EAGLE TRIAL

EVALUATION OF AI FOR DETECTION OF GASTROINTESTINAL LESIONS IN ENDOSCOPY (EAGLE)

Sponsor

ODIN MEDICAL Ltd.

(Trading as ODIN VISION)

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Confidentiality Statement

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1. PROTOCOL SIGNATURE PAGE

STUDY TITLE EVALUATION OF AI FOR DETECTION OF GASTROINTESTINAL LESIONS IN ENDOSCOPY (EAGLE)

Sponsor's Statement:

The Principal Investigator (CI) and the Sponsor have discussed this Clinical Investigation Plan (CIP). The investigator agrees to perform the investigation and to abide by this CIP.

The investigator agrees to conduct the Investigation in compliance with the approved CIP, EU Good Clinical Practice (GCP), ISO 14155, the Medical Device Regulation 2017/745 and UK Regulations for Devices (SI 2002/618; as amended), the UK Data Protection Act (2018), the General Data Protection Regulation 2016/679 (GDPR), the Trust Information Governance Policy (or other local equivalent), the UK policy framework for health and social care research, and other regulatory requirements as amended.

I have reviewed and approved this protocol in its entirety, agree to sponsor its implementation, and will ensure that the study is conducted in a scientific and ethical manner.

The clinical investigation shall not commence recruitment until all relevant ethics, regulatory and local approvals are received. All additional requirements imposed by the responsible Ethics Committees or regulatory authorities will be followed.

Signature Signature Date

_____ _____

PETER MOUNTNEY
Chief Executive Officer
ODIN Medical Ltd

Principal Investigator **Site**
Printed Name & Title

_____ _____

Signature Date

_____ _____

Co-Investigator (if applicable)
Printed Name & Title

_____

Signature Date

_____ _____

2. IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN

Study Title	EVALUATION OF AI FOR DETECTION OF GASTROINTESTINAL LESIONS IN ENDOSCOPY (EAGLE)
Study Acronym	EAGLE Trial
Reference Number	RCT-2022-01
Version and Date	Version 1.3 18 April 2023
EUDAMED	CIV-23-02-042352
Clinicaltrials.gov	NCT05730192
Sponsor:	ODIN MEDICAL Ltd. Contact Person: Peter Mountney, CEO Email: petermountney@odin-vision.com
Medical device:	CADDIE
Regulatory Status:	CE Marked in Europe.
EU Authorized Representative	Psephos Limited ATU iHub Galway, Dublin Road, Galway H91 DCH9, Ireland jhargreaves@psephos.com https://www.psephos.com/
Contract Research Organization:	Meditrial Europe Ltd. (Europe) / Meditrial USA Ltd. (USA) Contact Person: Dr. Monica Tocchi, Founder and CMO E-mail: m.tocchi@meditrial.net

Protocol Revision History

Version	Date	Summary of Changes
1.0	22 Dec. 2022	Initial release.
1.1	03. Mar. 2023	Explanation of baseline clinical assessment
1.2	10. Mar. 2023	Added NCT number (NCT05730192) Clarification of screening and informed consent process (section 3.1, schedule of assessments; section 9.2, informed consent process; and section 9.5.1, pre-colonoscopy assessment)
1.3	18 Apr. 2023	Added EUDAMED number. Modified wording of Inclusion Criterion #3 for clarity. Added exclusion criterion #12. Added 10.1 Anticipated benefits. Added in 13.3, definition of serious adverse event (Art. 2 No. 58 of Regulation (EU) 2017/745). Added 15.3 Study termination criteria.

List of Abbreviations

ACPGBI	Association of Coloproctology of Great Britain and Ireland
ADE	Adverse Device Effect
ADR	Adenoma Detection Rate
AE	Adverse Event
AI	Artificial Intelligence
APC	Adenomas Per Colonoscopy
BBPS	Boston Bowel Preparation Score
CA	Competent Authority
CAD	Computer Aided Diagnosis
CADDIE	Computer Aided Diagnosis and Detection for Intelligent Endoscopy
CE	Conformité Européenne
CIP	Clinical Investigation Plan
CNN	Convolutional neural network
CT	Computer Tomography
EC	Ethics Committee
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
CRC	Colorectal Cancer
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FIT	Faecal Immunochemical Test
FOBT	Fecal Occult Blood Test
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal
HDWL	High-definition white light
IBD	Inflammatory Bowel Disease
ISO	International Standard Organization
MDR	Medical Device Regulation 2017/745
MRMC	Multiple Reader Multiple Case
PI	Principal Investigator
PIS	Participant Information Sheet
PPA	Positive Percent Agreement
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Control Trial
ROC	Receiver Operating Characteristic
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSL	Sessile Serrated Lesion
TI	Terminal Ileum
TMC	Trial Management Group
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization

3. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Study Acronym	**EAGLE**
Protocol Title	**E**VALUATION OF **AI** FOR DETECTION OF **G**ASTROINTESTINAL **L**ESIONS IN **E**NDOSCOPY
Manufacturer, **Sponsor**	**ODIN MEDICAL Ltd** Charles Bell House, 43-45 Foley Street, London, W1W 7TS, UK
Medical Device	**CADDIE** CADDIE is a computer-assisted detection (CADe) device used in conjunction with endoscopy for the detection of abnormal lesions in the gastrointestinal tract. The device's advanced software algorithms bring attention to relevant images in order to aid the endoscopist in the detection of lesions. List of compatible endoscopes/equipment for EAGLE study: Olympus CF-HQ190L/I, CF-H190L/I, PCF-H190L/I, PCF-H190TL/I, PCF-PH190L/I, PCF-HQ190L/I, CF-HQ1100DL/I, CF-EZ1500DL/I List of compatible image processors for EAGLE study: Olympus X1 CV-1500
Indications for Use/Intended Purpose	CE Marked Intended Purpose: The CADDIE system is intended to be used by trained clinicians (users) as an accompaniment to video Endoscopy for the purpose of drawing attention to regions with visual characteristics consistent with different types of mucosal abnormalities. CADDIE is trained to process colonoscopy video frames that may contain regions consistent with colorectal lesions like polyps, including diminutive and flat polyps. CADDIE can analyse the visual characteristics and provide information to aid the user to characterize the tissue. This information is interpreted by the user and appropriate actions taken according to the standard clinical practice. Note: Availability of CADDIE's characterization feature depends on individual user configuration. The characterization feature will not be available during the EAGLE clinical investigation (which is focused on detection). Proposed US Indications for Use: The CADDIE computer-assisted detection device is intended to assist the gastroenterologist in identifying suspected colorectal polyps only. The gastroenterologist is responsible for reviewing CADDIE suspected polyp areas and confirming the presence or absence of a polyp based on their own medical judgment. CADDIE is not intended to replace a full patient evaluation, nor is it intended to be relied upon to make a primary interpretation of endoscopic

	procedures, medical diagnosis, or recommendations of treatment/course of action for patients. CADDIE has not been cleared by the FDA for sale in the US.
Study Objective	The EAGLE study is a prospective randomized controlled multicenter parallel design trial, for the assessment of clinical performance of the CADDIE device and to confirm that the device performs as expected.
Study Type	Prospective, Multi-Centre, Randomized Controlled, Parallel Design Study
Study Arms	The study will comprise two arms, with 1:1 randomization: 1. CADDIE colonoscopy (CADDIE Arm) 2. Standard high-definition white light colonoscopy (Control Arm)
Endoscopist Qualification	The study will only involve qualified endoscopists who have an ADR equal or above 25% and have completed a minimum of 1000 colonoscopies, as previously reported in other CADe studies. ADR ≥25% is an overall benchmark established by the American Society for Gastrointestinal Endoscopy and American College of Gastroenterology Task Force on Colonoscopy Quality.[1] All participating endoscopists will be trained in the use of the CADDIE device and in all the requirements of the study.
Study Design	The EAGLE study will be conducted with a parallel design. Patients who meet the study inclusion/exclusion criteria will be randomized in a 1:1 ratio to receive either computer-aided colonoscopy (CADDIE Arm) using CADDIE or standard colonoscopy without CADe (Control Arm). All resected polyps will be submitted for histologic examination.
Co-Primary Endpoints	The study is powered to allow for the assessment of two co-primary endpoints: 1. **Adenoma per Colonoscopy (APC)**. Superiority of CADDIE Arm vs. control. Where APC is the total number of histologically confirmed adenomas and adenocarcinomas divided by the total number of colonoscopies. 2. **Positive percent agreement (PPA).** Non inferiority of CADDIE Arm vs. control. Where PPA is the percent of histologically confirmed adenomas, sessile serrated lesions, and large (>10mm) hyperplastic polyps of the proximal colon (caecum, ascending colon, hepatic flexure, and transverse colon) out of total number of resections.
Secondary Endpoints	1. **Adenoma Detection Rate (ADR)** defined as the percentage of examinations with adenomas divided by total number of examinations. 2. **Sessile serrated lesions detected,** defined as the total number of polyps with histology of serrated adenoma, traditional serrated adenoma or serrated lesion with cytological dysplasia, excluding hyperplastic polyps. 3. **Colonoscope withdrawal time**, defined as the time it takes to withdraw the colonoscope from the furthest point (TI or caecum) back to the rectum. (Withdrawal times should be targeted to a minimum of 6 minutes.)

	4. **Total procedure time**, recorded as the entire duration of the procedure. 5. **Rate of adverse events**, recorded as the rate of adverse events related to the procedure for the duration of the study colonoscopies, for each study arm.
Statistical Sample Size	To satisfy both co-primary endpoints (APC and PPA), the sample size is selected as the highest between the two endpoints. We aim to recruit 860 subjects in total (430 per arm) to detect an absolute increase of 0.19 in APC (from 0.83 w/o CADe to 1.02 with CADe) between the two arms, using a two-group z-test with 80% power, a one-sided α level of 0.025. Accounting for an expected dropout rate of 10%, the total planned sample size consists of a total of 946 patients. Details of statistical assumptions, sample size calculation methods and methodologies are provided in Section 5 below.
Patient Selection	Patients who sign an informed consent are evaluated for eligibility. Patients who meet all study inclusion/exclusion criteria will be included in the study
Inclusion Criteria	1. Patients scheduled to undergo a screening or surveillance colonoscopy with a qualified endoscopist. (Surveillance colonoscopy; colonoscopy in subjects who have had one or more adenomatous polyp detected in a colonoscopy more than 3 years prior to the study) 2. Age 40 years or older at the time of informed consent. 3. The patient has been informed of the nature of the study and agrees to it's provisions and has provided written informed consent on a form, 4. Not more than 20 percent of patients who have undergone FIT or FoBT are allowed to randomization.
Exclusion Criteria	1. Emergency colonoscopies and/or inpatient colonoscopies. 2. Patients with inflammatory bowel disease (IBD) 3. Patients with Colorectal Cancer (CRC) 4. Patients with previous Colorectal Cancer (CRC) 5. Patients with previous colonic resection 6. Patients returning for a planned elective therapeutic colonoscopy. 7. Polyposis syndromes (familial adenomatous polyposis) 8. Patients with a contraindication for biopsy or polypectomy. These include: a. patients who have not withheld medications pre-disposing to bleeding at time of colonoscopy (antiplatelet agents, anticoagulants). b. Patients with a history of haemostasis disorders. 9. Surveillance colonoscopy where the last colonoscopy was performed less than 3 years before the scheduled colonoscopy 10. Patients undergoing diagnostic colonoscopy with high-risk indications including iron deficiency anemia, abnormal CT imaging, unexplained weight loss, Lynch Syndrome; 11. Patient is enrolled in another research study 12. Patients who have been placed in an institution on the basis of an official or judicial order

Histologic Examination	The resected polyps will be submitted for histologic examination by the gastroenterology pathologists at each site. Lesions will be classified according to World Health Organization (WHO) classification of tumors of the digestive system, 5th edition, 2019. [2, 3]
Planned Investigation Sites	Up to 10 investigational sites. 100% Europe. Sites must have the study endoscope
Estimated Study Duration	First patient in: Q1/2023 Enrollment completion: Q3/2023 Enrollment period: 9 months (80-120 patients per month) Enrollment per site: Up to 150 patients Enrollment rate: 5 to 12 patients per site per month Planned study end: Q3/2023
Justification of endpoint assumptions	Various studies were evaluated to select the APC value in the control group, as shown in Table 1. Based on an expected patient mix of screening ~66% and surveillance ~34%, the average value of APC in the control group was set at 0.83 and the APC difference with the CADe arm was estimated at 0.19.
Statistical Hypothesis	**APC statistical tests are defined as follows:** H0: APC of the active arm is lower or equal to the APC of the control arm (≤) H1: APC of the active arm is higher than the APC of the control arm (>) **PPA statistical tests are defined as follows:** H0: PPA of the active arm is higher or equal to the sum of PPA of the control arm and a safety margin Δ (≥) H1: PPA of the active arm is lower than the sum of PPA of the control arm and a safety margin Δ (<)
Assumptions for sample size	**APC Sample Size Computation:** ● One-tailed test for superiority of CADe versus standard colonoscopy ● Mean estimated APC value of the control arm: 0.83 (consistent with SKOUT, see Appendix 1); ● Expected difference with CADe: 0.19 ● Statistical test: z-test with two arms ● Significance level a is set to 0.025 ● Power: >80%. ● Sample size: 430 patients per arm ● Increase of 10% for attrition: total 946 patients **PPA Sample Size Computation:** The following methodology was applied for the PPA sample size simulations: ● Mean value of the control arm: 75.7% as reported in SKOUT 510(k) ● Non-inferiority margin: (15%) ● Statistical test: Wilcoxon test ● Significance level a is set to 0.025 ● One-tailed test for non-inferiority of CADe versus and standard colonoscopy

	● Power: > 80% ● Sample size: 125 patients per arm
Randomization methods	Randomization will be stratified by patients' age, sex and colonoscopy indication, to avoid bias related to patient characteristics.

