Short Title: Computer Aided Diagnosis and Detection for Intelligent Endoscopy

Clinical Investigational Plan (CIP) summary for Medical Device Studies

Full title of Investigation:	Multi-Centre, open-label, randomised, prospective trial to assess efficacy and safety of the CADDIE artificial intelligence system for improving endoscopic quality
Short title:	CADDIE Trial - Computer Aided Diagnosis and Detection for Intelligent Endoscopy
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Short Title: Computer Aided Diagnosis and Detection for Intelligent Endoscopy

Title:	Multi-Centre, open-label, randomised, prospective feasibility trial to assess efficacy and safety of the CADDIE artificial intelligence system for improving endoscopic quality.
Short title:	CADDIE Trial - Computer Aided Diagnosis and Detection for Intelligent Endoscopy.
Device:	CADDIE
Primary objectives:	To determine whether the CADDIE artificial intelligence system improves endoscopic detection of adenomas during colonoscopy.
Secondary objectives:	1. Evaluate the difference in number of adenomas detected per colonoscopy between intervention and non-intervention arm. 2. To determine whether the CADDIE artificial intelligence system improves endoscopic detection of all polyps during colonoscopy. 3. To determine whether the CADDIE system improves the accuracy of endoscopist optical diagnosis of diminutive polyps (≤5mm). 4. To determine whether using the CADDIE system improves the accuracy in assigning colonoscopy surveillance intervals. 5. To determine whether using the CADDIE system improves the accuracy of endoscopist optical diagnosis of diminutive (≤5mm) rectal polyps. 6. Evaluate the safety of the CADDIE in clinical application. 7. Assess integration of CADDIE into normal colonoscopy clinical workflow.
Type of Investigation:	Multi-Centre, open-label, randomised, prospective study.
Investigation design and methods:	The CADDIE system comprises a *computer* attached to the output of the endoscopy stack which detects polyps using an AI software and a *screen* which shows the normal video output of the colon in real-time with an overlay highlighting the presence and location of the polyp. The CADDIE device is capable of recording the video output of the colon in real time irrespective of whether the CADDIE's AI polyp detection system is active. In the run-in phase, we will verify individual endoscopists adenoma detection rates (ADR). We will then confirm their ADR by either extending the number of colonoscopies analysed to calculate their initial retrospective ADR or an additional prospective series of colonoscopies to calculate a confirmed ADR.

In the study phase of the trial, the endoscopists will be kept the same for the interventional and non-interventional arm. At the beginning of each procedure, patient information will be entered into an electronic system which will generate a random allocation into one of two arms (interventional and non-interventional arm). The intervention involves a colonoscopy assisted by the CADDIE system. The non-intervention (control) is a colonoscopy without the CADDIE system (i.e. standard practice). Each endoscopist will have the CADDIE device present during all endoscopy lists for the purpose of recording the colonoscopy. The CADDIE system (i.e. AI polyp detection function) will only be active in the interventional arm.

In both arms of the trial, for each polyp the endoscopist detects, they will:

1. *Measure polyp size, capture images, and optically diagnose polyp*
   For polyps measured to be <10mm, the endoscopist will capture a still image of the polyp in both white light and NBI (in NBI-near focus, if available) or equivalent imaging modality to NBI. The endoscopist will proceed with optical diagnosis of the polyp (noting whether they have high or low confidence in the diagnosis).
2. *Resect diminutive polyps*
   Management of rectal hyperplastic polyps will be standardised. Rectal polyps optically diagnosed by the endoscopist will be resected/biopsied. If multiple rectal hyperplastic polyps are optically diagnosed by the endoscopist, a minimum of 5 will be resected/biopsied for histopathology.
3. *Label each polyp resected*
   Each polyp resected (regardless of size) must be labelled according to instructions of the Specimen Handling SOP. Each unique polyp ID will need to be logged in chronological order on a per colonoscopy basis and sent for histopathology. Histopathology will be referenced as the gold standard for polyp diagnosis and characterisation.

