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A Comparison Of High Definition White Light And High Definition Virtual Chromoendoscopy For The Detection Of Intraepithelial Neoplasia In Longstanding Colitis: A Randomised Controlled Superiority Trial

(VIRTUOSO Study)

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	1.0	10/2/2016	Kesavan Kandiah	1st version

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2. SYNOPSIS

Study Title	**A Comparison Of High Definition White Light Chromoendoscopy and High Definition Virtual Chromoendoscopy for the Detection of Intraepithelial Neoplasia in Longstanding Colitis: A Randomised Controlled Superiority Trial**
Study acronym	**VIRTUOSO: Virtual Chromoendoscopy in Colitis Surveillance**
Internal reference number	PHT/2016/02
Problem statement	The risk for large bowel (colon) cancer in patients with longstanding ulcerative colitis exceeding the rectum is increased and therefore patients should be enrolled in a surveillance program eight years after the diagnosis. Up to date, official international guidelines for endoscopic screening in patients with ulcerative and Crohn's colitis advise to take 4 biopsies every 10 centimeters (with a minimum of 32) and of each suspected visible lesion. These guidelines are merely based on consensus during expert opinion meetings rather than evidence based. Recent studies have shown that chromoendoscopy guided biopsies reduced the number of biopsies for each procedure and detected more neoplastic lesions. However pan-colonic dye spraying is time-consuming, and tedious. The uptake of this technique in the UK has not been uniform. Therefore virtual chromoendoscopy has been studied as alternative method to improve intra-epithelial neoplasia (IN) detection in longstanding colitis. Virtual chromoendoscopy systems enhance surface patterns and mucosal vasculature thereby theoretically increasing the detection of IN compared to high definition white light endoscopy alone. Optical Enhancement or OE Scan by Pentax uses optical light filters to select particular narrow spectrums of red, green and blue light with a relative decrease in the proportion of red light. It provides the ability to enhance the mucosal surface to better highlight mucosal changes. There has been promising evidence that optical enhancement technology, such as OE scan, is efficient at detecting intraepithelial neoplasia in patients with long standing chronic inflammatory bowel disease.
Research question/Hypothesis	Is the use of high definition virtual chromoendoscopy (HDV), using Pentax OE scan, superior in the detection of intraepithelial neoplasia compared to the use of high definition white light (HDWL) endoscopy in the surveillance for neoplastic lesions in patients with longstanding colitis?
Study design	Parallel group, single blinded randomised controlled trial
Study participants	Patients with long standing colitis attending for their routine surveillance

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	colonoscopy
Planned sample size	204
Follow-up duration	N/A
Planned study period	Approximately 300 patients with long-term colitis undergo surveillance colonoscopy per year in Queen Alexandra Hospital, Portsmouth. Of these patients, we estimate 280 patients would be eligible to enter the study. Assuming a consent rate of 70%, we anticipate recruitment of 196 patients per year. Therefore, the planned study period is 14 months.
Primary objective	To compare the rates of neoplasia detection using virtual chromoendoscopy compared to high definition white light (HDWL) endoscopy
Secondary objectives	• To assess the neoplasia detection rate in targeted biopsies versus non-targeted (segmental) biopsies within each arm of the study • To compare the duration of time taken using each technique: i) Total endoscopic procedure time, ii) withdrawal time • To compare the difference in nurse recorded comfort scores
Primary endpoint	• The number of dysplastic areas detected during endoscopy
Secondary endpoints	• Total endoscopic procedure time • Withdrawal time • Nurse reported comfort score recorded at the end of procedure
Interventions	**Control group**: Surveillance colonoscopy with HDWL where targeted and mapping biopsies are taken **Intervention group**: Surveillance colonoscopy with HDV where targeted and mapping biopsies are taken

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3. LAY SUMMARY

The large bowel or colon is the last part of the digestive system where water and salt are extracted from solid waste before they are eliminated from the body. Colitis is an inflammation (redness and soreness) of the inner lining of the large bowel and it is often caused by conditions known as ulcerative colitis and Crohn's disease. In these conditions, the body attacks the bowel, and causes a lot of inflammation. We do not know exactly why this happens at the moment. However, there is evidence that patients who have had colitis affecting most of the large bowel for more than 8 years are at increased risk of abnormalities which may lead to cancer of the large bowel . To be able to pick up any areas of abnormalities that could lead to cancers, it is recommended that such patients have a colonoscopy (using a colonoscope which is a thin flexible tube that is used to look inside the bowel) at regular intervals. These regular colonoscopies are known as surveillance colonoscopies. If these abnormal areas are picked up early, they can be treated earlier with better outcomes for patients.

During a surveillance colonoscopy, doctors take around 4 tiny tissue samples of large bowel tissue (biopsies) for every 10 centimeters of bowel, and also take a sample of any areas that look abnormal. This is quite a lot of tissue samples to analyse for the laboratory, and because they are taken randomly there is no guarantee that they will detect abnormalities or cancer. However, studies carried out a decade ago have shown that spraying dye such as indigo carmine (a type of food dye) onto the lining of colon helps highlight abnormal areas that could indicate cells that could turn into cancer so that the endoscopist can remove them. This is a technique known as 'chromoendoscopy-guided biopsy' and it has been shown to reduce the number of biopsies needed for each procedure and is able to detect more pre-cancerous tissue.

