals NHS Foundation Trust, Portsmouth, United Kingdom
6. On behalf of the B-ADENOMA trial group

The B-ADENOMA trial group comprises

Professor Colin J Rees, Professor Matthew Rutter, Dr Ajay M Verma, Dr Tom Lee, Dr Jonathan Landy, Dr Andrew Veitch, Dr Andrew Higham, Dr Rodger Prudham, Dr Simon Hellier, Dr James Schutt, Ms Clare Westwood, Dr Ana Wilson, Dr James East, Dr Stuart Riley, Dr George Lipscomb, Dr Sara Koo, Dr Laura Neilson.

Corresponding author:

Professor Colin J Rees  
Population Health Sciences Institute  
Newcastle University Centre for Cancer  
Newcastle University  
Newcastle Upon Tyne  
NE2 4HH  
United Kingdom  
[Colin.Rees@newcastle.ac.uk](mailto:Colin.Rees@newcastle.ac.uk)

Word count : 3995

Keywords : Colonic adenomas  
Colorectal adenomas  
Colonic polyps  
Colorectal cancer screening  
Gastrointestinal endoscopy

## **Abstract**

### **Objectives**

Adenoma detection rate (ADR) is an important quality marker at lower gastrointestinal endoscopy. Higher ADRs are associated with lower post-colonoscopy colorectal cancer rates. The English flexible sigmoidoscopy screening programme (BowelScope), offers a one-off flexible sigmoidoscopy to individuals aged 55. However, variation in ADR exists. Large studies have demonstrated improved ADR utilising Endocuff Vision™ (EV) within colonoscopy screening but there are no studies within flexible sigmoidoscopy. We sought to test the effect of EV on ADR in a national flexible sigmoidoscopy screening population.

### **Design**

B-ADENOMA was a multicentre, randomised controlled trial involving 16 English BowelScope screening centres. Individuals were randomised to EV-assisted BowelScope (EAB) or Standard BowelScope (SB). ADR, polyp detection rate (PDR), mean adenomas per procedure (MAP), polyp characteristics and location, participant experience, procedural time and adverse events were measured. Comparison of ADR within the trial with national BowelScope ADR was also undertaken.

### **Results**

3222 participants were randomised (53% male) to receive EAB (n=1610) or SB (n=1612). Baseline demographics were comparable between arms. ADR in the EAB arm was 13.3% and in the SB arm was 12.2% (p=0.353). No statistically significant differences were found in PDR, MAP, polyp characteristics or location, participant experience, complications or procedural characteristics. ADR in the SB control arm was 3.1% higher than the national ADR.

### **Conclusion**

EV did not improve BowelScope ADR when compared to standard BowelScope. ADR in both arms was higher than the national ADR. Where detection rates are already high, EV is unable to improve detection further.

## Trial Registration

clinicaltrials.gov NCT03072472

International Standard Randomised Controlled Trials Number ISRCTN30005319

UK National Health Service NIHR portfolio CPMS ID 33224

## Summary

### **What is already known about this subject?**

We searched Medline and PubMed for publications in humans up to July 2019, using the terms 'Endocuff' and 'Endocuff Vision'. We identified 11 RCTs and 4 case series studies. This included our own group's study (the ADENOMA study) published in 2018. 2 other RCTs and the ADENOMA study utilised the Endocuff Vision™ (EV) device whilst the remainder used the original Endocuff™. The ADENOMA trial demonstrated an increase in ADR of 4.7% overall, driven by a bowel cancer screening subgroup increase of 10.8%. One EV study demonstrated an improvement in ADR of 7.8% which was not statistically significant but accompanied by a significant increased polyp detection rate of 11.9%. A single centre trial showed no increase in ADR with EV, influenced by exceptionally high ADR in both trial arms.

Of the RCTs which utilised the original Endocuff™ device, 3 showed increases in ADR of 3.3%, 8.9% and 14.7% respectively, one reported a lower adenoma miss rate of 23.7% but the rest did not demonstrate any significant difference in ADR. Findings from the case series reported improved mean number of adenomas detected per procedure and adenoma detection rates of up to 44.7%.

### **What are the new findings?**

To the best of our knowledge this is the first trial of EV in a flexible sigmoidoscopy population and it is the largest endoscopy randomised controlled device trial ever reported. The trial did not show an increase in ADR in the EV arm of this average risk population, however both the control arm ADR (12.2%) and the intervention arm ADR (13.3%) were significantly higher than the ADR in the broader national BowelScope programme (9.1%). EV was well tolerated.

### **How might it impact on clinical practice in the foreseeable future?**

EV has not been proven to increase ADR in an average risk population such as those undergoing flexible sigmoidoscopy screening. This contrasts with the increase in ADR in individuals at increased risk of adenomas (those who are faecal occult blood positive). Where ADR is high it is unlikely that EV can increase detection further however it may be of value to endoscopists with lower detection rates. Future EV research should focus on which specific endoscopy populations EV will benefit.

