Cover Page

Study Title	Gastroenterology Artificial INtelligence System for Detecting Colorectal Polyps (The GAIN Study)
Rev/Date	Rev C / 29Jul2022
Sponsor Name	Verily Life Sciences
NCT #	NCT05275556

Study Title	Gastroenterology Artificial INtelligence System for Detecting Colorectal Polyps (The GAIN Study)
Protocol Number	[redacted]
Version	[redacted]
Sponsor Name	Verily Life Sciences
Sponsor Address	[redacted]
Sponsor Contacts	[redacted]
Regulatory Identifiers	**IDE number:** Not Applicable

Protocol

Investigator's Agreement Signature Page

I, Principal Investigator, agree to conduct this study in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP), applicable legal and regulatory requirements, and in compliance with the provisions of this Protocol.

I am responsible for ensuring that the investigation is conducted according to this protocol and for protecting the rights, safety, and welfare of the research subjects. All personnel involved in the conduct of this study will complete Human Subject Protection training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator	Signature	Date

Confidentiality Statement

The information in the following document is provided to you as an investigator, potential investigator, or consultant, for review by you, your staff, and applicable Institutional Review Board, and is considered confidential. It is understood that the information will not be disclosed to others without written authorization from Verily Life Sciences LLC, except to the extent necessary to obtain informed consent from those persons to whom the product may be administered.

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1. Protocol Summary

Study Sponsor	Verily Life Sciences
Study Description	This is a prospective, multicenter, randomized controlled study to evaluate the effect of the Endoscopy Video Assistant for Colonoscopy (EVA-C) System on Adenomas Per Colonoscopy and Positive Percent Agreement for routine colonoscopies. The control arm is colonoscopy performed with High Definition White Light Endoscopy (HD-WLE) per standard of care. The intervention arm is colonoscopy performed with HD-WLE per standard of care plus the EVA-C System.
Study Objectives	Primary Objective ● To evaluate the effect of High Definition White Light Endoscopy with the EVA-C System on Adenomas Per Colonoscopy and Positive Percent Agreement relative to standard High Definition White Light Endoscopy alone. Secondary Objectives ● To evaluate the effect of High Definition White Light Endoscopy using the EVA-C System on Adenoma Detection Rate, False Alert Rate, Mean Withdrawal Time, and other endpoints related to polyp location, size, morphology, and histopathology.
Study Endpoints	Co-Primary Endpoints ● Difference in Adenomas Per Colonoscopy (APC) between the control and intervention arm, evaluated for superiority on the Intent To Treat (ITT) population ● Difference in Positive Percent Agreement (PPA) between the control and intervention arm, evaluated for non-inferiority on the Intent To Treat (ITT) population Secondary Endpoints ● Adenoma Detection Rate (ADR) evaluated on the ITT population ● APC, ADR and PPA endpoints evaluated on the Per-Protocol (PP) population ● APC, ADR and PPA endpoints evaluated on a modified Intent-to-Treat (mITT) population ● APC, ADR and PPA in subgroups defined by age group, sex, risk-group, race, ethnicity, colonoscopist, site, and country ● False Alert Rate (FAR) ● Mean Withdrawal (inspection) Time (MWT) ● Polyp Detection Rate (PDR) ● Proximal Adenoma Detection Rate (pADR) ● Flat Adenoma Detection Rate (fADR) ● Serrated Lesions per Colonoscopy (SLPC) ● Serrated Lesions Detection Rate (SLDR) ● Adenoma Detection Rate including Carcinoma (ADR*) ● Small Adenoma Detection Rate (sADR) ● Polyps per colonoscopy (PPC) ● Advanced Adenoma Detection Rate (aADR) ● False Positive Rate (FPR)

	[redacted]
Study Phase	Not applicable
Study Type	This is a prospective multicenter, randomized controlled study.
Regulatory Status/Trial Classification	Non-significant risk
Study Population	A minimum of 1,200 subjects will be enrolled at a minimum of 3 sites, with a possibility of a sample size increase up to 2,400. At least 51% of the study population will be enrolled within the United States.
User population	Colonoscopists having performed at least 1,000 colonoscopies with a self-reported Adenoma Detection Rate between 25% and 40%. No single colonoscopist will enroll more than 15% of the total patient population.
Description of Study Intervention	Subjects in the intervention arm will undergo a routine clinically-indicated colonoscopy using HD-WLE in conjunction with the EVA-C System. The control group will also undergo a routine clinically-indicated colonoscopy using HD-WLE not aided by the EVA-C System. The EVA-C System is designed to detect polyp-like morphologies. It does not differentiate between adenomatous and hyperplastic polyps. It is up to the colonoscopist's discretion, based on all available information, to decide whether to resect a given polyp, irrespective of the presence of an EVA-C System bounding box. The EVA-C System is not intended to change the colonoscopist's management of an identified lesion.
Subject Duration	The subject duration is approximately 1-2 hours, including informed consent process and colonoscopy procedure. There is no follow-up required.
Procedure	**Colonoscopy procedure** ● High Definition White Light Endoscopy will be used, per standard of care. ● Dye-based or virtual chromoendoscopy may be used for characterizing individual polyps at the colonoscopist's discretion, but may not be used for overall inspection of the colon. ● Bowel preparation will be evaluated after cleaning and will be scored using the Boston Bowel Preparation Scale (BBPS) separately in each of the three regions of the colon: the right colon (including the cecum and ascending colon), the transverse colon (including the hepatic and splenic flexures), and the left colon (including the descending colon, sigmoid colon, and rectum).[1] Subjects with a BBPS score of 0 or 1 in any of the three colonic regions of the colon will be excluded from the Per Protocol analysis.

