1) Protocol Title

Title: **Use of a Distal Colonoscope Attachment to Increase Detection of Sessile Serrated Adenomas**

Protocol Version Date: *October 29, 2018*

2) Objectives

We plan to compare standard colonoscopy to endocuff-assisted colonoscopy.

Primary Endpoint: Differences in sessile serrated adenoma detection rate (SSADR)

Secondary Endpoints: Differences in:

1. Adenoma Detection Rate
2. Proximal Colon Adenoma Detection Rate

3) Background

Colon cancer remains the second leading cause of death amongst both men and women in the United States.[1] With the advent of screening colonoscopy, mortality from colorectal cancer has decreased, and colonoscopy is the current gold standard for colorectal cancer screening and prevention by removing adenomatous polyps.

Different devices have been employed to assist the endoscopist in the detection of colon adenomas, as these lesions serve as precursors to colon neoplasia. One device of interest is the Endocuff Vision. The Endocuff Vision is a disposable device with a single row of soft, hair-like projections that aid in flattening colonic folds during colonoscope withdrawal to increase the detection of colon adenomas. Previous studies have compared endocuff to standard colonoscopy, and the results have indicated significant improvement in overall adenoma detection rates (ADR).[2-4] All of these studies have focused on the detection of conventional tubular adenomas as primary endpoints. However, there exists an additional serrated adenoma pathway that may give rise to about 15-20% of colon cancers.[5] These lesions tend to be flatter with subtler features that make them harder to detect. A recent meta-analysis suggested that the endocuff was more effective at detecting sessile serrated adenomas compared to standard colonoscopy; however, these findings are derived from secondary data analyses.[6] To the best of our knowledge, no study to date has examined the sessile serrated adenoma detection rate as a primary endpoint.

Our previous study examined the differences in overall adenoma detection between endocuff-assisted and standard colonoscopy.[7] Although there was no statistical difference in ADR between endocuff-assisted colonoscopy and standard colonoscopy, we did observe a numeric difference in sessile serrated adenoma detection rate (SSADR), 16.7% vs 23.8% ($p = 0.5$) between standard colonoscopy and endocuff-assisted colonoscopy, respectively. Given our previous sample size

was calculated to detect differences in overall ADR, we were not powered to determine whether this observed difference in SSADR was significant.

Therefore, the goal of our study is to compare standard colonoscopy to endocuff-assisted colonoscopy in patients undergoing colonoscopy for colon cancer screening to determine differences in sessile serrated adenoma detection rates.

References:

1 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
2 Biecker E, Floer M, Heinecke A, Strobel P, Bohme R, Schepke M, et al. Novel endocuff-assisted colonoscopy significantly increases the polyp detection rate: a randomized controlled trial. J Clin Gastroenterol. 2015;49(5):413-8.
3 De Palma GD, Giglio MC, Bruzzese D, Gennarelli N, Maione F, Siciliano S, et al. Cap cuff-assisted colonoscopy versus standard colonoscopy for adenoma detection: a randomized back-to-back study. Gastrointest Endosc. 2017.
4 Floer M, Biecker E, Fitzlaff R, Roming H, Ameis D, Heinecke A, et al. Higher adenoma detection rates with endocuff-assisted colonoscopy - a randomized controlled multicenter trial. PLoS One. 2014;9(12):e114267.
5 Obuch JC, Ahnen DJ. Colorectal Cancer: Genetics is Changing Everything. Gastroenterol Clin North Am 2016;45:459-76.
6 Chin M, Karnes W, Jamal MM, Lee JG, Lee R, Samarasena J, et al. Use of the Endocuff during routine colonoscopy examination improves adenoma detection: A meta-analysis. World J Gastroenterol. 2016;22(43):9642-9.

7 Marsano J, Johnson S, Yan, S, et al. Comparison of Colon Adenoma Detection Rate Using 2 Distal Colonoscope Attachments: A Single Center RCT. Am J Gastroenterol. 2017; S113-114.

4) Inclusion and Exclusion Criteria

Inclusion criteria:

(1) Patients between ages of 40 and 85 who are scheduled for screening colonoscopy with the following gastroenterologists at UC Davis :

Dr. Joseph Marsano
Dr. Sooraj Tejaswi
Dr. Asha Gupta
Dr. Amar Al-Juburi
Dr. Jesse Stondell
Dr. Juan Carlos Garcia
Dr. Eric Mao

Exclusion criteria:

The following patients will be excluded:

(1) Age less than 40 and greater than 85
(2) Prior history of colon adenomas (tubular adenoma,sessile serrated adenoma, tubulovillous or villous adenomas) and colon cancer
(3) Patients with inflammatory bowel disease
(4) Patients suspected to have colon cancer based on non-invasive tests such as stool tests for hemoglobin or DNA, or imaging finding suggestive of colon cancer (CT or barium enema).
(5) Patients undergoing colonoscopy for evaluation of symptoms such as abdominal pain, rectal bleeding, diarrhea, constipation, etc., or patient with iron deficiency anemia suspected to be due to ongoing bleeding inside the colon
(6) Patients with family history of hereditary polyposis syndromes such as Lynch syndrome, familial adenomatous polyposis etc., which are associated with an increased risk of colon cancer
(7) Patients unable to consent
(8) Pregnant patients
(9) Incarcerated patients
(10) Non-English speaking patients

Number of Subjects:
We plan on recruiting a total of 1374 subjects with 687 subjects randomized to each arm.

