Study Title: Real time computer aided detection and characterisation of colorectal polyps; a prospective multi-centre randomised controlled superiority trial (ColoVision)

Internal/Protocol Reference No: PHU/2022/09

Ethics Ref: 22/PR/1174

Date and Version No: 1.0 18-08-2022

IRAS ID: 313559

Chief Investigator:

Professor Pradeep Bhandari MD, MRCP
Portsmouth Hospitals University NHS Trust, UK

Investigators:

Miss Katie Siggens
Endoscopy Research Fellow
Portsmouth Hospitals University NHS Trust, UK

Dr Hein Htet
Endoscopy Research Fellow
Portsmouth Hospitals University NHS Trust, UK

Sponsor:

Portsmouth Hospitals University NHS Trust
Queen Alexandra Hospital, Cosham
Portsmouth, Hampshire,
England, UK
PO6 3LY

Funder: NEC Corporation Ltd. Japan

Signatures:

Protocol Development Team:

Professor Pradeep Bhandari, Consultant Gastroenterologist

Miss Katie Siggens, Research Fellow

Dr Hein Htet, Research Fellow

Dr Mohamed Abdelrahim, Research Fellow

Dr Gaius Longcroft-Wheaton, Consultant Gastroenterologist

Joanne Dash, Research Nurse

Michelle Baker-Moffatt, Research Nurse

Lucille Bombeo, Research Nurse

Laura Marshall, Research Facilitator

Sharon Court, PPI Facilitator

Paul Bassett, Statistician

TABLE OF CONTENTS

1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	**Real time computer aided detection and characterisation of colorectal polyps; a prospective multi-centre randomised controlled superiority trial (ColoVision)**
Internal ref. no.	PHU/2022/09
Problem statement	Colorectal cancer is a major health problem. Most colorectal cancers develop from precursor lesions (polyps), and early detection and removal of these polyps can reduce rate and improve outcome of colorectal cancer. Colonoscopy is the gold standard test to detect and remove polyps, however there is still significant polyp miss rate. Moreover, the concept of optical diagnosis of polyps has been recommended by various guidelines, however its implementation outside expert and academic centres is still limited. Computer aided detection (CADe) and computer aided diagnosis (CADx) of polyps is rapidly progressing and recent studies have shown promising results. However, there is still lack of high-quality data from well-designed and implemented randomised trials and hence the need for this study.
Research question / hypothesis	Our hypothesis is that the CAD device used in this study (WISE VISION®) can significantly improve endoscopists' adenoma detection rate (ADR) as well as their real time optical diagnosis to reach PIVI threshold of 90% NPV, compared to endoscopists not using the CAD device.
Study Design	This is an investigator initiated and led multi-centre randomised control superiority trial. The study will be using the NEC WISE VISION® device which has two functions: CADe and CADx and we will assess the impact of both. Participants will be randomised into two groups. The control group will have a standard colonoscopy (without CAD device support), and the intervention group will have colonoscopy with CAD device (both CADe and CADx) All patients (both in control and intervention group) will receive standard care. All decisions taken during the colonoscopy procedure will be taken by the endoscopists as per standard protocols.
Study Participants	Patients undergoing a colonoscopy

Planned Sample Size	CADe: 654 participants CADx: 200 diminutive rectosigmoid polyps (588 total polyps)
Follow-up duration	28 days (+/- 14 days)
Planned Study Period	12 months
Primary Objective	• To evaluate the impact of the CAD system on endoscopists' detection of colorectal polyps • To evaluate the impact of the CAD system on real time characterisation (optical diagnosis) of polyps compared to histology.
Secondary Objectives	• To evaluate the effect of the CAD device on other polyp detection parameters.
Primary Endpoints	Adenoma detection rate in both groups PIVI-2: NPV of adenoma diagnosis in diminutive (<5mm) rectosigmoid polyps in both groups
Secondary Endpoints	Polyp detection rate (PDR) in both groups Adenoma per colon (APC) in both groups PIVI-1: agreement between surveillance interval decisions based on histology and that based on the combination of histology of non-diminutive polyps and optical diagnosis in both arms Diagnostic performance measures in both groups (sensitivity, specificity, accuracy, NPV, PPV, AUC) according to various factors (eg endoscopist's experience) Withdrawal time in both groups
Intervention (s)	Colonoscopy plus WISE VISION® CAD device