Table 1. Studies Evaluated for Selection of APC reference value in Control Group

CADe Device	Population	Control APC	AI APC	Increase	% Increase
Skout A. Shaukat *et al*. 2022 [4]	Screening + Surveillance	0.83	1.05	0.22	26.51%
	Screening	0.67	0.85	0.18	26.87%
	Surveillance	1.17		0.24	20.51%
GI Genius RCT A. Repici *et al.* 2020[5]	23% Screening 25% Surveillance 30% FIT 22% Symptomatic	0.71	1.07	0.36	50.70%
Fujifilm RCT E. Rondonotti *et al.* 2022 [6]	FIT screening study	0.9	1.13	0.23	25.56%
Magentiq Eye M. Maas, 2022 [7]	Screening + Surveillance	0.51	0.7	0.19	37.25%

3.1. Schedule of Assessments

Table 1. Schedule of Assessments

Assessments	Baseline	Index Procedure	Post-colonoscopy
Study Windows	Up to one week	CADe or Standard Colonoscopy	24 hours
Patient Screening[1]	X		
Informed Consent[2]	X		
Inclusion/Exclusion Criteria	X		
Patient Hx & Meds[3]	X		
Randomization[4]		X	
Colonoscopy (CADe or HDWL)[5]		X	
Histopathology[6]		X	
Adverse Events		X	X

1 Patient screening is based upon routine patient care performed after the study patients are referred for colonoscopy. The following assessments are collected as part of routine care: demographic information (age, gender), medical history, gastrointestinal disease history, concomitant diseases, and medications assessment, physical examination and ASA Score based on the pre-operative health status. **See section 9.5.1 for details.**

2 On the day of the colonoscopy, subjects will be consented for enrolment in the study. Adequate time must be given for consideration by the patient before taking part. It is expected that an information leaflet will be sent to the patient by post or email within 7 days of the colonoscopy, and more than 24 hours prior to the colonoscopy. In some instances, patients may consent on the day of the procedure as it is common that endoscopy procedures are scheduled or rescheduled at short notice. In such instance, the PI or a GCP certified member of the local research team may offer the patient entry to the study at the time that consent is taken for the procedure itself. This must be undertaken outside the endoscopy room. **See section 9.2 for details.**

3 If patients meet study criteria and provide consent to participate, the data obtained during the routine pre-colonoscopy examination will be collected. This includes demographics and pre-colonoscopy clinical parameters, as available. In addition, ethnicity and race data will be collected as part of the study, as colorectal cancer risk is affected by these factors.

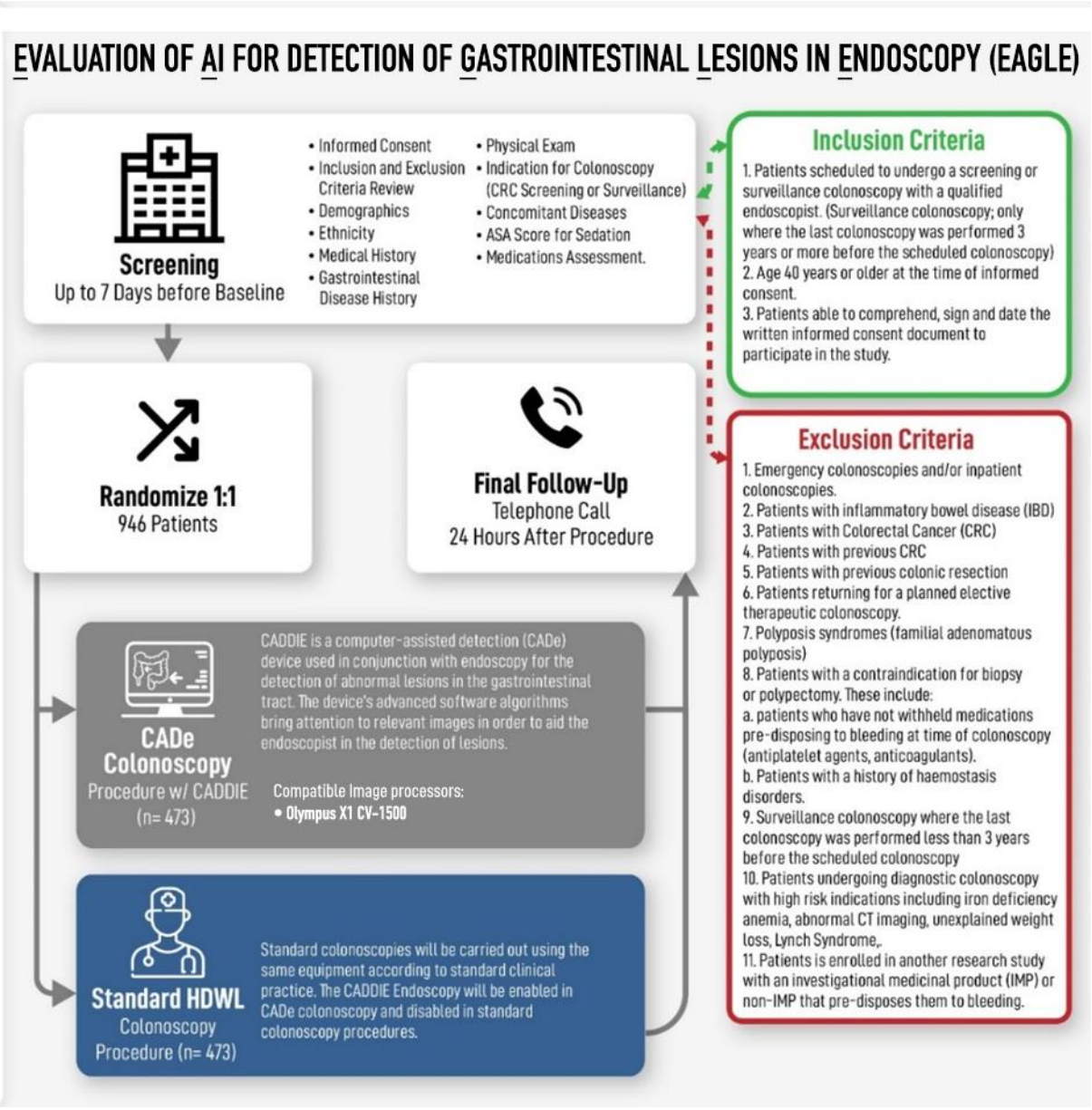
4 Patients will undergo either standard colonoscopy or CADDIE colonoscopy (randomization 1:1).

5 Both colonoscopies will be carried out using the same equipment according to standard clinical practice. The CADDIE AI system will be enabled in CADe colonoscopy and disabled in standard colonoscopy procedures.

6 All polyps, with the exception of hyperplastic rectosigmoid polyps <5mm, will be excised. Biopsies will be taken for non-resectable lesions, unless they are >2cm or where an endoscopic mucosal resection is expected. In these situations, biopsies are relatively contraindicated. Histopathology will be performed by the site pathologists, in accordance with the WHO classification of tumors of the digestive system, 5th edition, 2019. **See section 9.5.3 for details.**

3.2. Study Flowchart

Figure 1. Study Flowchart

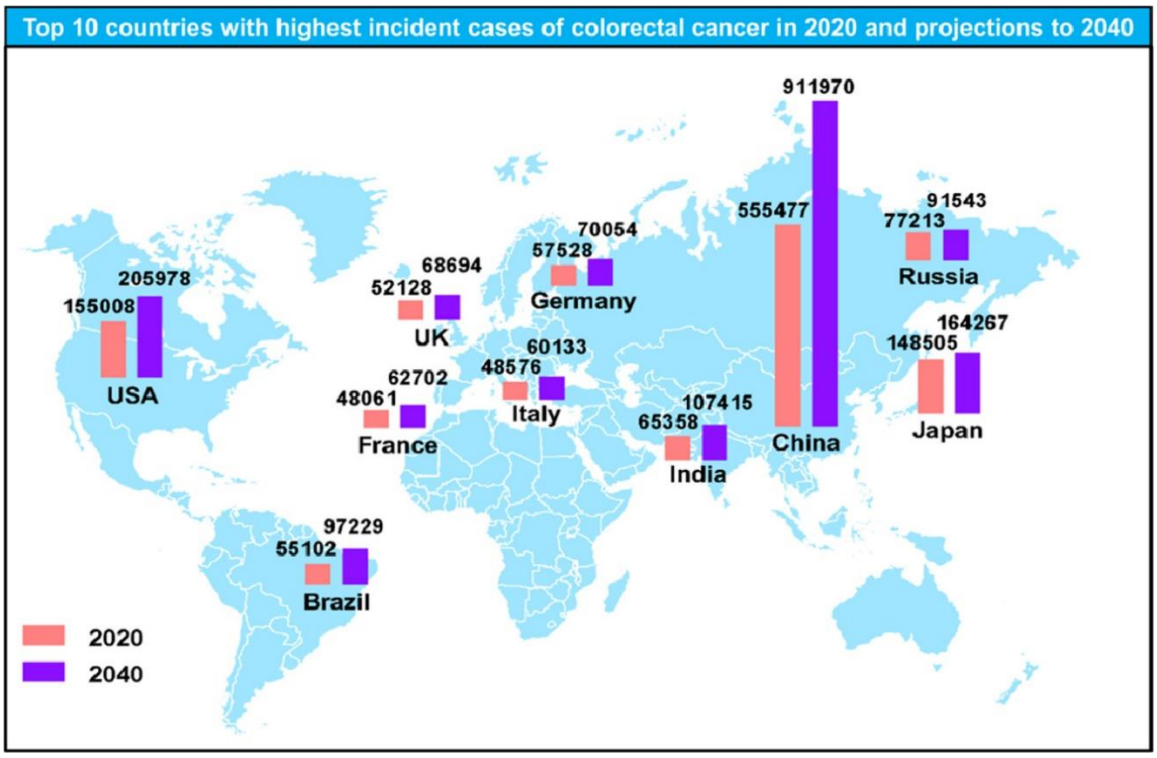


4. INTRODUCTION

4.1. Colorectal Cancer (CRC) Epidemiology

Colorectal Cancer (CRC) is the third most common cancer in both males (13% of all new male cancer cases) and females (10% of all new female cancer cases). [1] CRC is the second leading cause of cancer-related death worldwide. In 2020, CRC accounted for 10% of global cancer incidence and 9.4% of cancer deaths, just lower than lung cancer that comprises 18% of deaths. The global number of new CRC cases is predicted to reach 3.2 million in 2040, based on the projection of aging, population growth, and human development. [2]

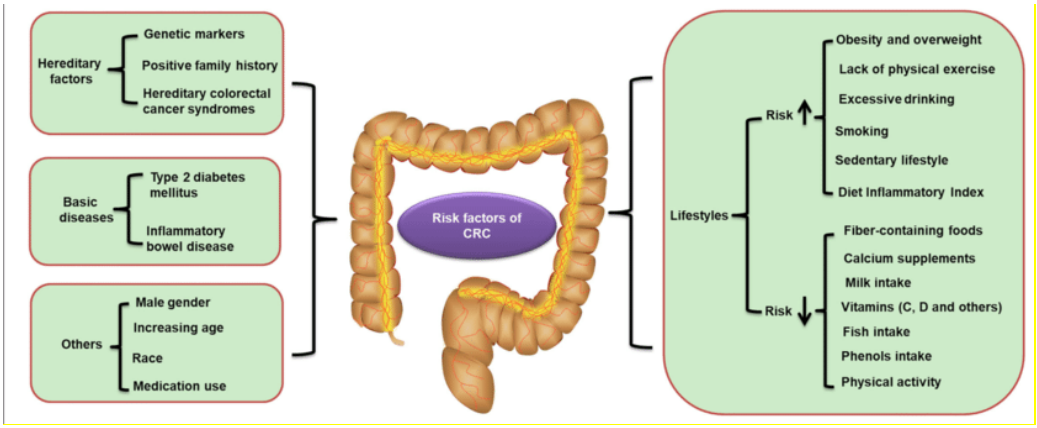
Figure 2. Global colorectal cancer burden in 2020



Source: Global colorectal cancer burden in 2020 and projections to 2040 [2]

The increase in CRC incidence is mainly attributed to the elevated exposure to environmental risk factors resulting from shifting lifestyle and diet toward westernization. In addition, male sex, increasing age, race, and medical intake have also been demonstrated to play critical roles in the progression and development of CRC (Figure 3). [3]