However, there are weaknesses to the dye spray technique. Studies of the dye spray technique were carried out using older endoscope technologies where the image quality is poor. In addition, using the dye spray takes a long time, which means the time taken for the whole colonoscopy is longer. Finally, there are not yet any set standards for what is considered a good dye spray colonoscopy. In

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view of all of this, dye spray colonoscopy is not yet used by every hospital in the UK.

Newer colonoscopes that are available at the moment can give a clearer picture of the bowel. This technology is known as high definition white light. A fair analogy is to compare the images seen with old television sets with new television sets that have high definition. The new generation of high definition colonoscopes without dye spray have been shown to be able to detect abnormal areas in the large bowel as well as using a standard colonoscope (colonoscopes with the older technology) with dye spray.

We would like to test a new technology, known as 'virtual chromoendoscopy', that is built into the colonoscope. This new technology uses different types of lights to highlight areas on the surface of the bowel that have changed from a normal appearance. Previous studies have shown that this technology is good at finding abnormal areas in the large bowel. However, there are no studies comparing this new technology of virtual chromoendoscopy with high definition white light colonoscopy.

In this study, 204 patients who have been referred to have a routine surveillance colonoscopy to assess their large bowel will be randomly assigned to have their colonoscopy done using either a high definition colonoscope without any dye or a high definition colonoscope with virtual chromoendoscopy. All patients will also have 4 tiny tissue samples of large bowel tissue (biopsies) for every 10 centimeters of bowel.

If virtual chromoendoscopy can be shown to make it easier to see abnormal areas on the bowel surface, then it could be a very good alternative to using the dye spray. This should reduce the time taken to carry out the colonoscopy whilst picking up more abnormal areas that might have otherwise been missed.

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4. ABBREVIATIONS AND DEFINITIONS

Abbreviations

BLI	----------	Blue Laser Imaging
CD	----------	Crohn's Disease
CRC	----------	Colorectal Cancer
FICE	----------	Fujinon Intelligent Colour Enhancement
GCP	----------	Good Clinical Practice
HD	----------	High Definition
HDC	---------	High Definition Chromoendoscopy
HDV	----------	High Definition Virtual chromoendoscopy
HDWL	---------	High Definition White Light
IBD	---------	Inflammatory Bowel Disease
IC	----------	Indigo Carmine
IN	----------	Intra-epithelial neoplasia
NBI	----------	Narrow Band Imaging
OE	----------	Pentax Optical Enhancement
PHT	----------	Portsmouth Hospitals NHS Trust
PPI	----------	Patient and Public Involvement
PSC	----------	Primary Sclerosing Cholangitis
SD	----------	Standard Definition
TSP	----------	Trial Specific Procedures
UC	----------	Ulcerative Colitis

Definitions

- **Neoplasia** – dysplasia, polyps, cancer
- **Dysplasia –** an abnormality in the development of cells

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- **Polyp –** a benign fleshy growth on the inner lining of the gastrointestinal tract. If not removed can potentially develop into cancer
- **Adenoma** – A type of polyp composed of glandular tissue. Most bowel cancers develop from adenomas.
- **Hyperplastic polyp** – a type of polyp with no malignant potential

5. BACKGROUND AND RATIONALE

5.1. Risk of Intraepithelial Neoplasia and Colorectal Cancer in patients with Colitis

Ulcerative Colitis and Crohn's colitis are both forms of inflammatory bowel disease causing chronic inflammation of the large bowel. It has long been recognised that both forms of colitis lead to a significantly increased risk of developing colorectal cancer (CRC) when compared to patients without colitis with a relative risk of approximately 2.7.[1,2,3] Rates of CRC between 7.6-18% have been reported in patients with ulcerative colitis of 30 years duration. CRC remains a major cause of mortality in this group, accounting for 1 in 3 to 1 in 6 deaths in patients with colitis.[4,5] Patients with concomitant UC and Primary Sclerosing Cholangitis (PSC) have a four fold increase of CRC compared to patients with UC alone.[6]

Because of this increased risk of CRC, patients with colitis are offered surveillance colonoscopy that aims to detect early cancers or preferably pre-cancerous areas of intraepithelial neoplasia (IN – previously referred to as dysplasia). Colonoscopic surveillance is recommended after 8 years disease duration in patients with colitis affecting the whole colon (large bowel) and after 15 years disease duration in those with colitis affecting the left side of the colon. Frequency of surveillance is now determined by severity of colonic inflammation plus other risk factors for CRC eg Family history of CRC, Primary Sclerosing Cholangitis, Strictures) and is performed at intervals of 1,3 or 5 years.[7]

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5.2. Detection of Neoplasia

Areas of IN within the colonic luminal surface in IBD are notoriously difficult to identify on standard white light endoscopy as it is often present in flat lesions and can be multifocal. Hence the traditional method of colonoscopic surveillance involves taking 4 quadrantic non-targeted biopsies every 10cm throughout the length of the colon. This policy aims to pick up any 'invisible' areas of IN. However this method has been shown to be time-consuming and costly with a very low yield for detecting IN - in the combined results of 8 studies an average of 1 biopsy detecting IN for every 1266 biopsies taken.[8]

Due to the lack of satisfaction amongst endoscopists with the policy of random quadrantic biopsies, various methods have been studied with the aim of increasing the visibility of IN within the colitic colon and therefore allowing targeted biopsies of visible abnormalities, rather then random 'non-targeted' biopsies. These methods can be divided into two main categories:

1) **Chromoendoscopy (dye-spraying)** involves the spraying of coloured contrast dyes onto the colonic mucosal surface, which highlight abnormal areas such as IN.
2) **Virtual chromoendoscopy** incorporates a number of techniques involving manipulation of the emitted or detected spectrum of light to enhance features of the colonic mucosal surface and thus highlight areas of IN.

