

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/119310/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Hurt, Chris , Ramaraj, Rajeswari, Farr, Angela, Morgan, Meleri, Williams, Namor, Phillips, Ceri J., Williams, Geraint T., Gardner, Georgina, Porter, Catharine , Sampson, Julian , Hillier, Sharon, Heard, Hayley, Dolwani, Sunil and CONSCOP Clinical Research Consortium 2019. Feasibility and economic assessment of chromocolonoscopy for detection of proximal serrated neoplasia within a population-based colorectal cancer screening programme (CONSCOP): an open-label, randomised controlled non-inferiority trial. *Lancet Gastroenterology and Hepatology* 4 (5) , pp. 364-375. 10.1016/S2468-1253(19)30035-4

Publishers page: [https://doi.org/10.1016/S2468-1253\(19\)30035-4](https://doi.org/10.1016/S2468-1253(19)30035-4)

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



## **Title page**

**Long title: Feasibility and economic evaluation of chromocolonoscopy for detection of proximal serrated neoplasia: a randomised controlled trial within a population based colorectal cancer screening programme (the CONSCOP study)**

## **Corresponding author:**

Dr. Sunil Dolwani, 1<sup>st</sup> floor Neuadd Meirionnydd, Division of Population Medicine, Cardiff University, Health Park, Cardiff CF14 4YS, UK. Email: [dolwanis@cardiff.ac.uk](mailto:dolwanis@cardiff.ac.uk). Tel: +442920687336. Fax: +442920715538

## **Author(s):**

**Chris Hurt (MSc)**, Centre for Trials Research, Cardiff University, Cardiff, UK\*

**Rajeshwari Ramaraj (MBBS MRCP)**, Division of Population Medicine, Cardiff University School of Medicine, Cardiff, UK\*

Angela Farr (BSc), Swansea Centre for Health Economics, Swansea University, Swansea, UK

Meleri Morgan (MBBS), Department of Pathology, Cardiff and Vale University Health Board

Namor Williams (MBBS), Department of Pathology, ABM University Health Board

Professor Ceri J. Phillips (PhD), College of Human and Health Sciences, Swansea Centre for Health Economics, Swansea University, Swansea, UK

Professor Geraint T. Williams (MD), Department of Pathology, Division of Cancer and Genetics, Cardiff University School of Medicine

Georgina Gardner (BTEC), Centre for Trials Research, Cardiff University, Cardiff, UK

Catherine Porter (PhD), Centre for Trials Research, Cardiff University, Cardiff, UK

Professor Julian Sampson (PhD), Division of Cancer and Genetics, Cardiff University School of Medicine

Sharon Hillier (PhD), Screening Division, Public Health Wales, Cardiff, UK

Hayley Heard (MSc), Bowel Screening Wales, Public Health Wales, Llantrisant, UK

Sunil Dolwani (MD), Division of Population Medicine, Cardiff University School of Medicine,  
Cardiff, UK

for the CONSCOP Clinical Research consortium\*\*

\*Joint first authors: CH and RR contributed equally to this paper

\*\*See acknowledgments

## **Abstract**

### **Background**

Most post-colonoscopy interval colorectal cancers are proximal. Serrated polyps are often precursors to these and considered hard to detect. We assessed the safety, feasibility and economic impact of chromocolonoscopy on detection of proximal serrated neoplasia.

### **Methods**

A parallel group randomised controlled, open label multicentre trial (ClinicalTrials.gov: NCT01972451) within Bowel Screening Wales (BSW). Participants positive for Faecal Occult Blood were randomised 1:1 (using minimisation stratified by centre with an 80:20 random element) to either standard white light colonoscopy or chromocolonoscopy (indigo carmine dye (0.2%)) using a secure, internet-based, computerised, randomisation system that used centralised, dynamic allocation. Participants were followed up for one year and data from index colonoscopies and associated clearance procedures were analysed. All proximal polyps were reviewed by an expert pathologist panel. The study was powered to see whether or not the extra procedure time taken to conduct chromocolonoscopy was acceptable (a non-inferiority design with an inferiority margin of 15 minutes) using a per protocol analysis.

### **Findings**

Between November 2014 - June 2016, 741 of 1031 were eligible and consented, 360 were randomized to white light colonoscopy and 381 to chromocolonoscopy. In the chromocolonoscopy arm, the procedure took an average of 6.3 (95% CIs: 4.2-8.4) minutes longer (well within the pre-specified inferiority margin of 15 minutes) but serious adverse reaction rates (two in the standard and four in the chromocolonoscopy arm with five of these being incidences of post polypectomy bleeding and one case of anxiety and hyperventilation), colonoscopy quality measures, comfort scores and sedation were similar in each arm. The proximal serrated polyp detection rate was significantly higher in the chromocolonoscopy arm

(45/381 (11.8%) vs 23/360 (6.4%); multivariable OR 2.04, 95% CI: 1.18-3.50, p=0.010). An additional investment of £81 (95% CI: £69.91- £92.09) per procedure is required to introduce chromocolonoscopy into routine practice.

### **Interpretation**

Chromocolonoscopy is feasible within a population based colorectal cancer screening programme, safe and significantly increased detection of proximal serrated neoplasia and other polyp types. Larger RCTs of chromocolonoscopy powered for improved detection of significant serrated polyps and for longer term follow up to investigate the impact on reduction of interval cancers within screening populations are warranted.

### **Funding**

Health and Care Research Wales (RfPPB –1021)

## **Research in context**

### ***Evidence before this study***

A systematic review of chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum was published in the Cochrane Database of Systematic Reviews in 2016. To capture randomised trial evidence published since then, on 7 December 2018, we searched Ovid MEDLINE using: ((randomised or randomized).ab. or trial.ti. or "Clinical trial".pt. or (exp Randomized Controlled Trials as Topic/ or randomised).mp.) and ("enhanced colonoscopy" or chromoscopy or chromocolonoscopy or panchromoendoscopy or chromoendoscopy or "pan-chromoscopy" or panchromoscopy).mp. and 2014:2018.(sa\_year). Titles and abstracts of 58 records were screened, and articles on narrow spectrum light/magnifying chromoendoscopy/electronic imaging/narrow band imaging/virtual chromoendoscopy/buscopan/side optic-enhancement/polypectomy technique interventions and gastric/oesophageal/Inflammatory Bowel Disease/Lynch syndrome cohorts were excluded leaving 4 studies. Of these, one was a review, one was a trial in patients with serrated polyposis syndrome only, one was a trial of the safety of oral methylene blue in 10 patients only, and one looked at the classification rather than detection of polyps.

Missed proximal serrated neoplasia may contribute to post-colonoscopy colorectal cancer. Chromocolonoscopy has been investigated in different settings and shown to increase adenoma detection rates. However, its use in the detection of proximal serrated polyps and implications for screening programmes and PCCRC has not been assessed.

### ***Added value of this study***

It is feasible to implement dye enhanced colonoscopy in a population based colorectal cancer screening program with an average 6.3 minutes of additional time taken per procedure. We

found more polyps of all types including significantly more proximal significant serrated lesions in the chromocolonoscopy group. An additional investment of £81 (95%CI: £69.9-£92.09) per procedure is required to introduce chromocolonoscopy into routine practice.

***Implications of all the available evidence***

This is the first study to demonstrate that, with rigorous trial design incorporating high quality standardised colonoscopy, chromocolonoscopy can be implemented within a population colorectal cancer screening programme with estimation of additional time and cost associated with it. It is the largest RCT of chromocolonoscopy in the detection of proximal serrated neoplasia and provides a screening population estimate of yield with minimisation of bias due to colonoscopist or pathology related factors. Further larger trials of chromocolonoscopy are warranted to look for a difference in proximal significant serrated lesion detection with full economic evaluation of follow up to assess clinical effectiveness over time and impact on clinical practice for surveillance.