Figure 3 Risk Factors Associated with CRC



There are several options to screen for colorectal cancer, each with a different level of evidence demonstrating its ability to reduce cancer mortality, its ability to detect cancer or precursor lesions, and its risk of harms. [4]

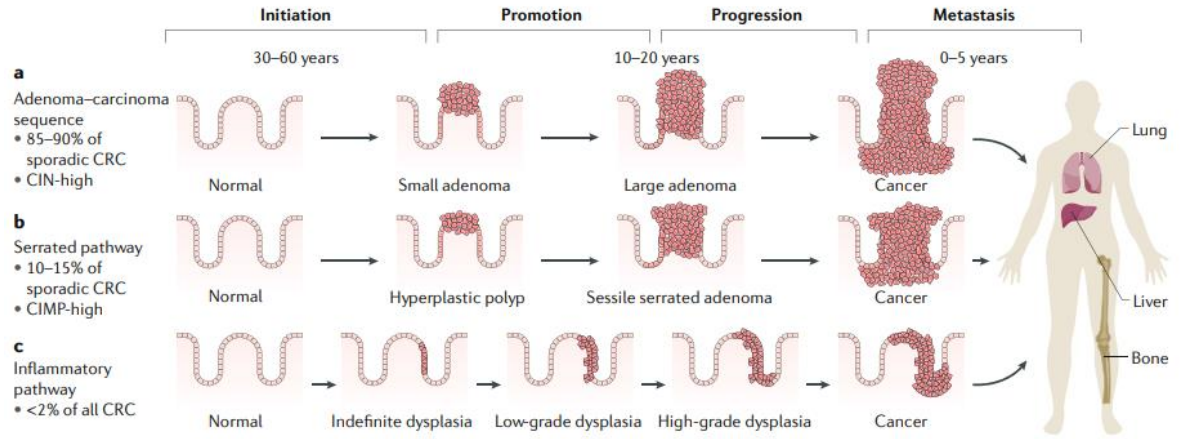
Most CRCs develop from adenomatous polyps, with colonoscopy accepted to be the gold standard for screening of CRC. [5, 6] In the UK, patients found to have adenomas are enrolled in a colonoscopy surveillance programme for surveillance of further polyps/CRC. Surveillance interval is calculated from the polyp's size, histology and the number of polyps detected during the patient's last colonoscopy. [7]

4.2. CRC Pathogenesis

Generally, CRC is considered to be developed from colorectal adenomatous polyps through the adenoma-carcinoma process. Therefore, early and timely removal of polyps and adenomas is of great significance to the prevention of CRC.

Colorectal carcinogenesis occurs through four stages: initiation, promotion, progression and metastasis (the liver is the most common metastatic site, followed by the lung and bone). Although the time span of each stage is difficult to estimate, decades are required for all stages to be completed. CRCs arise through distinct carcinogenic pathways: adenoma–carcinoma sequence, serrated pathway and inflammatory pathway.

Figure 4. Pathways of Colorectal Carcinogenesis.



a. Adenoma–carcinoma sequence. This classic pathway explains the majority of sporadic CRC. Normal cells progress to small adenoma, to large adenoma and, finally, to cancer. This pathway is predominantly associated with the development of the chromosomal instability (CIN)-positive subtype.

b. Serrated pathway. Accounting for 10–15% of sporadic CRC, this model is characterized by the progression from normal cells, to hyperplastic polyp, to sessile serrated adenomas and, finally, to cancer. The CpG island methylator phenotype (CIMP)-high subtype frequently arises from this pathway.

c. Inflammatory pathway. Driven by chronic inflammation, normal cells progress to indefinite dysplasia, to low-grade dysplasia, to high-grade dysplasia and, finally, to cancer. Due to the low incidence of inflammatory bowel diseases and treatment with prophylactic colectomy, this pathway explains less than 2% of all CRC. For all pathways, albeit more notable in the adenoma-carcinoma and serrated pathways, there are benign precursor lesions that are accessible and removable; because they take years to progress into cancer, there is a window of opportunity for secondary prevention of CRC.

4.3. Colonoscopy in CRC

Colonoscopy remains to be the gold standard test for CRC screening since it can detect and remove pre-cancerous lesions in the colon and decrease the mortality and morbidity of CRC in adults.[8] A colonoscopy is the most common endoscopic procedure. Because its use has turned mostly toward the prevention of colorectal cancer, there has been a relative decrease in its overall diagnostic yield.[9]

Adenoma detection rate (ADR) is one of the most important quality indicators in colonoscopy, and is known to be inversely correlated with the incidence of post-colonoscopy CRC and related mortality. [10]

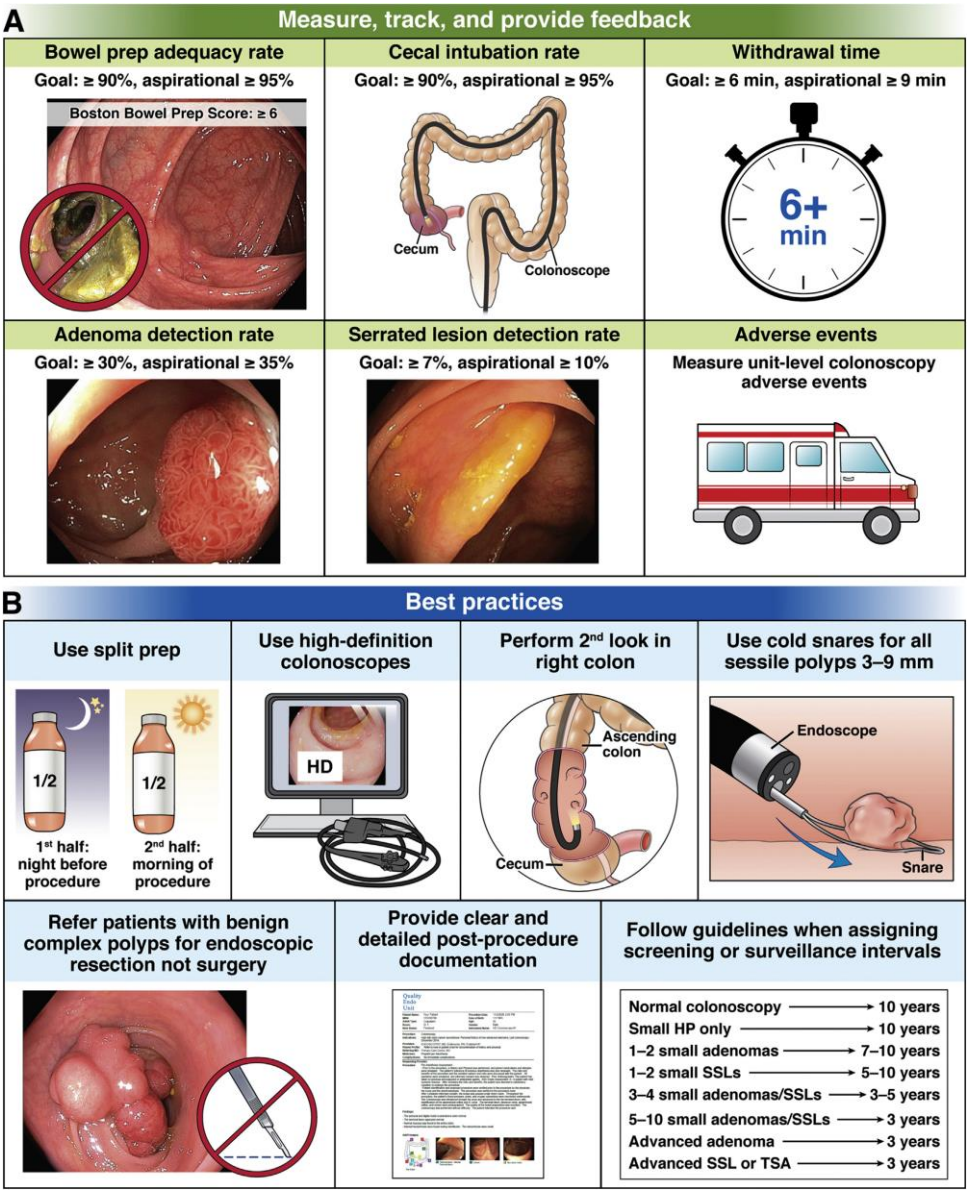
Key components of high-quality colonoscopy include ensuring effectiveness (detecting CRC and its precursors), safety (minimizing adverse events), and value (avoiding unnecessary costs). American Gastroenterological Association Institute Clinical Practice Update [11] provides a guidance on metrics and practices that contribute to high-quality screening and surveillance colonoscopy, see Figure 5.

Additionally, American Gastroenterological Association Institute Clinical Practice Update [11] provides key points for appropriate utilization of colonoscopy surveillance based on index examination findings include:

- Avoiding late surveillance in high-risk patients (such as those with advanced lesions or many adenomas) can help prevent interval development of metachronous advanced lesions or CRC.
- Conversely, avoiding overuse of surveillance in low-risk patients (such as those with negative examinations, hyperplastic polyps (HPs) only, or 1–2 small adenomas or serrated polyps) can help avoid unnecessary cost and risk associated with low-yield colonoscopies.

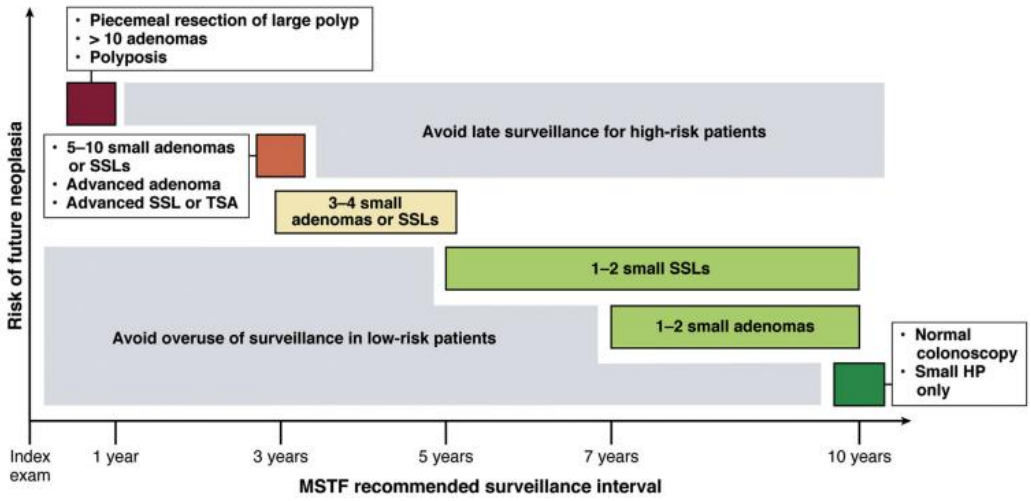
A major factor driving growth in colonoscopy procedures is the increasing public awareness of colon cancer, through media campaigns initiated by cancer awareness groups and government bodies, as well as an aging population that is recommended to receive regular screenings. The U.S. screening program, in particular, has been quite successful. One study compared practice patterns of GI endoscopy between two large national databases of the United States. The 5% sample of the CMS data from 1999 to 2003 contained 1,121,215 endoscopic procedures, of which 37.1% were EGDs, 52.7% were colonoscopies, and 10.2% were flexible sigmoidoscopies. By comparison, the CORI database contained 635,573 endoscopies, of which 32.2% were EGDs, 57.6% were colonoscopies, and 10.2% were flexible sigmoidoscopies. [9] The study revealed that women undergo both upper and lower endoscopic procedures more often than men. Nonwhite patients are underrepresented in the use of colonoscopy relative to the prevalence of non- white persons in the U.S. population. Increased use of a colonoscopy for colon screening and surveillance has been associated with a decreased rate of cancer diagnosis.[9]

Figure 5. Summary of best practice to improve quality of screening and surveillance colonoscopy



Source: AGA Clinical Practice Update, 2021 [11]

Figure 6. CRC Surveillance Considerations



HP – hyperplastic polyp, MSTF, Multi-Society Task Force; TSA, traditional serrated adenoma.

A colonoscopy is now the most common endoscopic procedure in the United States and varies based on age, gender, and race and often performed in patients less than 50 years old for irritable bowel symptoms; rectal bleeding; or average-risk screening, for which benefits are uncertain. In patients older than 50 years, surveillance after polyp removal is a common indication and may be overused. Understanding utilization can lead to further study to determine outcomes, to optimize utilization, and to provide a basis for shifting limited resources. [12]

The United States Preventive Services Task Force (USPSTF) and other expert panels have strongly recommended that average-risk adults, 50 years of age and older, receive colorectal cancer (CRC) screening. The options include a fecal occult blood test (FOBT) and a sigmoidoscopy, which, if positive, lead to colonoscopy. The most recent recommendations also include average-risk screening with colonoscopy. Despite these recommendations and Medicare coverage, only 30% to 40% of the population over 50 years of age receives colon cancer screening. There is concern that if colon cancer screening rates improve to 60% or 70%, the capacity to perform colonoscopy procedures may be exceeded and current resources may be insufficient.[12]

Colonoscopy combined with removal of neoplastic lesions (i.e., adenomas and, cancers) is believed to reduce the incidence and mortality of CRC. However, the quality of colonoscopy varies among endoscopists, which greatly affects the effectiveness of cancer reduction. [10]

4.4. Colonoscopy Quality Indicators

There has been extensive research on improving polyp detection. Polyps are frequently missed during colonoscopy, with the missed polyp rate reported to be up to 27%. [13] In a meta-analysis including six studies involving patients undergoing two same-day ‘back-to-back’ colonoscopies, the pooled miss rate for colonic polyps of any size was 22%. [14] Another meta-analysis identified a post colonoscopy cancer rate of 8.6% within three years of an apparently negative colonoscopy. Evidence suggests these cancers were most likely to be lesions missed during their previous colonoscopy, or incompletely resected lesions. [15, 16] These studies emphasise the importance of improving polyp detection. An endoscopist’s ability to detect polyps is assessed in the form of an Adenoma Detection Rate (ADR), an important quality indicator for colonoscopy. [17] An endoscopist’s ADR is defined as the proportion of patients first-time screening colonoscopy they have performed, where at least one adenoma was identified.

