PennState

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Hybrid APC assisted EMR for large colon polyps to reduce local recurrence, a prospective data collection Study

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1.0 Objectives

1.1 Study Objectives

The aim of this study to evaluate and examine, whether use of Hybrid Argon Plasma Coagulation (APC) as adjunct to endoscopic mucosal resection (EMR), will reduce the risk of residual or recurrent neoplasia at 6 months. Hybrid APC is an existing FDA approved device for ablation of abnormal tissue anywhere in GI tract. We hypothesis that with Hybrid APC assisted EMR there will be a decrease in recurrence rate after 6 months and it would be more effective compare to the standard EMR procedure.

1.2 Primary Study Endpoints

Measure Recurrent rate and efficacy of Hybrid APC assisted EMR. Assess rate of local recurrent or residual neoplasia at the EMR scar using optical and histologic classification at 6 months.

1.3 Secondary Study Endpoints

Evaluate rate of post-polypectomy bleeding and post-polypectomy syndrome and compare it to standard procedure.

2.0 Background

2.1 Scientific Background and Gaps

Colon Cancer is a major disease that effecting more than 1 million people per year globally. Adenomatous polyps have been identified as the main precursor in lesions leading to colorectal cancer.[1] Colon cancer screening the best way to detect and remove large, often asymptomatic polyps. Early detection and resection of these colorectal polyps can prevent the development of colon cancer. Endoscopic polypectomy introduced in 1970's, is an effective technique to prevent of colorectal cancer, as demonstrated in National Polyps Study. Endoscipc mucosal resection (EMR) is a technique used for resection of medium to large colon polyps. In this technique, fluid is injected into the submucosal creating a cushion between the mucosa and the muscolaris propria. An electrocautery snare is then deployed to resect the polyp in a single (en-bloc) or multiple (piecemeal) pieces. Most of polyps > 2cm are resected in piecemeal way. Although EMR is now considered standard of care with successful rate resection of 85 % and low risk of complication (3-10% bleeding and 1% perforation), this technique has inherent deficiencies, especially piecemeal EMR. This is particularly important if the polyp contains cancer. Resection of scarred polyps using this technique is particularly challenging due to the non-lifting of the polyp. Recurrence rates following piecemeal EMR can be as high as 20%.[1,2]
Endoscopic submucosal dissection (ESD) is an alternative approach that aims to remove non-pedunculated precancerous or cancerous lesions over 20 mm in one piece (en-bloc resection rate of 89.95% and lesion recurrence rate of 0.7%). However, due to its technical complexity and high complication risk (mainly bleeding and perforation, with complication rates approximately 8%), it is not the current standard of care and only performed by experts in the technique.[1]
Hybrid Argon plasma coagulation (APC) is a new technique in which the endoscopist reinjects the submucosal with fluid to create a cushion (normal saline/ diluted adrenaline and /or sodium hyaluronate solution) to protect the muscle layer and is then ablated using spray argon coagulation to treat any microscopic residual disease that is the seed for local recurrence .[3] Previous studies have shown that this technique is a safe and easily applicable technique to complete resection for recurrent polyps after first EMR.

In this present time there is no study to evaluate the safety and recurrence rate of the Hybrid-APC assisted EMR for large colon polyps at their initial resection attempt

2.2 Previous Data

In 2012 Tsiamoulos et.al. in a single-center, retrospective case series report their experience in regards to endoscopic mucosal ablation (EMA) technique that can be used to complement the eradication of recurrent fibrotic colon polyps. In this study, of consecutive patients referred for endoscopic excision of recurrent benign colon polyps with severe submucosal fibrosis, fourteen patients (mean age 73 years; 9 men, 5 women) with 15 recurrent colon adenomas (mean polyp size 30 mm, 9 proximal/6 distal) were included. EMA with a mean APC power setting of 55 W was applied. Complete polyp eradication was achieved in 9 of 11 patients (82%) at first or second completed follow-up. One patient needed laparoscopic colectomy because of cancer, and 1 underwent transanal endoscopic microsurgery for benign massive recurrence. The other 3 patients with small, easily treatable recurrence (≤3 mm) were followed by 1-year-surveillance. No perforations and no postpolypectomy syndrome were reported. They concluded that EMA appears to be a safe and easily applicable technique to assist the complete eradication of recurrent fibrotic colon polyps.[3]