	• In the right, transverse, and left colon, lesions are to be removed, at the colonoscopist's discretion, per standard of care. Notably, in the left colon, only those lesions that appear adenomatous are to be removed, per standard of care. **In the intervention arm only:** • The EVA-C System does not differentiate between adenomatous and hyperplastic polyps. It is designed to identify polyp-like morphologies. It is up to the colonoscopists' discretion, based on all available information, to decide whether to resect a given polyp or lesion, irrespective of the presence of the EVA-C System bounding box. The EVA-C System is not intended to change the colonoscopist's management of an identified polyp or lesion. • The colonoscopist is expected to interrogate any region of interest highlighted by the EVA-C System bounding box. • In the right, transverse, and left colon, lesions are to be removed, at the colonoscopist's discretion, and irrespective of the EVA-C System bounding box, per standard of care. Notably, in the left colon, only those lesions that appear adenomatous are to be removed, per standard of care. • For bounding boxes that persist on the screen for at least 2-3 seconds (per colonoscopist's discretion) but do not contain a polyp, the colonoscopist will verbally confirm a 'false alert' to the study personnel. **Polyp resection and pathology processing:** • Endoscopic images of each polyp will be acquired before polyp removal. • Study personnel will record the polyp size (≤ 5 mm, 6-9 mm, ≥ 10 mm), location (cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, rectum), and morphology (Pedunculated 0-Ip, Sessile 0-Is, Flat 0-IIa, or Depressed 0-IIc in accordance with Paris classification[2]), as reported by the colonoscopist. • Study personnel will record the time-of-day at the moment the colonoscopist says 'snare closed' (or as the snare is closed) and each polyp will be assigned a number or letter in the sequential order in which it is removed (eg. 1, 2, 3,… or A, B, C, …) per standard of care. • If the polyp is not able to be retrieved, the study personnel will note 'not retrieved' in the source documentation. • Each polyp will be placed into an individually labeled specimen jar with only one polyp per specimen jar. If a polyp trap is used on the endoscope, the polyp trap needs to be advanced/rotated for each new resected polyp. • The specimen jar will be labeled with the sequential number or letter correlating to the order in which the polyp was removed (eg. 1, 2, 3,… or A, B, C,...) per standard practice. • The pathology report will note each sequential polyp number or letter and location per standard practice.
Inclusion Criteria	• Scheduled to undergo routine screening (including, but not limited to, FIT/Cologuard positive), routine surveillance (≥3 years as scheduled since last colonoscopy), or diagnostic (symptomatic) colonoscopy with High Definition White Light Endoscopy.

	• Between the ages of 45 and 80 years, inclusive • Able and willing to provide written informed consent
Exclusion Criteria	• Self-reported pregnancy • Known diagnosis of Colorectal Cancer • History of, or referral for, Inflammatory Bowel Disease • Previous surgery involving the colon or rectum • Referral for known polyp or assessment of post-polypectomy site (i.e. less than 3 years since last colonoscopy). • High suspicion or diagnosis of genetic polyposis syndromes, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), or any other high-risk family history meeting Bethesda guidelines.[3] • Referral for overt, symptomatic gastrointestinal bleeding

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[redacted]	[redacted]

3. Prior Experience

[redacted]

[redacted]

4. Study Background and Rationale

4.1. Background

Reductions in the incidence of colorectal cancer (CRC) and age-related mortality have long been demonstrated through population-based screening programs.[5,6] Of these, regular cadence colonoscopy exams are the preferred cancer prevention screening test, for concurrent detection and removal of suspicious neoplasms.[7,8]

However, approximately 25% of adenomas and serrated polyps (primarily those ≤10mm) are missed during screening colonoscopies.[9,10]

The primary quality indicator relied upon by colonoscopists performing colonoscopies is adenoma detection rate (ADR)[11,12], defined as the percentage of patients undergoing screening colonoscopy who have one or more conventional adenomas detected and removed. Another important quality metric, particularly applicable to CADe technologies, is Adenomas Per Colonoscopy (APC), which is defined as the average number of histologically confirmed adenomas resected per colonoscopy. Polyp recognition or the failure to optimally recognize polyps is a major factor contributing to ADR and APC.[13,14]

Computer-aided polyp detection (CADe) systems show the ability to enhance polyp detection and recognition, thereby positively impacting ADR and APC.[15,16] Estimates report that every 1% increase in ADR lowers the risk of interval colorectal cancers by 3%-6%.[17] As such there is great importance in studying and developing CADe systems to enhance the diagnostic performance of screening colonoscopy, particularly as the recommended screening age in the United States has been reduced from 50 to 45[8], increasing the overall screening population.

There are multiple factors preceding missed polyps. Operator related factors including skill level, fatigue, and distraction, are known and reported previously.[18] Patient related factors include age, gender, and quality of bowel preparation. Algorithmic CADe solutions represent an attractive option to proactively mitigate some of these factors, and have the potential to improve polyp and adenoma detection in real-time.