Consent Process

Currently, the standard practice is to obtain informed consent prior to a colonoscopy. Some of the patients presenting for their colonoscopy are via open access, thus no colonoscopy specific clinic appointments are done before their actual procedure.

Patients that are identified as being eligible for the study will be contacted 3 weeks prior to their procedure (if possible) but no less than one week. They will be contacted by IRB- approved secured Mychart message via the electronic medical record or telephone by research personnel via IRB approved phone script to inform them of the study. Information regarding the procedure and goal of the study will be provided to allow for sufficient time prior to their procedure to consider participation. A copy of the consent form will also be sent to them via mychart or mail.

Patients agreeing to participate in the study will sign the informed consent form on the day of the scheduled colonoscopy procedure. Patients will be able to ask the consenting physician any questions regarding the study prior to signing the consent form.

As part of routine practice, our endoscopists will discuss with the patients about the colonoscopy - including consent, medication/ history review and discussions about the risks/benefits of the procedure. This conversation typically occurs in a quiet and private section in the pre-op rooms about 30-60 minutes before the procedure. The written consent discussion specific to our study will also be done in this same area. There is usually adequate time prior to the procedure for both the consents to be done.

Please see attached Consent form (HRP-502). Non-English speakers will not be included in the study due to the practical difficulty with translating the study materials and consents. Patients that are unable to provide consent for themselves will not be included in the study.

HIPAA Authorization for Research

With the approval of HIPAA Waiver of Authorization (HRP-441), the study coordinator may identify potential subjects through the Electronic Medical Record (EMR). Following the identification of a patient as a potential subject, the study coordinator may inform the potential subjects of the study via secured communication (MyChart messages) or telephone with an IRB-approved phone script.

5) Study Timelines

Timeline for enrollment of subjects will be November 2018 – May 2020. Data will be obtained from all patient medical records on an ongoing basis and completed once their pathology report is finalized (sessile serrated adenoma vs tubular adenoma vs. non-adenomatous polyps). Primary data analysis will begin immediately once all patients

have been enrolled, completed colonoscopy and all data collected. We anticipate that primary data analysis will be completed by June 2020. This will be a one-time participation during the date of their procedure only. Subjects will only be contacted by their endoscopist for communication of colonoscopy results per regular standard practice at UC Davis.

6) Study Endpoints

Primary Endpoint:
- Sessile Serrated Adenoma Detection Rate

Secondary Endpoints:
- Overall adenoma detection rate
- Proximal colon adenoma detection rate
- Mean number of adenomas per colonoscopy
- Mean number of sessile serrated adenomas per colonoscopy
- Adenomas per positive colonoscopy
- Sessile serrated adenomas per positive colonoscopy
- Colonoscope withdrawal time
- Differences if quality of colon preparation
- Major complication rates (perforation, major bleeding causing transfusion)

7) Procedures Involved

Our proposed study is a randomized control trial in which patients are randomized in a single-blinded fashion into one of 2 study arms. One arm of subjects will undergo their screening colonoscopy without any colonoscope attachments (conventional). A second arm of subjects will undergo their screening colonoscopy with the Endocuff Vision attachment.

All methods (colonoscopy without any attachment and colonoscopy with Endocuff Vision attachment) are approved standard of care options, and are already in clinical use.

Data that will be reviewed as part of the study includes: age, gender, smoking status, alcohol consumption, body mass index (BMI), history of diabetes, quality of bowel prep, withdrawal time, the number of polyps, location of polyps removed, size of the polyps removed, and histopathology of the polyps. These are data points that are routinely collected and reported as part of regular care of patients. This data will be reviewed and entered into the REDCap database by medical students, residents or fellows. GI faculty members' role will be to obtain consent, perform procedures, and analysis of the de-identified data.

8) Data and/or Specimen Management and Confidentiality

Data will be accessed from patient records using an encrypted, password-protected computer at UC Davis Medical Center. The computer is stored in the GI office in PSSB building. This room is accessible by staff/faculty members of the UC Davis Gastroenterology department. Each study patient will be assigned a unique study number. Patient identifier, including patient name (First and Last) and medical record number (MRN)associated with the study number will be entered into password protected REDCap along with other aforementioned data The principal investigators will not have access to the REDCap database, and research staff responsible for data entry will export de-identified data and distribute de-identified data to the investigators conducting data analysis.
As staff of UC Davis, each investigator will have completed HIPAA compliance training.