## INTRODUCTION

16,000 people die in the United Kingdom (UK) annually from colorectal cancer (CRC) with 1.4 million cases worldwide in 2012(1). The English National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) delivers two CRC screening programmes – a faecal occult blood (FOBT) based programme for people aged 60 -74 and one-off flexible sigmoidoscopy (FS) examination for people age 55 (termed BowelScope)(2). Evidence demonstrates that one-off FS between ages 55 to 64 can reduce CRC incidence by 23% and deaths by 31% (3). Flexible sigmoidoscopy and subsequent polypectomy interrupts the adenoma-carcinoma sequence, preventing progression to CRC(4). At BowelScope, if > 3 adenomas, a polyp with villous histology or high grade dysplasia, a polyp of >10mm in size, >20 hyperplastic polyps above the rectum, or a polyp which cannot be removed due to patient factors are found, individuals are referred for full colonoscopy. BowelScope is predicated on the ability of the investigation to maximise detection of adenomas present in the examined part of the colon. Details of BowelScope have been described elsewhere (2,5).

The most widely used measure of mucosal visualisation at lower gastrointestinal endoscopy is Adenoma Detection Rate (ADR)(6,7). ADR in BowelScope is lower than in FS trials, varying between centres and endoscopists(3,5,8,9). Factors influencing ADR at lower GI endoscopy include withdrawal time, use of antispasmodic medication, quality of bowel preparation and, crucially, adequate visualisation of the proximal aspect of mucosal folds(10,11). One approach to improve detection is using devices to hold back folds and enhance mucosal visualisation. Endocuff Vision™ (EV)(Figure 1), is a polypropylene device mounted onto the distal tip of a colonoscope(12). EV consists of a fixed portion and a row of eight soft projections which fold backwards during insertion but pull forwards during withdrawal to evert and slowly release colonic folds. This is a second-generation device with the earlier Endocuff™ (EC) improving ADR in some colonoscopy studies(13-15).

A recent multicentre randomised controlled trial (RCT), the ADENOMA trial, undertaken in participants attending for colonoscopy, demonstrated a significant increase in ADR using EV(16). ADENOMA demonstrated a 4.7% higher ADR in the intervention arm ( $p=0.02$ ) driven by a 10.8% higher ADR ( $p<0.001$ ) in FOBT positive BCSP participants undergoing colonoscopy. The greatest benefit was in the left colon, considered to be due to its increased tortuosity and prominent folds. No studies have investigated EV in FS. The effect of a device on total procedure time, completion rate, indirect health economic effects of finding more polyps and effect of a device on the experience of participants, particularly procedural comfort are important. The acceptability of an investigation is vitally important to screening tests(17,18). B-ADENOMA was an RCT comparing FS with and without EV in the English BowelScope screening programme. B-ADENOMA sought to determine the effect of EV on ADR, other detection markers and any other impact on BowelScope procedures.

## METHODS

### Study design

B-ADENOMA was a multicentre RCT recruiting patients from 16 hospitals in England between February 2017 and February 2018. All hospitals delivered dedicated BowelScope

lists. A short learning curve has previously been identified for EV use, therefore all endoscopists had to complete a minimum of 10 EV procedures prior to the study (16,19).

The B-ADENOMA protocol has been published (20), registered with clinicaltrials.gov NCT03072472, International Standard Randomised Controlled Trials Number ISRCTN30005319 and adopted onto the UK NHS NIHR portfolio (CPMS ID 33224). A favourable ethical opinion was received from UK West Midlands - Solihull Research Ethics Committee.

## **Participants**

BowelScope screening invites all 55-year-olds for a one-off procedure; however, individuals between 55 and 61 years may contact screening centres and opt into BowelScope.

Participants receive a BowelScope appointment at their closest local screening hospital. B-ADENOMA recruited BowelScope individuals aged 55 to 61 who were able to give informed, written consent. Exclusion criteria included absolute contraindications to FS, known or suspected bowel obstruction, colonic strictures, polyposis syndromes, known severe diverticular segment, active colitis, anticoagulation precluding polypectomy and pregnancy. BowelScope procedures are done without sedation. Reasons to withdraw participants from the trial after randomisation were withdrawal of consent, or new diagnosis of a polyposis syndrome. These individuals were excluded due to the different natural history of development of these polyps and significant malignant potential. All inclusion and exclusion criteria can be found in the protocol summary on the ISRCTN registry.

Standard BowelScope (SB) was undertaken in accordance with standard NHSBCSP procedures (22). Data were recorded on the Bowel Cancer Screening System (BCSS) database from which trial data were also reported.

Endocuff Vision™ - assisted BowelScope (EAB) was performed using the same protocol as SB with the following modifications: once in procedure room, endoscopist and staff were made aware of randomisation outcome and EV was attached to the tip of the endoscope according to manufacturer's instructions.

Removal of EV during BowelScope was advised if the endoscopist felt the device was hindering safe progression. Reasons for this included acute angulation in fixed sigmoid colon, colonic stricture, new diagnosis of malignancy or new diagnosis of active colitis (endoscopist concern over risk of mucosal damage).