The U.S. Multi-Society Task Force (MSTF) recommends minimum acceptable ADRs for direct screening colonoscopy (DSC) of 30% for men and 20% for women. In the higher yield FIT-positive population,

MSTF recommends minimum acceptable ADRs of 45% in men and 35% in women. Experience and a sufficient number of colonoscopy procedures are required for endoscopists to perform a high-quality colonoscopy to prevent the development of CRC. The evidence on ADR as the quality indicator has accumulated and organizations like the American Society for Gastrointestinal Endoscopy (ASGE) [18], European Society of Gastrointestinal Endoscopy (ESGE) [19] and British Society of Gastroenterology [17, 20] have set performance thresholds for this measure. Other metrics of success include Adenomas per colonoscopy (APC) which has become more widely used in the last few years and provides additional information about endoscopist performance.

4.5. Use of Artificial Intelligence in Colonoscopy

Colonoscopy cannot detect all colonic lesions and can even miss CRCs. Patients with adenoma resection and surveillance are still at 47% risk of a standardized incidence-based mortality from CRCs, which often occur in the interval between scheduled colonoscopies (i.e., interval cancers) and contribute to approximately 8%–9% of all CRCs. In addition, the lesions missed during the colonoscopy are responsible for 50%–60% of interval cancers, and the incidence of interval cancers from missed lesions is 3.5 per 1000 screened persons. [21]

Artificial intelligence (AI) is gaining attention as an attractive and reliable measure to tackle the challenges in colonoscopy. The latest AI technologies, such as deep neural networks (e.g., so-called deep learning), have enabled computer-aided polyp detection (CADe) and classification (CADx) in a real-time fashion during colonoscopy (Figure 8). CADe is designed to help endoscopists to avoid missing polyps, which might contribute to increasing their ADRs, while CADx is designed to help endoscopists to interpret polyp histology with greater accuracy than endoscopists themselves normally do.

The performance of both CADe and CADx has been assessed in several prospective studies, with surprisingly encouraging results, whereas retrospective bench-mark tests are considered as suboptimal for accurate assessment of AI tools because of selection bias. [10] AI tools possibly increase the adenoma detection rate by roughly 50% and contribute to a 7%–20% reduction of colonoscopy-related costs.[10]

According to the metanalysis, full implementation of CADx was estimated to reduce the average colonoscopy cost and gross annual reimbursement for colonoscopy by 18.9% and $149.2 million in Japan, 6.9% and $12.3 million in England, 7.6% and $1.1 million in Norway, and 10.9% and $85.2 million in the United States, respectively, compared with the resect-all-polyps strategy. [10]. The meta-analyses further reported that the use of CADe during colonoscopy is likely to increase ADR by ~50%, which may have great benefits in cancer prevention. Additionally, no major drawbacks to the use of AI, including serious adverse events, were confirmed in the trials. [10]

More recently, the use of artificial intelligence (AI) and computer aided diagnosis (CAD) in endoscopy has been gaining increasing attention for its role in automated lesion detection [20] and characterization. [22] Machine learning is closely related to artificial intelligence and allows systems to automatically learn and improve from experience without being restricted to only predefined simple decision rules. Advanced deep learning techniques through convolutional neural networks (CNN) are now being applied leading to more sophisticated and accurate image recognition tools. AI can potentially improve ADR, but previous AI related work has largely focused on retrospectively assessing still endoscopic images and selected video sequences which may be subject to bias and lack clinical utility. There are limited clinical studies evaluating the effect of AI in improving ADR. A recent prospective feasibility study demonstrated an inferior ADR for an AI device compared to the endoscopist and highlighted the difficulties of AICAD in detecting small polyps and flat polyps. [23]

5. CADDIE CLOUD-BASED AI COLONOSCOPY SOFTWARE

5.1. Device Overview

CADDIE is a computer-assisted detection (CADe) device used in conjunction with endoscopy for the detection of polyps in the gastrointestinal tract.

The device's advanced software algorithms bring attention to relevant images in order to aid the endoscopist in the detection of lesions.

The CADDIE device uses a computer (see white box in Figure 7 labelled with 'PC') attached to the output of the endoscopy stack. It receives the live image stream from the endoscopy screen, which is sent to the cloud in real-time via the frame capture device.

The secure cloud-based system processes the images through an **AI-based polyp detection algorithm**. After the image processing, the resulting information is returned and visualized to the user on the endoscopy screen. The endoscopy screen shows the normal video output of the colon in real-time with an overlay highlighting the suggested presence and location of a polyp (see Figure 8).

The device will not be in contact with any tissues or body fluids.

Figure 7. An example of the CADDIE system performing polyp detection.



Note the green bounding box delineating the mucosal area where the CADDIE suggests there may be a polyp present. The appearance of the bounding box is associated with a sounding alarm

5.2. Device Components

CADDIE is cloud deployed artificial intelligence software. It is intended to be used by trained clinicians (users) as an accompaniment to video endoscopy for the purpose of drawing attention to regions with visual characteristics consistent with different types of colonic mucosal abnormalities.

CADDIE is accessed using a secure Chromium web browser on an off-the-shelf computer (client system) that must meet minimum software and hardware requirements, (as specified below in section 3.1(g) and in the instructions for use document detailed in section 4.2 of this brochure).

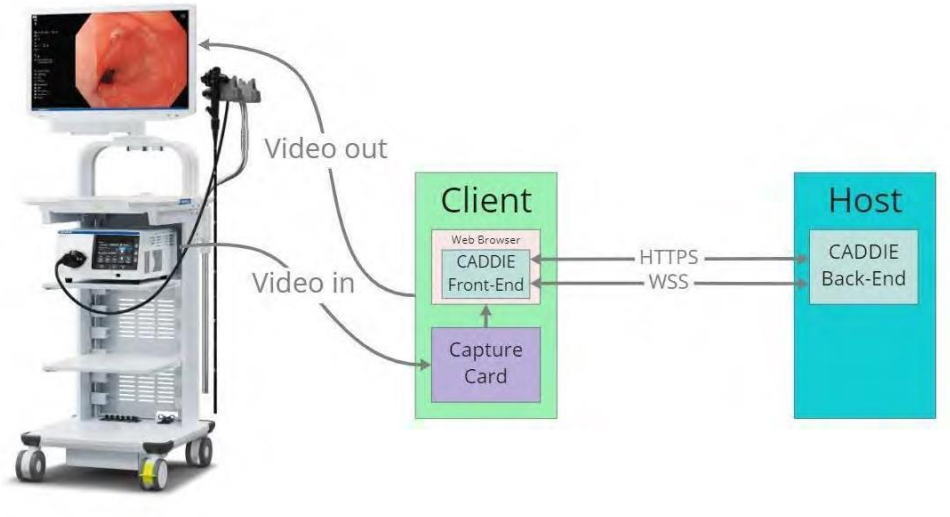
During colonoscopy procedures, there will be at least one monitor in use. This monitor is observed by the user of the endoscope and this is the monitor the CADDIE feed is inputted into (see Figure 3),

The computer accessing CADDIE must be equipped with a video (frame) capture card. This video capture device acquires the stream from the endoscopy video processor with a video cable. The computer takes the endoscopy video feed from the endoscopy video processor and displays it on the monitor.

CADDIE processes the video stream of the endoscope which is accessed through the video output of the endoscopy video processor by the compatible video capture device. The web browser accesses the video stream received and displays it through the webpage on the monitor.

CADDIE, which is deployed in the cloud, receives the video data through a secure internet protocol, analyses the video data and returns information to the website in the form of bounding box coordinates. The website overlays the bounding box onto the original video for display on the monitor.

Figure 8. CADDIE block diagram.



CADDIE is deployed on a host system which receives the endoscopic images from the video capture card and serves the front-end to a client. The client connects to the endoscope image processor and the monitor. The host is off-premises ("off-prem cloud"), but can also be on-premises ("on-prem cloud").

CADDIE is accessed using a secure Chromium web browser on an off-the-shelf computer (client system) that must meet minimum software and hardware requirements, as specified below.

Minimum client system specifications	CADDIE Cloud deployed version
CPU	Intel i3 (8th gen) or equivalent
RAM	4 GB
Network connection	8 Mbit upload, 1 Mbit download. For optimum performance a wired connection is required
Browser	Google Chrome or Chromium (v 83 or higher)
Frame capture device	Compatible with the endoscopy system to be used
Monitor resolution	To match the resolution of the endoscopy system
Audio speakers	Suitable for the work environment

Minimum host system specifications	CADDIE Cloud deployed version
CPU	Intel i7 (8th gen) or equivalent
RAM	16 GB
Network connection	1 Mbit upload, 8 Mbit download. For optimum performance a wired connection is required
GPU	NVIDIA Turing GPU, at least NVIDIA RTX 2070

5.3. Intended Use

CE Marked Intended Purpose

The CADDIE system is intended to be used by trained clinicians (users) as an accompaniment to video Endoscopy for the purpose of drawing attention to regions with visual characteristics consistent with different types of mucosal abnormalities.

CADDIE is trained to process colonoscopy video frames that may contain regions consistent with colorectal lesions like polyps, including diminutive and flat polyps.

CADDIE can analyse the visual characteristics and provide information to aid the user to characterise the tissue. This information is interpreted by the user and appropriate actions taken according to the standard clinical practice.

Note: Availability of CADDIE's characterization feature depends on individual user configuration. The characterization feature will not be available during the EAGLE clinical investigation (which is focused on detection).

Proposed US Indications for Use:

The CADDIE computer-assisted detection device is intended to assist the gastroenterologist in identifying suspected colorectal polyps only. The gastroenterologist is responsible for reviewing CADDIE suspected polyp areas and confirming the presence or absence of a polyp based on their own medical judgment.

CADDIE is not intended to replace a full patient evaluation, nor is it intended to be relied upon to make a primary interpretation of endoscopic procedures, medical diagnosis, or recommendations of treatment/course of action for patients.

Note: The study objective is to confirm CADDIE performs as intended under anticipated conditions of use. The CADDIE software will be used in the EAGLE study exclusively for computer-aided detection (CADe) of colorectal polyps. The results of the study will also be used to support pre-market submissions in other regions outside of Europe, including the US. The study data will be presented to the US FDA in order to support 510(k) clearance of the device in accordance with the applicable US regulation.

5.4. Manufacturer

The device is manufactured by Odin Medical Ltd., located in Charles Bell House, 43-45 Foley Street London, W1W 7TS, UK.

5.5. Model/Software

The software device intended to be used in the EAGLE clinical trial is CADDIE version 1.4.11 or higher.

5.6. Regulatory Status

CADDIE is CE marked in Europe as per Directive 93/42/EEC on Medical Devices (class I device). [24]

In the US, CADDIE is an Investigational Device. Limited by United States Law to Investigation Use.

Note: As specified in the intended use, this device is not intended to replace clinical decision making.

5.7. Traceability

CADDIE is cloud deployed artificial intelligence software; therefore, the sites will not receive a device, but only the web-based access to the software after study approval and after having received proper training. CADDIE's software version no. is the device's unambiguous reference allowing traceability.

5.8. Required Equipment

The CADDIE software is specifically designed to be used for colonoscopy only.

For the purpose of this study, the CADDIE software will be used exclusively with the following.