## Introduction

Screening has been shown to reduce colorectal cancer (CRC) incidence and mortality.<sup>1</sup> Studies suggest that this benefit is substantial in the reduction of distal colorectal cancers but modest for proximal colorectal cancers.<sup>2,3</sup> Additionally, most cancers developing after an index colonoscopy, i.e. interval cancers or post-colonoscopy CRCs (PCCRCs), are located proximally.<sup>4</sup> Studies have reported that interval CRC within 3 years after colonoscopy account for 3.4% to 9% of all CRCs and their incidence is associated with colonoscopy quality measures<sup>5,6</sup> therefore individuals may be falsely reassured by screening. Two types of factors may contribute to the occurrence of proximal interval CRCs: technical (operator/procedure) dependant factors which can result in missed lesions, lower detection rates, and incomplete resection of lesions,<sup>7</sup> and polyp biology dependent factors<sup>5,8</sup> which relate to the difficulty in detection due to morphology, potential accelerated rate of growth, and molecular characteristics.<sup>9,10</sup>

Apart from the traditional adenoma to carcinoma pathway, it has been recognised that subsets of serrated lesions (SLs) cause cancer via an alternative pathway (serrated neoplasia pathway).<sup>11</sup> This may be responsible for up to 20% of all sporadic CRCs.<sup>12</sup> Several studies have also demonstrated that SLs are common precursors to proximal interval cancers.<sup>10</sup> These polyps are flat or non-polypoid in morphology making them more difficult to detect endoscopically and studies show wide variation in detection rates (1-20%) amongst endoscopists.<sup>13,14</sup> There also remains considerable variability in histopathological interpretation of serrated polyp subtypes affecting the accurate categorisation of potential precursors to the serrated pathway.<sup>15,16</sup> This is further compounded by the existence of two different definitions of sessile serrated lesions (SSLs) promoted by the WHO<sup>17</sup> (World Health Organisation) and the AGA<sup>18</sup> (American Gastroenterological Association) and estimated prevalence rates vary according to

the criteria used.<sup>19,20</sup>

Pan-colonic chromocolonoscopy already forms part of standard practice in surveillance in high-risk cases of inflammatory bowel disease and is part of national and international guidelines.<sup>21</sup> Chromocolonoscopy has been investigated in different settings and shown to increase adenoma detection rates.<sup>22</sup> However, its use in the detection of proximal serrated polyps and implications for screening programmes and PCCRC has not been assessed. Technical factors affecting polyp and cancer detection rates include quality of bowel preparation, training and experience of the colonoscopist, and various procedural techniques.<sup>23</sup> Colonoscopists in the UK undergo a rigorous standardised assessment and accreditation process in order to achieve high quality minimum standard criteria (e.g. adenoma detection rates, withdrawal times, comfort scores) that are monitored regularly making a UK CRC screening programme the appropriate setting to investigate chromocolonoscopy.

The aims of this study were to assess: feasibility of implementation within a population wide screening programme and of recruitment to a larger definitive trial, whether chromocolonoscopy takes an acceptable length of additional time to conduct and the associated costs, and the proximal serrated polyp detection rates (with standardised and monitored operator and procedure quality and rigorous histopathology assessment) in the trial arms to inform the sample size of a future trial.

## **Methods**

### *Study design and participants*

This was a multicentre, randomized, open-label, feasibility trial of dye-enhanced chromocolonoscopy vs standard white light colonoscopy. All Bowel Screening Wales (BSW)

centres were encouraged to participate in the trial. All members of the public (aged between 60 and 74 years) testing positive on Faecal Occult Blood Testing (FOBT) in the BSW programme who were eligible for an index screening colonoscopy (i.e. this excluded Polyposis syndromes, Lynch syndrome and those under regular colonoscopic surveillance for chronic inflammatory bowel disease) were assessed for trial eligibility by Specialist Screening Practitioners during telephone assessment clinics to discuss their colonoscopy. People who had undergone previous colorectal surgery, or with known allergy to food colouring agents, were excluded. Eligible people had the study described to them and, if they were interested in participating, were sent more information (including a participant information sheet and consent form) along with standard information about the screening colonoscopy. Informed consent was taken by a Specialist Screening Practitioner when the patient attended for colonoscopy, prior to the patient being told which trial arm they had been allocated to.

#### *Randomisation and masking*

All potential participants were randomised 1:1 (using minimisation stratified by centre with an 80:20 random element) to either standard or chromocolonoscopy for their index procedure using a secure, internet-based, computerised, randomisation system that used centralised, dynamic allocation. It was not possible to blind either the patient or colonoscopist to trial arm but we did blind the expert panel of three GI pathologists (see below) who classified every proximal polyp.

#### *Procedures*

Participants randomised to white light colonoscopy had a colonoscopy conducted as per standard practice. For participants randomised to the chromocolonoscopy arm, once the caecum was reached, indigo carmine dye (0.2% as used in standard clinical practice;

manufactured by Diagmed (UK)) was sprayed on the surface of the proximal colon (caecum to splenic flexure) using a pump assisted spray through the colonoscope on withdrawal. This required specific training to all the colonoscopists and Specialist Screening Practitioners to ensure standardisation of technique of dye dilution and spray as well as detection, identification and removal of polyps under indigo carmine dye. We were aware that the colonoscopists undertaking screening in this cohort were all accredited to the same standard though some had previous experience of pan-colonic dye spray use in the context of chronic inflammatory bowel disease and Lynch syndrome whereas others did not. We ensured that all participating colonoscopists attended a day long training event including quizzes of images and video prior to and after the training, a training resource for reference, as well as lectures and video tutorials on technique and lesion detection with and without indigo carmine dye spray. We also included training on the PARIS classification, Kudo classification and lesion characterisation with virtual and dye based chromocolonoscopy. In participants allocated to this arm with inadequate bowel preparation on the day, dye was used at the subsequent adequately prepared colonoscopy, otherwise repeat procedures used standard white light colonoscopy. Colonoscopists were allowed to use the irrigation pump with water for washing colonic mucosa without any restriction in both trial arms. Ten sites used high-definition colonoscopes (not mandated), one high-resolution colonoscopes and one standard definition colonoscopes. All adverse events were reported until 30 days post-colonoscopy.

Polyps retrieved from all index colonoscopies and at associated clearance procedures up to one year after were included in the analysis. Surveillance procedures were not included. Polyps found on computed tomographic colonography (CTC) undertaken for incomplete procedures, were excluded from the analysis.

### *Outcomes*

The primary endpoint was time taken to perform the colonoscopy procedure defined as from the time when the scope was inserted to withdrawal from the anus. This, together with the data on colonoscopy outcomes, polyps found, bowel preparation, sedation, and technical quality indicators was collected by Specialist Screening Practitioners as part of routine data collection. Data on aspirin use, smoking, family history of bowel cancer, endoscopist assessment of procedural difficulty, the data in Supplementary Table S1, and data on resource use during index colonoscopy (probes, coagraspers, clips, snares, pots, etc) were not routinely collected and had to be collected on a trial specific case report.

All proximal (defined as at or above the splenic flexure) polyps included in the analysis, regardless of initial reported histology, were collected from local centres for central review by an expert panel of three GI consultant pathologists. All three were part of the national referral pathways for the bowel cancer screening programme reviews of pathology and have involvement in pathologist training and accreditation as well as regular review of “second opinion” lesions as part of a national pathology expert panel. Pre-defined standard diagnostic criteria were agreed to avoid variation in final reports and were based on the WHO classification,<sup>17</sup> though serrated lesions were also categorised according to AGA criteria.<sup>18</sup> In accordance with UK guidance,<sup>24</sup> the term ‘sessile serrated lesion’ (SSL) was used for lesions described elsewhere as ‘sessile serrated adenoma/polyp’ (SSA/P). The expert panel reviewed all slides independently and were blinded to the original report. Cases without diagnostic agreement were re-reviewed by all three pathologists to reach a consensus diagnosis. If this was not achieved, the lesion was deemed “unclassifiable”.