A systematic review and meta-analysis by Arezzo et.al in 2016 compares the safety and efficacy of endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) in the treatment of flat and sessile colorectal lesions >20mm. They reviewed the literature published between January 2000 and March 2014. Pooled estimates of the proportion of patients with en bloc, R0 resection, complications, recurrence, and need for further treatment were compared. A total of 11 studies and 4678 patients were included. The en bloc resection rate was 89.9% for ESD vs 34.9% for EMR patients (RR 1.93 p<0.001). The R0 resection rate was 79.6% for ESD vs 36.2% for EMR patients (RR 2.01 p<0.001). The rate of perforation was 4.9% for the ESD group and 0.9% for EMR (RR 3.19, p<0.001), while the rate of bleeding was 1.9% for ESD and 2.9% for EMR (RR 0.68, p=0.070). Therefore, the overall need for further surgery, including surgery for oncologic reasons and surgery for complications, was 7.8% for ESD and 3.0% for EMR (RR 2.40, p<0.001). They concluded that ESD achieves a higher rate of en bloc and R0 resection compared to EMR, at the cost of a higher risk of complications.[4]

Manner et.al in 2015 performed a prospective study, which evaluating the efficacy and safety of the new technique of Hybrid-APC which combines submucosal injection with APC in patients with dysplastic Barrett's esophagus. In this study Patients who had a residual Barret's Esophagus (BE) segment of at least 1 cm after endoscopic resection of early Barrett's neoplasia underwent thermal ablation of BE by Hybrid-APC. Prior to thermal ablation, submucosal injection of sodium chloride 0.9% was carried out using a flexible water-jet probe. Surveillence upper GI endoscopy was carried out 3 months after macroscopically complete ablation including biopsies from the neo-Z-line and the former BE segment, and recording of stricture formation. Total of 60 patients were included in the study [55 pt male (92%); mean age 62 ± 9 years, range 42-79]. Ten patients were excluded from the study. In the remaining 50 pt., Hybrid-APC ablation and surveillence endoscopy at 3 months were carried out. Forty-eight out of 50 pt. achieved macroscopically complete remission after a median of 3.5 APC sessions]. Freedom from BE was histopathologically observed in 39/50 patients (78%). There was one treatment-related stricture (2%). Minor adverse events of Hybrid-APC were observed in 11 patients (22%). It concluded that Hybrid-APC was effective and safe for BE ablation in a tertiary referral center. The rate of stricture formation was only 2%.[5]

2.3 Study Rationale

EMR has a recurrence rate of up to 20% in large ≥20 mm lesions with a relatively low risk profile. ESD has a low 1-4% recurrence rate but higher risk profile. We are assessing if adjuvant hybrid APC with EMR drop the recurrence rate near ESD levels while maintaining the safety profile of EMR.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Adult patient aged ≥18 and ≤89 of any gender, ethnicity and race referred to endoscopy for resection of large colon polyps
- Patients with a ≥20mm colon non-pedunculated polyp
- Ability to give written informed consent

3.2 Exclusion Criteria

- Patients with known (biopsy proven) invasive carcinoma in a potential study polyp
- Pedunculated polyps (as defined by Paris Classification type Ip or Isp)
- Patients with ulcerated depressed lesions (as defined by Paris Classification type III)
- Patients with inflammatory bowel disease
- Patients who are receiving an emergency colonoscopy
- Poor general health (ASA class>3)
- Patients with coagulopathy with an elevated INR ≥1.5, or platelets <50
- Poor bowel preparation
- Target sign or perforation during initial EMR
- Need for ESD for complete resection prior to APC
- Pregnancy and breast feeding

