Endocuff-assisted vs. standard colonoscopy in the fecal occult blood test-based UK Bowel Cancer Screening Programme (E-cap study): a randomized trial

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ABSTRACT
Background and study aims Up to 25 % colorectal adenomas are missed during colonoscopy. The aim of this study was to investigate whether the endocuff could improve polyp detection in an organized bowel cancer screening program (BCSP).

Patients and methods This parallel group, single-blinded, randomized controlled trial included patients with positive fecal occult blood test (FOBT) who were attending for BCSP colonoscopy. The primary outcome was the number of polyps per patient. Secondary outcomes included the number of adenomas per patient, adenoma and polyp detection rates, and withdrawal times.

Results A total of 534 BCSP patients were randomized to endocuff-assisted or standard colonoscopy. The mean age was 67 years and the male to female ratio was 1.8:1. We detected no significant difference in the number of polyps per patient (standard 1.8, endocuff 1.6; \(P=0.44\)), adenomas per patient (standard 1.4, endocuff 1.3; \(P=0.54\)), polyp detection rate (standard 69.8 %, endocuff 70.3 %; \(P=0.93\)), adenoma detection rate (standard 63.0 %, endocuff 60.9 %; \(P=0.85\)), advanced adenoma detection rate (standard 18.5 %, endocuff 16.9 %; \(P=0.81\)), and cancer detection rate (standard 5.7 %, endocuff 5.3 %; \(P=0.85\)). The mean withdrawal time was significantly shorter among patients in the endocuff group compared with the standard colonoscopy group (16.9 vs. 19.5 minutes; \(P< 0.005\)). The endocuff had to be removed in 17/266 patients (6.4 %) because of inability to pass through the sigmoid colon.

Conclusions This study did not find improved polyp or adenoma detection with endocuff-assisted colonoscopy in the FOBT-positive BCSP population. A shorter withdrawal time with endocuff may reflect improved views and stability provided by the endocuff.

Trial registered at ClinicalTrials.gov (NCT02529007).

Introduction
Bowel cancer is the third most common cancer in the UK and the second leading cause of cancer deaths [1]. Colonoscopy and the endoscopic removal of adenomas reduce colorectal cancer mortality [2–4]. For every 1 % increase in the adenoma detection rate (ADR), there is a 3 % decrease in the risk of interval colorectal cancer [5].

The UK Bowel Cancer Screening Programme (BCSP) uses fecal occult blood test (FOBT) to select high-risk individuals to undergo colonoscopy. However, colonoscopy has an inherent adenoma miss rate of up to 25 % [6]. Keeping this in mind, colonoscopy in the UK BCSP is restricted to very select colonoscopists who have been carefully selected based on their large lifetime experience and excellent performance indicators, and then ac-
credited by undergoing a theory-based exam and a clinical assessment.

Modifications of the endoscopic technique, such as by increasing withdrawal times [7], have been shown to increase lesion detection. The use of smooth muscle relaxants, such as hyoscine butylbromide, has shown mixed results [8]. In addition, a number of technologies and devices have been shown to improve polyp detection [9–12]. However, none have translated yet to mainstream practice, as we still need well-designed trials to prove the superiority and cost-effectiveness of devices over the expertise of a well-trained colonoscopist.

The Endocuff Vision (Arc Medical Design Ltd., Leeds, England) is a disposable device that attaches to the end of the colonoscope (►Fig. 1, ►Fig. 2). It has a single horizontal row of soft, flexible arms that remain collapsed during insertion but flare out on withdrawal to engage mucosal folds and flexures. This allows inspection of otherwise challenging areas and improves scope stability. It is a modification of the first-generation endocuff, which had two rows of flexible arms.