An ‘advanced adenoma’ was defined as a conventional adenoma with either high grade dysplasia (HGD), >25% villous histology, or measuring  $\geq 10$ mm in size.<sup>17</sup> ‘Serrated lesions’ (SLs) incorporated hyperplastic polyps, SSLs and traditional serrated adenomas (TSAs). ‘Significant SLs’ incorporated SSLs with dysplasia, SSLs measuring  $\geq 10$ mm and all TSAs. The term ‘advanced neoplasia’ incorporated all advanced adenomas and all significant SLs.

A cost consequence analysis evaluates the costs associated with the colonoscopy procedures within the study to compare resource utilisation. The costs were assessed from the perspective of the UK NHS. Assessed in two parts, the additional costs of providing new resources required to implement chromocolonoscopy and resources used during routine practice. Implementation costs of chromocolonoscopy included additional resources in the form of staff time (both “trainee” and “trainer”) to train in the new procedure and the cost of the contrast dye and dispersion equipment. Resource use data regarding staff time performing the procedure and medications/bowel preparation administered during a procedure were collected from all participating screening sites. Resources classified as consumables were only collected from one site during index colonoscopies. Details of resource use analysis methodology can be found in the Appendix 2 of the web appendix (pages 7-12).

### *Statistical analysis*

This feasibility study was powered to look for non-inferiority of time taken to perform the colonoscopy procedure. Experience suggested that chromocolonoscopy may take 12 minutes longer but should be no more than 15 minutes longer than standard. Assuming a common standard deviation of 15 minutes (normally distributed based on BSW data), this required 858 patients (power 90%,  $\alpha=0.05$  (one sided)) based on a two-group t-test. The protocol initially aimed to recruit 1052 patients to allow for ~18% loss to follow up for any reason.

However, the Trial Management Group decided to stop recruitment once 741 participants had been consented for the following reasons:

- i) set up of some centres took longer than anticipated
- ii) there was no loss to follow up after consent
- iii) 741 patients still gave 86% power.

Data were analysed according to a pre-specified analysis plan using the Stata SE 14 statistical package except where indicated as post hoc in the results section. All analyses were by intention-to-treat except the analyses of colonoscopy performance (including the primary endpoint of procedure time) and technical quality indicators (Table 2 and Supplementary Table S1) which were only in those participants who had adequate bowel preparation at the index or a subsequent procedure as this is when dye was administered. The primary endpoint was assessed by calculating the 95% confidence intervals around the mean difference and comparing them to the non-inferiority margin. Proportions were compared using chi square tests. For detection rates, univariable logistic regression was used to calculate odds ratios for the trial arm effect as well as important prognostic variables (smoking, obesity, sex, family history of cancer). Multivariable models included all these variables, as well as screening centre as a random effect, using multilevel mixed-effects logistic regression. Aspirin data was only collected after the first 210 patients had been recruited and this was included in the models in sensitivity analyses. Patients found to have cancer also had polyps removed if found and we included these patients in the analyses of polyp detection rates.

The analysis of the economic data was conducted on procedures with a complete set of original data across all resource use variables and on all available cases with mean imputation for sites that did not collect data on consumables. This allowed an overall resource use comparative cost

to be calculated for all patient procedures in the available cases analysis. T-tests was used to evaluate differences in resource use costs between the two trial arms. The cost-consequence analysis provides an indication of the additional costs associated with introducing chromocolonoscopy into routine practice.

The trial protocol (ClinicalTrials.gov: NCT01972451) was approved by a UK Multi-Centre Research Ethics Committee (ref: 14/WA/0004) and was sponsored by Cardiff University.

#### *Role of the funding source*

Neither the funder nor the Sponsor of the study had any role in study design, data collection, data analysis, data interpretation, or writing of the report. CH, RR, and CP had full access to the raw data. SD had final responsibility for the decision to submit for publication.

## **Results**

### *Patients*

Between 20 November 2014 and 16 June 2016, 1031 people testing positive on FOBT, and expected to proceed to colonoscopy after discussion with a Specialist Screening Practitioner, were assessed for eligibility from 12 out of 14 centres in the BSW screening programme with 20 out of 23 colonoscopists recruiting participants (Figure 1). 903 of the 1031 people assessed were considered eligible for the trial and of these 741 (82%) consented. Consent rates after randomisation were similar in each arm: 360/416 (87%) and 381/424 (90%) with standard and chromocolonoscopy respectively. Baseline characteristics were well balanced between trial arms (Table 1). Follow up of polyps collected at later polyp clearance procedures continued until 1 year after the last participant had their index procedure.

### *Procedures*

Participants in the chromocolonoscopy arm had more procedures (477 vs 427) than in the standard arm (Table 2). This was due to more repeats to remove polyps or check completeness of previous excisions in line with current guidelines. In the chromocolonoscopy arm, more participants had a final outcome of high risk (12 month) surveillance (76/381 (19.9%) vs 48/360 (13.3%); post hoc  $\chi^2=5.812$ ,  $p=0.016$ ) and fewer participants had an outcome of discharge back to routine FOBT testing (159/381 (41.7%) vs 162/360 (45.0%).

In the first (index) colonoscopy with adequate bowel preparation, the procedure time was longer in the chromocolonoscopy arm (mean 36.8 vs 30.6 minutes) (Table 2). However, the difference did not exceed the 15 minutes specified *a priori* as the non-inferiority margin (mean difference 6.3 minutes, 95% CIs: 4.2-8.4). The data showed some evidence of positive skew, but bootstrapping produced the same estimate for the confidence interval. The magnitude of this difference was reflected in the withdrawal times (mean 24.1 vs 18.7 minutes). The difference in procedure times was smaller when no polyps were removed (mean 28.6 vs 24.2 minutes) compared to when polyps were removed (mean 41.3 vs 35.2 minutes). The bowel preparation scores, completion rates, endoscopist assessment of procedural difficulties, and procedure comfort scores were similar in each arm (Table 2).

Technical quality indicators, percentage of participants who had a position change and other manoeuvres during the procedure, and use of antispasmodic and sedation at first colonoscopy were well balanced between trial arms (Supplementary Table S1 in web appendix p1). The mean volume of fluid sprayed (diluted dye 0.2%) in the chromocolonoscopy arm was 165.8ml (SD=62.3).

### *Adverse events*

Six Serious Adverse Reactions (SARs) were reported in the trial, two in the standard arm and four in the chromocolonoscopy arm of the trial with five of these being incidences of post polypectomy bleeding and one case of anxiety and hyperventilation). The rates of post-polypectomy bleeding were: 1/358 (0.3%) vs 2/378 (0.5%) in the standard and chromocolonoscopy arms respectively. None of these cases required any further interventional procedures related to the bleeding. There were no allergic reactions or deaths.

### *Polyps*

Figure 2 and Table 3 show the cancers detected and WHO classification of all polyps retrieved at index colonoscopy and associated clearance procedures up to one year afterwards. All but five proximal polyps were reviewed centrally by the expert panel. More polyps overall (903 vs 570), and more polyps of each type were found in the chromocolonoscopy arm. No patients had serrated polyposis as defined by WHO criteria though it is likely that some cases may fulfil these criteria at subsequent colonoscopy.