3. ABBREVIATIONS

ADR	Adenoma detection rate
AI	Artificial intelligence
AMR	Adenoma miss rate
APC	Adenomatous polyposis coli
BCSP	Bowel cancer screening programme
BLI	Blue Light Imaging
CADe	Computer aided detection
CADx	Computer aided diagnosis
CNN	Convolutional neural networks
CRF	Case report form
FAP	Familial adenomatous polyposis
GCP	Good clinical practice
HDWL	High definition white light
IBD	Inflammatory bowel disease
ITT	Intention to treat
KPI	Key performance indicators
MSI	Microsatellite instability
NBI	Narrow band imaging
PDR	Polyp detection rate
PIS	Patient information sheet
PIVI	Preservation and Incorporation of Valuable endoscopic Innovations
RCT	Randomised controlled trial

4. LAY SUMMARY

Bowel cancer is now the fourth most common form of cancer in the UK according to cancer research UK. We know that some small growths in the lining of the bowel called polyps can turn into cancers if left long enough and that early detection and removal of these polyps can prevent cancers developing.

Colonoscopy is the gold standard test to identify, diagnose and remove these polyps but we also know from research that polyps can be missed at colonoscopy. Artificial intelligence in health care is becoming increasingly common, and technology to improve detection of polyps has been developed, known as Computer Aided Detection CADe and Diagnosis (CADx). Early studies have shown promising results that CAD increases the detection of polyps and is able to recognise whether or not they are the type of polyps which have the potential to turn into cancers, however high-quality data from well designed randomised trials is still limited and hence the need for this study

Several devices for computer aided detection of polyps have been produced and are currently in use in endoscopy units around the world. In this study, we aim to examine how an approved device (WISE VISION®) can support endoscopists on detection and assessment of colorectal polyps.

5. BACKGROUND AND RATIONALE

Colorectal neoplasia and cancers

It is well recognised that colorectal cancer develops through the accumulation of series of mutations in a stepwise order. Different pathways have been identified in the pathogenic process. One of the first to be described was the adenoma-carcinoma sequence(1), or what is also known as the “traditional” pathway. The adenomatous polyposis coli (APC) tumour suppressor gene has been identified as one of the early mutations(2) occurring in the sequence. Germline mutations in the APC gene have been associated with familial cancer syndromes such as familial adenomatous polyposis (FAP) and Lynch syndrome, however most colorectal cancer are due to sporadic mutations. Further mutations in numerous genes including K-ras, p53 and 18q loss have also been identified. These occur in two main pathways- the chromosomal instability (CIN) or microsatellite instability (MSI) pathways(3) with the former accounting for approximately 85% of sporadic colorectal cancers(4).

More recently, the “serrated” pathway has been described in colorectal carcinogenesis. Serrated polyps form a heterogenous group of intestinal polyps including sessile serrated lesions as well as hyperplastic polyps which do not harbour malignant potential. This pathway only accounts for a small portion of colorectal cancers(3). Tumours which develop via the serrated pathway display early mutations in the BRAF(5) or K-ras oncogenes, distinct from the adenoma-carcinoma pathway. It is believed that the serrated pathway leads to accelerated cancer growths and are often the cause of interval cancers- those developing in shorter periods of time between surveillance. Sessile serrated lesions tend to be small, proximal lesions and can be easily missed without meticulous examination of the bowel.

Detection and characterisation of colorectal neoplasia

Our knowledge of the formation of colorectal cancers has led to the introduction of screening such as the Bowel Cancer Screening Programme (BCSP) in the UK. In addition, the need for surveillance has been recognised. Colonoscopy is the ‘gold standard’ test for assessment of the colon and rectum. Various key performance indicators (KPI) are in place to maintain standards in colonoscopy. This includes adenoma detection rate (ADR) where endoscopists should be aiming for 20%(6), although polyp detection rate (PDR) is often used as a surrogate marker. However, evidence shows that up to 23%(7,8) of polyps are missed on colonoscopy despite one study suggesting that for each 1% rise in ADR, there was a 3% reduction in the risk of cancer(9).

Once identified, polyp characterisation is essential to correctly manage them. There is now an array of enhanced imaging modalities available on modern colonoscopes to assist with differentiating lesions, such as blue light imaging (BLI), narrow band imaging (NBI) as well as standard high definition white light (HDWL) imaging. Estimating the size of polyps endoscopically can be challenging. We know the risk of a diminutive (<5mm) polyp harbouring a cancer is very low(10)(11) and there has been interest in “resect and discard” or “diagnose and leave” in these polyps(12,13). Similarly, the literature suggests polyps over 20mm are more likely to harbour a cancer with the risk being estimated between 2-6%(14). Knowing this, being able to estimate lesion size endoscopically has also drawn interest with the advances in CADx.

Computer aided detection and diagnosis and its use in the colon and rectum

Computer aided detection devices utilises artificial intelligence (AI) algorithms to perform various tasks. It is becoming increasingly utilised in medicine and has gained particular interest in the field of endoscopy due to the image-based nature of it and the use of pattern recognition. This uses a specific element of AI called Convolutional Neural Network (CNN)(15), involving complex matrix computations to predict the likelihood of what an image shows. Several CAD devices have already been validated (14) for in-vivo polyp detection.