5.3. Chromoendoscopy for detection of IN

Kiesslich et al examined IN detection in patients with colitis using the contrast dye methylene blue compared to standard white light endoscopy. [9] They demonstrated a 3-fold increase in the identification of areas of IN when using methylene blue chromoendoscopy compared to standard white light endoscopy. Rutter et al compared chromoendoscopy using another contrast dye, indigocarmine, to standard white light endoscopy with quadrantic biopsies in patients with longstanding colitis.[10] No areas of IN were detected in 2904 random biopsies. There was a strong trend towards increased IN detection with IC chromoendoscopy compared to standard white light endoscopy (7% vs 2%, P=0.06). Hurlstone et al also compared IC chromoendoscopy to standard white

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light endoscopy in patients with longstanding colitis.[11] A 2.5-fold increase in the number of areas of IN was demonstrated using IC chromoendoscopy compared to standard WL colonoscopy (P <0.0001). IN was found in 8% of chromoendoscopy guided targeted biopsies compared to 0.16% of non-targeted biopsies in this study. Marion et al showed that methylene blue guided targeted biopsies found IN in 16 of 34 patients compared to 3 of 34 patients with non-targeted biopsies (P=0.001).[12] These results have led to pan-colonic dye spray chromoendoscopy being the preferred method of IN surveillance recommended in national guidelines.

However, pan-colonic dye spraying is time-consuming (it can take approximately 5 to 10 minutes longer to a standard 20 minute procedure), tedious for the endoscopy team and not uniformly adapted by endoscopists in the UK. Additionally, there are no agreed and validated standards on what is considered good quality chromoendoscopy. In view of this, many centres throughout the UK continue to take segmental biopsies only.[13] Therefore virtual chromoendoscopy has been studied as alternative method to improve IN detection in longstanding colitis.

5.4. High definition white light (HDWL) for detection of IN

The majority of the studies looking at the IN detection rate with chromoendoscopy were done using standard definition (SD) endoscope systems in a research setting. Endoscope systems have since evolved and in the last decade, endoscopy units throughout the country have been switching over to high definition systems. HDWL has been shown to improve the detection of dysplastic lesions when compared to SD endoscopes in the detection of polyps in patients without colitis. In a meta-analysis comparing SD and HDWL colonoscopes, HDWL has been shown to detect more colorectal polyps and adenomas. [14] The additional benefit of chromoendoscopy when used with HDWL in the detection of colonic polyps and adenomas found only a marginal (non-significant) increase in adenoma detection.[15] HDWL has shown promise in improving the detection of dysplastic lesions in patients with colitis. A retrospective cohort study found that surveillance colonoscopy using HDWL detected more dysplastic lesions when compared to standard definition white

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light. In this study, no chromoendoscopy was used.[16] When chromoendoscopy is used in clinical practice, it does not increase dysplasia detection when compared to HDWL and random biopsies. [17]

5.5. Virtual chromoendoscopy for detection of IN

The principle of virtual chromoendoscopy is to filter white light images to enhance superficial structural and vascular changes in the mucosa. Three different commercially available systems are Narrow Band imaging (NBI, Olympus, Tokyo, Japan), Blue Laser Imaging or Fujinon Intelligent Chromo-Endoscopy (FICE, Fujifilm, Tokyo, Japan), and OE-Scan or i-Scan (Pentax, Tokyo, Japan).

NBI, BLI and OE are technologies that have been developed as an alternative to traditional dye-based chromoendoscopy. These technologies use optical light filters to select particular narrow spectrums of red, green and blue light with a relative decrease in the proportion of red light. This technique enhances surface patterns and mucosal vasculature and has been shown to be effective in the assessment of colonic polyps and neoplasia.[18,19,20,21] However, studies of NBI in the setting of IN detection in patients with longstanding colitis have shown conflicting results.[22,23,24]

The Fujinon Intelligent Chromo-Endoscopy (FICE) and Pentax i-Scan systems enhance the mucosal surface structures by using an image-processing algorithm. Unlike the light filtration technologies, these systems are software driven rather than using optical filters.

6. HYPOTHESIS

The use of high definition virtual chromoendoscopy (HDV) is superior in the detection of intraepithelial neoplasia compared to the use of high definition white light endoscopy (HDWL) in the surveillance for neoplastic lesions in patients with longstanding colitis.