Results from randomized controlled trials (RCTs) of the first-generation endocuff have demonstrated mixed success. Floer et al. demonstrated a 14.7 percentage point increase in ADR compared with standard colonoscopy [13]. Van Doorn et al. also reported an increase in ADR, but no difference in mean adenomas per patient and a lower cecal intubation rate when comparing endocuff with standard colonoscopy [14]. These studies did not specifically address a screening population and did not have strict standardization of the endoscopists’ expertise.

There are currently no studies investigating such devices within a screening population, where the gains could potentially be the greatest. We performed the first RCT comparing endocuff with standard practice in an organized bowel cancer screening program where the colonoscopy was performed by accredited experts.

**Aims and objectives**

The aim of the study was to establish whether endocuff-assisted colonoscopy improved polyp detection in the BCSP population.

**Patients and methods**

**Study design**

This was a parallel group, single-blinded, RCT carried out at a UK-based bowel cancer screening center. Ethics approval was obtained (ref: 14/SC/0207). The trial was adopted onto the National Institute of Health Research (NIHR) portfolio (UKCRN ID: 16985). The trial was registered at ClinicalTrials.gov (NCT02529007).
Participants
All patients attending the BCSP colonoscopy from 10-9-2015 to 10-9-2016 were included, provided they were able and willing to provide written informed consent. These patients were aged between 59 and 75 years and had a positive FOBT. Patients with a history of inflammatory bowel disease or polyposis syndromes were excluded.

Endoscopists
All procedures were performed by accredited bowel cancer screening colonoscopists. Screening colonoscopists need to have a minimum lifetime experience of 1000 colonoscopies and fulfill key performance criteria for sedation and adenoma detection before they are eligible to undergo the screening program accreditation process. This involves a theory test and then a practical assessment involving two real-time colonoscopy procedures assessed by two independent external assessors.

Colonoscopy procedure and pathology
The endoscopists in the study performed at least 15 endocuff-assisted colonoscopies before the commencement of the trial. Colonoscopy in both arms was standardized with the use of Olympus Spectrum CV260SL processor, Olympus CF-H260 endoscopes, CO₂, and Olympus scope guide (Olympus, Tokyo, Japan). Procedures were performed under conscious sedation with intravenous midazolam and fentanyl. All patients received hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Germany) on reaching the cecum, and had standard position changes during withdrawal (cecum, ascending colon, and hepatic flexure – left lateral position; transverse colon – supine position; splenic flexure and descending colon – right lateral position) [15].

The protocol for removing polyps and sending pathology specimens for assessment did not differ in any way from normal clinical practice. Pathology was reported by specialist gastrointestinal pathologists in an accredited NHS hospital laboratory (Clinical Pathology Accreditation ISO 15189). The pathologist was blinded to the use of the endocuff. An independent member of the research team recorded colonoscopy data directly onto a case report form.

Powering
Data from the center’s bowel cancer screening in previous years showed an average of 1.6 polyps detected per patient with a standard deviation of 2.05. Based on previous studies, we postulated that the endocuff could increase the polyp detection by 30%. To detect an absolute difference between mean counts per person of 0.5 with 80% power required 265 participants in each group, 530 in total.

Informed consent
Patients invited for BCSP colonoscopy were provided with the study information 1 week prior to their colonoscopy. On the day of the procedure, a good clinical practice-certified researcher met with the patient to obtain informed consent.

Randomization
Participants were stratified into two groups: those attending for index colonoscopy (screening population) and those attending for surveillance following previous polypectomy within the BCSP (surveillance population). Within each population, participants were randomized to either standard colonoscopy (standard group) or endocuff-assisted colonoscopy (endocuff group). Randomization was performed in a 1:1 ratio among the two study arms using random permuted blocks of randomly varying sizes. The successive participants were given a sequential study number and then assigned to the associated intervention from the random list. The generated list was concealed in sequentially numbered sealed opaque envelopes, which were only opened to reveal the allocation after verifying that the participant was eligible and had consented to enter the trial. The participant, but not the endoscopist, was blinded to the allocation.