Several recent studies have demonstrated promising performance of CAD devices in polyp detection and characterisation (15). However, most of these studies were performed on endoscopic images and videos, and the number of real time and randomised studies is still very limited. Only 5 randomised trials studying CAD polyp detection have been published and these are mostly done in the far East. Therefore, there is a significant need for Western and UK based randomised trials to study this important area of endoscopy research, and hence this study.

The CAD device in this study (WISE VISION® NEC Japan) is an approved device (CE marked) and already in use in different endoscopy departments around the world(17). This device is fully compatible with all major endoscopy processors. It has two main functions, detection of polyps (CADe) and characterisation of polyps (CADx). The characterisation function classifies polyps according to their likely precited histological diagnosis (neoplastic vs non-neoplastic). The device showed very promising results when evaluated on endoscopic images and videos(18) (ex-vivo), however it has not been assessed in a randomised trial in real time, hence this study.

6. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

The Chief Investigator of this study is experienced in running endoscopy clinical trials including studies on the application of AI in endoscopy. All co-investigators and members of the research team are GCP certified and have experience in running various endoscopy-based studies.

7. AIMS AND OBJECTIVES

The aim of this study is to assess whether CAD (NEC WISE VISION®) improves polyp detection and characterisation.

7.1 Primary Objective

- To evaluate the impact of the CAD system on endoscopists' detection of colorectal polyps
- To evaluate the impact of CAD characterisation system on endoscopists performance in optical diagnosis of diminutive colorectal polyps compared to histology

7.2 Secondary Objectives

- To assess the diagnostic performance of the CAD system on detection of colorectal polyps according to their size, location and morphology
- To evaluate the diagnostic performance of the CAD system on characterization of colorectal polyps based on size, location and morphology
- Evaluate the false positives and false negatives by the CADe system to understand predictors of wrong CADe detection
- Evaluate the cost implications of the CAD system
- Evaluate the impact of the CADe system on complications from colonoscopy and polyp removal