## **Randomisation and masking**

Stratified randomisation based on age, sex and hospital site was performed using a dynamic allocation algorithm created by the North Wales Organisation for Randomised Trials in Health Clinical Trials Unit using a computerised internet-based platform (21). It was not possible to blind endoscopists, endoscopy staff, research teams or participants to randomisation allocation as EV is visible on the end of the colonoscope.

## Outcomes

The primary outcome was the proportion of participants with one or more colorectal adenomas detected at BowelScope as measured by the ADR.

Secondary outcomes were: Polyp Detection Rate (PDR); Sessile serrated polyps detection rate; Advanced adenoma detection rate; Cancer (cancerous polyps (those found to be cancerous on histological assessment) or endoscopic cancer (lesion felt to be a cancer by the endoscopist)) detection rate; Mean number of Adenomas detected per Procedure (MAP); Mean number of Polyps detected per Procedure (MPP); Mean number of advanced adenoma detected per procedure; Polyp size (measured in mm); Polyp morphology (Paris classification); Polyp location (transverse colon, splenic flexure, sigmoid colon, or rectum); Procedure withdrawal time (in minutes – recorded in procedures where no lesions detected to remove confounder of time taken for lesion removal); Procedure completion time (in minutes – recorded in procedures where no lesions detected to remove confounder of time taken for lesion removal); Reach of procedure (transverse colon, splenic flexure, sigmoid colon, or rectum); Discomfort assessed by patient (0 to 9 scale); Discomfort assessed by nurse (0 to 4 scale); Complications rate (adverse events related to procedure); Rate of conversion colonoscopies generated; Rate of EV change (how often was cuff removed).

Additional explanatory analyses included: comparison of ADR of first 20% of participants scoped by each endoscopist compared to last 20% of participants scoped by each endoscopist in each arm to identify changes due to learning curve effect; comparison of endoscopist ADR pre-trial and within trial; post hoc explanatory comparison of ADR within the trial with NHSBCSP data were also undertaken.

The modified Gloucester score was used by nursing staff to record patient comfort as per BowelScope practice and a truncated Nurse-Assessed Patient Comfort Score (NAPCOMS) was given to participants pre-discharge and for completion at 24 hours(23,24). Participants were followed up for 14 days for late complications and to check polyp histology. Adverse Events (AEs) or Serious Adverse Events (SAEs) were defined a priori in the trial protocol and reported to the Data Monitoring Committee (DMC), with severity and relation to EV reviewed by 2 independent clinicians. A full list of endpoints can be found in the protocol summary on the ISRCTN registry.

## Statistical analysis

This trial was powered to detect a difference in ADR at BowelScope between EAB and SB. National BowelScope ADR at trial commencement was 8.8% (BCSP national data). This figure was used to power the trial; however subsequent analyses used the more up-to-date published national ADR of 9.1%(9). An increase in ADR of 3% was agreed to be clinically significant. Using a two-sided test with 5% significance level and 80% power, the trial required 1611 participants per group to detect a statistically significant difference in proportion of participants with adenomas, as measured by ADR, between trial arms.

All analyses were conducted on an intention-to-treat basis. Tests of non-inferiority (procedure withdrawal and completion time) were analysed on both per protocol and intention to treat basis. Secondary analyses (polyp detection rate, polyp location, comfort

scores) were adjusted for multiple comparisons using Bonferroni correction. All other analyses were performed using a 5% significance level with 95% confidence intervals are presented. All statistical tests and confidence intervals were two-sided. A fully defined statistical analysis plan was written and agreed prior to completion of data collection. When conducting analysis, trial statisticians were blinded as to which arm was which.

For the primary binary outcome, of whether an adenoma was detected or not, logistic regression was employed to compare the difference in primary outcome between groups, taking into account randomisation stratification variables (endoscopy site, sex and age group). Similarly, for secondary outcomes of polyp detection rates, sessile serrate polyps, advanced adenoma and cancer, logistic regression was employed to compare the difference between EAB and SB group adjusting for the effects of the randomisation stratification variables (endoscopy site, sex and age).

The secondary outcomes based on the number of adenomas, polyps and advanced adenomas detected were analysed using Analysis of Variance (ANOVA) models which adjusted for the effects of randomisation stratification variables. Secondary outcomes concerning characteristics of the detected polyps: polyp size, morphology and location were compared between the EAB and SB group. For polyp size, an ANOVA was conducted and for polyp morphology and location, multinomial logit regressions were conducted.

Non-inferiority testing, for withdrawal and completion times involved using an ANOVA and a non-inferiority margin of 1 minute, which was deemed a minimal clinically important difference. To determine whether the examination extent of EAB group was inferior to SB, descriptive analysis was used where the proportion of procedures for each extent of examination was calculated for both groups and clinician judgment used to determine if they were inferior. A Chi-squared test was also undertaken to compare examination extent between groups. Non-inferiority testing for participant experience of comfort involved conducting ANOVAs using a non-inferiority margin of one point for participant experience of comfort. Non-inferiority testing for complication rates involved conducting a logistic regression with a non-inferiority margin of 10%.