Outcome measures and analysis
The primary end point of the study was the mean polyps per patient (MPP), defined as the total number of polyps divided by the total number of patients in that group.

The secondary end points included polyp detection rate (PDR – the percentage of procedures in which at least one polyp was detected), ADR (the percentage of procedures in which at least one adenoma was detected), advanced ADR (the percentage of procedures with adenomas >10 mm in size), mean adenomas per patient (MAP – total number of adenomas divided by the total number of patients in that group), and cancer detection rate (total number of cancers divided by the total number of patients in that group). Fisher’s exact test was used to compare these outcomes.

The cecal intubation times and total procedure times were recorded. Withdrawal times (time taken from the start of withdrawal to the end of the procedure) were compared between the two arms. A log rank test was used to compare withdrawal times.

It can be challenging to obtain adequate views of the distal rectum and anal canal. We wanted to see whether the endocuff could improve views in these challenging areas. Endoscopists were asked to grade the views of the dentate line and anal canal on direct withdrawal in forward view as excellent, adequate or poor for all procedures. A chi-squared test was used to compare these data. Bowel preparation for each colonoscopy was graded as per the 3-point UK bowel preparation scoring system: good, adequate or poor [16].

Comfort scores were graded for all procedures as per the 5-point nurse-reported comfort levels used for UK national BCSP colonoscopy procedures, ranging from no discomfort to severe discomfort [17]. The distribution of scores across the two arms was compared using a chi-squared test.
Results

A total of 534 patients were recruited to the study between September 2014 and September 2015. Three patients were subsequently excluded following the unexpected finding of hyperplastic polyposis during the colonoscopy. The remaining 531 patients were included in the final analysis (Fig. 3).

The mean age of the patients was 67 years, and the male to female ratio was 1.8:1. Of the patients who were recruited, 371/531 (69.9%) attended for screening (index) colonoscopy and 160/531 (30.1%) attended for surveillance colonoscopy after previous polypectomies under the organized BCSP (Table 1).

A total of 265 patients were randomized to standard colonoscopy and 266 to endocuff-assisted colonoscopy. Of the 266 patients recruited to the endocuff arm, the endocuff had to be removed in 17 (6.4%) because the sigmoid colon was found to be too tortuous to negotiate with the device in situ. In 14 of these patients (82.4%), this resolved the problem and the colonoscopy could then be completed.

Polyp, adenoma, and cancer detection

Whole population

On intention-to-treat analysis, 470 polyps (MPP 1.7) were detected in the standard group compared with 436 polyps (MPP 1.6) in the endocuff group (Table 2). There was no significant difference between the two groups (P = 0.44). A total of 359 adenomas (MAP 1.4) were detected in the standard group vs. 336 adenomas (MAP 1.3) in the endocuff group (P = 0.54). The adenomas accounted for 76.4% of all polyps detected.

No significant difference was found between the two groups in PDR (standard 69.8%, endocuff 70.3%; P = 0.93), ADR (standard 63.0%, endocuff 60.9%; P = 0.85), advanced ADR (standard 18.5%, endocuff 16.9%; P = 0.81), and cancer detection rate (standard 5.7%, endocuff 5.3%; P = 0.85).

Screening and surveillance populations – subanalysis

A subanalysis was performed in the screening and surveillance populations separately. As expected, smaller numbers of polyps were detected in the surveillance population (266 polyps) compared with the screening population (640 polyps). However, no significant difference was seen between the two study arms for any of these outcomes in either the screening group or the surveillance group.
Polyp size-based analysis

A polyp size-based analysis was performed to investigate whether there was a difference in the size of polyps detected in the two groups (Fig. 4). A chi-squared test indicated that significantly more medium sized (6 – 10 mm) polyps were detected in the standard colonoscopy arm compared with the endocuff arm (76 vs. 46; P = 0.02). There was no significant difference between the two arms in the detection of diminutive (≤ 5 mm) and large (> 10 mm) polyps.