8. STUDY DESIGN

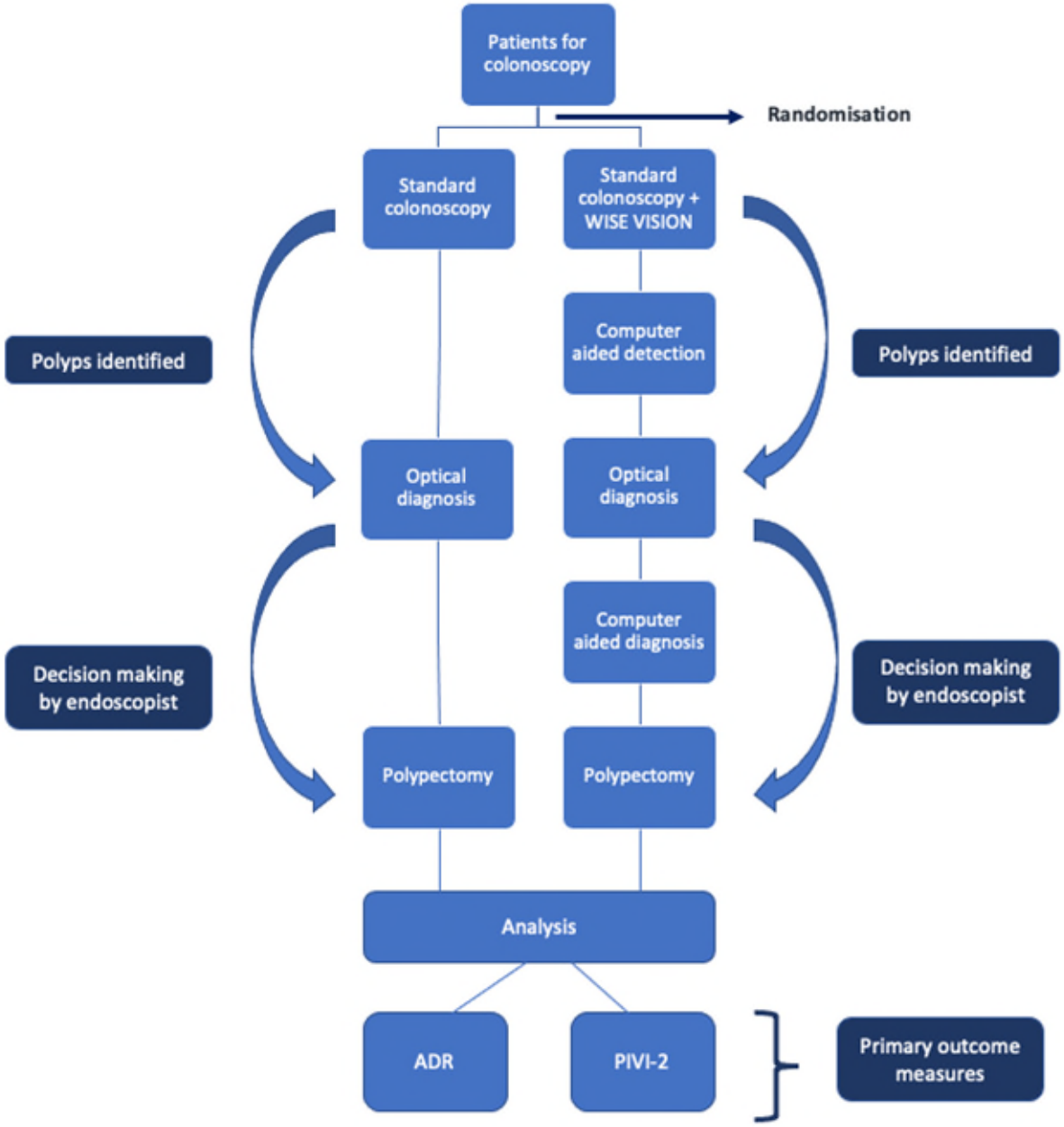
8.1 Summary of Study Design

This will be a multi-centre randomised control superiority trial. Participants will be randomised to either standard colonoscopy (control arm) or colonoscopy plus WISE VISION® CAD device (intervention arm). The CAD device has both detection and characterisation functions and there are 2 elements within the study. Firstly the study will aim to assess the impact of computer aided detection and secondly computer aided characterisation.

When polyps are identified, these will be recorded and the endoscopist will be required to assess this and indicate their optical diagnosis accordingly. For patients randomised to colonoscopy plus CAD, the CADx will then be carried out and the results recorded. Polyps will be treated according to standard care.

Polyps detected by the endoscopists but missed by the CADe device will also be recorded. The total number of polyps identified and the endoscopist diagnosis will be recorded for both arms. The histology results of the polyps removed will be collected.

Figure 1: Study Procedure Flowchart



8.2 Primary and Secondary Endpoints/Outcome Measures

Primary End points

Adenoma detection rate in both arms

PIVI-2: NPV of adenoma diagnosis in diminutive (<5mm) recto-sigmoid polyps in both arms

Secondary End points

Polyp detection rate (PDR) in both groups

Adenoma per colon (APC) in both groups

PIVI-1: agreement between surveillance interval decisions based on histology and that based on the combination of histology of non-diminutive polyps and optical diagnosis in both arms

Diagnostic performance measures in both groups (sensitivity, specificity, accuracy, NPV, PPV, AUC)

Diagnostic performance measures in both groups (sensitivity, specificity, accuracy, NPV, PPV, AUC) according to endoscopists experience

Diagnostic performance measures in both groups (sensitivity, specificity, accuracy, NPV, PPV, AUC) according to endoscopy imaging mode (WLI or EI)

The proportion of histological assessments that could have been avoided in both arms

The proportion of polyp removals that could have been avoided in both arms

Withdrawal time in both groups

9. STUDY PARTICIPANTS

9.1 Study Setting

This will be an international multi-centre trial being carried out at several secondary care endoscopy sites across Europe. All endoscopists working on the study at participating sites will have access to and be trained in the use of WISE VISION® device.

The trial will run at the following sites:

- Queen Alexandra Hospital, Portsmouth, UK (Sponsor & lead UK site)
- Royal Sussex County Hospital, UK
- St Georges Hospital, UK
- King's College Hospital, UK
- Humanitas Research Hospital, Milan, Italy
- GastroZentrum Lippe, University Medical Centre Mainz, Germany
- Sapienza University of Rome, Italy

9.2 Overall Description of Study Participants

All patients who are undergoing a colonoscopy at one of the participating sites will be screened, and those who meet eligibility criteria below will be invited to participate.