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7. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

Experience of Investigators

Professor Pradeep Bhandari – Professor of gastroenterology at Portsmouth University and Consultant Gastroenterologist at Queen Alexandra Hospital, Portsmouth. He is a leading and widely published UK expert in the field of in vivo diagnosis and the endoscopic treatment of early gastrointestinal neoplasia and advanced imaging of the gastrointestinal tract.
Dr Kesavan Kandiah – Research Fellow in gastrointestinal endoscopy, Queen Alexandra Hospital, Portsmouth. Research registrar with experience of participation in previous and on-going endoscopy-based trials. Current GCP certification. Experience in interaction with patients and gaining informed consent.
Ms Carole Fogg – Trials methodologist, University of Portsmouth. Expertise in design and delivery of clinical trials.
Mr Bernie Higgins – Statistician, University of Portsmouth. Expertise in analysis of trial data and methodology. Experience of previous clinical trials in gastroenterology.
Ms Lisa Gadeke – Research nurse, Portsmouth Hospitals NHS Trust. Expertise in the identification and recruitment of research participants to clinical trials, and maintaining Good Clinical Practice (GCP) standards in trial delivery.

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8. AIMS AND OBJECTIVES

8.1. Aims

- To investigate if HDV is superior to HDWL in the detection of intraepithelial neoplasia in patients with longstanding colitis

8.2. Objectives

Primary objective:

- To compare the rates of neoplasia detection using virtual chromoendoscopy compared to high definition white light (HDWL) endoscopy

Secondary objectives:

- To assess the neoplasia detection rate in targeted biopsies versus non-targeted (segmental) biopsies within each arm of the study
- To compare the duration of time taken using each technique:
    - Total endoscopic procedure time – defined as the duration of time between the insertion of the colonoscope into the patient and complete withdrawal of the same colonoscope out of the patient.
    - Total withdrawal time – defined as the duration of time between the start of the withdrawal of the colonoscope once the caecum is reached and the complete withdrawal of the same colonoscope out of the patient
- To compare the difference in nurse recorded comfort scores

9. STUDY DESIGN

9.1. Summary of study design

This will be a randomised controlled superiority trial in which patients with longstanding ulcerative colitis or Crohn's colitis will be randomised to have a surveillance colonoscopy with either high definition white light endoscopy or

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virtual chromoendoscopy. All the endoscopies performed will be with high definition systems by endoscopists trained in carrying out pan-colonic chromoendoscopy. The endoscopies will be carried out using a Pentax processor and Pentax high definition colonoscopes. The endoscopes used are not different in terms of design or size compared to standard colonoscopes and are all commercially available. All endoscopes and the processor are CE approved. The virtual chromoendoscopy is likely to have no influence on patient comfort or introduce any novel side effects as the function is switched on at a push of a button on the endoscope.

9.2. Surveillance colonoscopy

The endoscopic procedure is not much different from a standard colonoscopic procedure that patients would be advised to undergo according to current British Society of Gastroenterology guidelines. Bowel preparation will be administered according to the usual departmental colonoscopy protocol.

Currently, the policy on surveillance colonoscopy in patients with long standing colitis in our unit is to use either high definition or standard definition colonoscopes. All patients have non-targeted segmental biopsies taken every 10cms (also known as mapping biopsies). Depending on the endoscopist, patients may have indigo carmine dye spray and targeted biopsies.

In this study, all colonoscopies will be undertaken using the Pentax processor and colonoscopes, which have the capability of carrying out high definition colonoscopies and the ability of switching on the function of virtual chromoendoscopy at a push of a button. In other words, the Pentax system can be used to carry out colonoscopies for patients in either arm of the study.

10. ENDPOINTS

10.1. Primary Endpoint

The number of dysplastic areas detected during endoscopy

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10.2. Secondary Endpoints

- Total endoscopic procedure time
- Withdrawal time
- Nurse reported comfort score recorded at the end of procedure

11. STUDY PARTICIPANTS

11.1. Study setting

The study will be carried out in a single centre (Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust) and the colonoscopies will be carried out by endoscopists trained in colitis surveillance.

11.2. Overall description of study participants

All patients with colitis referred for colonoscopic surveillance for IN who meet the eligibility criteria will be invited to participate.

11.3. Eligibility criteria

Inclusion criteria

Eligible participants must meet **all** inclusion criteria:

- Ulcerative Colitis or Crohn's colitis with a disease duration of >8 years for pancolitis or >15 years duration for left-sided colitis
- Aged 18 years and above
- Patients able to give informed consent

Exclusion criteria

Eligible participants must **not** meet **any** exclusion criteria:

- Persistent coagulopathy or platelet count $<50x10^{12}$ which may preclude mucosal biopsy

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- Known colonic IN or CRC
- Fulminant colitis
- Patients who have been previously randomised and withdrawn on 2 occasions due to poor bowel preparation
- Patients who are pregnant

12. SAMPLING

We hypothesise that HDV is a superior endoscopic technique to detect dysplasia as compared to HDWL. A study carried out by Mohammed et al found that the neoplasia detection rate with HDWL is 9.4% and 22% with HD chromoendoscopy. [25] In previous studies using the older virtual chromoendoscopy technology, the neoplasia detection rate using HDV is between 12-39%.[22,24,26,27] This range is quite wide and the neoplasia detection rate is expected to be at the higher end of the range with the current technology. Therefore, we have used an expected neoplasia detection rate in the HDV arm of 24% and of 9% in the HDWL (control) arm.