4.2. Rationale

The clinical performance of the EVA-C System was previously tested in a prospective 100 patient pilot study where the use of the device was determined to increase the polyp detection rate in a colonoscopy practice outside of the United States.[4] The present global multicenter, randomized, controlled study is designed to determine the clinical performance of the EVA-C System compared to standard-of-care colonoscopy in patients undergoing clinically indicated colonoscopy. The co-primary outcomes of the study are to measure the difference in APC and PPA between routine colonoscopy procedures and those assisted by the EVA-C System. The

results of this study will provide further insight into the clinical impact of the use of the EVA-C System during colonoscopy.

5. Study Design

5.1. Overview

This is a prospective, multi-center, randomized controlled study.

5.2. Study Objectives and Endpoints

This study will evaluate the effect of the EVA-C System on Adenomas Per Colonoscopy and Positive Percent Agreement for routine colonoscopies. The control arm is colonoscopy with High Definition White Light Endoscopy (HD-WLE) per standard of care. The intervention arm is colonoscopy with HD-WLE per standard of care plus the EVA-C System.

Adenomas Per Colonoscopy (APC) is defined as the average number of histologically confirmed adenomas resected per colonoscopy.

The following findings are considered positive for the definition of APC, ADR, and other adenoma-related secondary endpoints (where specified):

- Adenoma
- Tubular adenoma
- Tubulovillous
- Villous
- High Grade Dysplasia

The following pathology findings are **not** considered positive for the definition of APC and ADR, and other adenoma-related secondary endpoints (where specified):

- Serrated-class lesions:
  - Hyperplastic polyps (HPs)
  - Sessile serrated lesions (with or without dysplasia) (SSLs)
  - Traditional serrated adenomas (TSAs)
- Inflammatory, lymphoid aggregate, normal mucosa

Positive Percent Agreement (PPA) is defined as the total number of histologically confirmed Clinically Significant Excised Lesions, divided by the total number of excisions.

For calculating PPA, Clinically Significant Excised Lesions are defined as follows:

- Neoplastic lesions (Adenoma, Tubular adenoma, Tubulovillous, Villous, High Grade Dysplasia, Intramucosal carcinoma, Adenocarcinoma);
- Serrated-class lesions classified according to the WHO serrated-class lesion classification below;
- Hyperplastic polyps of the proximal colon (caecum, ascending colon, hepatic flexure, transverse colon)

According to the World Health Organization (WHO), serrated-class lesions are currently classified into three main categories as follows:

- Hyperplastic polyps
- Sessile serrated lesions (with or without dysplasia), and

- Traditional serrated adenomas

5.3. Primary Endpoint(s)

- Both co-primary endpoints are evaluated on the Intent to Treat (ITT) population.
- **Adenomas Per Colonoscopy Co-Primary Endpoint**

  Difference in Adenomas Per Colonoscopy (APC) between the control and intervention arm, evaluated for superiority.

  The APC co-primary endpoint is a test of superiority. The null and alternative hypotheses for establishing superiority are as follows, where APC(I) and APC(C) are Intervention and Control arms APCs respectively:

  Ho: $APC(I) \leq APC(C)$

  Ha: $APC(I) > APC(C)$

  A statistical test of this hypothesis will be conducted.

- **Positive Percent Agreement (PPA) Co-Primary Endpoint**

  Difference in Positive Percent Agreement (PPA) between the control and intervention arm, evaluated for non-inferiority.

  The PPA co-primary endpoint is a non-inferiority comparison based on the difference in PPA across arms. For non-inferiority, the goal of the study is to show that the effect of Intervention (I) is not inferior to the effect of Control (C) by a pre-specified amount, i.e., the NI margin (M). The null and alternative hypotheses are as follows:

  Ho: $PPA(I) - PPA(C) \leq M$ (I is inferior to C)

  Ha: $PPA(I) - PPA(C) > M$ (I is not inferior to C)

  A statistical test of Ho will compare the lower bound of the two sided 95% confidence interval for PPA(I)–PPA(C) with M, which is pre-specified as -10%. If the lower bound lies above M, non-inferiority of I relative to C will be established.

- As co-primary endpoints, there are no issues related to multiple testing as both tests must successfully reject H0 in order to declare overall endpoint success.

5.4. Secondary Endpoints

- Adenoma Detection Rate (ADR)

  The Adenoma Detection Rate is defined as the number of patients with at least one histologically confirmed adenoma (the pathology findings that count as positive for adenoma are defined in Section 5.2) divided by the total number of patients enrolled per study arm.

- Evaluation of ADR on the ITT population
- Evaluation of the APC, ADR and PPA endpoints on the Per-Protocol (PP) population
- Evaluation of the APC, ADR and PPA endpoints on a modified Intent-to-Treat (mITT) population that includes only patients in the Screening and Surveillance risk groups

- Subgroup analysis of APC, ADR and PPA in groups defined by age group, sex, risk-group, site, race, ethnicity, colonoscopist, site, and country
- False Alert Rate (FAR)

  A false alert is defined as a bounding box that persists on the screen (approximately 2-3 seconds per the judgment of the colonoscopist) that is then determined by the colonoscopist not to contain a polyp. The false alert rate is calculated as the number of false alerts per procedure conducted in the intervention arm of the study.