9.3 Eligibility Criteria

Inclusion

- Adults over age 18 who are undergoing a colonoscopy

- Must be able to give informed consent

Exclusion

- Pregnant patients
- Poor bowel preparation
- Polyposis syndrome
- Active inflammation of the colon including inflammatory bowel disease
- Incomplete colonoscopy

10. SAMPLING

- This is powered as a superiority trial.
- For computer aided detection, the ADR of competent but non-expert endoscopists is assumed to be 20% and we believe that CADe will increase it to 30% (expert level). In order to demonstrate a difference of 10% between the two groups with an 80% power and a significance level (alpha) 0.05; we will need 588 patients (294 per group). We will over recruit by 10% (max total of 654) to allow for drop outs, poor bowel prep, incomplete dataset etc. Interim analysis will be done after 50% recruitment
- For computer aided diagnosis, the NPV of endoscopists is assumed to be 75%, and we believe the NPV of endoscopist plus CADx will be 90%. To achieve this with an 80% power and significance level (alpha) of 0.05, we will need to assess 200 diminutive recto-sigmoid (100 per group) polyps (588 total polyps), in an estimated 168 patients. We will plan to over recruit by 10% to allow for incomplete data (220 diminutive recto-sigmoid polyps, 647 total polyps). Interim analysis will be done after 50% recruitment

11. STUDY PROCEDURES

11.1 Recruitment

Patients booked for a colonoscopy will be screened prior to their procedure to identify potentially eligible participants. Recruitment will be carried out by suitably qualified members of the research team including research nurses, research fellows and consultants.

11.2 Screening and Enrolment

Patients will be approached and provided with information regarding the study to include a Patient Information Sheet (PIS). This, along with an invitation letter, will be posted to eligible participants by members of the research team with at least 1 week notice, where possible. If it is not possible to provide this notice, given the study does not alter standard treatment, patients would be approached on the day of the procedure instead. Each potential participant will be given as much time as they require to read and consider the information and ask questions to make an informed decision.

Patients who wish to participate will be able to provide informed consent to participate on the day of, and prior to, the procedure. Consent will be recorded on a paper form and obtained by a suitably qualified and delegated member of the local Research Team, in addition to the standard consent required for the procedure. There will be no financial remuneration for participating in the trial.

11.3 Randomisation

Participants will be randomised electronically in a 1:1 ratio into two groups. The intervention group will have their colonoscopy performed with the assistance of the WISE VISION® CAD system, the control arm will have standard colonoscopy. Randomisation will be carried out prior to the procedure being started. The randomisation will be stratified by site to ensure an equal allocation in each centre. Additionally, a blocked randomisation, with varying block sizes, will be performed to allow for a balance between groups throughout the trial.

The randomisation process will be managed using the built-in module within the project's REDCap eCRF database managed by Portsmouth Hospitals University NHS Trust. The Data Manager will generate the randomisation allocation table using statistical software, which will then be uploaded into REDCap before the first patient is consented.

11.4 Study Assessments

Baseline characteristics will be recorded for all participants. Basic demographics will be recorded to include:

- Age
- Sex
- Co-morbidities and ASA score
- History of previous polyps/bowel conditions

During the colonoscopy the following will be recorded in all patients:

- Endoscopist including level of experience (number of life time procedures)
- Indication
- Bowel preparation used and quality
- Use of sedation/general anaesthetic
- Procedure start and finish time and time of maximal intubation
- Comfort score
- Adverse events
- Polyps detected to include the endoscopists optical diagnosis and assessment of size, morphology using the Paris classification, site and details of their removal.
- Still image/video of polyp (where available)

For patients randomised to colonoscopy plus CAD the following additional data will be recorded:

- Total number of potential polyps identified by CADe
- CADx diagnosis of polyps identified
- Outcome of assessment by endoscopist e.g. confirmed as polyp, characterisation assessment

Post colonoscopy:

- Adverse events will be recorded
- Histology of any polyps removed will be recorded to correlate with the endoscopist/CADx assessment of the lesion.

11.5 Discontinuation/Withdrawal of Participants from Study Treatment

Participants are free to withdraw their consent at any point during the study if they wish. Data collected up to the point of withdrawal will still be included in the analysis.

The withdrawal of a participant in the study will also be required in the following situations:

- obstructing lesions
- inability to complete the procedure e.g. difficult colonoscopy

11.6 Definition of End of Study

The study will end 28 days(+/- 14 days) after the last participant has been recruited to allow for the reporting and collection of histopathology data. Patients will be followed up as per standard management, judged by the endoscopists (for example as per polyp surveillance guidelines). There is no additional follow up required.

11. INTERVENTIONS

11.1 Description of Study Intervention / Treatment

Colonoscopy is the gold standard technique for examination of the large bowel. Because of the knowledge of the long term risks polyps developing into cancers, when there are identified during colonoscopy it is standard practice to remove them where indicated and safe to do so. Removal of polyps is dependent on first identifying them, and secondly being able to accurately diagnose the type of polyp.

The use of Computer Aided Detection and Diagnosis (CAD) with the WISE VISION® is the intervention in this study. This is a CE marked device designed to improve both detection and diagnosis of polyps. The intervention in this study therefore aims to enhance polyp detection and diagnosis. Patients who do not consent to take part will still be treated in the same way.