With a significance level (alpha) of 5% and power of 80%, the number needed is 93 for the HDWL group and 93 for the HDV group, leading to a total of 186. However, we anticipate 10% of recruited patients will require withdrawal (e.g. poor bowel preparation, endoscopically confirmed moderate to severe colitis and new diagnosis of cancer) only after the colonoscopy has been started. To compensate for this, we would need to recruit 10% more patients in the HDWL and HDV groups. Therefore, the final number of patients that would need to be recruited are as follows:

HDWL: 102 patients
HDV: 102 patients

Total number of patients to be recruited = 204

Approximately 300 patients with long-term colitis undergo surveillance colonoscopy per year in Queen Alexandra Hospital, Portsmouth. Of these

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patients, we estimate 280 patients would be eligible to enter the study. Assuming a consent rate of 70%, we anticipate recruiting 196 patients per year. Therefore, the planned study period is 14 months.

13. STUDY PROCEDURES

13.1. Recruitment

Patients with ulcerative colitis and Crohn's colitis under regular follow up in the gastroenterology clinic at PHT referred for IN surveillance colonoscopy will be invited to participate in the study.

13.2. Screening and enrolment

Patients who meet the eligibility criteria can be provided with information about the study through a patient information sheet (PIS) when they are seen in the outpatients' clinic. A PIS will also be sent with their appointment for colonoscopy pre-assessment. A colonoscopy pre-assessment is carried out in all patients approximately 1-2 weeks prior to their colonoscopy. During this visit patients can discuss the study further with an endoscopy research fellow or research nurse, who will be able to answer any questions or concerns.

If a patient is willing to participate in the study then consent will be taken on the day of the procedure once inclusion and exclusion criteria have been checked and any further questions answered.

13.3. Randomisation

Patients who have consented to participate will be randomised to a 1:1 ratio among the 2 study arms (HDWL and HDV) by a computer-generated list using random permuted blocks of randomly varying sizes. The generated list will be submitted to 'Sealed Envelope', which will provide an online randomisation service. Once the patient is determined eligible and written consent to enter the trial is obtained, the successive patients will be given a sequential study number. The patient's trial number will be entered into the Sealed Envelope website which will then assign the associated intervention from the random list. A randomisation

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log will be kept and monitored by the Research and Development Department of the sponsor site.

13.4. Study assessments

13.4.1. Baseline

All baseline information will be collected by the endoscopy research team (consisting of research nurses and research fellows).

The following baseline information is recorded after written consent to enter the trial is obtained:

- Demographic data - Age, sex
- Colitis history – Year of first diagnosis, extent of colitis, co-existent primary sclerosing cholangitis
- Current disease activity:
    - Number of bowel movements per day (prior to starting bowel preparation for the surveillance colonoscopy)
    - Amount of rectal bleeding
- Smoking history
- Current medications – use of aminosalicylates, and immunomodulators such as azathioprine and anti-TNF therapy

The following baseline information will be recorded after the colonoscopy procedure (not recorded if patient is withdrawn due to poor bowel preparation):

- Haemoglobin
- Platelet count
- C-Reactive Protein
- Erythrocyte Sedimentation Rate
- Serum Albumin
- Serum/Faecal Calprotectin (if available)

13.4.2. During colonoscopy

- Endoscopist
- Amount of sedation administered
- Type and amount of pain relief used:
    - Fentanyl
    - Pethidine
    - Entonox (dose amount not required)

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- Whether HDWL or HDV was used
- Number and location of neoplastic lesions detected
- Paris classification of detected neoplastic lesions
- Total number and location of targeted biopsies taken
- The Baron's UC endoscopic severity score or the Simplified Endoscopic activity Score for Crohn's Disease (SES-CD)[28]
- Procedure time (from scope insertion into patient to final scope withdrawal from patient)
- Caecal intubation time (from scope insertion to time when caecum is reached)
- Withdrawal time (start of withdrawal from caecum to final scope withdrawal from patient)
- Patient comfort score recorded by nurse (not blinded) as described below:
    0. No discomfort
    1. Minimal discomfort
    2. Mild discomfort
    3. Moderate discomfort
    4. Severe discomfort
- Adverse events during the procedure

13.4.3. Post-colonoscopy

Adverse events will be recorded at the time of discharge from the recovery bay and the endoscopy suite. Participant follow-up ends at the time of discharge from the recovery bay.

13.4.4. When histopathology results of the obtained biopsies area available

- Number of IN detected
- Type of IN detected – e.g. Hyperplastic/sessile serrated polyp/dysplasia/cancer

Microscopic examination of all biopsy samples and resected polyps will be performed by expert consultant gastrointestinal pathologists, who will be blinded to whether virtual chromoendoscopy was used or not. Biopsy samples will be processed as per standard protocol.

13.5. Discontinuation or withdrawal of participants from study treatment

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The following are criteria for withdrawal of the patient from the study:

- Poor bowel preparation.

  The assessment of bowel preparation is made once the caecum is reached as follows:

  i. Excellent (Entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid)
  ii. Good (only liquid stool present removable with suction)
  iii. Adequate (some semi-formed stool obscuring < 20% of the mucosa after suction)
  iv. Poor (>20 % of the mucosa obscured by solid stool after suction)

  It is normal clinical practice for patients with poor bowel preparation to be offered to have a repeat colonoscopy. Such patients will be approached to be re-recruited into the study.