List of compatible endoscopes/equipment for EAGLE study:

- Olympus CF-HQ190L/I, CF-H190L/I, PCF-H190L/I, PCF-H190TL/I, PCF-PH190L/I, PCF-HQ190L/I, CF-HQ1100DL/I, CF-EZ1500DL/I

List of compatible image processors for EAGLE study:

- Olympus X1 CV-1500

Devices to be used in study including CE marked devices and non-CE marked devices (does not include devices not related specifically to use of CADDIE for the trial but that may be required as part of standard clinical practice for endoscopy)

Device/Items		Is the device CE marked under medical devices directive/regulation?	Device function/description	Will the device be supplied by Odin Medical for the trial?
1	**CADDIE**	Yes (CE marked by Odin Medical in accordance with Directive 93/43/EEC)	Cloud based AI colonoscopy software	Yes. Login information (username and password) to access CADDIE website will be provided to investigators/sites. More information on this will be provided during the training that will be provided by Odin Medical.
2	**Image processor:** • Olympus X1 CV-1500 **List of scopes**: • Olympus CF-HQ190L/I, CF-H190L/I, PCF-H190L/I, PCF-H190TL/I, PCF-PH190L/I,	Yes (CE marked by endoscopy system manufacturer)	Endoscopy system	No (sites are expected to have this on-site already)

	PCF-HQ190L/I, CF-HQ1100DL/I, CF-EZ1500DL/I			
3	**Foot Pedal**	Yes (should be CE marked by foot pedal manufacturer)	CADDIE is started by triggering a switch (e.g., pressing a foot pedal attached to the host PC). The detection can be enabled / disabled with a long press of the foot pedal.	No. However, if requested by the study site, Odin Medical can supply this item on loan.
4	**Keyboard with mouse/trackpad**	No – not medical device (but should be medical grade)	Instead of using a foot pedal to interact with CADDIE, the software can also be interacted with by using a standard keyboard attached to the user's computer (to start CADDIE or to enable / disable CADDIE's detection).	No. However, if requested by the study site, Odin Medical can supply this item on loan.
5	**Computer/ PC meeting following minimum client specification**: • CPU: Intel i3 (8th gen) or equivalent • RAM: 4 GB • Internet connection bandwidth: 8 Mbit upload, 1 Mbit download. For optimum performance a wired connection is required. • Google Chrome/Chromium Browser (v83 or higher) • Frame capture device to be compatible with the endoscopy system to be used • Monitor resolution: to match the resolution of the	No – not medical devices (off the shelf PC/items and peripherals)	CADDIE is accessed using a secure Chromium internet browser on an off-the-shelf computer (host system) that must meet these minimum software and hardware requirements The host computer of the device receives an endoscopy image stream from the endoscope through a frame capture device. This video capture device acquires the stream from the endoscopy video processor with a video cable.	No. However, if requested by the study site, Odin Medical can supply a PC on loan. A trained member of Odin Medical will liaise with each site to ensure that CADDIE is compatible with the user's existing hardware and that it meets the minimum client system specification. An on-premises host installation can also be arranged, where required.

	monitor of the endoscopy system • Audio speakers suitable for the work environment			

5.9. Performance Evaluation

CADDIE performance was assessed in bench testing executed on an independent Test dataset, comprising 268 full length HD white-light colonoscopies, during which a total of 630 polyps were excised and subsequently sent to histology from 219 cases. The total number of polyp frames of these videos was 582,891 frames. The dataset also comprised 49 full length white-light colonoscopies without polyps. The total number of frames of these videos was 1,110,552 frames. On testing CADDIE on this dataset, the mean per frame sensitivity was found to be 68.96% [67.05, 70.88] with a Object True Positive Rate of 100% (630/630 polyps). Additionally, the false alarms per minute, per patient with a persistence of 500ms was found to be 1.42 [1.20, 1.63].

6. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

6.1. Rationale for AI in Colonoscopy

Prospective randomized studies have established the clinical value of CAD devices in polyp detection [25]. Several devices are CE marked in Europe and are currently used in clinical practice. In addition three CADe devices have been cleared for marketing in the US by the Food and Drug Administration under product code QNP (Gastrointestinal Lesion Software Detection System): GI Genius (DEN200055, K211951), Endoscreener (K211326) and Skout (K213686).

A recent meta-analysis [26] demonstrated that the incorporation of Artificial Intelligence as aid for detection of colorectal neoplasia results in a significant increase of the detection of colorectal neoplasia, and such effect is independent from main adenoma characteristics. The enhancement with CADe compared with the traditional features of colorectal neoplasia was confirmed in all sub-analyses that were performed. CADe led to a statistically significant increase detection of diminutive, small, and large adenomas, of those located in the proximal as well as in the distal colon, and of those flat and polypoid. In addition, there was an increase detection of SSL and a trend for a nearly 2-fold increase in advanced neoplasia.

6.2. Rationale for Trial Population

This trial will involve patients referred for screening or surveillance colonoscopy, in whom polypectomy is being performed as part of routine medical care and in the interest of participant safety, we have excluded patients who have a medical condition which pre-disposes them to bleeding.

7. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

The EAGLE study is a prospective randomized controlled multicenter parallel design trial, for the assessment of clinical performance of the CADDIE device.

The study objective is to confirm and support existing data that the CE marked CADDIE device performs as intended under anticipated conditions of use. The CADDIE software will be used in the EAGLE study exclusively for computer-aided detection (CADe) of colorectal polyps. The study will also include evaluation of any adverse events.

The results of the study will also be used to support pre-market submissions in other regions outside of Europe, including the US. The study data will be presented to the US FDA in order to support 510(k) clearance of the device in accordance with the applicable US regulation

7.1. Hypotheses

Colonoscopy aided by the CADDIE system increases Adenoma per Colonoscopy (APC) and does not significantly decrease Positive Percent Agreement (PPA). The hypotheses of APC superiority and PPA non-inferiority are fully specified in Section 11.

7.1.1. Definition of Terms

The following definitions are used, in accordance with literature [17, 19, 20, 27, 28]

- **Adenoma:** Any dysplastic polyp with tubular, villous or tubule-villous histology. Sessile serrated lesions and hyperplastic polyps are excluded.
- **Adenoma Detection Rate (ADR):** Percentage of examinations with adenomas divided by total number of examinations.
- **Adenoma per colonoscopy (APC):** Total number of histologically confirmed adenomas and adenocarcinomas divided by the total number of colonoscopies.
- **Positive Percent Agreement (PPA):** Percentage of relevant extractions per all extractions. Relevant extractions include histopathologically confirmed adenomas, sessile serrated lesions, and large (>10mm) hyperplastic polyps of the proximal colon (caecum, ascending colon, hepatic flexure, and transverse colon).
- **Sessile serrated lesion (SSL):** Any polyp with histology of a sessile serrated adenoma, traditional serrated adenoma, or serrated lesion with cytological dysplasia. Hyperplastic polyps are excluded.
- **Total Withdrawal Time:** The time it takes to withdraw the colonoscope from the furthest point (TI or caecum) including time for polypectomy or other interventions.

7.2. Primary Objectives and Endpoints

The study is powered to allow for the assessment of two co-primary endpoints:

1. **Adenoma per Colonoscopy (APC).** Superiority of CADDIE arm vs. control arm. Where APC is the total number of histologically confirmed adenomas and adenocarcinomas divided by the total number of colonoscopies.

2. **Positive percent agreement (PPA).** Non inferiority of CADDIE arm vs. control arm. Where PPA is the percent of histopathologically confirmed adenomas, sessile serrated lesions, and large (>10mm) hyperplastic polyps of the proximal colon (caecum, ascending colon, hepatic flexure, and transverse colon) out of the total number of resections.

7.3. Secondary Objectives and Endpoints

1. **Adenoma Detection Rate (ADR)** defined as the percentage of examinations with adenomas divided by total number of examinations.
2. **Sessile serrated lesions detected**, defined as the total number of polyps with histology or serrated adenoma, traditional serrated adenoma or serrated lesion with cytological dysplasia, excluding hyperplastic polyps.
3. **Colonoscope withdrawal time**, defined as the time it takes to withdraw the colonoscope from the furthest point (TI or caecum) including time for polypectomy or other interventions (Withdrawal times should be targeted to a minimum of 6 **minutes.)**
4. **Total procedure time,** recorded as the entire duration of the procedure.
5. **Rate of adverse events,** recorded as the rate of adverse events related to the procedure for the duration of the study colonoscopies, for each study arm. Frequency of adverse events based on maximum severity of event for each patient in each arm. Any complications meeting the definition

of an adverse event will be recorded in the Adverse Event Log and reported in line with the procedures described in Section 13.

8. STUDY DESIGN

8.1. Study Design Overview

An overview of the EAGLE study design is given in Figure 1. Study Flowchart.

The EAGLE study is a prospective randomized controlled multicenter parallel design trial, for the assessment of clinical performance of the CADDIE device.

Patients who meet the study inclusion/exclusion criteria will be randomized in a 1:1 ratio to receive either computer-aided colonoscopy (CADe Arm) using the CADDIE System, or standard colonoscopy without CADe (Standard Colonoscopy Arm).

All resected polyps will be submitted for histologic examination.

8.1.1. Endoscopist Qualification

The study will only involve qualified endoscopists who have an ADR above 25% and have completed a minimum of 1000 colonoscopies, as previously reported in CADe studies. ADR ≥25% is an overall benchmark established by the American Society for Gastrointestinal Endoscopy and American College of Gastroenterology Task Force on Colonoscopy Quality. [18]

All participating endoscopists will be trained in the use of CADDIE device and all the requirements of the study.

8.1.2. Participating Histopathologists

The resected polyps will be submitted for histologic examination by the gastroenterology pathologists at each site. Lesions will be classified according to World Health Organization (WHO) classification of tumors of the digestive system, 5th edition, 2019. [29, 30] All participating histopathologists will be blinded to the assigned study arm.

8.1.3. Compatible Equipment with the Investigational Device

CADDIE is used in conjunction with endoscopy for the detection of abnormal lesions in the gastrointestinal tract. All procedures will be performed using standard clinical practice. Each endoscopist and facility can adopt their standard procedures for subject management and monitoring. CADDIE system is intended to be used only with the compatible equipment that was tested against during validation activities:

List of compatible equipment for EAGLE:

Olympus CF-HQ190L/I, CF-H190L/I, PCF-H190L/I, PCF-H190TL/I, PCF-PH190L/I, PCF-HQ190L/I, CF-HQ1100DL/I, CF-EZ1500DL/I

List of compatible Image processors

Olympus X1 CV-1500

CADDIE is a software system that does not come into contact with patients.

8.2. Target population

The study is expected to be representative of the intended use population and will include patients scheduled to undergo a screening or surveillance colonoscopy with a qualified endoscopist. Based on previous literature publications on studies of similar devices, it is expected that patient mix will consist of screening in approximately 66% of cases, and surveillance in the remaining 34%.

8.3. Subjects eligibility

8.3.1. Inclusion criteria

The Investigator at the clinical site has the responsibility of screening potential patients to determine if the patients meet all the inclusion criteria. The following are criteria for entry into study:

1. Patients scheduled to undergo a screening or surveillance colonoscopy with a qualified endoscopist. (Surveillance colonoscopy: only where the last colonoscopy was performed 3 years or more before the scheduled colonoscopy)
2. Age 40 years or older at the time of informed consent.
3. The patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent on a form,
4. Not more than 20 percent of patients who have undergone FIT or FoBT are allowed to randomization.

8.3.2. Exclusion criteria

The Investigator at the clinical site must exclude patients if any of the exclusion criteria are present. The following are the criteria for exclusion from participating in the study:

1. Emergency colonoscopies and/or inpatient colonoscopies.
2. Patients with inflammatory bowel disease (IBD)
3. Patients with Colorectal Cancer (CRC)
4. Patients with previous Colorectal Cancer (CRC)
5. Patients with previous colonic resection
6. Patients returning for a planned elective therapeutic colonoscopy.
7. Polyposis syndromes (familial adenomatous polyposis)
8. Patients with a contraindication for biopsy or polypectomy. These include:
    a. Patients who have not withheld medications pre-disposing to bleeding at time of colonoscopy (antiplatelet agents, anticoagulants).
    b. Patients with a history of haemostasis disorders.
9. Surveillance colonoscopy where the last colonoscopy was performed less than 3 years before the scheduled colonoscopy
10. Patients undergoing diagnostic colonoscopy with high-risk indications including iron deficiency anemia, abnormal CT imaging, unexplained weight loss, Lynch Syndrome.
11. Patients is enrolled in another research study.
12. Patients who have been placed in an institution on the basis of an official or judicial order.

8.4. Minimizing Bias

Subject demographics will be assessed by collecting information on possible differences that may affect the study outcome. Information will be gathered on the subject's relevant medical diagnosis and concomitant medication uses etc..

Before randomization, the endoscopist will inquire about bowel preparation to minimize the likelihood of inadequate exam leading to patient exclusion. Inadequate bowel preparation is defined as a segmental Boston Bowel Preparation Score (BBPS) of 5 or Aronchick score of 'inadequate' due to a single colonic segment with poor preparation.

Randomization will be stratified by patients' age, sex, colonoscopy indications (screening and surveillance) to avoid bias related to patient characteristics.

The gastrointestinal (GI) pathologist at site will be blinded to the study arm allocation.

8.5. Follow Up

Colonoscopy is a low-risk procedure and CADDIE is a non-invasive software device that does not come into contact with the patient. Complications from the device are not expected as it is a non-invasive device.

In this study, there is no clinical assessment required after the colonoscopy, except for a follow-up call at 24 hours to document any symptoms or complications. It is routine practice for patients to receive their colonoscopy report prior to leaving the endoscopy department with histology results available at a later date. Patients usually receive their histopathology results through a telephone consultation or review in clinic.

8.6. Study workflow

8.6.1. Enrolment period

The total planned sample size consists of a total of 946 patients. See Flowchart in Figure 1.

The study will be conducted at up to 10 clinical sites in Europe.

Overall estimated enrolment rate is 80-120 patients per month. Therefore, estimated time needed to select the sample size of 946 participants (i.e. enrollment period) is 9 months.