Detection rates for proximal SLs were significantly higher in the chromocolonoscopy arm with both univariable and multivariable analyses: 45/381 (11.8%); vs 23/360 (6.4%) univariable OR 1.96, 95% CI: 1.16-3.32,  $p=0.012$ ; multivariable OR 2.04, 95% CI: 1.18-3.50,  $p=0.010$ ) (Supplementary Table 2a in web appendix p2). A sensitivity analysis was conducted in the subset of patients with aspirin data ( $n=521$ ) and the trial arm effect in the multivariable regression was still found to be significant (OR 1.98, 95% CI: 1.05-3.74,  $p=0.036$ ), but the effect of currently taking aspirin was not (OR 1.79 in favour of taking aspirin, 95% CI: 0.72-4.50,  $p=0.21$ ). We also found a significantly higher detection rate in the chromocolonoscopy arm for SLs found anywhere in the colon: 81/381 (21.3%) vs 51/360 (14.2%), multivariable

OR 1.66, 95% CI: 1.12-2.46,  $p=0.012$ . SLs were more common in smokers (multivariable OR 1.79, 95% CI: 1.00-3.22,  $p=0.050$  for proximal SLs and multivariable OR 1.58, 95% CI: 1.03-2.42,  $p=0.038$  for all SLs).

Secondary regression analyses compared other rates of polyp detection. While absolute polyp numbers are small there is a suggestion that detection rates of “significant” SLs anywhere in the colon were higher in the chromocolonoscopy arm (Supplementary Table 2b in web appendix p2) (multivariable OR 2.18, 95% CI: 0.88-5.37,  $p=0.092$ ) and also in males (multivariable OR 3.23, 95% CI: 0.94-11.2,  $p=0.063$ ). Histological criteria for distinguishing hyperplastic polyps from SSLs differ between the WHO and AGA definitions of SLs. For a diagnosis of SSL the WHO recommendations<sup>17</sup> require two or three contiguous crypts showing characteristic SSL-type appearances whilst the AGA proposals<sup>18</sup> require only one such crypt. Accordingly, when the AGA definition of SSL was used, 13 proximal hyperplastic polyps were re-classified as SSLs (one  $\geq 10$ mm in the chromocolonoscopy arm). This marginally increased the detection rate of “significant” SLs in the chromocolonoscopy arm: 17/381 (4.5%) vs 7/360 (1.9%); multivariable OR: 2.31, 95% CI: 0.94-5.67,  $p=0.066$ ). The detection rate of proximal SSLs was significantly higher in the chromocolonoscopy arm (Supplementary Table 2c in web appendix p3) (multivariable OR 1.91, 95% CI: 1.02-3.59,  $p=0.045$ ), but this difference disappeared when the AGA definition of SSL was used: 34/381 (8.9%) vs 22/360 (6.1%), multivariable OR 1.58, 95% CI: 0.90-2.78,  $p=0.11$ . Higher adenoma detection rates were found in the chromocolonoscopy arm (60.9% vs 56.4% in Table 3). Analyses of advanced neoplasm detection rates suggest that obesity and male gender may be important risk factors (Supplementary Table 2d in web appendix page 3). A further multivariable analysis (data not shown) of advanced neoplasm detection rates conducted in the subset of patients with aspirin

data (n=521) in both arms of the trial combined found a significant protective effect of aspirin (23/103 (22.3%) vs 153/418 (36.6%), OR 2.11 95% CI: 1.27-3.51, p=0.004).

Of the 85 SSLs (24 in standard and 61 in chromocolonoscopy arm) identified in both arms of the study combined, six of the ten (60.0%) with dysplasia were  $\geq 10$ mm compared with only 13 of the 75 (17.3%) without dysplasia ( $\chi^2=9.25$ , p=0.007). Surprisingly, none of the four proximal SSLs with dysplasia was  $\geq 10$ mm while all six distal SSLs with dysplasia were  $\geq 10$ mm.

Univariable logistic regression analysis identified statistically significant associations between the finding of any SSL and the presence of synchronous advanced adenoma(s) (OR 2.42, 95% CI: 1.19-4.93, p=0.015) and between any proximal “significant” SL and advanced adenoma(s) (OR 4.10, 95% CI: 1.01-16.7, p=0.049) in the chromocolonoscopy arm but not in the standard arm (Supplementary table S3 in web appendix p4).

### *Economic evaluation*

The economic evaluation case analysis included 899 procedures (904 index and associated non-surveillance repeat procedures conducted within one year (Table 2) minus five procedures (four from the chromocolonoscopy arm and one from the standard arm) with missing data). 183 (20%) of these (91 standard arm and 92 chromocolonoscopy arm) were first procedures conducted at the site that documented the use of consumables constituted the complete case analysis. Mean training cost per procedure was £4.94 and mean equipment cost £47.99 (a total implementation cost per procedure of £52.93). A spray catheter attached to the pump was used in only 30% of procedures with a higher cost of £40 per colonoscopy. This compared to the technique used in 70% of procedures of adapting existing pumps with tubing and a valve which

added £8.88 to the cost of the colonoscopy. Supplementary Tables S4 to S6 (web appendix p5-6) show the higher costs associated with chromocolonoscopy. This is primarily due to the extra time required by staff to perform the chromocolonoscopy (£26.15 per procedure) and additional implementation costs (£52.93 per procedure). When all resource use for all procedures conducted (index and repeat Supplementary Table S4) by each arm was compared, standard colonoscopy cost per procedure was £190.60 compared to £271.60 per procedure for the chromocolonoscopy resulting in a mean cost difference of £81 (95% CI: £69.91-£92.09). Examining procedures separately produced the following results:

- Index procedures only (available cases Supplementary Table S5): mean cost difference between arms £87.68 (95% CI: 76.83-98.53) more expensive per procedure than standard colonoscopy;
- Repeat procedures only (available cases Supplementary Table S6): mean cost difference between arms £49.11 (95% CI: 11.33-86.88)

## **Discussion**

Within the lack of reduction in mortality from proximal colon cancer with screening, an intervention that improves detection of proximal serrated lesions must be feasible within a screening programme and the proportion of significant proximal precursor lesions detected must be of the order that might affect surveillance and outcomes in the longer term. This study demonstrates the feasibility of recruitment of patients (82% of those eligible) and colonoscopists to a trial of standard versus chromocolonoscopy within a population based CRC screening programme. Although the procedure time took approximately 6 minutes longer in the chromocolonoscopy arm, we can be 95% confident that using chromocolonoscopy does not increase the mean time by more than 10 minutes. The dye is safe and consequent polyp detection and resection is associated with a very low rate of post-polypectomy bleeding, similar

to the standard arm. The chromocolonoscopy arm demonstrated higher detection rates for proximal serrated lesions, all serrated lesions and proximal sessile serrated lesions, and there was more advanced neoplasia and significant serrated lesions in this arm. Colonoscopy performance and technical quality indicators and patient comfort scores were similar in each trial arm whilst the additional costs of adopting the chromocolonoscopy technique would be £81 per procedure. More follow up work is required to assess the extent of further costs involved in screening surveillance as a result of improved detection.

Our study identified a number of other interesting findings. First, while dysplasia in distal SSLs only occurred in lesions  $\geq 10\text{mm}$ , all proximal SSLs with dysplasia were smaller than this. This is consistent with another recent study that found the majority of proximal dysplastic SSLs to be  $<10\text{mm}$ <sup>25</sup> and suggests the need for caution in setting guidelines for clinical significance based solely on the size of serrated polyps. Second, in the chromocolonoscopy arm (but not the standard arm), advanced adenomas (of conventional type) were more common in individuals harbouring SSLs. The reasons for this are unclear but the improved identification of otherwise occult SLs by chromocolonoscopy may go some way in explaining the appearance of post-colonoscopy interval cancers in conventional screening programmes. Thirdly, there was evidence that aspirin protects against advanced neoplasia.

