Prospective, Multicenter Study for the Evaluation of Safety and Performance of the Interscope EndoRotor® Endoscopic Mucosal Resection System for the Removal of Alimentary Tract Mucosa in the Colon

Protocol Number: CLIN 0001-US
Revision A
19 April 2019

Sponsor:
Interscope, Inc.
100 Main Street, Suite 108
Whitinsville, Massachusetts, USA 01588

Investigator's Protocol Signature Page

STUDY TITLE: **PROSPECTIVE MULTICENTER STUDY FOR THE EVALUATION OF SAFETY AND PERFORMANCE OF THE INTERSCOPE ENDOROTOR® ENDOSCOPIC MUCOSAL RESECTION SYSTEM FOR THE REMOVAL OF ALIMENTARY TRACT MUCOSA IN THE COLON**

PROTOCOL NUMBER: **CLIN 0001-US, Revision A**

STUDY CENTER: _____

(Print name of study center)

By signing below, I confirm that I will not enroll subjects in this study until IRB approval has been obtained at my site. I have read this protocol and agree to adhere to the protocol and study requirements. I will discuss this protocol and all related study material with the research team at my institution and ensure that they are fully informed regarding the study requirements and use of the EndoRotor® device. I will also ensure that the study is conducted in accordance with all applicable standards and regulations; including, but not limited to, the Declaration of Helsinki, Good Clinical Practices (GCP), FDA Regulations, the Sponsor, the IRB and any other applicable local or national requirements.

_____

Principal Investigator – Printed Name

_____

Principal Investigator – Signature

_____

Date

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List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CIP	Clinical Investigational Plan
CV	Curriculum Vitae
DMC	Data Monitoring Committee
EndoRotor®	The EndoRotor® is a powered tissue resection system produced by Interscope, Inc. of Whitinsville, MA, USA.
EU	European Union
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IRB	Institutional Review Board
MREC	Medical research ethics committee
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical or medical device company
WIRB	Western Institutional Review Board

Protocol Summary

PROTOCOL NUMBER	CLIN 0001-US / Revision A
Study Title:	Prospective, Multicenter Study for the Evaluation of Safety and Performance of the Interscope EndoRotor® Endoscopic Mucosal Resection System for the Removal of Alimentary Tract Mucosa in the Colon
Study Objective:	To collect data in support of the safety and performance of the Interscope EndoRotor® Endoscopic Mucosal Resection System on a post-market basis. The study will confirm that the EndoRotor® resections are safe and effective.
Study Device:	Interscope EndoRotor® Endoscopic Mucosal Resection System
Indication for Use:	The EndoRotor® is intended for use in endoscopic procedures by a trained gastroenterologist to resect and remove tissue, not intended for biopsy, of the gastrointestinal (GI) system including post-endoscopic mucosal resection (EMR) tissue persistence with a scarred base and residual tissue from the peripheral margins following EMR.
Regulatory Status:	The Interscope EndoRotor® Mucosal Resection System is a cleared Class II medical device per 21CFR 807.92 and 21 CFR 884.1690 under 510(K) K181127. The EndoRotor is also approved under MDD 93/42/EEC on Medical Devices Annex II, excluding Section 4. The device bears the CE Mark as a Class IIa under Rule 5 of Annex IX where it is indicated for excision/resection of alimentary tract lesions including pan necroses via direct endoscopic necrosectomy (CE 613797). According to the CFR and MDD the EndoRotor® is not an investigational product. The study does not include any non-standard of care assessments; therefore, the study is classified as a non-interventional (or observational) study. The device has been designed and is manufactured under the control of the Interscope, Inc. Quality Management System. Interscope, Inc. is ISO 13485 certified (FM 61310).
Study Design:	Post-market, prospective, non-randomized, multi-center study for the treatment of subjects with the need for resection of recurrent flat or sessile colorectal lesions where EndoRotor is the primary resection modality of persistent adenoma with a scarred base.
Enrollment:	Total enrollment is at least 60 evaluable subjects at up to 15 clinical sites