Enrollment per site:	Up to 150 patients
Enrollment rate:	5 to 12 patients per site per month
Planned study end:	Q3/2023

The total expected duration of the study is 9 months. Timelines may be prolonged if the activation of the clinical study sites is delayed due to administrative procedures, contracting, and enrollment problems.

8.6.2. Randomization methods

Patients who sign the informed consent and meet the study inclusion/exclusion criteria will be randomized in a 1:1 ratio to receive either computer-aided colonoscopy (CADe Arm) using the CADDIE System, or standard colonoscopy without CADe (Standard Colonoscopy Arm). Randomization will be stratified by patients' age, sex, colonoscopy indications (screening and surveillance) to avoid bias related to patient characteristics.

8.6.3. Criteria and procedures for subject withdrawal or lost to follow-up

Patients may be withdrawn from the study for the following reasons:

- Patient Voluntary Withdrawal

The patient may voluntarily withdraw from the clinical study at any time, without penalty or loss of benefits to which they are otherwise entitled.

- Physician Withdrawal

The Principal Investigator also has the right to withdraw a patient if they feel it is in the best interest of the patient to do so.

- Follow-up

If a patient cannot be reached for a follow-up phone call within 24 hours of colonoscopy completion, the investigator will document the contact efforts made to the patient and/or effort to obtain hospital records in the appropriate electronic case report form.

As the study does not require additional follow-up, procedures for tracing subjects that are lost to follow-up are not planned.

8.6.4. Expected duration of each subject's participation

Each participant will be contacted by phone within 24 hours of colonoscopy procedure, with no additional follow up required for the study.

9. STUDY CONDUCT

9.1. Statement of compliance

This study will be conducted in compliance with the approved protocol, applicable regulatory requirements, and good clinical practices. The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable national regulations. The applicable regulation include Medical Device Regulation 2017/745 as amended, and UK Regulations for Devices (SI 2002/618; as amended), the UK Data Protection Act (2018), the General Data Protection Regulation 2016/679 (GDPR), the Trust Information Governance Policy (or other local equivalent), the UK policy framework for health and social care research,

The clinical investigation shall not commence recruitment until all relevant ethics, regulatory and local approvals are received. All additional requirements imposed by the responsible Ethics Committees or regulatory authorities will be followed.

9.2. Informed Consent Process

Information to patients

Patient should always be given adequate time to consider whether they wish to take part in the trial. This duration is defined on a per trial basis and must be balanced against the potential risks to the patient and the complexity of the decisions they need to make.

The CADDIE technology and participation in the study is considered low risk. The AI polyp detection system is CE marked, it is commercially available in Europe being used in many centers on a routine clinical basis. There are multiple similar CE Marked products on the market from other companies including Medtronic and Olympus and collectively AI has been used on over 10,000 patients worldwide with no serious adverse events related to the medical devices identified.

Whenever possible, information on the study will be provided to patients 24 hours in advance, but patients may also consent on the day of the procedure as it is common that endoscopy procedures are scheduled or rescheduled at short notice. Consent on the day is considered acceptable due to the low-risk nature of the medical device and the fact that this type of device is already routinely used in many centres in Europe and the USA.

Benefit for trial operations

This trial will be limited to specific types of patients, who are being scoped by specific clinicians in specific endoscopy rooms where the artificial intelligence CADDIE system has already been installed. This reduces the pool of patients available to join the study. Furthermore, endoscopy procedures can be arranged at less than 24 hours' notice and patients can even be moved from one room to another at very short notice for operational reasons. Published data demonstrate that this type of AI trial confers a negligible risk to patients. In instances where a patient has not received information about the trial at least 24 hours in advance, excluding them from the trial will deny these patients the opportunity for them to participate in clinical research if they choose to do so.

Informed Consent Process

On the day of the colonoscopy, subjects will be consented for enrolment in the study. Adequate time must be given for consideration by the patient before taking part. It is expected that an information leaflet will be sent to the patient by post or email within 7 days of the colonoscopy, and more than 24 hours prior to the colonoscopy. There may, however, be changes to endoscopy lists at short notice. Given the low impact of this study on the procedure, it is proposed that where the information leaflet has not been sent in advance, the PI or a GCP certified member of the local research team who has been delegated the duty of consent by the PI on the delegation log may offer the patient entry to the study at the time that consent is taken for the procedure itself. This must be undertaken outside the endoscopy room.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the Investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The person taking consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the PI on the delegation log.

The Investigator or designee will explain the patients are under no obligation to enter the Investigation and that they can withdraw at any time during the Investigation, without having to give a reason. No clinical investigation procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the trial. A copy of the signed Informed Consent Document will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes. Alternatively, an electronic consent form, which is signed electronically, may be used via EDC.

All efforts will be made to enter all eligible patients into the trial. Research sites will be permitted to use interpreters as part of the informed consent process, and should a patient consent to enter, throughout their participation in the study. Research sites must ensure that language is not a barrier to further explanations during the course of the participant's participation in the study, or for completion of the participant questionnaire. If local interpreters are not available at the site, or if there are any concerns over the participant's understanding and fully informed consent is not deemed possible, the patient will not be considered for the trial.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

9.3. Study Arms

After informed consent has been obtained, eligible patients will be randomized (1:1) into one of the study arms:

1. CADDIE colonoscopy (CADe Arm)

2. Standard high-definition white light colonoscopy (HDWL Arm)

9.4. Study Visits and Procedures

Baseline

- Patient Screening

Patient screening is based upon routine patient care performed after the study patients are referred for colonoscopy. Participant recruitment at a site will only commence when the trial has been initiated by the Sponsor or its delegated representative and issued with the 'Site Activation/Open to Recruitment' letter. The subjects will be recruited from the clinical practices of the investigators. Additionally, at the Gastroenterology or Colorectal clinic, potential participants will be asked by a member of the healthcare team whether they are interested in receiving information about the study for potential participation.

Screening endoscopy lists

A member of the research team at participating hospitals will screen the endoscopy list of endoscopists enrolled in the trial. Potentially eligible participants (referencing the exclusion criteria outlined in this protocol) will be told about the study and the participant information sheet (PIS) will be provided in advance of their scheduled procedure (by post, email or weblink) and where possible telephoned in advance to discuss the study. If they have not received the PIS, then this will be provided to them during their admissions process to read prior to the endoscopy procedure.

All patients will be given sufficient time to read the PIS and prepare any questions they may have. They will be encouraged to ask questions and the person taking informed consent will check their understanding before registering them onto the study. Patients do not have to give a reason for not wanting to participate in the study, but sites should capture this information is available.

- Informed Consent

The Investigator, or a person delegated by the Investigator, will obtain written informed consent from each subject prior to participation in the Investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Details of Informed Consent Process are described in Section 8.2.

- Inclusion/Exclusion Criteria

Once written informed consent has been obtained, participants will be assessed against the eligibility criteria. If eligible, participants will be registered into the study, generating a participant study ID. The eCRF for the participant will then be updated to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will need to be documented. The signed consent form will be filed in the medical notes and a copy retained by the Principal Investigator. The subject will not be advanced any further into this clinical investigation.

Colonoscopy

Patients will undergo either standard colonoscopy or CADDIE colonoscopy (randomization 1:1). Both colonoscopies will be carried out using the same equipment according to standard clinical practice. The CADDIE AI system will be enabled in CADe colonoscopy and disabled in standard colonoscopy procedures.

Post-colonoscopy

A phone call will be conducted within 24 hours of colonoscopy procedure completion, with primary aim to record adverse events.

9.5. Study Assessments

Following consent and registration of the endoscopist, baseline endoscopist data will be collected and the endoscopist initial retrospective ADR calculation will be verified.

9.5.1. Pre-colonoscopy assessments

1) Demographic and Medical history data collection

As part of routine care, on the day of the colonoscopy but prior to the procedure, patients will undergo the following standard pre-procedure assessments:

Demographic and medical history data will include the following minimum dataset:

- Indication for colonoscopy (FIT+, Primary CRC Screening, Surveillance, GI Symptoms)
- Demographic Information (age, sex, ethnic group)
- Medical history, gastrointestinal disease history, concomitant diseases, and medications assessment.
- Physical examination.
- ASA Score based on the pre-operative health status

If patients meet the EAGLE study criteria and provide consent to participate, the data obtained during the routine pre-colonoscopy examination will be collected. This includes demographics and pre-colonoscopy clinical parameters, as available. In addition, ethnicity and race data will be collected as part of the study, as colorectal cancer risk is affected by these factors.

Ethnicity and race will be classified according to the recommendations in the FDA guideline: Collection of Race and Ethnicity Data in Clinical Trials, October 2016.

2) Randomisation

Within each investigational site, randomisation will be stratified by endoscopist and indication for colonoscopy (i.e., surveillance or screening). Patients will be block randomised, in a 1:1 ratio, within either the “CADe” or “Standard Colonoscopy” control arm. Prior to commencing the colonoscopy

procedure, patient information (e.g. patient study ID) and endoscopist information (e.g. endoscopist study ID number) will be entered into the study database, which is available 24 hours a day. The online randomisation tool will automatically generate an allocation into one of two arms (CADe and non-Standard Colonoscopy arm) when the participant is registered.

9.5.2. Colonoscopy assessments

1) Colonoscopy

In both arms of the trial, the entire colonoscopy procedure will be recorded via the CADDIE device. The CADDIE device will be connected to the endoscopy generator/screen and the video stream will be captured by the CADDIE in real time.

The CADDIE device will only be active in the CADe arm. As CADDIE is a cloud deployed software, mitigating processes will be implemented during the course of the study to monitor the internet network speed for the procedures of participants recruited to the study. This is to detect internet network issues and avoid recruiting further patients whilst this issue is occurring. If internet network goes down during the procedure, the corresponding data should be excluded from the data analysis.

Images and videos that are recorded as part of routine clinical care do not usually contain any patient identifying information. If any patient identifiable information is present on the endoscopy monitor display, this will be removed prior to the start of the colonoscopy.

For each polyp diagnosed by the endoscopist (CADe and non-CADe arm), the endoscopist will be required to:

1. Measure the polyp size and capture images of the polyp

Polyps are to be measured using an instrument of known size.

2. Resect the diminutive polyp (if safe to do so) as per standard of care, using standard techniques and send for histopathology

- All diminutive polyps detected will be included in the trial, regardless of the presence of larger polyps in the patient.

3. Label each polyp resected

- All polyp samples (regardless of size) must be labelled according to the instructions of the Specimen Handling SOP.

- For each participant, each unique polyp ID will need to be labelled in chronological order of resection.

4. Documentation (per standard of care)

For each polyp, the endoscopist must document in the endoscopy report the polyp site, size, morphology (e.g. Paris Classification), the segmental Boston Bowel Preparation Score and capture an image when the caecum is detected.

2) Colonoscopy – CADe arm only

During the colonoscopy, the CADDIE software processes each individual frame captured and where it detects a possible polyp, it will simultaneously sound an alarm and the area of interest will be bound by a coloured bounding shape on the CADDIE monitor. Where the device sounds an alarm, the endoscopist will inspect the mucosal area where the CADDIE device has detected a possible polyp (without any assistance). If it is deemed to be a polyp, the endoscopist will follow the steps documented above.

9.5.3. Post colonoscopy assessments

1) Endoscopy meta-data collection

At the end of each colonoscopy, a colonoscopy report is generated as per standard of care. A series of metadata will be recorded from the medical notes into the participant's eCRF.
This includes the following minimum dataset:

- Type of sedation (None, Benzodiazepine and narcotics, or Propofol)
- Bowel preparation used (BBPS, Aronchick)
- Segmental Bowel Preparation (as identified by endoscopist): Overall bowel preparation Left Colon bowel preparation, Transverse Colon bowel preparation, Right Colon bowel preparation, or Aronchick Scale: Excellent, Good, Fair and adequate)
- Withdrawal time defined as the time it takes to withdraw the colonoscope from the furthest point (TI or caecum) including time for polypectomy or other interventions
- Total procedural time
- Number of Polyps detected during colonoscopy
- Polyp site (Location: Cecum, Ascending colon, Hepatic flexure, Transverse colon, Splenic flexure , Descending colon, Rectosigmoid)
- Polyp size (<5 mm, 5-9 mm, >10 mm)
- Polyp morphology (e.g. Paris Classification Ip, Is, IIa, IIb)
- Polyp histopathology (once available - Tubular adenoma, Tubulovillous Adenoma, Villous adenoma, Adenoma with high-grade dysplasia, Sessile serrated adenomas, Traditional serrated adenomas, Hyperplastic polyps >10 mm)
- If colonoscopy is incomplete, a reason will need to be recorded
- Adverse events (Gastrointestinal disorders, General disorders and administration site conditions, Injury, poisoning and procedural complications, Neoplasms benign, malignant and unspecified including cysts and polyps, Nervous system disorders)

Further metadata may be recorded if deemed necessary.

2) Histopathology samples

As part of routine clinical care, histology samples are labelled with patient identifiable information and unique polyp ID label.

The pathologist at site will be blinded to the assigned arm randomization of the patient. When the pathologist reports the polyps, it is recommended that they include the same unique polyp ID that the endoscopist used to label the sample after resection (in addition to standard of care).