Logistic regression was employed to compare the rate of conversion colonoscopies generated by EAB and SB groups. Repeated measures t-tests were computed to examine comparisons and relationships between ADR for the first 20% of procedures versus ADR for the last 20% procedures.

Dropouts were defined as patients who were randomised to enter the study but for some reason did not complete it (i.e. withdrew). Given the low percentage of missing data the complete case approach to dealing with missing data was employed in line with the recent recommendations of best practice (25). As this trial was aimed to detect differences in detection rates at Bowelscope as affected by EV the detection rates for subsequent colonoscopy procedures were not measured.

### **Patient and public involvement**

Patient and public involvement informed the development, conduct and reporting of this study with a patient representative on the trial steering committee. Input was also obtained

from local patient groups and patient and public representation on the National Cancer Research Institute CRC screening and prevention group.

## RESULTS

6579 individuals were identified and assessed for trial eligibility between 14<sup>th</sup> February 2017 and 13<sup>th</sup> February 2018 (Figure 2). 3357 individuals were excluded with the most common reasons being ineligibility (438), not attending for BowelScope (214), declining the study (1485), individuals who were not recruited at procedure e.g. unavailable research staff (899) and procedure cancellation (292). 3222 individuals were randomised into the study with one found to be ineligible post randomisation.

Patient demographics were balanced across arms. The mean age of participants was 55 years. 53% of participants were male and 22% had prior abdominal surgery (Table 1). Dropout rates were comparable across arms EAB (0.4%, n= 7), SB (0.3%, n = 5). Data from participants (n=12) who dropped out were not analysed; the percentage of missing data was 0.33% across the analysed dataset.

		<b>EAB (n=1609) (%)</b>	<b>SB (n=1612) (%)</b>
<b>Sex</b>	<b>Female</b>	757 (47)	758 (47)
	<b>Male</b>	852 (53)	854 (53)
<b>Previous abdominal surgery</b>	<b>No</b>	1243 (77.3)	1276 (79.2)
	<b>Yes</b>	365 (22.7)	334 (20.7)
	<b>Unknown</b>	1 (0.1)	2 (0.1)

**Table 1:** Summary of Participant Characteristics

No significant difference was demonstrated in the primary outcome. ADR in EAB and SB arms was 13.3% and 12.2% respectively. Results of logistical regression analyses for other detection markers were adjusted to account for randomisation stratification variables (age group, sex and endoscopy site) and are summarised in Table 2.

	<b>EAB % (n#)</b> <b>N=1578</b>	<b>SB (% , n#)</b> <b>N=1578</b>	<b>Odds Ratio</b>	<b>95% CI Odds Ratio</b>	<b>p value</b>
<b>Adenoma Detection Rate (ADR)</b>	13.3 (209)	12.2 (193)	1.11	0.90 - 1.37	0.353
<b>Polyp Detection Rate (PDR)</b>	28.6 (451)	26.6 (420)	1.11	0.89 - 1.39*	1*
<b>Sessile Serrated Polyps</b>	0.3 (5)	0.3 (4)	1.32	0.34 - 5.42	0.686
<b>Advanced Adenoma</b>	6.1 (95)	5.0 (80)	1.23	0.90 - 1.69	0.200
<b>Cancer</b>	0.2 (3)	0.4 (6)	0.48	0.10 - 1.85	0.292

\* In accordance with the pre-defined statistical analysis plan only the key secondary analyses were adjusted for multiple comparisons.

#Raw frequency

**Table 2:** Summary of Detection Rate Results from the Logistic Regression and adjusted to account for randomisation stratification variables (age group, gender and endoscopy site)

Results for the number of lesions detected using ANOVA and adjusted to account for randomisation stratification variables (age group, gender and endoscopy site) are summarised in Table 3.

	<b>EAB</b> <b>(Mean, SD, N)</b>	<b>SB</b> <b>(Mean, SD, N)</b>	<b>Mean Difference</b>	<b>95% CI Mean Difference</b>	<b>p value</b>
<b>Mean Number of Adenomas</b>	0.23, 0.47, 1578	0.21, 0.43, 1578	0.02	-0.01 - 0.05	0.153
<b>Mean Number of Polyps</b>	0.53, 0.92, 1578	0.49, 0.85, 1578	0.04	-0.02 - 0.12	0.190
<b>Mean Number of Advanced Adenomas</b>	0.07, 0.28, 1578	0.06, 0.25, 1578	0.01	-0.02 - 0.10	0.216

**Table 3:** Summary of the Quantity of lesions detected Results

Regarding characteristics of the detected polyps, no statistically significant differences were observed between EAB and SB groups for the size of polyps detected, 4.68mm vs 4.79mm, mean difference = -0.11, p = 0.635, 95% CI [-0.58, 0.35]. Similarly, there were no statistically significant differences between the EAB and SB groups for polyp morphology,  $\chi^2(6) = 8.04$ , p = 1 (Table 4) and polyp location,  $\chi^2(4) = 3.88$ , p = 1 (Table 5).