- Obstructing tumour

  Large tumours that prevent the safe passage of the colonoscope past the obstruction caused by the tumour.

- Acute severe colitis

Patients will have the right to withdraw from the study at any time for any reason. This will not compromise their care in any way. The reason for withdrawal will be recorded. This will be reflected in the caecal intubation rate. These patients will be included in the intention to treat analysis but not in the per protocol analysis.

It is understood by all concerned that an excessive rate of withdrawal can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

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13.6. Definition of end of study

The study will end when the required numbers of patients (102 in the control group and 102 in the intervention group giving a total of 204 patients) have been randomised and colonoscopy attempted. There is no study follow up once they have been discharged from the recovery area following the colonoscopy.

Kandiah K, *et al. Gut* 2020;0:1–7. doi: 10.1136/gutjnl-2020-320980

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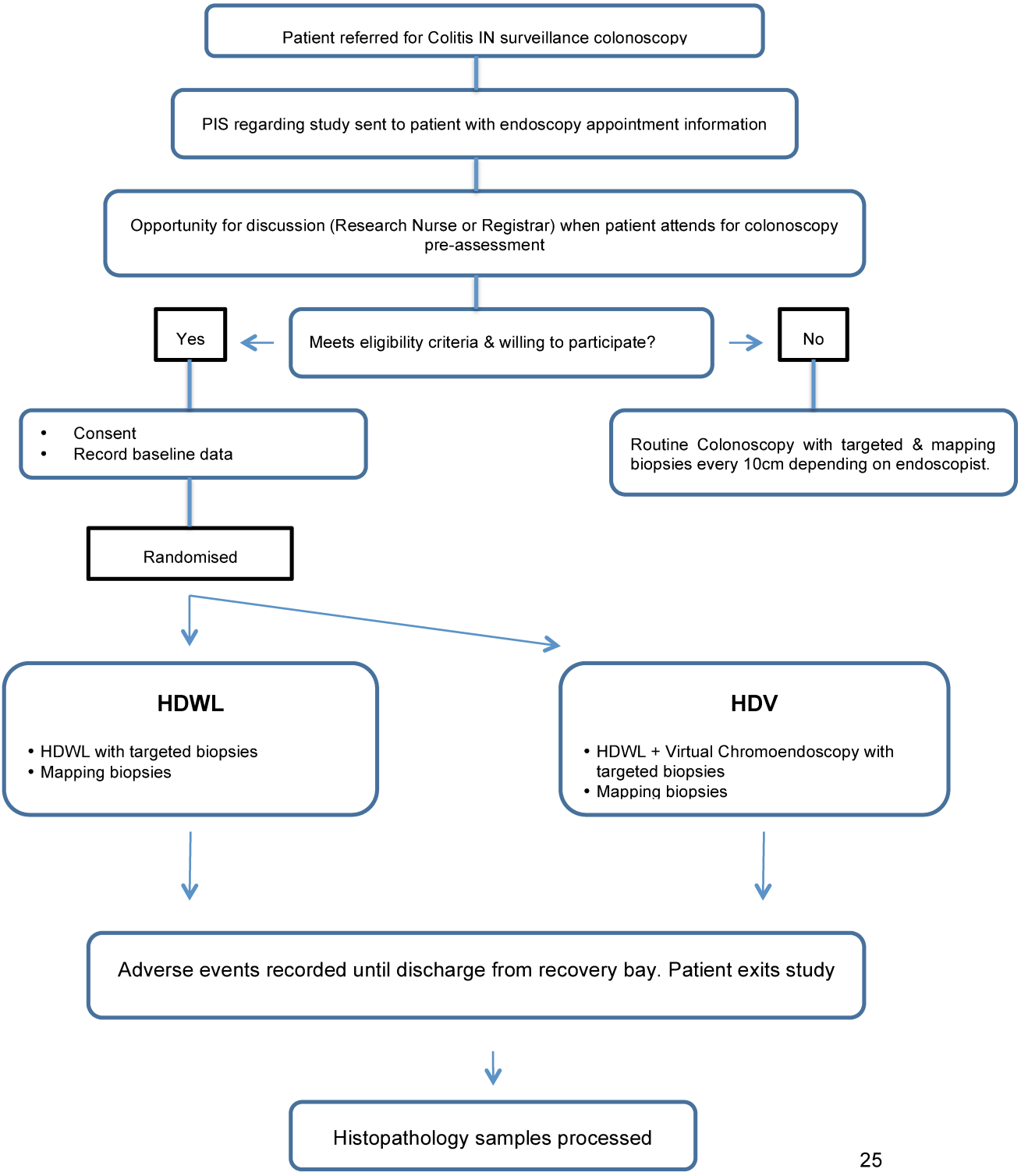
14. TRIAL FLOWCHART



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15. INTERVENTIONS

15.1. Description of study interventions

Each patient will attend for a single visit during which a surveillance colonoscopy procedure will be performed as described. Patients will be randomized between one of the following techniques:

I. HDWL

The patient will undergo a colonoscopy where a Pentax high definition colonoscope is used. Once the caecum is reached, the colonoscope will be withdrawn using high definition white light only. Any mucosal abnormalities identified will be documented and biopsied or removed. In addition, mapping biopsies will be taken routinely.