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

A patient will be removed from the study for any following reasons:

- The patient desires to discontinue participation
- The investigator believes that discontinuation is in the best interest of patient

3.3.2 Follow-up for withdrawn subjects

Patients will be informed that participation in this study is voluntary and that they do not to have to participate in this research. If patients choose to participate, they have the right to stop any time. If a patient decides not to take part in the research or decides to stop taking part in the research at later date, there will be no penalty or loss benefits to which he/she is entitled. The PI of this study has the right to remove patients from the study without their permission. If the investigator determines that the subject does not fulfill the criteria to be in the study, or the subject's condition becomes worse, he may remove the subject from the study.
Information obtained prior to withdrawal may continue to be used if is necessary for the soundness of the overall research. Furthermore, records of the care that we provided will be retained as long as the law requires.
As this is a single point of care investigation, the process of withdrawal may occur between the time of consent and the administration of sedative. Withdrawal may occur either with a written or vocalized desire to retract one's consent.
If a subject is removed from the study prior to completion, the reason for doing so and the date the subject is discontinued will be documented.

4.0 Recruitment Methods

4.1 Identification of subjects

We will recruit patients presenting with a known ≥ 20mm polyp prior colonoscopy and referred for resection of this polyp to Hershey Medical Center.

4.2 Recruitment process

All patients in our institute with a known ≥ 20mm polyp detected at a prior colonoscopy who are referred for colonoscopy procedure will be identified as potential study participants.

4.3 Recruitment materials

Not applicable

4.4 Eligibility/screening of subjects

All prospective subjects undergoing colonoscopy with a ≥ 20mm colon non-pedunculated polyp will be seen prior to the procedure to discuss and review the details of the study. Interested individuals will be screened to ensure that they meet inclusion and exclusion criteria.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Consent and basic demographics will be garnered by the PI, one of the co-investigators or research associate prior to bringing the patient into the endoscopy suite, discussions about the research and obtaining informed consent will occur in curtained endoscopy pre-procedure room. Patients will be giving adequate time to review consent form and consult with family if they wish. Patients are not sedated at the time of consent.

5.1.1.2 Coercion or Undue Influence during Consent

Patients will have time to review the consent form and ask questions. Patients will be informed that Colonoscopy procedure will take place even if the patient chooses not to participate in the study.

5.1.2 Waiver or alteration of the informed consent requirement

Partial Waiver of informed consent is requested pre – recruitment purpose. The chart and Medical record review pre-recruitment poses no more than minimal harm to subject (i.e. loss of confidentiality/privacy). Given the number of subjects and the

possibility that not all subjects that look at their medical record may not eligible for the study this part of research would not be practical without waiver

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Consent will be performed by the PI, co-investigators or research associate prior to the procedure. A discussion about the research study will be initiated prior to bringing the patient into the endoscopy suite. Written consent will be obtained by the PI, co-investigators or research associate prior to the procedure and that a copy of the signed consent form will be given to the subject. Patients will be informed that colonoscopy procedure will take place even if they chose to decline participation.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not planned at this time, although, if subjects who do not speak English will be enrolled, short form and oral translation process will be used to obtain informed consent.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent
Not applicable

5.3.2.2 Adults Unable To Consent
Not applicable

5.3.2.3 Assent of Adults Unable to Consent
Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable

5.3.3.2 Assent of subjects who are not yet adults
Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Not applicable

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Not applicable

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

The information to be gathered is just for the recruitment purpose. Without it the PI could not identify the eligible subjects. This partial waiver is only for recognize the eligibility of study subjects. Obtaining consent from every subjects come for EMR would be prohibitive, resource exhaustive, and potentially cause confidentiality issues for the ones not be eligible for the study.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The projects requires look at medical records to identify eligible subjects.
Obtaining consent from every subjects come for EMR would be prohibitive, resource exhaustive, and potentially cause confidentiality issues for the ones not be eligible for the study.