There is a perception that chromocolonoscopy is time consuming and this study provides quantification of the additional time taken per procedure and of the additional costs associated with chromocolonoscopy. The cost-consequence analysis provides an indication of the additional resources required to adopt this technique and shows that additional costs are primarily due to implementation. Some screening colonoscopists are already familiar with the

concept of chromocolonoscopy from their inflammatory bowel disease surveillance procedures and will consequently have less training requirements.<sup>26</sup>

### *Strengths*

With 20/23 colonoscopists from 12/14 screening centres in the BSW programme participating in the current study, we demonstrate the feasibility and results from a real world programme-wide roll out of chromocolonoscopy. By contrast, previous studies have largely focused on expert centres and expert colonoscopists.<sup>27</sup>

Previous estimates of prevalence of SLs have demonstrated significant variation possibly partly due to inconsistency in histopathological categorisation of these lesions.<sup>13,20,28</sup> In order to address this, unlike the previous RCTs involving chromocolonoscopy, this study included an expert GI central pathology panel reviewing all slides of proximal colonic polyps.<sup>22</sup> Randomisation was stratified by centre to ensure that any centre effects were balanced across trial arms. We demonstrated very little difference between arms in technical factors affecting mucosal visualization and consequent polyp detection and addressed most major sources of bias in previous studies due to procedure quality. To our knowledge this study is also the first to estimate the resource utilization associated with training and implementation of this intervention in routine clinical practice.

### *Limitations*

It is difficult to completely remove bias in chromocolonoscopy as it is impossible to blind assessors. Withdrawal times in both groups, even where polyp resection was not required, were higher than the pre-specified minimum withdrawal time of 7 minutes in the quality assurance criteria for BSW. Previous studies suggest that longer withdrawal times may improve detection

rates for serrated polyps.<sup>14,29</sup> It may be that the dye promotes longer withdrawal times which in turn led to the higher detection rates. However, none of the previous studies suggest that a withdrawal time greater than 11 minutes would be effective in independently achieving a significant improvement in detection rates for both adenomas as well as serrated lesions supporting our findings of an independent and significant positive effect of the chromoendoscopy.<sup>30</sup> We did not specify the use of high definition colonoscopes as a prerequisite but data from previous studies suggests that this would be unlikely to influence the results of this study.<sup>31,32</sup> Aspirin use was only collected for a subset of patients and the results should be treated with caution, especially in this selected screening population, although sensitivity analysis in that subset supported the main finding of the study in proximal serrated polyp detection rate. This was a feasibility study not powered to find differences in detection rates and a definitive trial with longer follow up and high definition colonoscopy mandated in both arms is planned. Finally, some variables were subject to recall bias e.g. smoking and family history of cancer/polyps.

### *Conclusion*

It is safe and feasible to use index chromocolonoscopy within the CRC screening setting with an acceptable increase in procedure time of approximately 6 minutes. It is also feasible (in terms of safety, recruitment rates, procedure time, and trial logistics) to conduct a larger individually randomised trial comparing chromocolonoscopy to standard white light colonoscopy. Such a trial could be powered to find a difference in significant SSL detection rate at index since a study powered to detect a difference in PCCRC would require tens of thousands of participants. The higher proximal serrated polyp detection rates and advanced neoplasia found on chromocolonoscopy in this study contribute data to the discussion around its impact on colonoscopy quality and PCCRC.

## **Contributors**

All authors were involved in acquisition of the data, and critical revision of the manuscript for important intellectual content. SD, CH, RR contributed to drafting the manuscript. CH performed the statistical analysis. AF and CPh performed the economic analysis. CH, SD, CPh, JS, SH, HH were responsible for the study concept and design and obtained the funding. GTW, MM and NM undertook the pathology expert review.

## **Declaration of interests**

The authors have no competing interests to declare.

## **Data sharing**

We do not have permission to share data from this study with other researchers. However, we can share the study protocol, statistical analysis plan, and informed consent form upon request to the corresponding author.

## **Acknowledgments**

The CONSCOP trial was funded by the National Institute for Social Care and Health Research (Wales) (RfPPB –1021) and Cancer Research UK core funding to the Centre for Trials Research at Cardiff University. We thank current and former staff of Cardiff University for supporting the development and running of this trial, members of the trial steering committee, Kate Lifford for her editorial input, and our patient representatives who contributed to the design and management of the study (Bob McAllister and Jeff Horton). We also thank the members of the CONSCOP Clinical Research Consortium, on behalf of whom we ran the

study, and who recruited patients, performed the colonoscopies, collected data and approved the final manuscript:

Faiz Ali, Consultant Gastroenterologist, Hywel Dda Health Board

Aram Baghomanian, Consultant Gastroenterologist, Betsi Cadwaladr University Health Board

Dafydd Bowen, Consultant Gastroenterologist, Hywel Dda Health Board

Gillian Bishop, Specialist Screening Practitioner, Cardiff & Vale University Health Board

Sarah Buckley, Specialist Screening Practitioner, Hywel Dda Health Board

Pamela Clarke, Specialist Screening Practitioner, Aneurin Bevan Health Board

Rhodri Davies, Consultant Gastroenterologist, Aneurin Bevan University Health Board

Stephen Dias, Consultant colorectal surgeon, Hywel Dda Health Board

Jaber Gasem, Consultant Gastroenterologist, Betsi Cadwalader University Health Board

T Paulose George, Consultant Gastroenterologist, Betsi Cadwalader University Health Board

Vivek Goel, Consultant Gastroenterologist, Aneurin Bevan University Health Board

John Green, Consultant Gastroenterologist, Cardiff and Vale University Health Board

Jane Gray, Specialist Screening Practitioner, Aneurin Bevan Health Board

Hamid Khan, Consultant Gastroenterologist, Betsi Cadwaladr University Health Board

Jane Harrison, Specialist Screening Practitioner, Powys Teaching Health Board

Neil Hawkes, Consultant Gastroenterologist, Cwm Taf University Health Board

Barney Hawthorne, Consultant Gastroenterologist, Cardiff and Vale University Health Board

Joanna Hurley, Consultant Gastroenterologist, Cwm Taf University Health Board

Catherine Lewis, Specialist Screening Practitioner, Hywel Dda University health Board

Peter Marsh, Consultant colorectal surgeon, Betsi Cadwaladr University Health Board

Andrew Maw, Consultant colorectal surgeon, Betsi Cadwaladr University Health Board

Mark Narain, Consultant Gastroenterologist, Hywel Dda Health Board

Sara Osmond, Specialist Screening Practitioner, Aneurin Bevan University Health Board

Joy Owens, Specialist Screening Practitioner, Betsi Cadwaladr University Health Board

Joanna Popham, Specialist Screening Practitioner, Cardiff & Vale University Health Board

David Ramanaden, Consultant Gastroenterologist, Betsi Cadwalader Health Board

Linzi Thomas, Consultant Gastroenterologist, ABM University Health Board

Jared Torkington, Consultant colorectal surgeon, Cardiff & Vale University Health Board

Finally, we thank all patients who participated in the trial.

