CAD-EYE in the Middle East

Investigator-initiated Protocol

Study Title:

A multi-center randomized control study to determine the efficacy of CADEYE in detecting colon polyps in comparison to standard of care

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Introduction

I. Objectives

The objective of this study is to assess the sensitivity and added benefits of CADEYE compared to standard care (white-light) in detecting colon polyps in patients undergoing colonoscopy.

a. Primary objective

The primary objective of this study is to assess the efficacy of CADEYE compared to the sensitivity and specificity of standard of care (SOC) in detecting colon adenomas.

b. Secondary objective

- To compare both methods in clean withdrawal time
- Evaluate if there is an increase in unnecessary resections
- To evaluate if CADEYE overcomes the following challenges of polyp detection:
    - Quality of bowel preparation
    - Operator dependent factors
        - Fatigue (better performance in the morning)
        - Successive repetitive procedures

II. Hypothesis:

The use of CADEYE in patients undergoing colonoscopy will lead to significantly higher detection rate of colonic polyps than SOC.

III. Endpoints:

a. Primary endpoint

Adenoma detection rate is the primary end point which is the percentage of patients with at least 1 histologically proven adenoma or carcinoma.

b. Secondary endpoint

- Adenomas detected per colonoscopy
- Proximal ADR

- Withdrawal time
- Non-neoplastic resection rate

IV. Background:

One fourth of colorectal neoplasms are missed during screening colonoscopies. These neoplasms can develop into colorectal cancer (CRC). Due to the high rate of missed lesions, there is a wide range of adenoma detection rates (ADR) among endoscopists throughout regions. However, ADR is a significant parameter as or every 1% increase in ADR, there is an associated 3% decrease in the incidence of CRC. While there is data available on the ADR throughout Europe and the United States, there is very little data on ADR throughout the Middle East.

Failure in polyp recognition is a major determinant for the high rate of missed colorectal neoplasms. In response, technological advances have paved the way for Computer-Aided Polyp Detection (CAD-e) systems. Artificial intelligence systems allow of real-time computer-aided detection of polyps with high-accuracy. CADEYE is a CAD-e system (FUJIFILM) that enables real-time video processing at the same rate as the standard procedure.

The data generated from this study will provide an estimate of the ADR throughout the Middle East as well as assess the accuracy of CADEYE in detecting adenomas in comparison to standard of care.

JAMA Intern Med. 2016 Jul 1;176(7):894-902.

Gastroenterology. 2019 Feb 6.

Endoscopy. 2020 Jan;52(1):61-67.

N Engl J Med. 2014 Apr 3; 370(14):1298-306.

V. Study Design

This is a multi-center randomized control trial of CADEYE compared to SOC (white-light) in detecting colon polyps.

For each center, the following design will take place:

- Subjects will be randomized in a 1:1 ratio
- All subjects in Experimental Arm A will undergo SOC (white-light endoscopy).
- All subjects in Experimental Arm B will undergo CADEYE endoscopy.
- All subjects in Experimental Arm A & B will otherwise undergo identical preparation, procedures and post-procedure protocols.
- The target number of procedures to be done in total by each center (including both Experimental Arm A and B) is 100

Data will be collected and recorded by each individual center. All data and recordings will ultimately be gathered at the central database located at ROEYA Gastroenterology, Hepatology and Endoscopy Center in Cairo, Egypt.

VI. Inclusion criteria

- 40–80 years old subjects
- Subjects undergoing colonoscopy for the following:
    - Primary CRC screening
    - Post-polypectomy surveillance
    - Work up following FIT positivity
    - Symptoms/signs suspicions of CRC
- Subjects must be willing to give written informed consent for the trial

VII. Exclusion Criteria

- Unable to consent
- Contraindicated to undergo endoscopy

- Hospitalized patient
- Patients with the following conditions:
    - History of colon resection
    - History of CRC
    - Antithrombotic therapy precluding colon resection
    - Inflammatory Bowel Disease (IBD)
    - Familial Adenomatous Polyposis (FAP)
- Pregnant or lactating
- Poor bowel preparation: BBPS 0 or 1 in a segment

VIII. Patient randomization

In each center, 100 subjects will be randomized to one of the 2 treatment arms in a 1:1 ratio. The sample size was calculated to allow for the greatest, yet achievable, sample size possible.