6.3 Waiver or alteration of authorization statements of agreement

Not applicable

7.0 Study Design and Procedures

7.1 Study Design

This is a prospective data collection study which patients with non-pedunculated large polyps ≥ 20mm undergoing endoscopic mucosal resection (EMR with adjuvant Hybrid Argon Plasma Coagulation (APC) of the base and edges of the polypectomy site to fulgurate any potential microscopic residual disease. Resected polyps will be sent to the pathology laboratory where pathologist determine the final diagnosis of the polyps as per standard of care. We will collect the detail of the procedure, including,

general procedure details, polyp characteristic, details of any adverse event may happen and the details of 6 months follow up colonoscopy procedure.

7.2 Study Procedures

Consent and basic demographics will be garnered by the PI, Co-investigators or research associate in the pre-procedure area prior to bringing the patient to the endoscopy unit.
Whether or not the patients choose to participate in this study, subject will undergo the scheduled colonoscopy in the same manner as any patient presently referred for resection of large polyps. Patients will have undergone colonoscopy prep as it is standard at each center. All exams will be performed using high-definition colonoscopes with digital chromoendoscopy capability (e.g. Olympus 190 series).
Lesions will be identified using conventional colonoscopic views. Polyp characteristics will be recorded. Endoscopic mucosal resection (EMR) will be used for all resections: the polyp will be submucosally injected, so that the lesion will lift and demarcate from the submucosal layer. The submucosal injection creates a “cushion” between the mucosa and the muscularis propria. The idea is that mucosal lesions can be more safely removed. The applied injectate fluid will contain a lifting agent e.g. NaCl 0.9% and a dye agent e.g. methylene blue. The polyp will be resected with electrocautery snare. Following the resection of the polyp with the snare the submucosal area will be reinjected with saline (NaCl 0.9%) and then thermally ablated using APC (Erbe Hybrid APC). Finally thermal ablation of the resection site with the hybrid APC will occur using start settings. Once resection is considered complete the mucosal defect may be closed with clips for situations include but not limited to control bleeding during the polyp resection. Patients will be monitored continuously as is routine for any colonoscopy performed in our institution. Patients will be observed for in the recovery room before discharge for any sign of complications. (See appendix 1) We will collect the detail of the procedure, including, general procedure details, polyp characteristic, details of any adverse event may happen and the details of 6 months follow up colonoscopy procedure.

7.2.1 EXAMPLE: Visit 1 or Day 1 or Pre-test, etc. (format accordingly)

Patients will be contacted by phone 30 days post procedure to assess for any possible complications. (See appendix 2).

7.2.2 EXAMPLE: Visit 2 or Day 2 or Post-test, etc. (format accordingly)

A follow-up colonoscopy will be scheduled 6 months following the EMR procedure to evaluate for any recurrent polyp.
This is a standard of care for resection of large polyps

7.3 Duration of Participation

For all of the subjects it will be take 6 months to complete the study. A follow up colonoscopy will schedule and preform 6 months post-procedure to assess recurrence rate.

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8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We're going to enroll 40 patients with detected colon polyps ≥20 mm that referred to Hershey Medical Center for EMR colonoscopy.

8.2 Sample size determination

We shall assume a recurrent rate of 5% for the APC assisted EMR. A sample size of 40 subjects provide 60% power of rejecting $\boldsymbol{H_0}$: $\boldsymbol{\pi = 15\%}$ in a one-sided test, which is reasonable for a pilot study.

8.3 Statistical methods

The statistical plan for this study was designed with the assistance of Dr. Jason Liao with Penn State Public Health Sciences. The primary end point is the rate (proportion of patients) of local recurrent or residual neoplasia at 6 months for the Hybrid Argon Plasma Coagulation (APC) assisted EMR. Estimate of this recurrent rate will provided with 95% exact binomial confidence limits, which will then be compared to the historical rate of 15-20% recurrent rate for EMR alone. Statistical significance will be declared if the upper limit is smaller than 15%. Even when significance is not reached, the confidence interval provides the plausible range of the local recurrent rate of the APC assisted EMR and helps to decide if a future study with a larger sample size is warranted.