11.2 Adherence to Study Treatment

All patients undergoing colonoscopy are managed according to local and national guidelines including the decision to remove polyps and the follow up following the procedure. Given this, management of patients and adherence to treatment should not be altered as a direct result of this trial.

12. ASSESSMENT OF SAFETY

12.1 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.

Adverse Device Effect (ADE)

Adverse Device Effects (ADEs) are all untoward and unintended medical occurrences in response to a medical device.

All cases judged by either a medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualify as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- 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.

A non-CTIMP *Suspected Unexpected Serious Adverse Reaction (SUSAR)*

is defined as any Serious Adverse Event judged to be:

- Related to the administration of any intervention or any study procedure of interest to the study i.e. having a reasonable causal relationship to that procedure or intervention
- Unexpected, i.e. not listed in the protocol (or product information) as an expected occurrence for those specified procedures/intervention, and
- Unrelated to the administration of an IMP i.e., having no reasonable causal relationship to an IMP

12.2 Reporting Procedures for Serious Adverse Events

All SAE/SADEs occurring to a participant will need to be initially recorded in the study CRF and reported to the Chief Investigator and Sponsor (unless exempt from being reported) in line with PHT/RDSOP/007 – SOP for Investigators: Recording, Assessing and Reporting Adverse Events in Clinical Research (found at 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. Listings of adverse events will be provided to the Sponsor by the TMG/TSC, when requested, for safety oversight.

Exemptions to SAE reporting:

Complications arising from colonoscopy or polypectomy (bleeding, perforation, etc.) would not be classed as adverse events of the study, and therefore for the purpose of the study would not be considered to be reportable SAEs. In the event these occur they should still be recorded in the study CRF. These include the following:

- ***Bleeding: this includes intra procedural, early or delayed bleeding.***
- ***Perforation***
- Hospital admission
- Missed pathology
- Recurrence of pathology
- Death

12.3 Recording and Reporting Procedures for non-CTIMP SUSARSl

It is extremely unlikely that any research related SUSARs will occur given the intervention (addition of CAD device) does not alter standard care. If however, in an unforeseen way a

non-CTIMP SUSAR does occurs during the study, it should to be reported to the Sponsor, within 24 hours, as per Portsmouth Hospitals University NHS Trust's standard operating procedure PHT/RDSOP/007 (see details above) and the Chief Investigator. The REC that approved the study will also need to be notified within 15 days of the Chief Investigator becoming aware of the event as per Health Research Authority safety reporting guidelines.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Collection

Patients will be allocated a unique anonymised study ID number, in which their data will be collected against, to maintain participant confidentiality. A paper Case Report Form (CRF) will be created for data collection for those participating in the trial. This will be contemporaneously populated by a delegated member of the research team during the procedure. This will then be uploaded onto the REDCap database by a delegated member of the research team. Query reports will be run on the database regularly throughout the study and where data is missing or incorrect this will be chased. Missing/incorrect data will also be reviewed and discussed at the Trial Steering Meetings.

13.2 Data Management

All data will be handled in line with the Data Protection Act 2018. The data recorded on the paper CRF will be entered onto the REDCap online database by an approved and delegated member of the research team. Where still images are obtained during the colonoscopy these will be uploaded onto the electronic database. Each participating site will have a unique login for the REDCap system. A list of users for the database will be created and will be approved by the Chief Investigator. Information input to REDCap will be anonymised prior to uploading and patients will only be referred to by their participant ID number for all data and images collected. Original paper copies of the CRF will be safely stored according to Good Clinical Practice (GCP)

14. DATA ANALYSIS

14.1 Description of Analysis Populations

Analysis will be carried out on an intention to treat basis.

14.2 Analysis of Endpoints

The primary outcome, ADR, will be compared between groups using the Chi-square test. The difference in the proportion of patients with an adenoma detected between groups will be quantified, along with a corresponding 95% confidence interval.

Within both groups, a descriptive analysis of percentage of polyps correctly identified, relative to the histological diagnosis, will be reported.

For all detection outcomes, a series of sensitivity analyses will be performed, repeating the analyses, but this time only considering polyps in the CAD intervention group if they were correctly identified based on their histology.

Binary secondary outcomes will be analysed using the Chi-square test. Continuous secondary outcomes will be compared between groups using the unpaired t-test, if found to be normally distributed, or the Mann-Whitney test otherwise.

14.3 Procedure for Dealing with Missing, Unused and Spurious Data

We expect very little missing data due to non-response given the nature of the intervention in this study. If the amount of missing data is not significant, we will use listwise deletion (i.e. only subjects with complete data will be included in the full ITT primary analysis). If the amount of missing data is significant, we will use standard statistical/imputation methods to deal with that and minimise data loss.