II. HDV

The patient will undergo a colonoscopy where a Pentax high definition colonoscope is used. Once the caecum is reached, the virtual chromoendoscopy, The Pentax OE Scan, setting will be switched on. Any mucosal abnormalities identified will be documented and biopsied or removed. In addition mapping biopsies will be routinely taken.

Each patient will have 2 sets of biopsies taken:

1) HDWL targeted biopsies OR HDV targeted biopsies
2) Non-targeted quadrantic biopsies

Blinding of the endoscopist will not be done, as the endoscopist will have to be aware of whether or not virtual chromoendoscopy is switched on. All the endoscopists would have done at least 400 colonoscopies and trained to carry out colitis surveillance colonoscopies.

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15.2. Adherence to study treatment

The endoscopist's adherence to either the HDWL or HDV colonoscopy (as per randomisation) will be monitored during the procedure and the reasons for any deviation, if any, will be recorded using a study deviation form.

15.3. Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Sponsor (oversight provided by the Research Quality Committee). If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected. There is no expectation that there will be significant safety concerns or early evidence of significant efficacy difference of the two trial arms.

15.4. Concomitant medication/therapy

No additional concomitant medications or therapies will be required or recorded as part of this study.

16. ASSESSMENT OF SAFETY

16.1. Definitions

- **Adverse Event (AE)** - Any untoward medical occurrence in a patient taking part in a clinical trial which does not necessarily have to have a causal relationship with the device under investigation.
- Serious Adverse Event **(SAE)** – Any untoward medical occurrence that:
  - Results in death
  - Is life threatening – life threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event. It does not

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refer to an event that hypothetically might have caused death if it were more severe.

- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Results in other important medical events

Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction). The event itself however, may be of relatively minor medical significance (such as severe headache).

This is not the same as 'serious', which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

16.2. Safety reporting procedures

As part of the department policy, any serious adverse events are routinely reported and the data collected. However, additional safety monitoring will be undertaken during this study as outlined below.

16.3. Recording and reporting procedures of all adverse events

As with any interventional medical procedure, there are certain expected risks associated with colonoscopy. The risks of complications would be the same as

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any standard colitis surveillance colonoscopy. Patients are counselled in detail about these risks before they provide informed consent.

- Perforation – making a hole in the bowel wall as a result of trauma from the colonoscope. Depending on the type of perforation, this can be managed endoscopically during the procedure or may require surgery.
- Bleeding – Small amounts of bleeding can happen during colonoscopy, especially if polyps or dysplastic appearing lesions are removed. Any significant amounts of bleeding may require specific endoscopic therapy to stop the bleeding or very rarely, surgery.

- Any of the above possible adverse events are likely to occur during the procedure, or in the period immediately after the procedure, Therefore all Adverse events that occur before discharge from the recovery area shall be recorded in the CRF recording the following as a minimum data set:
    - A verbatim description of the event
    - The date of onset
    - Intensity (mild, moderate, severe)
    - Relatedness to the study intervention (unrelated, unlikely, possibly, probably, definitely)
    - Serious adverse event (yes, no)
    - Action taken
    - Outcome of the event
    - The date of resolution (if resolved)

    Any of the above possible adverse events are likely to occur during the procedure, or in the period immediately after the procedure. We will be monitoring for these during the actual procedure and in the recovery room thereafter till their discharge from the unit. There will be no further follow up as part of the study.

All Serious Adverse Events (SAEs) occurring during this time will be reported immediately to the sponsor's research office in line with PHT/RDSOP/007 – SOP for

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Investigators: Recording, Assessing and Reporting Adverse Events in Clinical Research **http://www.porthosp.nhs.uk/Research-Department/policies.htm**. All assessments shall be made in accordance with this SOP and all recorded adverse event data shall be collated and included in the study analysis.

17. DATA HANDLING AND RECORD KEEPING

17.1. Case report forms

The case report form, including baseline data and primary and secondary endpoints will be filled out by the research assistant together with the endoscopist and then collected by the trial coordinator. The pathology reports will also be entered on the CRF when they become available on the computerised result reporting system.

17.2. Data management

Study data including the primary and secondary outcome measures will be collected on a case report form at the time of the colonoscopy. The data collection forms will be stored in a secure location in the research office and data will subsequently be entered onto a secure password protected access custom built database.

The Investigator(s) will permit trial-related monitoring and audits by providing the Sponsor(s) with direct access to all trial documents plus source data (e.g. patients' medical records and study digital photographs).

The Chief Investigator will act as custodian for the trial data. The following will be strictly adhered to:

- Patient data will be anonymised
- All anonymised data will be stored on a password protected computer in a bespoke database
- Data will be held on a protected area of the trust's shared drive to ensure that it is backed up on a regular basis.
- All trial data will be stored in line with the Data Protection Act and archived in line with Trust procedures.

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17.3. Data protection

Following publication of the results the trial documentation will be stored for 10 years in a secure environment that complies with the Data Protection Act (1998).