	<b>EAB (%)</b>	<b>SB (%)</b>
<b>lp</b>	31 (6.8%)	30 (7.0%)
<b>lps</b>	36 (7.9%)	28 (6.6%)
<b>ls</b>	244 (53.6%)	209 (48.9%)
<b>0-IIa</b>	136 (29.9%)	156 (36.5%)
<b>0-IIa/c</b>	2 (0.4%)	3 (0.7%)
<b>0-IIb</b>	5 (1.1%)	1 (0.2%)
<b>0-IIc</b>	0 (0%)	0 (0%)
<b>0-IIc/IIa</b>	1 (0.2%)	0 (0%)

**Table 4:** Summary of the modal polyp morphology for each procedure as a function of group

	<b>EAB (%)</b>	<b>SB (%)</b>
<b>Rectum</b>	184 (40.3%)	176 (41.0%)
<b>Sigmoid</b>	232 (50.1%)	212 (49.4%)
<b>Descending</b>	35 (7.7%)	33 (7.7%)
<b>Splenic flexure</b>	6 (1.3%)	7 (1.6%)
<b>Transverse</b>	0 (0%)	1 (0.2%)

**Table 5:** Summary of the modal polyp location for each procedure as a function of group

Analyses of withdrawal time and overall procedure time (in procedures where no lesions were detected), demonstrated no inferiority of EAB relative to SB. The difference in withdrawal duration between the EAB group (mean = 3.32, SD =2.05) and the SB group (mean = 3.44, SD =2.00) was -0.11 minutes, 95% CI [-0.25, 0.03] which did not cross the specified non-inferiority boundary of 1 minute. The difference in procedure duration between the EAB group (mean = 7.80, SD =3.49) and the SB group (mean = 8.03, SD=3.69) was -0.23 minutes, 95% CI [-0.48, 0.03] which also did not cross the specified non-inferiority boundary of 1 minute. Intention to treat and per protocol analyses were comparable, since there were only 5 protocol deviations: three in EAB and two in SB.

The reach of the procedures for the EAB and SB group are summarised in Table 6. There was a statistically significant difference in extent reached, as judged by endoscopist, between EAB and SB,  $\chi^2(4) = 18.99$ ,  $p < 0.001$  with further extent reached in the SB arm. Post-hoc testing showed that there were statistically significant differences between EAB and SB for sigmoid,  $\chi^2(1) = 9.81$ ,  $p = 0.002$ ; splenic flexure,  $\chi^2(1) = 6.72$ ,  $p = 0.010$  and transverse  $\chi^2(1) = 6.13$ ,  $p = 0.013$  extent.

	<b>EAB (%)</b>	<b>SB (%)</b>
<b>Rectum</b>	7 (0.4)	7 (0.4)
<b>Sigmoid</b>	372 (23.2)	301 (18.7)
<b>Descending</b>	762 (47.6)	738 (45.9)
<b>Splenic Flexure</b>	367 (22.9)	432 (26.9)
<b>Transverse</b>	93 (5.8)	129 (8.0)

**Table 6:** Anatomical location, as judged by endoscopist, reached during procedure as a function of group

Analyses of comfort demonstrated non-inferiority of EAB compare to SB. Greater discomfort was reported by patients (+0.26 point, 95% CI [0.1, 0.43]) and endoscopy nursing staff (+0.11 point, 95% CI [0.03, 0.19]) in EAB arm compared to SB arm, however although these differences were statistically significant, they did not reach the level of clinical significance as agreed pre-trial, which was set at 1 point of difference on both assessment scales.

Complication rates (adverse events related to procedure) were identical between the EAB (0.3%) and SB groups (0.3%) hence non-inferiority of EAB compare to SB was demonstrated.

Logistic regression adjusting for randomisation stratification variables revealed no statistically significant differences in the number of conversion colonoscopies generated between the EAB (8.4%) and SB (6.8%) groups (OR = 1.27, 95% CI [0.97, 1.67]). As a consequence, there was also no difference in workload of colonoscopy or surveillance generated based on polyp follow up by guidelines(26). The rate of EV exchange in the EAB group was 4.21% (95% CI [2.97, 5.95]). Endoscopists performed procedures using both SB and EAB and the distribution of number of procedures performed is depicted in Figure 3.