14.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

The Trial Steering Committee will meet on a bi-annually basis. If it is felt that a deviation in the initial analysis is needed this will be discussed in the meeting to obtain consensus that this is the appropriate way forward. A substantial deviation (classified as a substantial amendment) will be reported and submitted to the ethics committee for approval.

15. ETHICS

15.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained throughout. No information will be disclosed or reproduced through which patients could be identified, except when reporting serious adverse events. Participants will be allocated a unique study number and all data will be collected against this number therefore no information such as name or date of birth is used. All study documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act (2018) which requires data to be anonymized as soon as it is practical to do so. It will also conform to Caldicott principles in full and comply with Portsmouth Hospitals University NHS Trust's confidentiality code of conduct.

15.2 Declaration of Helsinki

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).

15.2 Other Ethical Considerations

This study is not designed to alter standard treatment. The CAD device will be used as an adjunct to see if this enhances endoscopist experience, it is not designed to replace endoscopists. The endoscopist will still be expected to use their own clinical judgment. This will be made clear to patients in the PIS.

The trial will be carried out in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines, Research Governance Framework for Health and Social Care and World Association Declaration of Helsinki (1964) and Scotland (2000) amendments.

The study will not be initiated before the protocol and all study relevant material such as the informed consent forms and participant information sheets have received favourable opinion from the Research Ethics Committee (REC), Health Research Authority (HRA) and the respective National Health Service (NHS) Research & Development (R&D) departments. Any changes to protocol or relevant study documents will be approved by the Sponsor. Should an amendment be made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC is notified as soon as possible, and an approval is requested. Minor amendments as defined by REC as a non-substantial amendment, may be implemented immediately; and the REC will be informed.

15.3 ICH Guidelines for Good Clinical Practice

All research staff will be required to have up to date ICH GCP training and certification prior to commencing work on the study and throughout the study duration. The study will be monitored by the Sponsor according to the agreed risk-based monitoring plan to ensure adherence to GCP throughout.

16. PATIENT PUBLIC INVOLVEMENT (PPI)

This study was reviewed prior to NHS ethics submission by Portsmouth Hospitals University NHS Trust's Research Ambassador/PPI group. Feedback was received and no concerns were raised.

17. FINANCING AND INSURANCE

The trial is funded by NEC Corporation Japan. The Sponsor is Portsmouth Hospitals University NHS trust. The NHS indemnity scheme shall apply for the management, design and conduct of the study. The device has a CE mark.

The WISE VISION® system will be provided on long term loan to participating sites by NEC Japan.

18. STUDY SPONSORSHIP, MANAGEMENT & OVERSIGHT

Portsmouth Hospitals University NHS Trust shall act as Sponsor for the UK sites only. A research fellow will be responsible for overseeing the study and data collection, acting as the Trial Co-ordinator (TC). The TC will also be responsible for co-ordinating the set-up of the study at the international sites.

The study will also have a dedicated Trial Manager who will work alongside the Trial Co-ordinator to ensure the study runs efficiently and according to protocol and relevant Sponsor and study specific Standard Operating Procedures (SOPS).

A Trial Management Group (TMG) will convene quarterly and will oversee the day-to-day co-ordination and progress of the study. The TMG will consist of study representatives selected from the Chief Investigator which will include the Trial Co-ordinator (TC), Trial Manager (TM), and Research Nurses based at the lead/Sponsor site. The TM & TC will manage the project across all sites; ensuring co-ordination and communication between organisations. The TMG will be the primary point of contact for the study with responsibility for the delivery of approvals and permissions; initiation and training of sites, adverse event and progress reporting to the Sponsor and Trial Steering Committee (TSC), data collection, close-out procedures and archiving. The Trial Manager & Trial Co-ordinator will ensure all preparatory REC work is conducted, and coordinate NHS permissions with each UK site. All relationships and any delegation of duties will be formalised in written agreements facilitated by the Sponsor.

A Trial Steering Committee (TSC) will be set-up at the start of the study and shall convene to oversee the running and performance of the study against its key milestones at appropriate

intervals during the study. This committee will include an independent clinician as Chair of the committee, along with the Chief Investigator, independent clinicians, representatives from the TMG, Sponsor representatives and independent lay members. Safety events will be reviewed by the TSC with oversight and management of these by the Sponsor's research governance team.