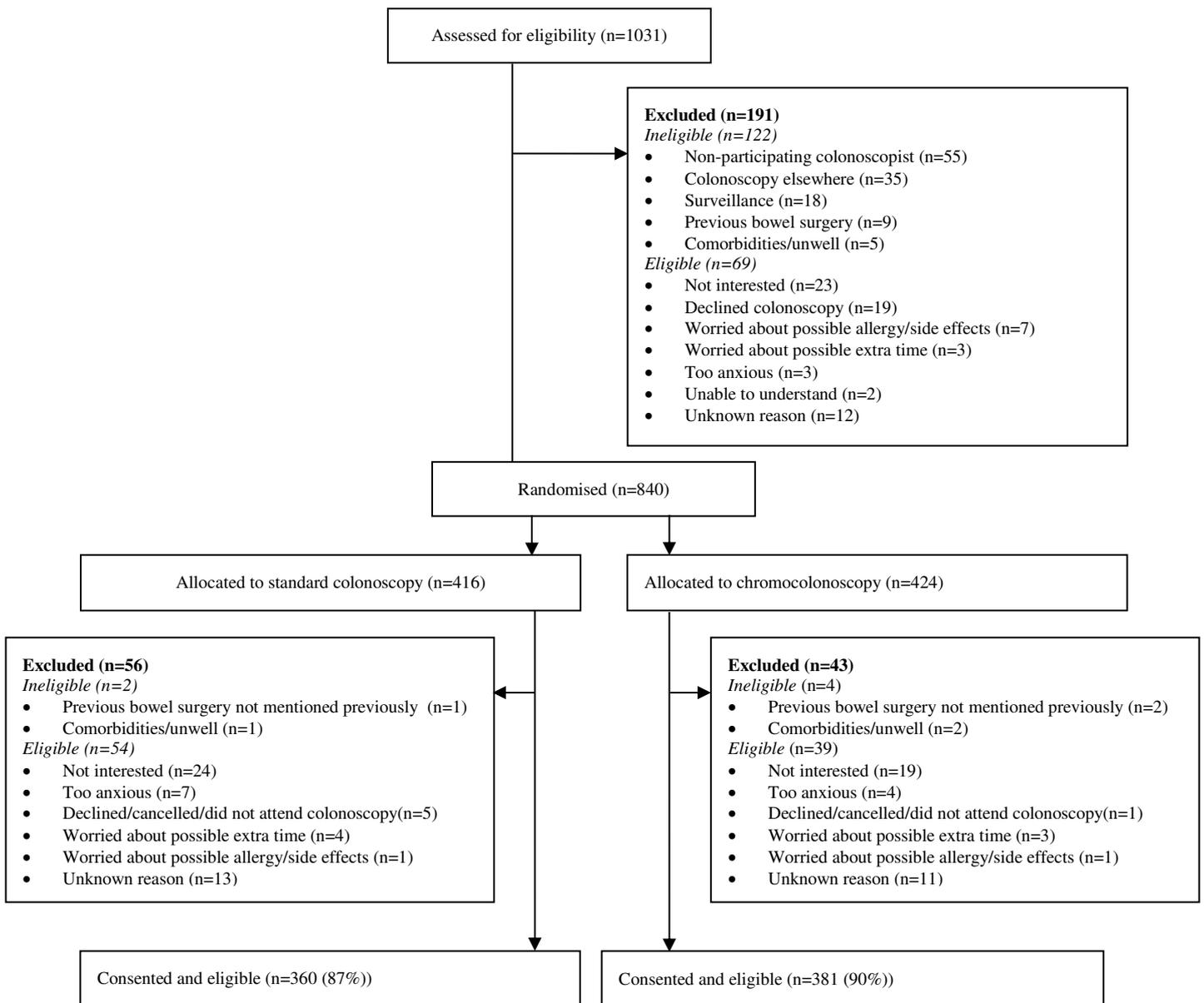
## References

1. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): An update. *American Journal of Gastroenterology* 2008; **103**(6): 1541-9.
2. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ* 2014; **348**: g2467.
3. Nishihara R, Wu K, Lochhead P, et al. Long-Term Colorectal-Cancer Incidence and Mortality after Lower Endoscopy. *New England Journal of Medicine* 2013; **369**(12): 1095-105.
4. Adler J, Robertson DJ. Interval Colorectal Cancer After Colonoscopy: Exploring Explanations and Solutions. *The American journal of gastroenterology* 2015; **110**(12): 1657-64; quiz 65.
5. Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of New or Missed Colorectal Cancers After Colonoscopy and Their Risk Factors: A Population-Based Analysis. *Gastroenterology* 2007; **132**(1): 96-102.
6. Baxter NN, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. *Gastroenterology* 2011; **140**(1): 65-72.
7. Wallace MB, Crook JE, Thomas CS, Staggs E, Parker L, Rex DK. Effect of an endoscopic quality improvement program on adenoma detection rates: a multicenter cluster-randomized controlled trial in a clinical practice setting (EQUIP-3). *Gastrointestinal endoscopy* 2017; **85**(3): 538-45 e4.
8. Bressler B, Paszat LF, Vinden C, Li C, He J, Rabeneck L. Colonoscopic miss rates for right-sided colon cancer: A population-based analysis. *Gastroenterology* 2004; **127**(2): 452-6.
9. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. *New England Journal of Medicine* 2010; **362**(19): 1795-803.
10. Arain MA, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. *The American journal of gastroenterology* 2010; **105**(5): 1189-95.
11. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology* 2013; **62**(3): 367-86.