- Mean Withdrawal and Inspection Time (MWT)

  The withdrawal time is defined as the time measured from the moment the withdrawal phase of the procedure begins (with the scope in the cecum) to the moment the scope is withdrawn from the patient. The mean Inspection time measurement (also called net withdrawal time) will exclude resection time, and other peri-resection activity not deemed to be colonic inspection. Inspection times for both the control arm and intervention arm will be calculated retrospectively upon review of the video recordings.

- Polyp Detection Rate (PDR)

  Polyp detection rate is defined as the proportion of patients with at least one histologically-confirmed polyp detected.

- Proximal Adenoma Detection Rate (pADR)

  pADR is defined as the proportion of patients with at least one histologically-confirmed adenoma (the pathology findings that count as positive for adenoma are defined in Section 5.2) detected in proximal colon (caecum, ascending colon, hepatic flexure, transverse colon).

- Flat Adenoma Detection Rate (fADR)

  fADR is defined as the proportion of patients with at least one histologically-confirmed non-polypoid adenoma (the pathology findings that count as positive for adenoma are defined in Section 5.2) detected;

- Serrated Lesions per Colonoscopy (SLPC)

  SLPC is defined as the number of histologically confirmed serrated lesions detected, divided by the total number of colonoscopies

- Serrated Lesions Detection Rate (SLDR)

  SLDR is defined as the proportion of patients with at least one histologically confirmed serrated lesion detected

- Adenoma Detection Rate including Carcinoma (ADR*)

  ADR* is defined as ADR (see above), but also includes histologically-confirmed intramucosal carcinoma and adenocarcinoma.

- Small Adenoma Detection Rate (sADR)

sADR is defined as proportion of patients with at least one adenoma 5mm or smaller detected (the pathology findings that count as positive for adenoma are defined in Section 5.2);

- Polyps per Colonoscopy (PPC)

  PPC is defined as the total number of histologically-confirmed polyps found divided by the total number of colonoscopies performed, per study arm.

- Advanced Adenoma Detection Rate (aADR)

  aADR is defined as the proportion of patients with at least one adenoma (the pathology findings that count as positive for adenoma are defined in Section 5.2) ≥ 10 mm, or any adenoma < 10 mm, which was either of high-grade dysplasia (HGD) or villous or tubulovillous;

- False Positive Rate (FPR)

  Defined as the proportion of colorectal lesions resected or biopsied and subsequently not histologically-confirmed to be clinically relevant colorectal polyps (e.g. a pathology finding of normal mucosa, inflammatory tissue, stool or debris, lymphoid aggregates)

[redacted]

5.6. Comparator or Control Groups

Patients randomized to the control arm of the study will undergo a standard-of-care colonoscopy procedure (using High Definition White Light Endoscopy) without the EVA-C System turned on.

6. Study Population

6.1. Sample Size and Number of Participating Sites

A minimum of 1,200 subjects will be enrolled at a minimum of 3 sites, with a possibility of a sample size increase up to 2,400. At least 51% of the study population will be enrolled within the United States.

6.2. Inclusion Criteria

Prospective subjects must meet all of the following criteria to be eligible for participation in the study:

1. Scheduled to undergo routine screening (including, but not limited to, FIT/Cologuard positive), routine surveillance (≥3 years as scheduled since last colonoscopy), or diagnostic (symptomatic) colonoscopy with High Definition White Light Endoscopy
2. Between the ages of 45 and 80 years, inclusive
3. Able and willing to provide written informed consent

6.3. Exclusion Criteria

Prospective subjects must be excluded from participation in this study if any of the following criteria are met:

1. Self-reported pregnancy
2. Known diagnosis of Colorectal Cancer
3. History of, or referral for, Inflammatory Bowel Disease
4. Previous surgery involving the colon or rectum
5. Referral for known polyp or assessment of post-polypectomy site (i.e. less than 3 years since last colonoscopy).
6. High suspicion or diagnosis of genetic polyposis syndromes, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), or any other high-risk family history meeting Bethesda guidelines
7. Referral for overt, symptomatic, gastrointestinal bleeding

6.4. Discontinued/Withdrawal of Study Subjects

Participation in this research study is voluntary and subjects may withdraw at any time. In the event the subject chooses to withdraw, he/she will be instructed to contact the Investigator immediately and may be asked the reason for their withdrawal from the study. The subject may also be terminated from the research study at any time if the Investigator considers it to be in his/her best medical interest. The Investigator may withdraw the subject any time due to the non-compliance with respect to the provisions of the protocol. If a subject withdraws prior to study completion, no new health information identifying him/her will be gathered after that date.

Information that has already been gathered may still be used and given to others. Subjects will be informed of any new significant information regarding new findings related to the study device that may develop during the course of the study that may be related to his/her willingness to continue participation as a research subject.

Subjects will either satisfactorily complete all requirements set forth in the Clinical Investigation Plan or their participation in the clinical study will be prematurely terminated. The completion of a subject's participation in the study or early departure from the study, including reasons for early discontinuation, will be fully documented on the appropriate case report form.

7. Study Assessment Plan and Methods

7.1. Schedule of Study Procedures Table

Procedures[a]	Screening	Enrollment	
		Control (Colonoscopy)	Intervention (Colonoscopy + EVA-C System)
Informed Consent	✔		
Inclusion/Exclusion Criteria	✔		
Medical History	✔		
Demographics	✔		
Current Medications	✔		
Randomization		✔	✔
Colonoscopy		✔	✔
Colonoscopy Recording		✔	✔
Device Accountability			✔
Histology		✔	✔
Adverse Event Evaluation		✔	✔
Protocol Deviation Evaluation		✔	✔
Device Deficiency Evaluation			✔
[a] Case Report Forms not limited to the below listed data			

7.2. Study Conduct and Procedures

The study is conducted in accordance with this clinical investigational plan and ethical principles consistent with GCP and applicable regulatory requirements to protect the rights, safety, and well-being of the study subjects.