19. TIMETABLE AND ORGANISATIONAL CHART

Timeline (months)	**1-3**	**3-6**	**6-9**	**9-12**	**12-18**	**18-24**
Study set up						
Protocol development						
Collaboration with PPI steering group						
Submission for ethics and R&D approval						
Recruitment						
Patient invitation and recruitment open at QAH						
Recruitment open at other sites						
Study closure						
Data Cleaning & Database Lock						
Analysis						
Data analysis						
Dissemination at conferences						
Publication in peer reviewed journals						

20. RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

Additional equipment required for the trial, such as the WISE VISION® device and software, will be provided directly by NEC on long term loan to each recruiting site.. The existing endoscopy department equipment at each participating site will be utilised as part of standard care. A research team consisting of nurses and research fellows are employed for trial

management and data collection. Designated office space is available for work to be carried out.

21. DISSEMINATION AND OUTCOME

The result of this RCT will be presented at national and international conferences. Work will be submitted for publication in peer review journals.

22. REFERENCES

1. Wardener de, Hill B C Morson H J R Bussey MJ. AEITIOLOGY OF ADENOMA-CARCINOMA SEQUENCE IN LARGE BOWEL. Vol. 9, Bio-chem. Pharmac. 1973.
2. Sparks AB, Morin PJ, Vogelstein B, Kinzler KW. Mutational Analysis of the APC/β-Catenin/Tcf Pathway in Colorectal Cancer. Cancer Research. 1998;58(6).
3. de Palma FDE, D'argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F. The molecular hallmarks of the serrated pathway in colorectal cancer. Vol. 11, Cancers. 2019.
4. Leslie A, Carey FA, Pratt[2] NR, Steele RJC, Leslie MA. The colorectal adenoma±carcinoma sequence [Internet]. Vol. 89, British Journal of Surgery. 2002. Available from: www.bjs.co.uk
5. H D, GR B, C C, P S, S E, S C, et al. Mutations of the BRAF gene in human cancer. Nature [Internet]. 2002 Jun 27 [cited 2021 Oct 26];417(6892):949–54. Available from: https://pubmed.ncbi.nlm.nih.gov/12068308/
6. Rees CJ, Gibson ST, Rutter MD, Baragwanath P, Pullan R, Feeney M, et al. UK key performance indicators and quality assurance standards for colonoscopy. Available from: http://gut.bmj.com/
7. Heresbach D, Barrioz T, Lapalus MG, Coumaros D, Bauret P, Potier P, et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back−to−back video colonoscopies.
8. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: A systematic review. Vol. 101, American Journal of Gastroenterology. 2006. p. 343–50.
9. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma Detection Rate and Risk of Colorectal Cancer and Death. http://dx.doi.org/101056/NEJMoa1309086 [Internet]. 2014 Apr 2 [cited 2021 Oct 26];370(14):1298–306. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1309086
10. Bhandari P. Polyp cancers: Size matters! Vol. 51, Endoscopy. Georg Thieme Verlag; 2019. p. 407–8.
11. Ponugoti PL, Cummings OW, Rex DK. Risk of cancer in small and diminutive colorectal polyps. Digestive and Liver Disease. 2017 Jan 1;49(1):34–7.

12. Ignjatovic A, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. Lancet Oncol [Internet]. 2009 Dec [cited 2022 Mar 24];10(12):1171–8. Available from: https://pubmed.ncbi.nlm.nih.gov/19910250/

13. Rees CJ, Rajasekhar PT, Wilson A, Close H, Rutter MD, Saunders BP, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. [cited 2022 Mar 24]; Available from: http://www.stard-statement.org

14. KO T, RM G, A S. Lesions of All Types Exist in Colon Polyps of All Sizes. Am J Gastroenterol [Internet]. 2018 Feb 1 [cited 2021 Oct 26];113(2):303–6. Available from: https://pubmed.ncbi.nlm.nih.gov/29231190/

15. Ebigbo A, Palm C, Probst A, Mendel R, Manzeneder J, Prinz F, et al. A technical review of artificial intelligence as applied to gastrointestinal endoscopy: clarifying the terminology. Endoscopy International Open. 2019 Dec;07(12):E1616–23.

16. Yamada M, Saito Y, Imaoka H, Saiko M, Yamada S, Kondo H, et al. Development of a real-time endoscopic image diagnosis support system using deep learning technology in colonoscopy. Scientific Reports. 2019 Dec 1;9(1).

17. Product Information: WISE VISION | NEC [Internet]. [cited 2022 Mar 28]. Available from: https://www.nec.com/en/global/wisevision/products.html

18. Yamada M, Saito Y, Imaoka H, Saiko M, Yamada S, Kondo H, et al. Development of a real-time endoscopic image diagnosis support system using deep learning technology in colonoscopy. Scientific Reports 2019 9:1 [Internet]. 2019 Oct 8 [cited 2022 Mar 29];9(1):1–9. Available from: https://www.nature.com/articles/s41598-019-50567-5