Summary statistics such as percentage of male/female patients, percentage of polyps within the different location of colon, mean diameter of polyps, percentage rate of neoplasia recurrence after 6 months , the percentage of each type of Polyps (Ip, IIa, IIb, IIc, etc), and Percentage of successful resection will also be provided. SPSS 22 statistical software shall be used to perform statistical analysis.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

9.1.1.1 Use of Codes, Master List

9.1.2 Storage of Data and/or Specimens

9.1.3 Access to Data and/or Specimens

9.1.4 Transferring Data and/or Specimens

9.2 Subject Privacy

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The study involves minimal risk to subjects as it involves evaluate Hybrid APC assisted EMR, which is FDA approved equipment and standard care procedure in U.S. for resection of large polyps.

Oversight for the conduct of the study will be provided by the PI, John M. Levenick, MD and the clinical research associate. Any adverse event may occurring will

be documented and reported according to HSPO policies and procedures. The principal investigator and co-investigators will be responsible for data collection and verification, and review of cumulative adverse events. Confidentiality will be protected by utilizing a code number as the only identifier for each subject and the master list will be kept under lock and key with access limited to the PI and research associate. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review.

10.2 Data that are reviewed

All adverse events will be documented and entered into the Redcap® data management system for centralized data storage and documentation. The following information will be entered: adverse event type, onset/resolution date and time, intensity/severity, action taken, and outcome. All deaths on the study, not related to progression of underlying disease will be reported to the IRB immediately. All unanticipated AE's related or possibly related to study will be reported by PI to the IRB according to HSPO policies and procedures.

10.3 Method of collection of safety information

Patient demographics, risk factors, EMR procedural elements, Pathology results, complications, and all follow up data will be entered into the Redcap® data management system for centralized data storage and documentation.

10.4 Frequency of data collection

Data will be collected at the time of enrollment, the initial procedure, 30 days post procedure phone call (adverse events), 2-3 weeks post-procedure pathology results and 6 month follow-up colonoscopy examination .

10.5 Individuals reviewing the data

The PI and clinical research associate will review cumulative adverse events and accrual every 3 months and report any issues requiring modification of the study or alternation of the risk: benefit ratio to IRB immediately. A summary of adverse events, study progress and protocol modification will be included for IRB review in the continuing progress report.

10.6 Frequency of review of cumulative data

The PI and the clinical research associate will review cumulative adverse events and accrual every 3 months.

10.7 Statistical tests

Not applicable

10.8 Suspension of research

The study team will make decisions regarding cessation of accrual. This trial will be suspended for review for any patient death during, or up to 30 days after participating in the trial if felt to be causally related to participation in this trial. The study team and the Office of Human Protection will then decide after review whether it is safe to continue the trial.

11.0 Risks

The research involves no more than minimal risk to participants because it involves prospective review of the patient's medical records, procedure details and any adverse events may occur for limited and in-sensitive

information. The only risk is the loss of patient confidentiality and the risk will be minimized by coding the research data and keeping separate list that links code number with identifiers.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There are no guarantees that subjects will benefit from participating in a research study, however, we hope there is a benefit of reducing recurrence rate while maintaining safety.

12.2 Potential Benefits to Others

The results of this research may lead to a technique for better way of complete resection of large polyps and safer one for future patients.

13.0 Sharing Results with Subjects

Data and results of the study outcome will not be shared with either the patient, primary provider, or referring provider. The results of the colonoscopy will be shared as per normal routine of the endoscopist.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not Applicable

15.0 Economic Burden to Subjects

15.1 Costs

Participant will not bear any costs which are not part of standard care.