Prior to any study-related procedures, informed consent must be obtained (Section 12.3).

7.2.1. Screening/Screen Failures

The following will be conducted during the Screening Visit:

1. Both the subject and the investigator (or designee) will sign the Informed Consent Form (ICF).
2. The Investigator (or designee) will complete an assessment to determine that the subject still meets eligibility criteria.
3. The Investigator (or designee) will review the subjects' current medication, medical history, and collect demographics.

4. If the subject does not meet all eligible criteria, the subject will be exited from the study.

Screen failures are defined as subjects who consent to participate in the clinical trial but are not randomized into the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

This data will be documented on the appropriate case report form.

7.2.2. Enrollment

Subjects will be considered enrolled in the study when they have signed the IRB/EC approved ICF and have met all eligibility criteria.

7.2.3. Randomization/Blinding/Masking

Enrolled subjects will be randomized into control or intervention arms in a 1:1 allocation using block randomization within subjects strata defined by age-group, sex, and risk-group. Subjects will be assigned to control or intervention arms within each colonoscopist based on a predetermined randomization schedule.

Subjects, investigators, study site personnel, and pathologists will not be blinded to treatment assignments. All Verily personnel involved in the statistical analysis of this study will be blinded to treatment assignment. For the interim analysis, unblinded analysis will be performed by an independent statistician, the results of which will be communicated to a select group of Verily personnel not involved in the study management.

7.2.4. Subject Compensation

Subjects may be compensated for their participation in the study. The details of compensation will be provided to the subjects in the informed consent form.

7.2.5. Visit Schedule

After confirmation that the ICF has been signed by both the investigator (or designee) and the subject and eligibility has been confirmed, the following assessments will be performed.

- Subjects will be randomized using the randomization system within the EDC system provided by Sponsor.
- If a subject is assigned to the intervention group, the EVA-C System will be turned on prior to scope insertion and will remain on for the duration of the colonoscopy.
- If a subject is assigned to the control group, the EVA-C System will not be used and will remain turned off during the colonoscopy.
- In both the control and intervention groups, the colonoscopy video feed will be recorded from scope-in to scope-out, while the scope is inside the subject. Any

protected health information (PHI) in the colonoscopy video feed will be masked prior to recording or removed after recording, but prior to sending to Sponsor.

Colonoscopy procedure

- High Definition White Light Endoscopy will be used, per standard of care.
- Dye-based or virtual chromoendoscopy may be used for characterizing individual polyps at the colonoscopist's discretion, but may not be used for overall inspection of the colon.
- Bowel preparation will be evaluated after cleaning and will be scored using the Boston Bowel Preparation Scale (BBPS) separately in each of the three regions of the colon: the right colon (including the cecum and ascending colon), the transverse colon (including the hepatic and splenic flexures), and the left colon (including the descending colon, sigmoid colon, and rectum).[1] Subjects with a BBPS score of 0 or 1 in any of the three colonic regions of the colon will be excluded from the Per Protocol analysis.
- In the right, transverse, and left colon, lesions are to be removed, at the colonoscopist's discretion, per standard of care. Notably, in the left colon, only those lesions that appear adenomatous are to be removed, per standard of care.

In the intervention arm only:

[redacted]The EVA-C System is not intended to change the colonoscopist's management of an identified polyp or lesion.

- The colonoscopist is expected to interrogate any region of interest highlighted by the EVA-C System bounding box.
- In the right, transverse, and left colon, lesions are to be removed, at the colonoscopist's discretion, and irrespective of the EVA-C System bounding box, per standard of care. Notably, in the left colon, only those lesions that appear adenomatous are to be removed, per standard of care.
- For bounding boxes that persist on the screen for at least 2-3 seconds (per colonoscopist's discretion) but do not contain a polyp, the colonoscopist will verbally confirm a 'false alert' to the study personnel.

Polyp resection and pathology processing:

- Endoscopic images of each polyp will be acquired before polyp removal.
- Study personnel will record the polyp size (≤ 5 mm, 6-9 mm, ≥ 10 mm), location (cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, rectum), and morphology (Pedunculated 0-Ip, Sessile 0-Is, Flat 0-IIa, or Depressed 0-IIc in accordance with Paris classification[2]), as reported by the colonoscopist.

- Study personnel will record the time-of-day at the moment the colonoscopist says 'snare closed' (or as the snare is closed) and each polyp will be assigned a number or letter in the sequential order in which it is removed (eg. 1, 2, 3,… or A, B, C, …) per standard of care.
- If the polyp is not able to be retrieved, the study personnel will note 'not retrieved' in the source documentation.
- Each polyp will be placed into an individually labeled specimen jar with only one polyp per specimen jar. If a polyp trap is used on the endoscope, the polyp trap needs to be advanced/rotated for each new resected polyp.
- The specimen jar will be labeled with the sequential number or letter correlating to the order in which the polyp was removed (eg. 1, 2, 3,… or A, B, C,...) per standard practice.
- The pathology report will note each sequential polyp number or letter and location per standard practice.