There was no difference at the level of individual endoscopists between ADR 6 months pre-trial and the ADR of those endoscopists in the control arm (SB) of the trial, 10.1% vs. 11.4%,  $t(44) = 0.93$ ,  $p = 0.355$ , mean difference = 1.3%, 95% CI [-0.01, 0.04]. For the EAB arm, there was a statistically significant difference in ADR for the first 20% of patients compared to the last 20% of patients per endoscopist: 8.6% vs 16.6%,  $t(51) = 2.23$ ,  $p = 0.030$ , mean difference = 8.0%, 95% CI [0.81, 15.09]. For the SB arm, there was no statistically significant difference in ADR for the first 20% of patients compared to the last 20% of patients per endoscopist: 9.2% vs 14.2%,  $t(51) = 1.77$ ,  $p = 0.083$ , mean difference = 5.0%, 95% CI [-0.68, 10.59]. However, although this difference was not statistically significant, it is substantial, especially given that a difference of 3% or greater had been deemed clinically significant. Furthermore, further explorative analysis (shown in Figure 4) strongly suggests that there is

evidence for a trial progression effect in the both the EAB and SB groups; i.e in both arms, the ADR rose as recruitment to the trial proceeded.

## DISCUSSION

B-ADENOMA was a multicentre RCT delivered across 16 English endoscopy units. This is, to our knowledge the largest endoscopy device trial ever conducted. There are no other trials examining the use of EV during flexible sigmoidoscopy. The trial did not demonstrate a significant difference in ADR detection between EAB and SB in the English NHS BowelScope Flexible Sigmoidoscopy Cancer Screening Programme.

EV previously demonstrated improved detection at colonoscopy in the ADENOMA trial but only amongst participants recruited through the BCSP and thus FOBt positive (16) – i.e. a population with high rates of pathology. No increase in detection was demonstrated in an average risk population in the ADENOMA trial. BowelScope invites unselected asymptomatic 55-year olds who are at average population risk of colorectal neoplasia.

It is important to explore why EV improves detection in some settings and not others. ADR in the control arm of this study was much higher than in standard BowelScope practice and It is likely that the high detection rates of pathology in the control arm could not be improved upon with EV. At the beginning of this study, ADR in the national BowelScope programme was 8.8% (Public Health England figures) and, more recently, several years into the programme, had only risen to 9.1% (9). The high control arm ADR of 12.2 % in this trial is well above (3.1% higher) national ADR and is likely that this high ADR meant that EV was unable to confer additional improvements in ADR. In contrast to the ADENOMA trial, a single centre UK EV study demonstrated no difference in ADR using EV in FOBt positive screening patients undergoing colonoscopy (19). In that trial, ADR in the control arm was much higher (63%) than national figures. Similarly, a Netherlands study, whilst using the original Endocuff™ (EC), found a higher than expected ADR in the control arm (52%) and did not see an increase in ADR when EC was used(27). These results demonstrate a consistent pattern: where control arm ADR is high (higher than reported ADR in those populations) the intervention arm (EV) does not demonstrate an increase in ADR. In any population endoscoped there will be a ceiling where all present polyps have been detected and the addition of a device or technology to improve detection will not be able to raise that ceiling and increase detection further. In 3 other trials utilising the original EC where baseline ADRs were comparatively low (13.5%, 20.7%, 26.3% respectively), ADR improvements were demonstrated(13-15). EV and the original EC are not the same device so direct comparisons are not possible, however these findings reinforce the same message that low ADR may be improved but there will be a level at which further improvement is not possible.

High ADRs seen in the control group arms of the current and previous trials may be influenced by high ability of endoscopists operating in centres participating in clinical research or influenced by research causing a change in practice(19,27). Individuals who agree to participate as endoscopists in research may self-select and be detectors with higher performance levels. This principle was suggested by the Netherlands study (27) where it was noted that endoscopists who had a high ADR prior to the use of EC benefitted little from addition of the device. Change in behaviour amongst practitioners participating in trials is

well recognised. Whilst the Hawthorne effect refers to changes in behaviour of individuals when they are being studied, it may be that endoscopists participating in research change practice and become more thorough in their mucosal inspection with or without device enhancement leading to above normal performance (28,29). It is also possible that endoscopists performing both control and intervention endoscopies change their technique both with and without the EV. This effect was suggested in a pilot study where an increase in ADR using EV in a colonoscopy screening population persisted when EV was no longer used when compared to the period before introduction of the device, although this difference did not achieve statistical significance(12). The current trial demonstrates ongoing rise in ADR throughout the study providing evidence that endoscopist practice changed throughout the trial.

A number of patient factors are known to affect polyp prevalence including sex, age, ethnicity, smoking and obesity(9,30). This was a multi-site study of 16 centres across wide English geography with equivalent characteristics across the two arms so this is unlikely to have influenced the outcome. We have no evidence to suggest the population studied was unrepresentative of the English BowelScope screened population with pre-trial ADR for participating sites comparable to national figures. By randomising by participant and not endoscopist, this trial has demonstrated the effect of EV on detection. An alternative could have been to employ a cluster methodology whereby endoscopists rather than participants were randomised and only performed either EAB or SB. This could potentially have limited the influence of practice changes using a device being employed without the device, however this could have introduced other confounders around endoscopist characteristics, and we believe the current trial design to be better. If the true difference between the groups was smaller than anticipated (e.g. 1.1% as seen rather than the 3% used for power calculation) the study would not have been adequately powered to demonstrate statistical significance. However, were this to be the case, the clinical significance of a 1% increase in ADR would be small and the authors would consider this not to be a clinically important value.