15.2 Compensation for research-related injury

Subjects will not receive any compensation for being in this research study. As this is a low risk study, the like-hood of complications or injury is very small. Is it possible however, that the subject could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, medical treatment is available but will provide at the usual charge.
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

All study procedures including colonoscopy will be conducted at Gastrointestinal Endoscopy and Motility Center at UPS (suite 2000) at Hershey Medical Center. The fully-staffed Gastrointestinal Endoscopy and Motility Center features 8 endoscopy rooms with state of the art Olympus endoscopes. Two of the room designed to accommodate advanced therapeutic procedures, and have fluoroscopic capabilities. The suite has several onsite anesthesiologists, nurses and physicians. Measures in place to maintain patient privacy include: procedures that are performed in private studios or rooms and recovery that occurs in curtained rooms. If required, continuous emergency care is available. The primary investigator Dr. John Levenick is an Assistant Professor of Medicine. He has extensive experience with colonoscopy and EMR procedures. Additionally Dr. Levenick has several years of research experience as PI or Co-Investigator.

16.2 Feasibility of recruiting the required number of subjects

A total of 40 patients are needed for this study. Approximately, 170 colonic EMR performed at Hershey medical center per year. 100-125 of these EMR are done to remove polyps >2cm. We anticipate complete enrollment in 6 months.

16.3 PI Time devoted to conducting the research

As the principal investigator, Dr. Levenick has devoted a set amount of time to oversee the administration and surveillance of this study and to perform the procedures. He has been given a dedicated amount of academic time to pursue research, and while limited, it is sufficient to oversee and execute this trial safely and effectively.

16.4 Availability of medical or psychological resources

Patients will have continuous monitoring of vital signs during and after the colonoscopy procedure as is standard of care for this procedure as outlined in the protocol. Continuous emergency medical care is available for any patient undergoing colonoscopy and to this study population as standard of care. Physician, nursing, and support staff are available continuously while the patient is in the endoscopy suite.

16.5 Process for informing Study Team

The study team will meet to review the study procedures every month at the therapeutic pod meeting. All team members will be up to date on the progress of the study and any adverse events that may occur.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans

Not Applicable

18.2 Data Submission and Security Plan

Not Applicable

18.3 Subject Enrollment

Not Applicable

18.4 Reporting of Adverse Events and New Information

Not Applicable

18.5 Audit and Monitoring Plans

Not Applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE 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.

19.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

Note: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

Not Applicable

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

Not Applicable

19.7 Stopping Rules

Not Applicable

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The study involves minimal risk to subjects as it involves evaluate Hybrid APC assisted EMR, which is FDA approved equipment and EMR is standard care procedure in U.S. for resection of large polyps.

Oversight for the conduct of the study will be provided by the PI, John M. Levenick, MD and the clinical research associate. Any adverse event may occurring will

be documented and reported according to HSPO policies and procedures. The principal investigator and co-investigators will be responsible for data collection and verification, and review of cumulative adverse events. Confidentiality will be protected by utilizing a code number as the only identifier for each subject and the master list will be kept under lock and key with access limited to the PI and research associate. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review.

20.1.2 Safety Monitoring

All adverse events will be documented and entered into the Redcap® data management system for centralized data storage and documentation. The following information will be entered: adverse event type, onset/resolution date and time, intensity/severity, action taken, and outcome. All deaths on the study, not related to progression of underlying disease will be reported to the IRB immediately. All unanticipated AE's related or possibly related to study will be reported by PI to the IRB according to HSPO policies and procedures.