The data collected will be analyzed using a one-way ANOVA. Using a baseline incidence of sessile serrated adenoma detection rate of 10%, and to detect an effect size of 50%, with a power of 0.809, we would need 687 subjects in each study arm. We therefore aimed to enroll 687 subjects into each arm (2 arms for a total of 1374 subjects) to ensure we have enough subjects in each arm to detect an effect if present.

9) Data and/or Specimen Banking

Linkage between patient identifiers(First Name, Last Name, and MRN) and study number including other data will be saved on the UC Davis REDcap database using an encrypted, password-protected computer at UC Davis Medical Center, division of Gastroenterology office located at 2315 Stockton Boulevard, South 3 Room 3016 and Ticon I. Only study staff designated for data entry will have access to the REDCap database. Upon request, the de-identified data will be exported from the REDCap database and distributed to the investigators for analysis. De-identified data used for this study will not be banked for future use. At the completion of the study, all linkage between the patient identifiers and the study number will be destroyed.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

This research does not involve more than minimal risk to the subject.

The PI affirms to uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of subject's unique identification number.

11) Withdrawal of Subjects

Participation in the study is completely voluntary, thus patients can withdraw at any time during or after the procedure. Written consent will be obtained from all subjects. Withdrawing from the procedure has no negative implication on their colon cancer screening and subsequent clinical care. If a subject desires to withdraw from the study, all information associated with the particular subject will be discarded immediately.

A patient may also be withdrawn from the research at the discretion of the endoscopist or PI. The PI may withdraw a subject if there is a clinical suspicion for hereditary polyposis syndrome and/or new case of inflammatory bowel disease (IBD) based on the colonoscopy. Also, there are scenarios where the regular colonoscope is switched to a pediatric colonoscope. This occurs in patients with altered/ post-surgical anatomy, preventing completion of the procedure using a standard colonoscope. In these cases, subjects may be withdrawn from the study.

12) Risks to Subjects

The attachment device proposed in our study is currently FDA approved for use in colonoscopy. There is no added risk to participating subjects. There is an overall minimal risk to subjects and that risk is similar to any and all risks for conventional colonoscopy. Although we will make every effort to ensure that all patient health information remains confidential, there is the risk of loss of confidentiality.

13) Potential Benefits to Subjects

Subjects may benefit from increased sessile serrated adenoma detection.

14) Multi-Site Research

Only UC Davis Medical Center Endoscopy suites will be involved in this study.

15) Community-Based Participatory Research

Not applicable

16) Sharing of Results with Subjects

Under current standard of practice, patients are contacted by the endoscopist either through the phone, mail, my chart or in person during a clinic visit to discuss endoscopic and pathology results. The results of the study will not be shared with subjects until the study has been completed and all of the data has been analyzed.

17) Prior Approvals

Not applicable

18) Provisions to Protect the Privacy Interests of Subjects

The only people that will have access to subject personal information are the principal investigators, sub-investigators and research personnel during the study period. All information collected (including age, gender, smoking status, alcohol consumption, BMI, diabetes status, withdrawal time, bowel prep quality, size, number and types of polyps removed, cecum intubation time and complications of procedure) will be de-identified.

19) Compensation for Research-Related Injury

No compensation will be provided.

20) Economic Burden to Subjects

Patients presenting for colonoscopies are typically insured and are not expected to pay for screening colonoscopies. The study will not provide or pay for the endocuff since it is already approved for use at each study site as standard practice. The endocuff is an additional tool to detect polyps at the discretion of the endoscopist. There is no additional billing code when this device is used, and it is included in the standard screening colonoscopy visit. Therefore, there is no expectation that patients who are randomized to

the endocuff arm will incur additional costs versus those that are randomized to colonoscopy without endocuff.

21) Drugs or Devices

The Endocuff Vision device being used is FDA approved for use during colonoscopy. No investigational devices are being used in this study.

22) ClinicalTrials.gov Registration

FDAAA 801 establishes penalties for Responsible Parties who fail to comply withClinicalTrials.gov registration or results submission requirements. **Penalties include civil monetary penalties and, for federally funded studies, the withholding of grant funds.**

For additional information on registration and results submissions requirements click here.
If registration is necessary the following are required:

- *Registration and, in some instances, submission of results at Clinicaltrials.gov*
- *Specific clinicaltrials.gov language in the consent form for this research. The language can be found in HRP 502 Template Consent under the heading "What happens to the information collected for the research?"*

Complete each section below. If you finish a section indicating the research must be registered on Clinicaltrials.gov is required you do not have to complete the remaining sections.

Section 1: NIH Funded Studies
If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☐	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☒	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction
If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
☒	This is a prospective clinical study of health outcomes in human subjects that

	compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric post market surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
☒	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☐	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

23) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
☒	This research involves no more than minimal risk.
☒	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
☒	This research is not subject to FDA jurisdiction.
☒	This research does not include prisoners as participants.
☒	This research is not subject to SCRO oversight.
☒	This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).
☒	This research does not involve identifiable information held by the State of

	California Department or Agency
☒	No personnel involved in the design, conduct, or reporting of this research have a new unreported related financial interest (RFI) in this study.