Comfort, procedural time and complications rates are crucial to the success of screening procedures which must be effective, safe and acceptable to the screened population (17,18). In our study, EV was associated with a statistically significant increase in participant and endoscopy nurse reported discomfort. However, this was not deemed clinically significant as set out by pre-trial levels for non-inferiority analysis of 1 point on the 0-9-point modified NAPCOMS score used by participants and the 0-4 point modified Gloucester scale used by endoscopy nursing staff. EV demonstrated a trend towards shorter withdrawal and overall procedural times, consistent with other studies. EV was not associated with an increase in complications(12,27).

We summarise that EV does not increase detection in an average risk population amongst endoscopists who already have high ADRs. It is possible that endoscopists with ADRs more consistent with or below national detection rates might benefit from EV use but we are unable to prove that assertion. It should be noted that whilst EV did not enhance detection, although the extent of the procedure was less with EV, this did not equate to a reduction in ADR. EV was safe and not associated with any increase in complication rates. Patient comfort was not adversely affected significantly.

B-ADENOMA is to our knowledge the largest endoscopy device trial ever reported and it recruited from 16 units in half the anticipated time of nine rather than 18 months. This study demonstrates the ability of a well-motivated network of endoscopy units to achieve rapid large-scale recruitment.

## **CONCLUSION**

The B-ADENOMA trial did not demonstrate increased detection with EV in an average risk population undergoing flexible sigmoidoscopy. The ADR in both the control arm and the intervention arm were significantly higher than in standard BowelScope flexible sigmoidoscopy screening practice.

## **THE B-ADENOMA TRIAL GROUP**

Professor Colin Rees, Professor Matthew Rutter, Dr Ajay M Verma, Dr Tom Lee, Dr Jonathan Landy, Dr Andrew Veitch, Dr Andrew Higham, Dr Rodger Prudham, Dr Simon Hellier, Dr James Schutt, Ms Clare Westwood, Dr Ana Wilson, Dr James East, Dr Stuart Riley, Dr George Lipscomb, Dr Sara Koo, Dr Laura Neilson.

## **ACKNOWLEDGEMENTS**

We would like to thank members of the Trial Steering Committee (John McLaughlin – Chair, Matt Brookes, Christian Von Wagner, Venketaraman Subramanian, Nigel Hesleton – participant representative, Sharon Love); Data Monitoring Committee (Mike Bramble – Chair, John DeCaestecker, Colin Everett, Andrew Higham); South Tyneside Research Department (The sponsor site - Claire Livingstone, Amy Burns, Paula Madgwick), research nurses, the Bowel Cancer Screening Programme, Specialist Screening Practitioners, members of the research team, and participants at all participating sites who took part in the study.

## **COMPETING INTERESTS**

Colin Rees has received grant funding from ARC medical, Norgine and Olympus medical. He was an expert witness for ARC medical. Pradeep Bhandari has received grant funding from Norgine. No other authors declare competing interests.

## **FUNDING**

B-ADENOMA was an investigator led study funded by ARC Medical and adopted onto the English National Institute for Health Research Portfolio.

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of this manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

## **LEGENDS FOR FIGURES**

**Figure 1:** Endocuff Vision™ (EV) Photograph taken by author

**Figure 2:** CONSORT Flow Diagram

**Figure 3:** Total number of Procedures performed by an Endoscopist for each Group

**Figure 4:** ADR for the First Proportions of Procedures versus ADR for the Last Proportions of Procedures as a function of Split size and Group Allocation.

## REFERENCES

1. Cancer Research UK. Bowel Cancer Statistics. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer#heading-Zero>. Accessed August 28, 2018.
2. NHS Bowel Cancer Screening. <https://www.nhs.uk/conditions/bowel-cancer-screening/>. Published 2018. Accessed August 28, 2018.
3. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010;375(9726):1624–1633. doi:10.1016/S0140-6736(10)60551-X.
4. Leslie A, Carey FA, Pratt NR, Steele RJC. The colorectal adenoma-carcinoma sequence. *Br J Surg*. 2002;89(7):845–860. doi:10.1046/j.1365-2168.2002.02120.x.
5. Bevan R, Blanks RG, Nickerson C, et al. Factors affecting adenoma detection rate in a national flexible sigmoidoscopy screening programme : a retrospective analysis. *Lancet Gastroenterol Hepatol*. 2019;4(3):239–247. doi:10.1016/S2468-1253(18)30387-X.
6. Lee TJW, Rutter MD, Blanks RG, et al. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. *Gut*. 2012;61(7):1050–1057. doi:10.1136/gutjnl-2011-300651.
7. Rees CJ, Thomas Gibson S, Rutter MD, et al. UK key performance indicators and quality assurance standards for colonoscopy. *Gut*. 2016;65(12):1923–1929. doi:10.1136/gutjnl-2016-312044.
8. Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. *Scand J Gastroenterol*. 2003;38(6):635–642.
9. Segnan N, Senore C, Andreoni B, et al. Baseline findings of the Italian multicenter randomized controlled trial of “once-only sigmoidoscopy” --SCORE. *J Natl Cancer Inst*. 2002;94(23):1763–1772. doi:10.1093/jnci/94.23.1763.
10. Rees CJ, Rajasekhar PT, Rutter MD, Dekker E. Quality in colonoscopy: European perspectives and practice. *Expert Rev Gastroenterol Hepatol*. 2014;8(1):29–47. doi:10.1586/17474124.2014.858599.
11. Faiss S. The missed colorectal cancer problem. *Dig Dis*. 2011;29 Suppl 1:60–63. doi:10.1159/000331119.
12. Tsiamoulos ZP, Misra R, Rameshshanker R, et al. Impact of a new distal attachment on colonoscopy performance in an academic screening center. *Gastrointest Endosc*. 2018;87(1):280–287. doi:10.1016/j.gie.2017.04.001.
13. Gonzalez-Fernandez C, Garcia-Rangel D, Aguilar-Olivos NE, et al. Higher adenoma detection rate with the endocuff: a randomized trial. *Endoscopy*. 2017;49(11):1061–