	in the United States and Europe.
Subject Population:	Adult subjects aged ≥18 to ≤85 years who have one or more recurrent flat or sessile rectal/colon mucosal polyps measuring up to 6 cm in diameter and/or length.
Estimated Study Duration:	First subject enrolled: June 2019 Last subject enrolled: December 2019 Study completion (final 90-day visit, closeout visit): June 2020
Primary Endpoints:	**Primary Effectiveness Endpoint (Performance):** Technical Success, defined as the ability of the EndoRotor device to resect recurrent flat or sessile colorectal lesions without concomitant use of other resection modalities for mucosectomy and no definitely or probably device-related serious adverse events (SAEs) throughout the 90-day follow-up period. **Primary Safety Endpoint:** Assessment of Serious Adverse Events (incidence, relationship to device and severity) at index procedure and at 90 days, post-procedure.
Secondary Endpoints:	1. Completeness, in percentage, of resection based on endoscopy film and/or photographs and in addition to diagnostic assessment of specimen graded by the independent pathologist. 2. Presence of colon stenosis based on endoscopy film and/or photographs. 3. Rate of persistence of disease at the location of resection at 90 days. 4. Histologic assessment of the diagnostic value of the collected specimens.
Primary Analysis:	The Per Protocol (PP) analysis population will be the primary effectiveness analysis population.
Inclusion Criteria:	1. Subjects aged ≥18 to ≤85 years. 2. At least one recurrent flat or sessile colorectal lesion measuring up to 6 cm in diameter and/or length. 3. Presence of recurrent flat or sessile lesion where the EndoRotor® may be used to resect recurrent neoplasia. 4. Favorable anatomy that allows the investigator to access the lesion. 5. Subject is able and willing to comply with site standard medical follow-up, including the 90-day follow-up visit. 6. Subject has been informed of the nature of the study, agrees to participate and has signed the consent form.

Exclusion Criteria:	1. Inability to give informed consent. 2. Subject age is <18 years of age or >85 years of age. 3. Presence of a lesion that represents cancer or has a high chance of harboring submucosal invasive cancer. 4. Presence of synchronous lesions intended for resection that would require use of a concomitant resection modality 5. Medical reasons the procedure cannot be performed (i.e. labile blood pressure, anticoagulation laboratory levels that are too high and risk excessive bleeding, systemic infection, etc.) 6. Active antiplatelet therapy (Plavix®, 325mg aspirin therapy) – patient off treatment for < 1 week. 7. Inability to undergo a procedure under propofol sedation or General Anesthesia. 8. Female patients who are known to be pregnant. 9. Co-morbid conditions that place the subject at an unacceptable surgical risk (e.g., severe chronic obstructive pulmonary disease, hepatic failure, cardiac disease, autoimmune disorders or conditions of severe immunosuppression). 10. Any clinical evidence that the investigator feels would place the subject at increased risk with the deployment of the device. 11. Subject is participating in another study of a device, medication, biologic, or other agent within 90 days and could, in the opinion of the investigator, impact the results of this study. 12. Subject has other medical, social or psychological problems that in the opinion of the investigator would preclude them from receiving this treatment and the procedures and participating in evaluations pre- and post-treatment.

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1.0 INTRODUCTION AND BACKGROUND

1.1 Introduction

The EndoRotor® Endoscopic Mucosal Resection System is a non-thermal mechanical endoscopic mucosal resection system for use in the gastrointestinal tract for benign neoplastic or pre-malignant tissue removal by interventional gastroenterologists and GI surgeons. The EndoRotor® System performs both tissue resection and extraction with a single device. The EndoRotor® System allows a gastroenterologist to access and remove polypoid or abnormal mucosa through an endoscope's instrument biopsy channel without removing and re-inserting the scope and without having to use multiple instruments. A motorized rotating cutting tool driven by an electronically controlled console performs tissue resection. Because the system automatically suctions and cuts about 1750 times a minute, resected tissue is immediately aspirated away from the resection site and collected onto a micron filter. Tissue collected on the filters can be used for pathological examination using standard methods.

Although the EndoRotor® was designed to be used within the esophagus, stomach, small and large intestine, in this study, Interscope will evaluate the use of the EndoRotor® to resect diseased colorectal mucosa only.

- In this study, recurrent flat or sessile lesions up to 6 cm in diameter and/or length in the appropriate patient will be removed using the EndoRotor®.

- Various parameters, such as bleeding requiring intervention, perforation, speed of resection, and adequacy of the specimens to produce a diagnosis will be assessed. Routine endoscopic surveillance at 90 days will allow the endoscopist to assess adequacy of resection, the presence of persistent lesions and resection-associated stenosis.