Endoscopist-based analysis

The data for each endoscopist were evaluated separately to look for any significant differences in lesion detection rates between the four different endoscopists in the study. When individual endoscopists were analyzed, no significant difference was found in these outcomes between the standard and endocuff groups (Table 3).

Effect of trial on the performance of the endoscopists (study bias)

We examined the ADRs of the study endoscopists in the 6 months prior to the start of the study and compared these with their ADRs in the standard arm during the study. The pre-study ADR averaged 58.9% and did not change significantly during the study.

Withdrawal and intubation times

The mean withdrawal time for all cases in the study was 18.16 minutes. The mean withdrawal time was 19.5 minutes in the standard arm, which was significantly longer than the 16.9 minutes in the endocuff arm (P<0.005) (Table 1).

There was no significant difference in the intubation times between the two groups (standard 15.89 minutes vs. endocuff 15.75 minutes; P=0.86).

The mean total procedure time was shorter in the endocuff group (32.8 minutes) compared with the standard group (35.28 minutes); however, this difference was not statistically significant (P=0.11).

Views of the dentate line and anal canal

Views were graded as excellent in 67.6% of patients in the endocuff group and in 61.9% of those in the standard group; however, this failed to achieve significance. All endoscopists graded the views as excellent more frequently for the endocuff group; however, the difference was not significant compared with the standard group (P=0.05).

Comfort scores

Comfort scores were graded for all procedures on a 5-point scale, with no discomfort being scored as 0 and severe discomfort scored as 4. A chi-squared test of homogeneity demonstrated no significant difference in comfort scores between the standard and endocuff arms (P=0.27), with a mean comfort score of 1.46 and 1.57, respectively.

Complications

No significant complications were seen in either study arm. Postpolypectomy bleeding occurred in one patient in the standard arm. The bleed was identified immediately and was controlled with the application of clips.

Discussion

This is the first RCT to evaluate any generation of endocuff in an organized national bowel cancer screening population.

The endocuff did not increase polyp or adenoma yield in the hands of highly experienced colonoscopists in this FOBT-positive screening population. The overall MPP, MAP, PDR, and

<table>
<thead>
<tr>
<th>Polyp size-based analysis</th>
<th>Standard colonoscopy (n = 265)</th>
<th>Endocuff-assisted colonoscopy (n = 266)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Polyps, n</td>
<td>470</td>
<td>436</td>
<td>0.44</td>
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<tr>
<td>MPP, mean ± SD</td>
<td>1.8 ± 2.0</td>
<td>1.6 ± 1.9</td>
<td>0.44</td>
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<tr>
<td>Adenomas, n</td>
<td>359</td>
<td>336</td>
<td>0.54</td>
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<tr>
<td>MAP, mean ± SD</td>
<td>1.4 ± 1.5</td>
<td>1.3 ± 1.8</td>
<td>0.93</td>
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<tr>
<td>PDR, %</td>
<td>69.8</td>
<td>70.3</td>
<td>0.85</td>
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<tr>
<td>ADR, %</td>
<td>63.0</td>
<td>60.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Proximal1 polyps, n (%)</td>
<td>169/470 (36.0)</td>
<td>148/436 (33.9)</td>
<td>0.52</td>
</tr>
<tr>
<td>Proximal1 adenomas, n (%)</td>
<td>140/359 (39.0)</td>
<td>128/336 (38.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Advanced ADR2, %</td>
<td>18.5</td>
<td>16.9</td>
<td>0.81</td>
</tr>
<tr>
<td>Cancer detection rate, %</td>
<td>5.7</td>
<td>5.3</td>
<td>0.85</td>
</tr>
</tbody>
</table>

1 Proximal, proximal to the splenic flexure.
2 Advanced ADR, proportion of cases in which at least one adenoma > 10 mm in size was detected.
ADR were similar in the standard and endocuff arms. The study demonstrated that it was possible to achieve cecal intubation in 93.6% of patients without removing the endocuff attachment. There were no safety concerns and the device did not increase patient discomfort. However, the mean withdrawal time was significantly shorter in the endocuff arm (16.9 minutes vs. 19.5 minutes; $P<0.005$).