In the intervention arm, the endoscopist will use the normal endoscopy video system including the standard screen. When the CADDIE system detects a possible polyp, it will simultaneously sound an alarm and overlay the area of interest on the endoscopy screen with a bounding box. The endoscopist will then inspect the mucosal area. If it is deemed to be a polyp, the endoscopist will follow the steps documented above. When an image of the polyp is captured in NBI mode, the endoscopist will press on the foot pedal to reveal the CADDIE's polyp characterisation. Using this information and the endoscopist own assessment, the endoscopist will log an optical diagnosis of the polyp and confidence in diagnosis (high or low) on a paper case report form (CRF). The optical diagnosis will be assessed against the polyp's histopathology.

On three occasions, the endoscopist will complete a brief questionnaire regarding their views on safety and efficacy of the system and how they feel it affected performance. The endoscopy nurses in the interventional arm will complete the

	questionnaire once. Each patient will also complete a questionnaire to ascertain their experience. The ADR for each endoscopist will be calculated in the run-in phase. Selected endoscopists will be invited to proceed with the study phase of the trial. In the study phase, we will compare endoscopist ADR between the non-intervention and intervention arms. This will allow us to evaluate whether the process of using AI software improves endoscopist ADR. Safety of the device will be assessed through monitoring of adverse events. Acceptability will be assessed through a qualitative questionnaire for the endoscopist, endoscopy nurse and patient in addition to measuring endoscopy markers such as caecal intubation time, procedural time, withdrawal time.
Investigation duration per participant:	From written consent to completion of questionnaire.
Estimated total investigation duration:	3 years
Planned Investigation sites:	University College London Hospitals NHS Foundation Trust Cambridge University Hospitals NHS Foundation Trust West Hertfordshire Hospitals NHS Trust Barts Health NHS Trust Surrey and Sussex Healthcare NHS Trust Imperial College Healthcare NHS Trust The Princess Alexandra Hospital NHS Trust Bradford Teaching Hospitals NHS Foundation Trust Sheffield Teaching Hospitals NHS Foundation Trust
Total number of participants planned:	654 subjects will be enrolled in the study-phase of the trial. As per the data monitoring committees (DMC) recommendation following the interim analysis, this has been increased to 766 subjects.
Main disease/area:	Main disease: Colorectal Polyps Main area: Colon and Rectum
Main inclusion/exclusion criteria:	**Inclusion Criteria**: - Participants scheduled to undergo a surveillance or symptomatic colonoscopy with an endoscopist participating in the study phase of the trial. - Male and female participants aged 18 years or older at the time of informed consent.

- Participants able to comprehend, sign and date the written informed consent document to participate in the study.

Exclusion criteria:

- Emergency and/or inpatient colonoscopies
- Patients with inflammatory bowel disease (IBD)
- Patients with current Colorectal Cancer (CRC)
- Patients with previous CRC
- Patients with previous colonic resections
- Polyposis syndrome
- Patients returning for a planned elective therapeutic colonoscopy.
- Current or relevant history of a physical or psychiatric illness or any medication condition that in the opinion of the investigator could affect the patient's safety or interfere with the study assessments.
- Patients with a contraindication for biopsy or polypectomy. These include:
    - Patients who have not withheld medications pre-disposing to bleeding at time of colonoscopy as per local site /national guidelines.
    - Patients with a history of haemostasis disorders (Haemostasis disorders will include but will not be limited to: patients with haemophilia or other congenitally acquired clotting factor deficiencies, patients with cirrhosis with coagulopathy, patients known to have thrombocytopenia (<80,000 platelet/ul) and individuals with Von Willebrand's disease or other known platelet malfunction disorders)
- Patients is enrolled in another research study with an investigational medicinal product (IMP) or non-IMP that pre-disposes them to bleeding.

Statistical methodology and analysis:

We aim to recruit 327 subjects per arm to detect a 10% difference in ADR (from 20% to 30%) between the two arms, using a two-group z-test with 80% power, a two-sided α level of 0.05, and accounting for an expected dropout rate of 10%. Thus, the total planned sample size consists of 654 patients in the study phase of the trial. As per the DMC recommendation following the interim analysis, the dropout rate has been increased to 15% and an additional 66 patients are to be recruited to account for local technical issues encountered during the initial recruitment of 66 patients across two sites. The total planned sample size therefore consists of 766 patients.

The difference in the primary outcome measure between the intervention and control groups will be estimated using regression models. Significance will be considered at the 5% level and confidence intervals will be at the 95% level. Secondary outcomes will also be assessed by means of appropriate regression models depending on the nature of the outcome.