IX. Study Procedures

a. Clinical assessment

- A standard full clinical assessment will be carried out by each center.
- All past medical history, drug history, family history, etc. will be recorded in detail.

b. Laboratory testing

Initial assessment will by done including CBC, coagulation profile, liver profile , kidney profile, tumor markers , occult blood in stools and fecal calprotectin.

c. Colonoscopy

- Procedures will be performed with high-definition scopes
- Bowel preparation will be evaluated and graded by the endoscopist performing the exam using the Boston Bowel Preparation (BBPS) scale
- Each endoscopist and facility can adopt their standard procedures for subject management and monitoring (including sedation procedures)

- Cecal intubation will be assessed by the endoscopist by the identification of the ileocecal valve and the appendix orifice via photo documentation
- Intubation time and inspection time during withdrawal will be measured using a stopwatch with pauses during therapeutic intervention, washing and characterization time
- Endoscopists will comply to a minimum of 6 minutes of inspection (clean withdrawal time)
- Polyps will be classified according to their location, size and morphology
- All polyps will be removed and biopsies taken for non-resectable lesions, regardless of size, color or subjective interpretation with exception to diminutive hyperplastic appearing polyps located in the rectum

d. Histopathology

- All resected or biopsy specimens will be fixed, processed, and stained for histopathology using standard methods
- Specimens will be evaluated by expert pathologists (one for each center) – they will be blinded
- All lesions will be classified according to a chosen classification system (i.e Vienna).
- Criteria for advanced adenomas will be defined

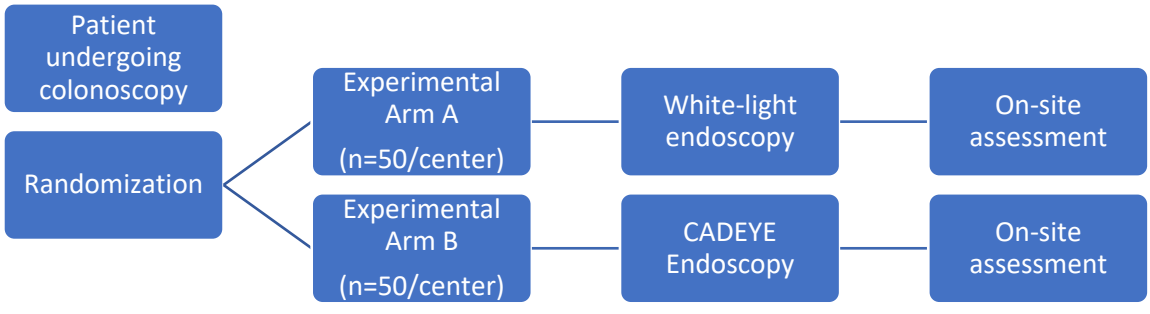
X. <u>Assessment of Endpoints</u>

The primary endpoint is adenoma detection rate (ADR) which is the proportion of patients with at least one histologically proved adenoma or carcinoma.

Secondary endpoints will include mean number of adenomas detected per colonoscopy, proximal ADR, total number of adenomas detected, withdrawal time, cecal intubation rate and non-neoplastic resection rate. Mean number of adenomas detected per colonoscopy is the total number of adenomas divided by the number of colonoscopies performed. Proximal ADR is the prevalence of patients with at least one adenoma detected proximal to the splenic flexure. Non neoplastic resection rate is defined as the proportion of patients with no adenoma or Sessile Serrated Lesions (SSLs), within any excised lesion who had undergone at

least one excision with histopathological examination. SSLs will not be included when calculating ADR.

XI. Flow Chart



XII. Study Duration

Study duration will vary depending on the access of the centers to the CADEYE device and the flow of patients.

XIII. Statistical Analysis

Two randomized group (equilibrium between age, sex).

For each center:

- Group 1: 50 cases
- Group 2: 50 cases

- Data will be collected on standardized forms by each center. This form will then be sent to the central database to be entered into SPSS (IBM SPSS Statistics) or using R software by **one** research assistant.

- A dedicated software will be used in data entry.
- The chi-square, Fisher's exact test, and Mann-Whitney's *U*-tests will be used to analyze the differences of background features and biochemical data between the two groups.
- The obtained clinical data will be analyzed on an intention-to-treat basis (and per protocol). Differences will be expressed as relative risk (RR) with 95% CIs.
- Categorical variable will be described by frequency counts and percentages.
- Quantitative variables will be described by mean and standard deviations.
- Incidence rate ratios to assess the relationship between study arm, age, gender and colonoscopy indication will be calculated using Poisson regression.
- A per-polyp analysis to assess the differences in adenoma location, size and morphology will be performed to control for multiple lesions per patient.
- Data will be reported as odds ratios.

XIV. Adverse Experience Reporting

- All adverse events in both arms will be documented.

XV. Publication Plan

- 1 submission as a poster to UEG is anticipated
- 1 subsequent manuscript is anticipated