The most significant finding from this study is the lack of an improvement in polyp or adenoma detection with the use of the endocuff attachment. Our data demonstrate that if endoscopists have a very high PDR and ADR in a BCSP, then devices such as the endocuff are unlikely to be of benefit.

To date, three large RCTs comparing the first-generation endocuff with standard colonoscopy have been published [13, 14, 18]. A large study from the Netherlands with over 1000 participants suggested a trend toward improved adenoma detection, although this was not statistically significant and there was no significant increase in the number of adenomas per patient with the endocuff [14]. Our study did not suggest any trend toward significance, although it should be noted that our patient population was quite different, being entirely FOBT positive. It is important to note that the authors in the above study performed a subanalysis of patients with positive fecal immunochemical tests and noted no significant difference in adenoma detection ($P=0.52$). This would be in keeping with our findings, and reflects the importance of examining a device within a specific patient population.

There are a few studies, however, that have reported an improvement in polyp/adenoma detection with the use of the endocuff attachment. The consistent observation from these studies is a low polyp/adenoma detection in the control arm, and the reason behind this is not clear. This could potentially be related to either the endoscopists or population included in these studies. The other observation of note here is that the MPP and ADR in the control arm of the study from the Amsterdam group [14] and our current study are very high, and in both these studies the endocuff has shown no improvement in MPP or ADR. Given the above observations, it is not unreasonable to speculate that the observed benefits of endocuff in some of the studies could be a reflection of poor polyp detection in the control arms, as the reported polyp and adenoma rates in the control arms of these studies is lower than expected. We believe that future studies with similar devices should consider these factors when designing the study and interpreting the results.

We have reported significantly shorter withdrawal times (approximately 15% reduction) in the endocuff arm compared with the standard arm. This could be due to improved views and stability provided by the endocuff during withdrawal. This is really important, as the endoscopists in the endocuff arm have detected the same number of polyps and adenomas as in the standard arm but in a much shorter time. The small additional cost of the endocuff device could potentially be neutralized by the reduction in withdrawal and overall procedure times, there-

### Table 3  Results by endoscopist.

<table>
<thead>
<tr>
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<th>Endoscopist 1</th>
<th>Endoscopist 2</th>
<th>Endoscopist 3</th>
<th>Endoscopist 4</th>
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<tr>
<td>Participants, n</td>
<td>122</td>
<td>108</td>
<td>90</td>
<td>107</td>
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<tr>
<td>Polyps, n</td>
<td>234</td>
<td>194</td>
<td>138</td>
<td>138</td>
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<tr>
<td>MPP, mean ± SD</td>
<td>1.9 ± 2.2</td>
<td>1.8 ± 2.2</td>
<td>1.5 ± 1.4</td>
<td>1.3 ± 1.5</td>
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<tr>
<td></td>
<td>$P=0.66$</td>
<td>$P=0.11$</td>
<td>$P=0.66$</td>
<td>$P=0.11$</td>
</tr>
<tr>
<td>Adenomas, n</td>
<td>183</td>
<td>156</td>
<td>107</td>
<td>110</td>
</tr>
<tr>
<td>MAP, mean ± SD</td>
<td>1.5 ± 1.7</td>
<td>1.4 ± 2.2</td>
<td>1.2 ± 1.2</td>
<td>1.0 ± 1.4</td>
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<tr>
<td></td>
<td>$P=0.52$</td>
<td>$P=0.06$</td>
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<tr>
<td>PDR, %</td>
<td>66.4</td>
<td>72.2</td>
<td>75.6</td>
<td>63.5</td>
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<tr>
<td></td>
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<td>$P=0.06$</td>
<td>$P=0.34$</td>
<td>$P=0.06$</td>
</tr>
<tr>
<td>ADR, %</td>
<td>57.4</td>
<td>62.0</td>
<td>67.8</td>
<td>51.4</td>
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<td></td>
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<td>$P=0.47$</td>
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</tr>
<tr>
<td>Cancer detection rate, %</td>
<td>4.9</td>
<td>2.8</td>
<td>6.7</td>
<td>5.6</td>
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<tr>
<td></td>
<td>$P=0.40$</td>
<td>$P=0.75$</td>
<td>$P=0.40$</td>
<td>$P=0.75$</td>
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</table>