3) Safety

Complications from the CADDIE device are not expected as it is a non-invasive device and therefore no clinical follow up visit is required.

Any adverse event will be recorded and reported in line with the procedures described in the protocol Section, “Safety reporting”. Patients will be instructed to seek medical advice in the routine way if complications occur. The central research team is to be informed about all complications.

In the event that there is a higher rate of adverse events associated with the CADe arm, data will be analysed to assess if the device was a contributing factor.

9.6. Device traceability

Good Clinical Practices require accounting for the disposition of all investigational devices received by each investigational site. As CADDIE is a software as medical device, no physical device will be provided to the site. CADDIE’s software version number is the device’s unambiguous reference allowing traceability.

Odin will provide any equipment to the sites, such as the PC, when required

9.7. Monitoring Plan

The Sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

9.8. Confidentiality

All data will be handled in accordance with the General Data Protection Regulation (GDPR) and applicable national regulations. The eCRFs will not bear the subject's name (subject refers to both trial patients and endoscopists).

Subjects will be assigned an Investigation identification number by the EDC system sequentially upon enrolment into the study. The study site will maintain a master Subject Identification Log. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, General Data Protection Regulation and Ethics Committee Approval.

All endoscopy data (i.e. frames from the colonoscopy video stream) will already be de-identified at the time of image acquisition. As a safety measure to preserve the confidentiality of patients, the CADDIE cloud has an automatic anonymization tool that removes optical characters (e.g. patient name) from imaging data in the event that a site has uploaded identifiable patient information.

9.9. Record keeping and archiving

Principal Investigators are responsible for the secure archiving of essential Investigation documents in electronic or paper form as per their Trust policy. All essential documents will be archived for at least 5 years after completion of Investigation. Destruction of essential documents will require authorization from the Sponsor.

9.10. Clinical Investigation Amendments

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the Investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff has been trained. This process does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

9.11. Procedures for Recording, Reporting and Analysing CIP Deviations

A deviation is considered a departure from the conditions and principles of GCP in connection with that Investigation; or the CIP relating to that Investigation, as amended from time to time.

The Investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation.

If possible, prior approval from the sponsor and EC, if appropriate, shall be obtained by the investigator. All spontaneous CIP deviations shall be recorded and reported to the sponsor as agreed. A deviation log shall be maintained by the study site. Deviations shall be reported to the EC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

10. RISKS AND BENEFITS

10.1. Anticipated Benefits

AI can detect previously unrecognized lesions and act as a "second pair of eyes" through a continuous monitoring mechanism. Since AI works as a visual aid, AI-aided colonoscopy can become an important approach, especially for inexperienced endoscopists. [8]

The AI system can improve the detection rate of adenomas or polyps in all positions except for cecum and has high accuracy, consistency, and fidelity. This advantage also extends to the more favorable detection of flat and sessile polyps, which are often neglected by naked eye. This study found that AI system cannot further improve the detection rate when it comes to pedunculated adenomas or polyps comparing with RC. This may be due to the high recognition ability of the naked eye for the pedunculated adenoma or may be explained by stalks with variable lengths that can interfere with AI detection in pedunculated adenomas.

Meta-analyses reported that the use of CADe during colonoscopy is likely to increase ADR by ~50%, which may have great benefits in cancer prevention. Additionally, no major drawbacks to the use of AI, including serious adverse events, were confirmed in the trials. [10]

Previous studies have also shown that sessile adenomas or polyps have a higher risk than pedunculated lesions to cause cancer formation. Therefore, the increase resulted from the assistance of AI in detection rate of sessile adenomas is of great significance when considering the prevention of CRC.[8]

10.2. Anticipated CADDIE software risks

There are minimal anticipated adverse device effects associated with the CADDIE device. There is a risk of false positive with the CADDIE system which could theoretically lead to unnecessary interventions. A false positive occurring where the device detects a polyp but the endoscopist deems there not to be a polyp. To minimise risks associated with false positives, the endoscopist is mandated to inspect the area where the device detects a polyp and the endoscopist is responsible for diagnosing and managing as per normal endoscopy practice.

There is a risk of false negative associated with the CADDIE system which will be assessed in the data analysis phase of the trial. A false negative occurs where the device deems there to be normal mucosa when in-fact there is a polyp present. It is important to appreciate that the CADDIE device is intended to aid the endoscopist in detecting polyps, not to replace the endoscopist's diagnosis. Ultimate responsibility for the procedure lies with the endoscopist who is responsible for the final diagnosis. If the endoscopist diagnoses a polyp which is not detected by the CADDIE, the endoscopist should proceed with managing as per routine clinical practice.

There is a potential risk of anxiety for patients in using a new medical device during their colonoscopy. The sounding alarm associated with the CADDIE device detection of polyps may also induce anxiety in patients during the procedure, although this risk is limited as the procedure is performed under sedation. This will be clearly explained in the PIS. "Adequate time" must be given for consideration by the patient before taking part. Participants will be given the opportunity to address any concerns prior to enrolling into the trial.

10.3. Residual Risks Associated with Study Procedures

It is likely that the participants enrolled in this trial will have an increased number of polypectomies performed for various reasons. Firstly, this could be due to an anticipated increased detection of polyps using the CADDIE system. This means that less polyps are being missed which is actually to the patient's benefit. Secondly, there could be an increased number of polypectomies/biopsies performed due to our study standardising diagnosis of rectal hyperplastic polyps, as explained above.

The risk of major complications from polypectomies, such as perforation or major bleeding, is associated with the size of the polyp. [31, 32] The MUPS study identified a risk of 0.1% and 1.6% for major complication associated with polypectomies of polyps <1cm and 1-1.9cm respectively. [31] To minimise the risk of complications, the EAGLE will exclude patients on medications or suffering with medical conditions which pre-dispose to bleeding. [32]

Table 2. Investigation Procedures - Summary of the risks and mitigations

CADDIE	Potential risk	Risk Frequency	Risk Management
To be invited in the study and given patient information sheet (PIS)	Anxiety	Expected to be low	The sounding alarm will be clearly explained in the PIS. "Adequate time" must be given for consideration by the patient before taking part. Participants will be given the opportunity to ask as many questions as they would like prior to enrolling into the trial. It will be emphasised that declining to enroll in the trial will not affect the care they receive.
False Positive by CADDIE	Misdiagnosis resulting in unnecessary intervention.	Expected to be low	Endoscopist will be mandated to inspect any area where the device deems to have detected a polyp. Endoscopist is responsible for diagnosing and management as per normal endoscopy practice.
False Negative by CADDIE	CADDIE misdiagnoses polyp as normal mucosa.	Expected to be low	If a false negative occurs, the endoscopist is responsible for the final diagnosis (as per usual clinical practice).
Increased number of polypectomies due to increased polyp detection with CADDIE.	Risk of perforation Risk of bleeding	0.058%[33] 0.24% [33]	To minimise the risk of complications, we will exclude patients on anticoagulants/antiaggregant medications or suffering with medical conditions which pre-dispose to bleeding.

10.4. Risks Associated with Participation in The Clinical Investigation

Table 3. Summaries of the risks and mitigations of all test above standard care

Intervention	Potential risk	Risk Management
Increased number of polypectomies compared to standard care because: 1. Potential increase in polyp detection with CADDIE 2. Standardisation of diagnosing rectal hyperplastic polyps	Risk of perforation 0.058%[33] Risk of bleeding 0.24%[33]	To minimise the risk of complications, the Eagle study will exclude patients on medications or suffering with medical conditions which pre-dispose to bleeding. Where polyps are identified as a rectal hyperplastic polyp, it will be resected/biopsied. If multiple rectal hyperplastic polyps are diagnosed, a minimum of 3 rectal hyperplastic polyps will be resected/biopsied.

11. STATISTICAL ANALYSIS PLAN

11.1. Statistical Hypothesis

The study is powered to allow the assessment of two co-primary endpoints: Adenomas Per Colonoscopy (APC), as co-primary efficacy endpoint, and the Positive percent agreement (PPA) as co-primary safety endpoint.

The statistical test is defined as follows:

- H_0: APC of the active arm is lower or equal to the APC of the control arm (≤)
- H_1: APC of the active arm is higher than the APC of the control arm (>)

For the safety co-primary endpoint Positive Percent Agreement (PPA) the statistical test is defined as follows:

- H_0: PPA of the active arm is higher or equal to the sum of PPA of the control arm and a safety margin Δ (≥)
- H_1: PPA of the active arm is lower than the sum of PPA of the control arm and a safety margin Δ (<)

The following pass criteria will be applied to the results of the study:

- APC: Expected increase in APC with CADDIE CADe compared to Standard colonoscopy arm: 0.19
- PPA: Non-inferiority margin: (15%)

11.2. Justification of Primary Endpoints Assumptions

Various studies were evaluated to select the APC value in the control group, as shown in **Table 1** (see study synopsis). Based on an expected patient mix of screening ~66% and surveillance ~34%, the average value of APC in the control group was set at 0.83 and the APC difference with the CADe arm was estimated at 0.19.

11.3. Sample Size Computation

APC Sample Size Computation:

- One-tailed test for superiority of CADe versus standard colonoscopy
- Mean estimated APC value of the control arm: 0.83 (consistent with SKOUT study [28]);
- Expected difference with CADe: 0.19
- Statistical test: z-test with two arms
- Significance level a is set to 0.025
- Power: >80%.
- Sample size: 430 patients per arm
- Increase of 10% for attrition: total 946 patients

PPA Sample Size Computation:

- Mean value of the control arm: 75.7% as reported in SKOUT 510(k)
- Non-inferiority margin: (15%)
- Statistical test: Wilcoxon test
- Significance level a is set to 0.025
- One-tailed test for non-inferiority of CADe versus and standard colonoscopy
- Power: > 80%
- Sample size: 125 patients per arm

To satisfy both co-primary endpoints (APC and PPA), the sample size is selected as the highest between the two endpoints. We aim to recruit 860 subjects in total (430 per arm) to detect an absolute increase of 0.19 in APC (from 0.83 w/o CADe to 1.02 with CADe) between the two arms, using a two-group z-test with 80% power, a one-sided α level of 0.025. Accounting for an expected dropout rate of 10%, the total planned sample size consists of a total of 946 patients.

11.4. Descriptive statistics

Summary measures f the baseline characteristics of the overall population and each study group will be presented as mean and standard deviation for continuous, symmetric variables, medians and inter-quartile ranges for continuous variables and frequencies and percentages for categorical variables.

Comparison of the study endpoints between the CADe and control groups will be performed using regression models to adjust for centre and endoscopist experience. The primary analysis will be performed

on an intention to treat basis and no adjustments for missing data will be made. Significance will be considered at the 5% level and confidence intervals will be at the 95% level.

Additionally, analyses will be performed for each of the secondary outcome variables, using appropriate regression models for continuous and categorical variables. These analyses shall be considered exploratory, as the study design was not powered to assess these independently.

A dropout rate of about 10% is expected. Potential bias due to missing data will be investigated initially by comparing the baseline characteristics of the trial participants with complete measurements compared to those who have incomplete or no outcome data, using appropriate statistical comparisons.

Protocol deviations that could impact on the results of the analyses will be described. All individuals who withdraws consent shall be excluded from the analyses from the point of withdrawal, although any data collected from such patients prior to the point of withdrawal shall be included unless otherwise specified by the patient. Reasons for withdrawal from the trial will be summarised.

11.5. Analysis population

Similar to previous studies evaluating the efficacy of AI algorithms to detect polyps, APC and PPA will be calculated. [34, 35]

Where a polyp(s) is detected, but resection deferred for a repeat procedure, the histology will be collected from the repeat procedure and included in the trial's data analysis as the polyp(s) was detected during the index procedure. In rare occurrences, polyp(s) resected cannot be retrieved for histopathological analysis. These polyps will be excluded from the data analysis due to the absence of the gold standard histopathology result.

Regarding the extent of the colonoscopy procedure, analysis of polyp detection metrics will be performed twice. The first will be for all procedures. For the second analysis, incomplete procedures (i.e. procedures that do not reach the caecum) are to be excluded from the data analysis except where intubation is complicated by a histologically proven large lesion such as a malignant adenocarcinoma stricture.

11.6. Bowel Preparation

Regarding bowel preparation, analysis of polyp detection metrics will be performed twice. The first will be for all procedures and the second will be for procedures where bowel preparation was adequate (BBPS score ≥6 Or Aronchick score of 'fair' or above). To avoid inappropriately scoring procedures as inadequate bowel preparation, procedures scored with a BBPS of 5 or Aronchick score of 'inadequate' due to a single colonic segment of poor preparation, will be independently reviewed by two endoscopists, at least one will be an expert consultant gastroenterologist with an ADR of at least 30%. The reviewer will be blinded to the randomisation of the procedure, and their bowel preparation score will be used to determine the procedures bowel preparation score.

Regarding patients who are newly diagnosed with inflammatory bowel disease (IBD) during their colonoscopy, analysis of polyp detection metrics will be performed twice. The first will be for all procedures. For the second analysis, patients with a new diagnosis of IBD (ulcerative colitis, Crohn's disease or indeterminate colitis) will be excluded from the data analysis.