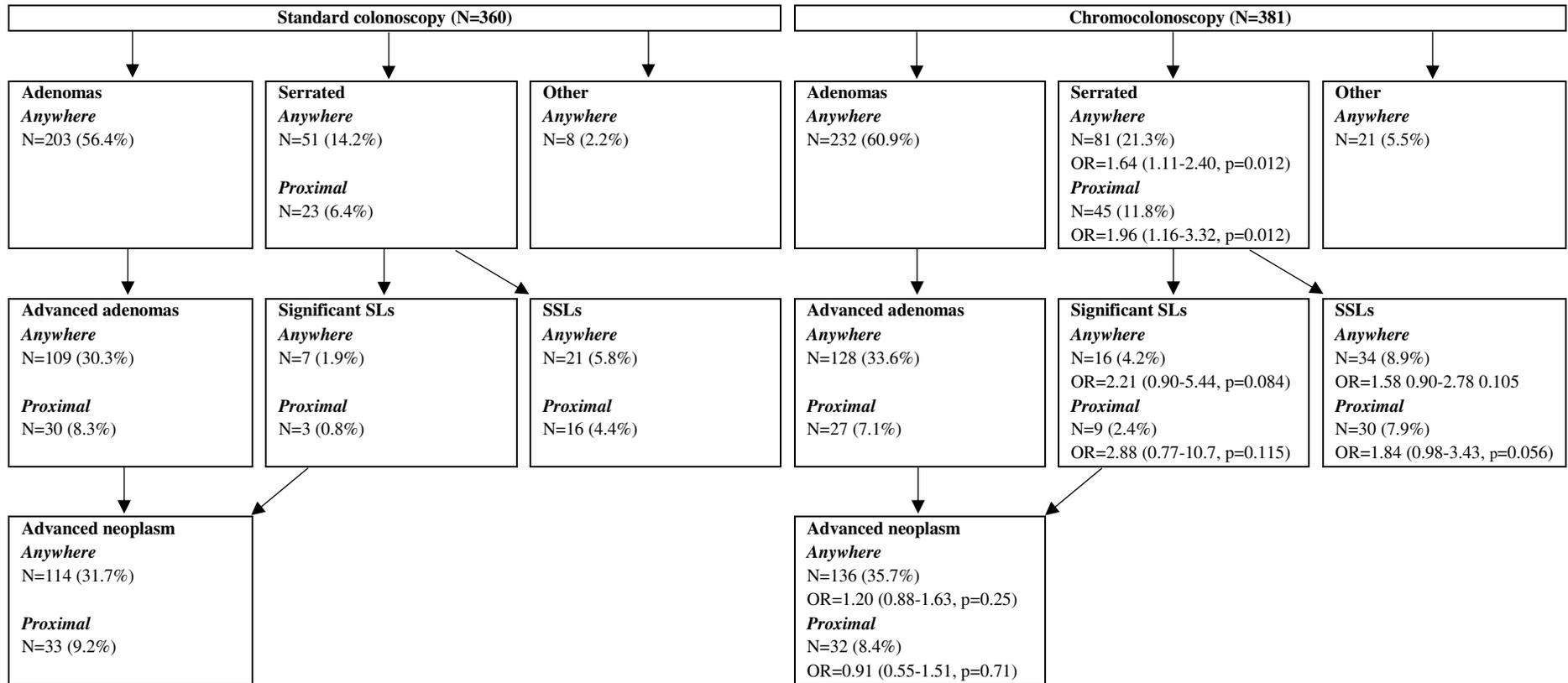
12. Snover DC. Update on the serrated pathway to colorectal carcinoma. *Human pathology* 2011; **42**(1): 1-10.
13. JEG IJ, Bevan R, Senore C, et al. Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. *Gut* 2017; **66**(7): 1225-32.
14. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. *Gastrointestinal endoscopy* 2013; **77**(4): 617-23.
15. Abdeljawad K, Vemulapalli KC, Kahi CJ, Cummings OW, Snover DC, Rex DK. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. *Gastrointestinal endoscopy* 2015; **81**(3): 517-24.
16. Rau TT, Agaimy A, Gehoff A, et al. Defined morphological criteria allow reliable diagnosis of colorectal serrated polyps and predict polyp genetics. *Virchows Archiv : an international journal of pathology* 2014; **464**(6): 663-72.
17. Bosman FT, World Health Organization., International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
18. Rex DK, Ahnen DJ, Baron JA, et al. Serrated Lesions of the Colorectum: Review and Recommendations From an Expert Panel. *American Journal of Gastroenterology* 2012; **107**(9): 1315-30.
19. Bettington M, Walker N, Rosty C, et al. Critical appraisal of the diagnosis of the sessile serrated adenoma. *The American journal of surgical pathology* 2014; **38**(2): 158-66.
20. Chetty R, Bateman AC, Torlakovic E, et al. A pathologist's survey on the reporting of sessile serrated adenomas/polyps. *Journal of clinical pathology* 2014; **67**(5): 426-30.
21. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointestinal endoscopy* 2015; **81**(3): 489-501 e26.
22. Brown SR, Baraza W, Din S, Riley S. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *The Cochrane database of systematic reviews* 2016; **4**: CD006439.
23. Hilsden RJ, Dube C, Heitman SJ, Bridges R, McGregor SE, Rostom A. The association of colonoscopy quality indicators with the detection of screen-relevant lesions, adverse events, and postcolonoscopy cancers in an asymptomatic Canadian colorectal cancer screening population. *Gastrointestinal endoscopy* 2015; **82**(5): 887-94.
24. East JE, Atkin WS, Bateman AC, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. *Gut* 2017; **66**(7): 1181-96.
25. Bettington M, Walker N, Rosty C, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. *Gut* 2017; **66**(1): 97-106.
26. Picco MF, Pasha S, Leighton JA, et al. Procedure time and the determination of polypoid abnormalities with experience: implementation of a chromoendoscopy program for surveillance colonoscopy for ulcerative colitis. *Inflammatory bowel diseases* 2013; **19**(9): 1913-20.
27. JE IJ, de Wit K, van der Vlugt M, Bastiaansen BA, Fockens P, Dekker E. Prevalence, distribution and risk of sessile serrated adenomas/polyps at a center with a high adenoma detection rate and experienced pathologists. *Endoscopy* 2016; **48**(8): 740-6.
28. Turner JK, Williams GT, Morgan M, Wright M, Dolwani S. Interobserver agreement in the reporting of colorectal polyp pathology among bowel cancer screening pathologists in Wales. *Histopathology* 2013; **62**(6): 916-24.

29. Shaukat A, Rector TS, Church TR, et al. Longer Withdrawal Time Is Associated With a Reduced Incidence of Interval Cancer After Screening Colonoscopy. *Gastroenterology* 2015; **149**(4): 952-7.
30. Butterly L, Robinson CM, Anderson JC, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. *The American journal of gastroenterology* 2014; **109**(3): 417-26.
31. Singh M, Sacatos M, Laine L. Impact of Changeover to Newer Endoscopic Systems on Quality and Efficiency of Screening and Surveillance Colonoscopy: Equipment or Endoscopist. *Journal of clinical gastroenterology* 2017.
32. Subramanian V, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011; **43**(6): 499-505.

**Figure 1. CONSORT diagram**



**Figure 2. Flow diagram for key polyp detection rates by trial arm (ORs are given with 95% CIs with standard as the reference arm)**



**Table 1. Baseline Demographics**

	<b>Standard colonoscopy</b>	<b>Chromocolonoscopy</b>
	<b>N=360</b>	<b>N=381</b>
<b>Current smoking status</b>		
Smoker	37 (10.3%)	45 (11.8%)
Ex-smoker	180 (50.0%)	196 (51.4%)
Never smoker	143 (39.7%)	139 (36.5%)
<i>Missing</i>	0 (0.0%)	1 (0.3%)
Pack years for smoker/ex-smoker – median (IQR, n, missing)	20 (10-39, 205, 12)	16 (8-34, 231, 10)
<b>Family history of bowel cancer</b>		
No	302 (83.9%)	318 (83.5%)
Second degree	9 (2.5%)	13 (3.4%)
First degree	45 (12.5%)	48 (12.6%)
Both	3 (0.8%)	0 (0.0%)
<i>Missing</i>	1 (0.3%)	2 (0.5%)
<b>Family history of bowel polyps</b>		
No	340 (94.4%)	349 (91.6%)
Second degree	2 (0.6%)	2 (0.5%)
First degree	15 (4.2%)	29 (7.65)
<i>Missing</i>	3 (0.8%)	1 (0.3%)
<b>Previous abdominal/pelvic surgery</b>	96 (26.7%)	108 (28.3%)
<i>Missing</i>	5 (1.4%)	4 (1.0%)
<b>Presence of diverticular disease</b>	201 (55.8%)	195 (51.2%)
<i>Missing</i>	6 (1.7%)	5 (1.3%)
<b>BMI – mean (SD); Obese <math>\geq 30</math> - n (%)</b>	28.8 (5.1); 134 (37.2)	28.9 (5.6); 128 (33.6)
<i>Missing</i>	2 (0.6%)	5 (1.3%)
<b>Age - median (IQR)</b>	67.6 (62.6-70.7)	67.7 (62.7-70.8)
<b>Sex</b>		
Male	234 (65.0%)	256 (67.2%)
Female	126 (35.0%)	125 (32.8%)
<b>Aspirin data was only collected after the first 210 patients</b>		
	<b>N=254</b>	<b>N=277</b>
<b>Does the patient take daily aspirin?</b>		
Currently	52 (20.5%)	57 (20.6%)
Previously	21 (8.3%)	24 (8.7%)
Never	181 (71.3%)	196 (70.8%)
<b>If currently taking aspirin, what is daily dose?</b>		
75mg	49/52 (94.2%)	55/57 (96.5%)
>75mg	3/52 (5.8%)	1/57 (1.8%)
<i>Missing</i>	0/57 (0.0%)	1/57 (1.8%)

**Table 2. Index colonoscopy and associated polyp clearance procedures up to one year later (surveillance procedures not included)**