Pathology processing guidelines:

- Histopathology will be performed per standard of care with the following recommended guidelines. As assessed by pathologists:
    - For polyp sizes of 1 cm and greater:

      Recommend allowing at least 24 hours in formalin for fixation prior to sectioning. Serial section (through stalk, if present) into a maximum of 3 mm blocks. For each block, recommend at least 2 sections will be acquired.
    - For polyp sizes greater than 6mm and less than 1cm:

      Bisect or serial section (through stalk, if present) into a maximum of 3 mm blocks. For each block, recommend at least two sections will be acquired.
    - For polyp sizes between 3mm and 6mm, inclusive:

      Recommend at least two slides with 8 ribbon sections per slide. For 'no significant abnormality' findings, at least 3 serial sequential deeper levels will be performed. Exhaust the block on Pathologist's discretion.
    - For polyp sizes less than 3mm:

      Recommend to ribbon section block entirely ('exhaust the block' – at least 3 slides)
    - Histopathology sections shall be stained and imaged as per standard of care.

Review of Adverse Event, Protocol Deviation, and Device Deficiencies will be completed from time of consent to study exit.

7.2.6. User Experience

Colonoscopists using the EVA-C System as a part of this study may be asked to provide their written or electronic feedback about their experiences with using this system throughout the course of the study.

7.2.7. Investigational Product

The study device will be used on the day of the study visit. The investigator is responsible for accountability at the study site as indicated in Section 11.3, and the study devices will be stored in a locked cabinet and/or in a locked office at the site.

7.2.8. Adverse Events

Adverse events related to study device and study procedures, all serious adverse events, and all unanticipated adverse device effects will be reported on the appropriate CRF in a timely manner as indicated in Section 9. They will be collected from time of consent to study exit and will be reviewed by the Sponsor. The investigator will provide further information regarding adverse events as requested by the Sponsor.

7.2.9. Protocol Deviations

A protocol deviation is when the procedures that are outlined in the Protocol are not followed. There are two types of protocol deviations in this study: major deviations and minor deviations.

A major deviation is defined as an event that resulted in an increased risk to a subject or others; affecting the rights, safety and/or welfare of the subject; or affecting the integrity of the clinical study. Major deviations include (but are not limited to): failure to obtain Informed Consent prior to enrollment, enrolled subject who participated in the study session does not meet inclusion/exclusion criteria or unauthorized use of study device on a subject not enrolled in the study; AEs that are not reported by the Investigator during the protocol-specified timeframe.

A minor protocol deviation is defined as deviating from the protocol and include (but are not limited to): protocol-required testing and/or study visit were not completed.

All deviations will be reported on the appropriate CRF.

7.3. Test Procedures

7.3.1. Laboratory parameters

This section is not applicable for this study.

7.3.2. Special Methodologies and Evaluations

7.3.2.1. Retrospective Review of Colonoscopy Video Recording

Inspection time, defined as time when not resecting, washing, or preparing for resection, will be calculated retrospectively from colonoscopy video recording (subtracting out the non-inspection time).

8. Risk Analysis

This study is a non-significant risk device study and subjects in this study will not be exposed to significant risk. The risks of participation in this study are not expected to be different from patients' routinely scheduled colonoscopy visit.

8.1. Risk Analysis

Verily Life Sciences has conducted an analysis of the benefits and risks of the EVA-C System.

Verily Life Sciences has determined that this clinical investigation is justified, as the overall potential benefit to the population outweighs its risks.

8.2. Benefits

There is no direct benefit to the participating subjects for this study, but the information obtained will be used in scientific research and may be helpful to others in the future.

8.3. Risks

This study is a non-significant risk device study, and this study exposes subjects to minimal risks not expected to be significantly different from patients' routinely scheduled colonoscopy visit.

Possible risk, in addition to risks associated with the clinical colonoscopy, may include:

- Algorithm malfunction or misinterpretation leading to:
    - False positive detection potentially resulting in procedural delays due to prolonged interrogation/examination. However, the software is not designed to replace clinical decision making.
    - False negative missed detection, potentially resulting in delayed patient treatment. However, this delay would have occurred regardless of device use. Additionally, it is possible physicians could develop an overreliance on the device.
- Failure to identify lesions, potentially resulting in delayed patient treatment, because of software or hardware malfunction. Such malfunctions might include:
    - Incompatibility with hardware and/or data source
    - Inadequate mapping of software architecture
    - Degradation of image quality
    - Prolonged delay of real-time endoscopic video

In all cases of device malfunction, the device may be turned off or unplugged by the colonoscopist or the study team at any time, to avoid further procedural risk, and the procedure would continue as planned without the use of the EVA-C System.

Another risk of this study includes breach of privacy and confidentiality of protected health information (PHI).

The following measures will be implemented to help minimize risks to subjects during the study:

- All PHI will be stored in a secure locked office on a password protected computer. The informed consent forms will be stored in a locked cabinet in a locked office at the site. Measures to ensure complete de-identification prior to data transfer and analysis will be taken.

9. Adverse Events (AE), Serious Adverse Events (SAE), and Unanticipated Problems

During and following a subject's participation in the study, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

In the event medical care to a subject is required, the medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

9.1. Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury in subjects, users or other persons, that is considered a change from baseline or pre-study status, whether or not related to the investigational medical device.