11.7. Management of Bias and Potential Confounding Factors

The study design accounts for both reader and case variability (MRMC). Endoscopists will evaluate a similar number of patients in both arms (with and without CADe arms), both overall and with respect to the stratifications considered. Randomization will be stratified by patients' age, sex and colonoscopy indication (screening or surveillance), to avoid bias related to patient characteristics.

11.8. Missing, Unused or Spurious Data, Including Drop-outs

Procedures that should be excluded from the data analysis are termed "dropouts". These include:

- The CADDIE AI device is mistakenly switched off during the colonoscopy procedure for a patient randomised to the CADDIE arm.
- The endoscopist performing the colonoscopy changes during the procedure to an endoscopist not enrolled in the trial. For example, the trial endoscopist encounters a difficult intubation to the caecum and to prioritise the patient's safety, a second endoscopist who is not enrolled in the trial performs the remainder of the procedure.
- An endoscopist exits the study before completing the minimum number of procedures as per the study protocol.

Whether and how subjects are to be replaced

A dropout rate of about 10% is expected and its extent will be summarised in each arm and at each time point. Potential bias due to missing data will be investigated initially by comparing the baseline characteristics of the trial participants with complete measurements compared to those who have incomplete or no outcome data, using appropriate statistical comparisons.

Protocol deviations that could impact on the results of the analyses will be described. All individuals who withdraw consent shall be excluded from the analyses from the point of withdrawal, although any data collected from such patients prior to the point of withdrawal shall be included unless otherwise specified by the patient. Reasons for withdrawal from the trial will be summarised.

Prior to performing analyses, basic checks shall be performed on the collected data to ensure accuracy. Each outcome variable and baseline demographic variable shall be checked for:

- missing values;
- values beyond an acceptable range;
- other inconsistencies.

If missing values or other inconsistencies are present the corresponding data shall be checked with the aid of the central research team and local site research team and, where necessary, either corrected or deemed to be missing. Any such changes made to the dataset shall be documented fully.

Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data) will be performed.

12. DATA MANAGEMENT

Data Management procedures are detailed in trial specific Data Management plan. The handling of all data entered onto the trial databases will be the responsibility of the Sponsor or delegate CRO. It will be the responsibility of the investigator to ensure the accuracy of all data entered in the trial databases. The site delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

12.1. Completion of Case Report Forms

Data in the trial will be collected by the local research team using a web-based EDC system provided by an independent third-party. Only designated site personnel who are delegated this duty on the delegation log will be able to enter and modify data onto the online EDC system. Access to the EDC system is strictly user-controlled. Data for each participant will be entered into the CRFs using the participant's unique trial identification number only.

If additional documentation (e.g. clinic or procedural notes, adverse event summaries, test reports) are required for any reason it must be appropriately redacted to block the trial participant's name and any additional identifying information, and the participant's unique study ID code inserted, prior to being sent.

The principal investigator will be responsible for the timing, accuracy and completeness of the eCRF for each individual subject. This will be maintained by the local PI or delegated research staff. The personal data recorded on all documents will be regarded as confidential.

The PI must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the PI must keep a separate list of all subjects entered into the clinical investigation showing each subject's initials, date of birth and assigned subject number (for identification purposes). A Subject Identification Log will be provided in the Investigation Site File to record this.

All data will be handled in accordance with the Data Protection Act 2018 and General Data Protection Regulation.

12.2. Data Review, Database Cleaning, and Issuing/Resolving Data Queries.

All data entered on the eCRFs will be monitored (100% monitoring) by a sponsor representative trained on the CIP and who has current GCP training. Data Clarification or queries will be issued to the Investigator should a discrepancy be found between the source and eCRF. The Investigator will be required to verify and correct all errors or provide an explanation for the discrepant data. Sponsor representatives will re-verify the corrected data and mark the clarification as resolved at the next monitoring visit.

12.3. Procedures for Verification, Validation and Securing of EDC Systems

All source documents shall be maintained by the investigational sites throughout the course of the investigation. All findings in this investigation must be documented as source data, and therefore can be verified (and audited). Source documentation may be paper or electronic and is defined as the first time the data appears and may include for example; phone interview notes, clinical records, hospital records, colonoscopy reports, death/autopsy reports, and any other material that contains original information used for clinical study data collection or adverse event reporting. It should be possible to verify the inclusion and exclusion criteria for the investigation from available source

Access to the eCRF data shall be limited to site representatives directly involved in the collection, analysis, maintenance or safety monitoring of the data. The research team will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

Data will be stored in a secure manner and the trial will be registered in in accordance with the Data Protection Act 2018 and General Data Protection Regulation (GDPR).

Data collected from trial participants will be submitted to two study databases. The first is an electronic data capture (EDC) database via eCRFs. This will include all trial participant data that is non-image related. The second is the video database which will be stored in the CADDIE cloud storage system. The data in the two databases will be correlated through pseudonymized patient IDs.

In both arms of the trial, the entire colonoscopy procedure will be recorded via the CADDIE device and uploaded in a pseudo-anonymised format to the central research team using a secure stand-alone cloud-based storage system for data management.

The site research team will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified, in accordance with the Data Protection Act 2018 and General Data Protection Regulation.

13. SAFETY REPORTING

13.1. Reporting requirements

CADDIE is a CE marked device. As such, safety reporting will follow the applicable requirements for the Vigilance System as outlined in Medical Device Regulation No. 2017/745, Article 87, and the guideline MEDDEV 2.12-1 rev. 8, which can be found at this link: https://ec.europa.eu/docsroom/documents/36292

Table 4. Safety Definitions

Term	Definition
Adverse Event	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. **Note 1:** This definition includes events related to the investigational medical device or the comparator **Note 2:** This definition includes events related to the procedures involved **Note 3:** For users or other persons, this definition is restricted to events related to investigational medical devices
Incident / Device Malfunction	Any malfunction or alteration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effects (adverse events)
Serious Incident	Any incident that directly or indirectly led, might have led or might lead to any of the following (serious adverse event): (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat;
Serious Adverse Event (Art. 2 No. 58 of Regulation (EU) 2017/745)	'serious adverse event' means any adverse event that led to any of the following: (a) death, (b) serious deterioration in the health of the subject, that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalisation or prolongation of patient hospitalisation, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (v) chronic disease, (c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect;
Serious Public Health Threat	An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time
Device Deficiency (DD)	DD is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling; device deficiencies may relate to the investigational or the comparator device.

13.2. Reporting Procedures

All adverse events listed in Table 4 will be reported to the CA of each Country according to the local regulations and laws.

All adverse events occurring to a participant will be initially recorded in the study CRF and reported to the Principal Investigator and Sponsor (unless exempt from being reported). All assessments shall be recorded and adverse event data shall be collated and included in the study analysis.

13.3. Assessments of Adverse Events

The Principal Investigator will use the following criteria in the assessment of adverse events:

13.3.1. Severity

Each adverse event will be assessed for the following criteria:

Severity Category	Definition
Mild	The adverse event does not interfere with the subject's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subject's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health Note: A severity rating of severe does not necessarily categorise the event as an SAE.

13.3.2. Expectedness

Category	Definition
Expected	An adverse event that is consistent with the information about the device listed in the Instructions for Use, Risk Assessment or clearly defined in this CIP.
Unexpected	An adverse event that is not consistent with the information about the device listed in the Instructions for Use, Risk Assessment or clearly defined in this CIP.

There are no foreseeable anticipated adverse device effects (i.e. it is not expected for the investigational device to directly cause any adverse events). The CIP will be used as the reference document to assess disease related and/or procedural expected events.

13.3.3. Causality

The assessment of relationship of adverse events to the study procedures/interventions and the CADDIE device will be a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

- Causal Relationship – the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or

procedures;
- the event involves a body-site or organ that
- ›the investigational device or procedures are applied to;
- ›the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/clinical condition and/or an effect of another device, drug, or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

- Probable – the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- Possible – the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition and/or an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible
- Unlikely – the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- Not Related – relationship to the device or procedures can be excluded when:
  - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has no temporal relationship with the use of the investigational device or the procedures;
  - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - the event involves a body-site or an organ not expected to be affected by the device or procedure;
  - the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
  - harms to the subject are not clearly due to use error;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

14. STUDY MANAGEMENT

14.1. Financing and Insurance

The study will be funded by the Sponsor ODIN Medical Ltd.

Study participants will be insured by the Sponsor for study related injuries according to local regulatory requirements.

The Sponsor will be responsible for the review and approval of the Investigators financial disclosure or certification. The Sponsor will cover the cost of the study through contracts with each clinical institution.

14.2. Sponsor Oversight

As the study Sponsor, ODIN Medical Ltd. has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the pertinent regulatory agencies.

14.3. Study Equipment

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.

Since CADDIE is a software accessed through a regular web browser, no installation of it is required by the user. CADDIE is logged into with a username and password on a webpage. The username and password will be provided by email (further information on this will be provided during training).

A trained member of Odin Medical will ensure that CADDIE is compatible with the user's existing hardware and accessories and that these meet the minimum host system specification as detailed in the instructions for use. This initial set-up and access to CADDIE software on the site's PC will involve checks and recorded tests to verify the set-up and access to CADDIE has been successful.

15. COMPLETION OF THE TRIAL

Both the Sponsor and the Principal investigator reserve the right to terminate the clinical investigation at any time. In terminating the clinical investigation, the clinical site and the principal investigator will assure that adequate consideration is given to the protection of the subject's interests.

15.1. Subject Withdrawals and Discontinuation

Patients will be reassured that their participation in the trial is entirely voluntary, and that they are free to withdraw their consent from the trial at any time. During the course of this clinical investigation, subjects may elect to withdraw from further treatment through any of the following reasons:

- Subject's rescission of consent.
- Any unexpected adverse device effect which is, in the opinion of the PI, related to the device and will endanger the wellbeing of the subject if the treatment is continued.
- The development of any undercurrent illness(es), infection or condition(s) that might interfere with the Clinical Investigation Plan.
- Any problem deemed by the PI and/or the investigational site to be sufficient to cause discontinuation.

All subjects discontinued from the clinical investigation due to an unexpected adverse device effect, directly related to the clinical investigation, will be treated until the effect resolves. The PI will clearly document the date and reason(s) for subject withdrawal in his/her eCRF and the monitor must be notified.

Subjects who are withdrawn will not be replaced if they have received the investigational device. If possible, any procedures or assessments planned for the subject on withdrawal from the clinical investigation should be performed when intention to withdraw the subject is announced.

Subjects who are withdrawn prior to receiving investigational device will be replaced.

15.2. End of the trial

The expected duration of the trial is 9 months from recruitment of the first participant.

The end of trial is the date of the colonoscopy of the last participant/collection of the last histology result (whichever is later).

15.3. Study termination criteria

As discussed in section 9.2, CADDIE technology and participation in the study is considered low risk. The AI polyp detection system is CE marked, it is commercially available in Europe being used in many centers on a routine clinical basis. There are multiple similar CE Marked products on the market from other companies including Medtronic and Olympus and collectively AI has been used on over 10,000 patients worldwide with no serious adverse events related to the medical devices identified.

In addition, risk mitigations have been applied for this study (see 10-3 and 10.4) and the overall risk of the CADDIE is extremely low. CADDIE is a software installed on a separate computer and does not have any contact with the patient. It does not interfere with the standard colonoscopy examination. Although endoscopist will be expected to inspect any area where the device deems to have detected a polyp, the endoscopist is responsible for diagnosing and management as per normal endoscopy practice.

The entire study may be suspended or prematurely terminated by the Sponsor in the following cases:

- Serious adverse events as defined in Section 13 attributable to the investigation.
- If new data become available which raises concern about the safety of the study device, so that continuation of the study might cause unacceptable risks to the subjects.
- If suspicion of an unacceptable risk to subjects arises during the clinical investigation, the Sponsor may suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed.
- National regulatory authority withdrawal of study approval.
- On recommendation by the EC for any perceived safety concern based on clinical judgment, including, but not limited to, a higher than anticipated rate for any component of the safety endpoint, device failures resulting in AEs or unexpected SAEs.
- Administrative decision by the Sponsor.

16. PUBLICATION POLICY

Upon completion or premature termination of the trial, the sponsor will prepare, in cooperation with the leading clinical investigators, the final version of the clinical trial report which will be signed by all principal investigators and the sponsor.

A single comprehensive publication may be authored on the procedure and outcomes of this study. The principal investigator shall be listed as the last author on the publication. All authors will be given a minimum of two weeks to review the manuscript and comment prior to submission.

The publication should be submitted to a peer-reviewed journal of significant quality in relation to the acquired data. The publication should be made in accordance with all participating clinical investigators and in strictly adherence to the Declaration of Helsinki (as amended). Odin Medical Inc. will have the right to review the publication for correctness and technical aspects prior to submission within a 60-day period.

The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multi-center results, any exceptions would require a written approval from the Sponsor. All proposed publications will be discussed with and reviewed by the Sponsor for technical accuracy prior to publishing or presentation at scientific forums/meetings. For purposes of abstract presentation and publication, any secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multicenter data will require the approval of the Sponsor.

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