	Standard colonoscopy	Chromocolonoscopy
<b>Number of participants</b>	<b>360</b>	<b>381</b>
<b>Number of procedures</b>		
Total number	427	477
Per person rate	1.19	1.25
Number of people receiving >1 procedure	53 (14.7%)	65 (17.1%)
<b>Nature of procedure</b>		
Index	360	381
Repeat to check completeness of polyp resection	26	33
Repeat due to incomplete previous procedure	2	0
Repeat due to poor bowel preparation at previous procedure	11	8
Repeat for therapeutic indication	28	55
<b>Type of procedure</b>		
Colonoscopy	399	430
Flexible sigmoidoscopy <sup>A</sup>	28	47
<b>Final outcome</b>		
Repeat	21 (5.8%)	20 (5.2%)
Discharge back to routine FOBT screening	162 (45.0%)	159 (41.7%)
No further colonoscopies required due to age limit/other bowel condition	22 (6.1%)	19 (5.0%)
3 year surveillance – intermediate risk	64 (17.8%)	63 (16.5%)
12 month surveillance – high risk	48 (13.3%)	76 (19.9%)
Refer to surgery for non-cancer indication	2 (0.6%)	4 (1.0%)
Cancer <sup>B</sup>	41 (11.4%)	40 (10.5%)
<b>Inadequate bowel preparation at index then no further colonoscopies</b>	<b>2 (0.6%)</b>	<b>3 (0.8%)</b>
<b>First colonoscopy with adequate bowel preparation</b>		
<b>Number of participants</b>	<b>358</b>	<b>378</b>
<b>Bowel preparation score</b>		
Adequate	237 (66.2%)	240 (63.5%)
Excellent	120 (33.5%)	135 (35.7%)
Missing	1 (0.3%)	3 (0.8%)
<b>Completion rate</b>		
Complete (caecum/ileum)	345 (96.4%)	366 (96.8%)
Incomplete (other)	13 (3.6%)	12 (3.2%)
<b>Average procedure time (minutes) – mean (SD); median (IQR)</b>	30.6 (13.7); 28 (22-36)	36.8 (15.0); 34 (27-45)
Missing	0 (0.0%)	1 (0.3%)
When polyps removed – mean (SD); median (IQR); n	35.2 (14.2); 33 (25-42); 207	41.3 (15.2); 39 (30-50); 244
When no polyps removed – mean (SD); median (IQR); n	24.2 (9.8); 24 (17-28); 151	28.6 (10.5); 28 (21-34); 133
When endoscopist assessed procedure as difficult – mean (SD); median (IQR); n	41.4 (14.8); 40 (31-48); 58	47.4 (15.9); 44 (36-58); 66
<b>Average withdrawal time (minutes) – mean (SD); median (IQR)<sup>C</sup></b>	18.7 (11.3); 16 (11-22)	24.1 (12.7); 21 (15-31)
Missing	0 (0.0%)	1 (0.3%)
When polyps removed – mean (SD); median (IQR); n	23.0 (12.2); 20 (15-28); 204	28.5 (12.8); 25.5 (19-35); 242
When no polyps removed – mean (SD); median (IQR); n	12.5 (5.6); 11 (8-16); 141	15.4 (6.6); 15 (10-18); 123
<b>Endoscopist assessment of procedural difficulty</b>		
Easy	108 (30.2%)	106 (28.0%)
Average	172 (48.0%)	190 (50.3%)
Difficult	58 (16.2%)	66 (17.5)
Unable to complete	13 (3.6%)	12 (3.2%)
Missing	7 (2.0%)	4 (1.1%)
<b>Procedure comfort score (Gloucester)</b>		
1	73 (20.4%)	72 (19.0%)
2	158 (44.1%)	180 (47.6%)
3	107 (29.9%)	101 (26.7%)
4	17 (4.7%)	23 (6.1%)
5	2 (0.6%)	2 (0.5%)
Missing	1 (0.3%)	0 (0.0%)

<sup>A</sup>All repeats; <sup>B</sup>In each arm, one found at first repeat, all others at index; <sup>C</sup>Only recorded for complete procedures

**Table 3. Polyps (WHO classification) retrieved over first and repeat procedures**

	Standard colonoscopy (N=360)				Chromocolonoscopy (N=381)			
	Number of participants		%		Number of participants		%	
<b>No polyps or cancer</b>	116		32.2		98		25.7	
<b>Cancers</b>	41		11.4		40		10.5	
<i>Proximal</i>	33		9.2		26		6.8	
<i>Distal</i>	8		2.2		14		3.7	
	Number of polyps		Polyp detection rate		Number of polyps		Polyp detection rate	
	n	per patient	n	%	n	per patient	n	%
<b>Polyps (any)</b>	570	1.583	217	60.3	903	2.370	258	67.7
<b>Adenomas</b>	482	1.339	203	56.4	734	1.927	232	60.9
1. <i>HGD or villous features</i>	36	0.100	33	9.2	39	0.102	34	8.9
2. <i>Other</i>	446	1.239	193	53.6	695	1.824	220	57.7
<i>a. Other ≥ 10mm</i>	122	0.339	85	23.6	152	0.399	105	27.6
<b>Serrated lesions (SL)</b>	78	0.217	51	14.2	141	0.370	81	21.3
1. <i>Any SSL</i>	24	0.067	21	5.8	61	0.160	34	8.9
<i>a. SSL no dysplasia</i>	20	0.056	17	4.7	55	0.144	31	8.1
<i>ai. SSL no dysplasia ≥ 10mm</i>	2	0.006	2	0.6	11	0.029	8	2.1
<i>b. SSL with dysplasia</i>	4	0.011	4	1.1	6	0.016	5	1.3
<i>bi. SSL with dysplasia ≥ 10mm</i>	2	0.006	2	0.6	4	0.010	3	0.8
2. <i>TSA</i>	1	0.003	1	0.3	5	0.013	5	1.3
3. <i>HP</i>	53	0.147	37	10.3	75	0.197	54	14.2
<b>Other</b>	8	0.022	8	2.2	27	0.071	21	5.5
1. <i>Mixed polyp</i> <sup>A</sup>	2	0.006	2	0.6	4	0.010	4	1.0
2. <i>Inflammatory</i>	3	0.008	3	0.8	14	0.037	11	2.9
3. <i>Dysplasia and inflammation</i>	0	0.000	0	0.0	3	0.008	1	0.3
4. <i>Unclassifiable</i>	3	0.008	3	0.8	6	0.016	6	1.6
<b>Proximal SLs</b>	28	0.078	23	6.4	60	0.157	45	11.8
1. <i>Any SSL</i>	18	0.050	16	4.4	39	0.102	30	7.9
<i>a. SSL no dysplasia</i>	16	0.044	14	3.9	37	0.097	28	7.3
<i>ai. SSL no dysplasia ≥ 10mm</i>	1	0.003	1	0.3	9	0.024	7	1.8
<i>b. SSL with dysplasia</i>	2	0.006	2	0.6	2	0.005	2	0.5
<i>bi. SSL with dysplasia ≥ 10mm</i>	0	0.000	0	0.5	0	0.000	0	0.0
2. <i>TSA</i>	0	0.000	0	0.0	1	0.003	1	0.3
3. <i>HP</i>	10	0.028	9	2.5	20	0.052	19	5.0
<b>“Advanced neoplasia”<sup>B</sup></b>								
<i>Overall</i>	164	0.456	114	31.7	214	0.562	136	35.7
<i>Proximal</i>	45	0.125	33	9.2	57	0.150	32	8.4
<b>“Advanced adenomas”<sup>C</sup></b>								
<i>Overall</i>	156	0.433	109	30.3	190	0.499	128	33.6
<i>Proximal</i>	42	0.117	30	8.3	43	0.113	27	7.1
<b>“Significant SLs”<sup>D</sup></b>								
<i>Overall</i>	7	0.019	7	1.9	22	0.058	16	4.2
<i>Proximal</i>	3	0.008	3	0.8	12	0.031	9	2.4
<b>At least one SL and adenoma</b>								
<i>Overall</i>			39	10.8			61	16.0
<i>Proximal</i>			13	3.6			28	7.3

<sup>A</sup>One polyp in standard arm was advanced, two in chromo colonoscopy arm were advanced

<sup>B</sup>Advanced adenoma or “Significant SL” or advanced mixed polyp

<sup>C</sup>HGD or villous features or ≥10mm

<sup>D</sup>SSL with dysplasia or any SSL≥10mm or TSA