Any pre-existing medical condition or symptoms present in a subject will not be considered an AE in this study, unless it worsens as a result of this study.

For this study, AEs related to the study device and study procedures will be reported on an AE Case Report Form and will include the following: Date/time of onset, date the site first becomes aware of the event, description of the event, the duration of the event, the severity of the event, assessment of the relation of the event to the study device and study procedure, description of action taken, if any, and the event outcome.

In the event medical care to a subject is required, the medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.

9.2. Serious Adverse Events

A Serious Adverse Event (SAE) is defined as an adverse event that is anticipated or unanticipated and which reasonably suggests that one of the manufacturers' devices has or may have caused or contributed to a death or serious injury.

A Serious Adverse Event is an Adverse Event that led to: (a) death, (b) serious deterioration in the health of the subject that either resulted in a (i) life-threatening illness or injury or (ii) permanent impairment of a body structure or a body function, or (iii) in-patient or prolonged hospitalization or (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or (c) fetal distress, fetal death or a congenital abnormality or birth defect.

These events are typically reportable to health authorities. For this study, all serious Adverse Events will be reported to the Sponsor within 24 hours of knowledge of the event.

9.3. Unanticipated Adverse Device Effects (UADE)

An Unanticipated Adverse Device Effect (UADE) is a serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or

welfare of subjects. Anticipated potential adverse device effects have been identified in the Sponsor Risk Management files.

The Principal Investigator will assure that all unanticipated adverse device effects (UADE) involving risk to subjects or others will be reported to the Sponsor within 24 hours of knowledge of the event. All UADE's will be evaluated and the results of such evaluation will be reported to the IRB within ten (10) working days after the event is reported by the study subjects. The Sponsor will report all SAE's and UADE's to the appropriate regulatory authority. All Serious and Unanticipated Adverse Effects will be reviewed by a Medical Monitor.

10. Device Deficiencies

A device deficiency is an observed or detected inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety or performance/efficacy. Device deficiencies will be collected on the Device Deficiency CRF. Any adverse events resulting from a device deficiency will be collected on the Adverse Event CRF as appropriate.

If the EVA-C System breaks or malfunctions, the device will be returned to the Sponsor and may be replaced with a new device.

Verily will manage the EVA-C System troubleshooting with sites and as well as logistics of device returns and replacement if necessary.

11. Investigational Product(s)/Medical Device

11.1. Investigational Product(s)/Device Description

The EVA-C System is a computer-aided detection (CADe) system that uses artificial intelligence to aid in identifying colorectal polyps during High Definition White Light Endoscopy (HD-WLE) based colonoscopies.[redacted]

[redacted]

[redacted]

11.2. Control Product/Device Description

This section is not applicable for this study.

11.3. Investigational Device Labeling & Accountability

The Investigator is responsible for accountability at the study site. The Investigator should take adequate precautions, including storage of the investigational study devices to prevent diversion of the products into unauthorized channels of distribution. All unused products will be returned to the Sponsor.

The EVA-C System is an investigational device and will be packaged with a label with the name and place of business of the manufacturer and distributor. The device will also be labeled with the following: "CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use." Devices used outside the United States will be labeled with the following: "CAUTION: Investigational device. For use in clinical studies only."

The investigational device label information will be transcribed to the appropriate case report form as well as for device accountability and traceability.

Only sites/Investigators participating in the clinical study will be eligible to receive the EVA-C System after Verily has declared the site ready to start the clinical study.

At the end of the study, all investigational devices must be returned to the Sponsor. To return the devices to Verily, a Return Material Authorization (RMA) number is required. The site will contact Verily to issue an RMA number, and Verily will provide the site with appropriate device return packaging and shipment materials. The Sponsor-issued RMA number will be captured within the appropriate shipping and/or device accountability documentation.

12. Regulatory, Ethical and Study Oversight Considerations

12.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures; and

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.3. Informed Consent Process

Subjects must be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study before informed consent is obtained and per sites' local and IRB guidelines. The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

There must be a source document that includes a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

12.4. Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the subject. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the study subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.5. Interim Analysis Structure

An independent statistician will be utilized for the interim analysis. Within Verily and/or a designee, data and programming for the interim analysis will be performed by an interim analysis dedicated group who are not involved in the management of the study. This group will

communicate with the independent statistician and will provide the unblinding codes. The independent statistician will execute the unblinding with the set of programs prepared by the interim analysis dedicated group and will then communicate the results to a pre-selected group within Verily not involved in the management of the study. A detailed unblinding and a communication plan will be provided in the statistical analysis plan.

12.6. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- If study data is recorded directly on the CRFs (i.e., no prior written or electronic record of data), it is considered to be source data.
- Definition of what constitutes source data can be found in CRF completion guidelines.

12.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

12.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multisite studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13. Statistical Considerations

Based on previous feasibility data, a sample size of 600 patients per arm (1:1 allocation, 1,200 total in both arms) would provide >99% Power to detect superiority for APC assuming a data loss of 15%. This same number of patients would also provide 90% Power to detect superiority for ADR, based on the expected ADR of 35% in the control arm, and 45% for the intervention arm.. Based on the assumption that PPA will be at least 70% in both arms, Power for the PPA non-inferiority comparison will be > 90%.