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

Not applicable

21.2 Location of storage

Not applicable

21.3 Duration of storage

Not applicable

21.4 Access to data and/or specimens

Not applicable

21.5 Procedures to release data or specimens

Not applicable

21.6 Process for returning results

Not applicable

22.0 References

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2. Kandiah K, Subramaniam S1, Bhandari P. Polypectomy and advanced endoscopic resection. Frontline Gastroenterol. 2017 Apr;8(2):110-114
3. Tsiamoulos ZP, Bourikas LA, Saunders BP. Endoscopic mucosal ablation: a new argon plasma coagulation/injection technique to assist complete resection of recurrent, fibrotic colon polyps (with video). Gastrointest Endosc. 2012 Feb; 75(2):400-4.
4. Arezzo A, Passera R, Marchese N., et.al. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. United European Gastroenterol J. 2016 Feb; 4(1):18-29.
5. Manner H, May A, Kouti I, et.al. Efficacy and safety of Hybrid-APC for the ablation of Barrett's esophagus. Surg Endosc. 2016 Apr;30(4):1364-70

Appendix 1: Schedule of events/study calendar, including screening, treatment, and follow-up

TimeLine	Before Colonoscopy	During Colonoscopy		30 days post EMR Procedure	6 months follow up Colonoscopy procedure
Tasks	-Screen patient for eligibility from Medical records and previous reports. - Explain study and obtain informed consent prior to colonoscopy	-Assess polyp eligibility -Decide whether to resect or not include patient in the study	- Perform EMR Followed by Hybrid APC	-Follow up phone call and pt. interview	-Assesse interim events Assess the resection site
Location	Endoscopy unit	Endoscopy unit		Phone	Endoscopy unit
Data	Patient characteristic and See checklist for inclusion/ exclusion criteria. Upload data into RedCap®	See checklist. Polyp characteristic data + EMR procedure details using Hybrid APC study Data Acquisition Form. Upload data into RedCap®		Minor and major complications (Bleeding, abdominal pain, etc.)+ Pathology results. Upload data into RedCap®	Resection site procedure details using Hybrid APC study Data Acquisition Form. Upload data into RedCap®

Appendix 2: Following questions will ask from the patients at the time of the 30 days follow up. The answer from patients and information from medical records will be transfer to Hybrid APC study Data Form and upload into RedCap®

1. Did you have any bleeding within 30 days following the EMR colonoscopy?
   - ❑ Yes
   - ❑ No
2. If yes when did this start? Date of AE start: ___ ___/ ___ ___/___ ___ (mm/dd/yy)
3. If yes when did this end? Date of AE end: ___ ___/ ___ ___/___ ___ (mm/dd/yy)
4. If yes how much bleeding did you have?
5. If yes did you need a treatment?
   - ❑ No treatment
   - ❑ Outpatient treatment
   - ❑ Inpatient treatment, specify days of admission: N= ____
   - ❑ Other, specify _____
6. Did you need Blood transfusion:
   - ❑ Yes
   - ❑ No
   - ❑ Don't know

   a. If yes, number of transfused units: N= _____
7. Did you have any fever within 30 days following the EMR colonoscopy?
   - ❑ Yes
   - ❑ No
8. If yes when did this Start? Date of AE start: ___ ___/ ___ ___/___ ___ (mm/dd/yy)
9. If yes when did this End? Date of AE End: ___ ___/ ___ ___/___ ___ (mm/dd/yy)
10. What was you temperature during this time?
11. If yes did you need a treatment?
    - ❑ No treatment
    - ❑ Outpatient treatment
    - ❑ Inpatient treatment, specify days of admission: N= ____
    - ❑ Other, specify _____
12. Did you have any abdominal pain within 30 days following the EMR colonoscopy?
    - ❑ Yes
    - ❑ No

13. If yes what is the score of your pain from 0-10 (10 is the worst pain)?

14. If yes where was the location?

15. If yes did you need a treatment?
    - ❑ No Intervention
    - ❑ Outpatient treatment
    - ❑ Inpatient treatment, specify days of admission: N= ____
    - ❑ Other, specify _____

16. If yes did a Colonoscopy performed?
    - ❑ Yes
    - ❑ No
    - ❑ Don't know

17. If yes did a CT performed?
    - ❑ Yes
    - ❑ No
    - ❑ Don't know

18. If yes did surgery required to repair/ resect your colon?
    - ❑ Yes
    - ❑ No
    - ❑ Don't know