1068. doi:10.1055/s-0043-117879.
14. Floer M, Biecker E, Fitzlaff R, et al. Higher adenoma detection rates with endocuff-assisted colonoscopy - a randomized controlled multicenter trial. *PLoS One*. 2014;9(12):e114267. doi:10.1371/journal.pone.0114267.
  15. De Palma GD, Giglio MC, Bruzzese D, et al. Cap cuff-assisted colonoscopy versus standard colonoscopy for adenoma detection: a randomized back-to-back study. *Gastrointest Endosc*. 2018;87(1):232–240. doi:10.1016/j.gie.2016.12.027.
  16. Ngu WS, Bevan R, Tsiamoulos ZP, et al. Improved adenoma detection with Endocuff Vision: the ADENOMA randomised controlled trial. *Gut*. 2019;68(2):280–288. doi:10.1136/gutjnl-2017-314889.
  17. Public Health England. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. <https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme>. Published 2015. Accessed August 28, 2018.
  18. Wilson J, Junger G, World Health Organization. *Principles and Practice of Screening for Disease*. Vol 34. World Health Organisation. 1968.
  19. Bhattacharyya R, Chedgy F, Kandiah K, et al. Endocuff-assisted vs. standard colonoscopy in the fecal occult blood test-based UK Bowel Cancer Screening Programme (E-cap study): a randomized trial. *Endoscopy*. 2017;49(11):1043–1050. doi:10.1055/s-0043-111718.
  20. Ngu WS, Walls M, Bhandari P, et al. The B-ADENOMA Study: Bowelscope - Accuracy of Detection using Endocuff Optimisation of Mucosal Abnormalities: Study Protocol for randomised controlled trial. *Endosc Int open*. 2018;6(7):E872–E877. doi:10.1055/a-0591-9308.
  21. Russell D, Hoare ZSJ, Whitaker R, Whitaker CJ, Russell IT. Generalized method for adaptive randomization in clinical trials. *Stat Med*. 2011;30(9):922–934. doi:10.1002/sim.4175.
  22. Public Health England. Bowel scope screening: standard operating procedures. Guidance. <https://www.gov.uk/government/publications/bowel-cancer-screening-bowel-scope-standard-operating-procedures/bowel-scope-screening-standard-operating-procedures>. Published 2018. Accessed August 28, 2018.
  23. Chilton A, Rutter M. Quality assurance guidelines for colonoscopy. *NHS BCSP Publ No 6*. 2011.
  24. Rostom A, Ross ED, Dube C, et al. Development and validation of a nurse-assessed patient comfort score for colonoscopy. *Gastrointest Endosc*. 2013;77(2):255–261. doi:10.1016/j.gie.2012.10.003.
  25. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple

imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17(1):162. doi:10.1186/s12874-017-0442-1.

26. Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut*. 2002;51(Supplement 5):v6–v9. doi:10.1136/gut.51.suppl\_5.v6.
27. van Doorn SC, van der Vlugt M, Depla A, et al. Adenoma detection with Endocuff colonoscopy versus conventional colonoscopy: a multicentre randomised controlled trial. *Gut*. 2017;66(3):438–445. doi:10.1136/gutjnl-2015-310097.
28. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *BMJ*. 2015;351:h4672. doi:10.1136/bmj.h4672.
29. Sanaka MR, Super DM, Feldman ES, Mullen KD, Ferguson DR, McCullough AJ. Improving compliance with postpolypectomy surveillance guidelines: an interventional study using a continuous quality improvement initiative. *Gastrointest Endosc*. 2006;63(1):97–103. doi:10.1016/j.gie.2005.08.048.
30. Corley DA, Jensen CD, Marks AR, et al. Variation of adenoma prevalence by age, sex, race, and colon location in a large population: implications for screening and quality programs. *Clin Gastroenterol Hepatol*. 2013;11(2):172–180. doi:10.1016/j.cgh.2012.09.010.