The co-primary endpoint of PPA will be tested for non-inferiority using a non-inferiority margin of 10%. PPA will be calculated for each arm as the number of positive biopsies of total removed lesions. A resampling distribution of the difference in PPA will be used to calculate a two-sided 95% confidence interval for the difference: PPA(intervention)-PPA(control). Non-inferiority will be concluded if the lower confidence limit of the 95% two-sided confidence interval is above -10%. For APC, superiority will be assessed based on a one-sided test of the difference in mean rates at a 0.025 level of significance. For ADR, superiority will be assessed using a stratified CMH test at a one-sided 0.025 level of significance.

Interim analysis: When approximately 600 subjects have completed the trial, an interim analysis will be conducted, and a conditional power analysis will be performed. The conditional power will assess the probability (power) that the study will meet its objectives on the superiority endpoint of APC and ADR, and on the non-inferiority of the PPA endpoint. If the conditional power is below 90% for either one of the co-primary endpoints or for ADR, an increase in the sample size from 1200 up to 2400 will be considered.

The increase in the sample size will be based on the probability of achieving success on both co-primary endpoints (APC and PPA) and success on the ADR endpoint. If the increase in sample size leads to an increase in the power for these endpoints to approximately 90%, then the study will enroll the additional subjects to allow the increase in power. Otherwise, the study may continue to the originally planned sample size of 1200 or stopped for futility. Due to a possible increase in the sample size, the final analysis will be done using a simple combination test, by transforming the test statistics of the interim patients, and the test statistic of the post-interim patients to standard normal (Z) statistics. Using prespecified weights of w1 = 1/2 and w2 = 1/2, the final Z = √w1 * interim Z + √w2 * post-interim Z. The interim analysis will be conducted by an independent statistician. Recommendations will be communicated confidentially to a select committee within Verily not directly involved in the study. Communication processes will be laid out in the interim analysis section of the statistical analysis plan.

The co-primary endpoints of APC and PPA will be analyzed using the ITT population. Sensitivity analyses will be conducted to assess the effect of missing complete or partial data by considering various imputation methods and will be described in the Statistical Analysis Plan. Subgroup analysis will include assessments of APC, ADR and PPA in groups defined by age-group, sex, race, ethnicity, site, colonoscopist and country

Of the subjects receiving intervention, a subset of subjects may receive an iteration of the device that incorporates varying hardware and software configurations (see Section 11.1). The predicted result of these variations is not expected to significantly impact primary or secondary endpoints.

The Intent to Treat (ITT), modified Intent to Treat (mITT) and Per Protocol (PP) populations will be further defined within the Statistical Analysis Plan.

[redacted]

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16. Glossary

Term	Abbr.	Definition
Adverse Event	AE	Any untoward medical occurrence, unintended disease or injury in subjects, users or other persons, that is considered a change from baseline or pre-study status, whether or not related to the investigational medical device.
Case Report Form	CRF	A set of documents, designed for complete recording of all relevant subject and device related data, as required by the clinical investigation plan.
Trial Master File	TMF	Contains essential documents for a clinical trial that may be subject to regulatory agency oversight.
Clinical Investigation	N/A	Any controlled systematic study in human subjects, undertaken to verify the safety and performance of a specific medical device, under normal conditions of use. This is also known as a Clinical Study or Clinical Trial.
Clinical Research Associate	CRA	A person appointed by the sponsor and responsible for monitoring and reporting on the progress of the clinical investigation. This is also known as a Monitor.
Contract Research Organization	CRO	Contract research organizations are independent contractors who assume, by contract, some or all of the regulatory responsibilities of a sponsor and/or monitor.
Informed Consent	IC	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects that are relevant to the subject's decision, including potential risks and benefits to participate. Informed consent is documented by means of a written, signed, and dated informed consent form. Informed consent continues throughout the trial.
Intent to treat	ITT	All randomized subjects.
Investigational Device	N/A	Any medical device intended for use by an appropriately qualified practitioner when conducting clinical investigations in an adequate clinical environment.
Modified Intent to treat	mITT	The subset of ITT subjects, including only those indicated for Screening or Surveillance
Per Protocol	PP	The subset of ITT subjects, excluding those whose procedure could not be completed per protocol (e.g. poor bowel prep).
Principal Investigator	PI	The investigator responsible for the conduct of a clinical investigation and who takes the clinical responsibility for the well being of the subjects involved.
Serious Adverse Event	SAE	A Serious Adverse Event (also referred to as Adverse Incident) is defined as an adverse event that is anticipated or unanticipated and that reasonably suggests that one of the manufacturers devices has or may have caused or contributed to a death or serious injury. A Serious Adverse Event is an Adverse Event that led to: (a) death, (b) serious deterioration

		in the health of the subject that either resulted in a (i) life-threatening illness or injury or (ii) permanent impairment of a body structure or a body function, or (iii) in-patient or prolonged hospitalization or (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or (c) fetal distress, fetal death or a congenital abnormality or birth defect. These events are typically reportable to health authorities.
Sponsor	N/A	An individual or an organization which takes responsibility for the initiation and/or implementation of a clinical investigation.
Sub-Investigator	Sub-I	A member of the clinical study team with appropriate credentials and is supervised by the Principal Investigator at a site and allowed to perform critical trial-related procedures and/or to make key trial-related decisions.
Subject/ Research Subject	N/A	A human being, either a patient or a non-patient volunteer, participating in a clinical investigation.
Unanticipated Adverse Device Effect	UADE	Serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.