MPP, mean polyps per patient; MAP, mean adenomas per patient; PDR, polyp detection rate; ADR, adenoma detection rate.
by making colonoscopy more time efficient. Similar findings were observed by the Netherlands group and we suspect that this is not artifactual. However, this needs to be formally evaluated.

There was a trend toward significance in the endoscopists’ grading of mucosal views in the area around the dentate line, with views being graded as excellent in 67.6% patients in the endocuff group and 61.9% in the standard group ($P = 0.05$).

A surprising finding from our study was a reduction in the number of medium-sized (6–10 mm) polyps with endocuff compared with standard colonoscopy ($P = 0.02$). This could reflect the change in technique required to withdraw the scope with the endocuff attached. Traditional colonoscopy requires repeated reinsertion and withdrawal to visualize all of the folds with maximal distension. To use the endocuff effectively, over-distension should be avoided to enable the flanges to engage with the folds, and less slippage will make the endoscopist feel less inclined to reinsert and re-examine areas. These findings should be interpreted with caution, as the study was not powered to investigate this. The most likely explanation is that it is a statistical artifact, but it could be a focus for further investigation.

The endocuff attachment did not fall off the scope during the examination in any case and was a good fit for the scope. Difficult sigmoid colons with complex diverticulosis are always challenging. As our study population was aged between 59 and 75 years, the prevalence of diverticulosis was high. Despite this, the endocuff had to be removed in only 6.4% of patients in order to negotiate a tortuous sigmoid.

The study has a number of strengths. It is the first study to investigate the endocuff in an organized FOBT-based national bowel cancer screening population. It is large and well powered. The endoscopists, colonoscopy technique, and the study population were all very well standardized and controlled. We also controlled for a study-related in-trial bias by comparing the pre-trial ADR of the endoscopists with the ADR during the study. Our endoscopists were highly experienced with excellent performance indicators including a baseline ADR of 58.9% in the FOBT-positive screening population before the start of the study.

A potential criticism of our study is that the primary endpoint was polyp rather than adenoma detection rates. However, there are growing data to support the importance of right-sided serrated polyps in the development of cancer. Given that there is a need within bowel cancer screening to reduce right-sided bowel cancer risk, it is our contention that ADR is not an adequate measure of the effectiveness of the device. In the current study, the endoscopists could not be blinded to the randomization. However, the ADR (63% for standard vs. 60.9% for endocuff) and the number of adenomas per patient (1.4 for standard vs. 1.3 for endocuff) were closely comparable. These are the most important surrogate markers of the quality of colonoscopy. Comparable values in the two arms therefore make selection/observer bias unlikely. In addition, the in-trial ADRs of the endoscopists compared very closely with the pre-trial ADRs, thus further ruling out in-trial observer bias.

Conclusion
This is the first RCT of the endocuff in an organized FOBT-based national bowel cancer screening population. Results showed no significant difference in poly or adenoma detection between standard and endocuff-assisted colonoscopy. The withdrawal times were significantly faster in the endocuff arm, which could be due to improved views and stability provided by the endocuff. No significant adverse events were seen. We conclude that while the endocuff is safe and reduces withdrawal time, it does not improve polyp detection during FOBT-positive screening colonoscopy in an organized screening program.

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Competing interests
None

References