17.4. Data analysis

Baseline characteristics will be presented descriptively. The endpoints `will be represented by their statistical means or medians where appropriate. To compare detection rates, categorical variables will be compared using Chi-Square or Fisher's exact test:

- The difference in total number of neoplastic lesions detected by targeted biopsies using HDWL and virtual chromoendoscopy
- The difference in the proportion of neoplastic lesions/ total number of lesions between HDWL and virtual chromoendoscopy

In view of the large sample size, the dysplasia detection rate on per biopsy basis, the patient comfort score and the time taken for each endoscopy procedure (i.e. the continuous variables) will be compared using a two-sample t-test (Welch version) or a Mann–Whitney sum of ranks test as appropriate. For advanced analysis, Poisson regression may used for the detection rates and the Log-rank test for the duration of the colonoscopy. Outcomes will be adjusted for withdrawal time, family history of CRC, and previous history of a dysplastic lesion.

18. ETHICS AND REGULATORY APRROVAL

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related documents will be submitted for review to a regional Research Ethics Committee (REC).

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19. PATIENT AND PUBLIC INVOLVEMENT

By patient and public involvement (PPI), we mean patient and members of the public who are not part of the study as participants, but invited to share a collaborative relationship with the researchers. Our Gastroenterology Research Nurse identified patients and a member of the public to be contacted. Those identified were previously involved in other studies run by our department. Initial contact was made via telephone by the gastroenterology research nurse and consent to discuss the study was obtained. Following this, the lead research registrar contacted each PPI team member individually and discussed in detail the research proposal.

19.1. Study design

The proposal was originated from clinicians but supported by the PPI as the study outcome has the potential to change current practice of colitis surveillance to the benefit of patients.

The PPI group was involved in the study design and protocol preparation stage. The group is happy with the current study design for several reasons. The first is that all patients recruited will be receiving the minimum standard of care, which is colonoscopy with segmental biopsies. They feel that the current design does help address the question asked. They are pleased that patients do not have to go through two colonoscopies (i.e. a cross-over trial design) and therefore avoiding taking the bowel preparation twice. The group has reviewed the lay summary, patient information sheet, letter of invitation and consent form.

19.2. Screening and enrolment

During this visit patients can discuss the study further with an endoscopy research fellow or research nurse, who will be able to answer any questions or concerns. This approach in recruiting patients was discussed and approved to be ideal by the PPI group.

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19.3. Post-colonoscopy follow up

This was discussed with the PPI group who agrees that as patients will be undergoing a standard colonoscopy without any additional interventions, there is no requirement for further follow up outside that of normal clinical practice.

19.4. Study dissemination

The PPI members are keen to assist in the dissemination of the results of this study, and will work with the study team to write a summary of results, which can be shared with the participants, the wider patient group and bowel cancer charities.

20. RESEARCH MANAGEMENT

The trial will be carried out by the endoscopy research group, who will meet together with sponsor representatives prior to the study start, after enrolment of the first ten patients or 1 month of study process (whichever comes first), and at regular intervals thereafter.

21. FINANCING AND INSURANCE

The trial coordinator (TC) is funded by Portsmouth Hospitals NHS Trust as part of the Trust Research Fellowship scheme. The TC Is also part of the clinical care team for these patients and is expected to conduct most of the direct research activities supported by specialist nurses and an experienced departmental research team.

Pentax Medical UK will support this study by supplying equipment valued at £150,000. The equipment includes an EPK-i7010 processor and EC38 i10F colonoscopes. Pentax will also contribute £20,000 towards research expenses.

The NHS indemnity scheme shall apply for the management, design and conduct of the study. All the endoscopes and processors have a CE mark and are covered by product liability insurance from the company, the evidence of which can be provided upon request. There are no excess treatment costs associated with the study.

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22. STUDY SPONSORHSIP

Portsmouth Hospitals NHS Trust shall act as sponsor

23. TIMETABLE

Month 1 and 2: ethical and R+D approvals, set-up of randomisation procedure, finalisation and piloting of CRF, completion of trial specific procedures (TSPs)

Month 3: begin patient recruitment

Month 4: review current recruitment, CRF and TSPs

Month 16: complete recruitment

Month 17 and 18: final data checks, analysis, meeting with PPI group and dissemination

24. RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

This study will be conducted for patients who require surveillance colonoscopy and no added procedures are being undertaken. All colonoscopies will be undertaken using a Pentax high definition processor and high definition colonoscopes. The Endoscopy department is experienced in conducting clinical research and has the physical facilities to host this activity to high standards of GCP. The Trust pathology department shall provide pathology resources.

25. LAB METHODS

Pathology samples will be reported by accredited GI pathologists as per normal clinical practice. These will be reviewed by the study coordinator to confirm neoplasia detection rate and the number of neoplasia per patient.

26. DISSEMINATION AND OUTCOME

It is intended that the results of the study will be reported and disseminated at international conferences such as the British Society of Gastroenterology annual meeting, the United European Gastroenterology Week (UEGW) and the Digestive Diseases Week (DDW) and in peer-reviewed scientific journals such as *Endoscopy, Gastrointestinal Endoscopy* and *Gut.*

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Results will also be disseminated to the local primary care groups, the Oxford and Wessex 'Gut Club' and also to patients via the endoscopy staff and patient forum.

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Signatures

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Chief Investigator Date

Print name

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Statistician (if applicable) Date

Print name