1.2 Background

1.2.1 Gastrointestinal Polyps

The gastrointestinal tract is the system of organs that is responsible for consuming and digesting foodstuffs, absorbing nutrients and expelling waste. In humans, it consists of the esophagus, stomach, small intestine (duodenum, jejunum & ileum) and large intestine (cecum, colon, rectum & anal canal), with the upper GI tract comprising the mouth to the duodenum and the lower GI tract comprising the cecum to the anus. The structure of the gastrointestinal wall is relatively consistent throughout the length of the tract and involves four layers, the mucosa, submucosa, muscularis propria, and serosa or adventitia. The mucosa is the innermost layer that surrounds the lumen and is exposed to the contents of the tract. It is itself composed of 3 layers: epithelium, lamina propria, and muscularis mucosa, and is highly specialized in each organ of the GI tract. The submucosa consists of connective tissue and supplies blood vessels, lymphatic vessels, and nerves to the mucosa. The muscularis propria, also known as the muscularis

externa, consists of 2 layers of smooth muscle and controls peristalsis. The serosa, or adventitia, is the outermost layer of the GI tract and consists of several layers of connective tissue.

A polyp is an abnormal growth of tissue protruding from the mucosal membrane into the lumen of a hollow vessel, anywhere in the gastrointestinal, genitourinary or respiratory tracts. Within the gastrointestinal tract polyps can be found within the esophagus, the stomach, the duodenum, the colon, and the rectum, with colorectal polyps accounting for the vast majority of polyps found in the GI tract. While most polyps are largely asymptomatic and despite the majority of polyps being benign, if left untreated certain types of polyps can become malignant and develop into cancer.

Polyps can be classified by their malignant potential:

- Non-malignant potential polyps. Hyperplastic polyps are the most common type of polyp in the colon, accounting for 90% of all polyps detected. Hyperplastic, harmartomatous/juvenile and inflammatory polyps are also considered to have no malignant potential.
- Low/Moderate-malignant potential polyps. Although only 5% of adenomas evolve to cancer, it is accepted that the majority of carcinomas evolve from adenomatous polyps. Adenomatous polyps should be considered as precursors to carcinomas and should be removed whenever possible.
- High-malignant potential polyps. Serrated-adenoma polyps have recently been identified and display features of both non-malignant and moderate-malignant potential polyps.

In addition, polyps can also be classified by their visual appearance:

- Sessile polyps are broad-based without a connecting stalk. They arise directly from the mucosal layer and account for approximately 50% of all polyps.
- Pedunculated polyps are defined by a head connected to a stalk or pedicle and account for approximately 5% of all polyps.
- Flat polyps are non-protruding or non-raised lesions with a height of less than one-half the diameter of the lesion.
- Depressed polyps are very uncommon and are particularly likely to harbor high- grade dysplasia or be malignant, even when small.

Although the majority of polyps are non-malignant, it is known that the risk of malignancy increases with polyp size, with polyps < 10 mm having < 1% risk of cancer, polyps of 10 mm having a 10% risk of cancer and polyps of 20 mm having a greater than 10% risk of cancer. It is also understood that a polyp of < 1 cm takes approximately 10 years to transform into invasive

colorectal carcinoma. Therefore, adenomas greater than 5 mm are normally treated. Polyps with tethered bases resulting from scarring are often the most challenging to resect endoscopically. The scarring can be caused by previous attempts at resection, previous deep biopsies, or tattoos placed too closely. These polyps often do not lift and can be impossible to snare even when stiff snares are used. Endoscopic submucosal dissection (ESD) and knife-assisted resection (KAR) are techniques that have been shown effective in the management of scarred polyps, however these techniques have not been widely adopted in the West. Argon plasma coagulation has been more commonly used to ablate adenomatous tissue in scarred polyps but this technique does not allow for the histological assessment of the scarred polyp and is less effective than ESD. The EndoRotor provides a technique whereby the lesion can be effectively removed without adjunct procedures with collection of tissue for histological assessment.

1.3 Literature Summary

1.3.1 Rectum/Colon Polyps

Although most colon polyps are small (90% are less than 1cm) and never progress to cancer[1,2], the larger polyps have a higher chance of harboring advanced histology and even cancer. Larger polyps and sessile polyps present the endoscopist with technical challenges in their resection that current instrumentation is not well-suited to address. EMR and Endoscopic Submucosal Dissection (ESD) are the main advanced techniques used to remove larger lesions by interventional endoscopists. When comparing the two, there are some striking differences between them. EMR involves the piecemeal resection of the lesion and is relatively quick depending on the endoscopist's skill and the size of the lesion. EMR is more widespread and is easier to learn (30-40 cases) than ESD that requires from 60 to 80 cases to become proficient. ESD requires the lifting of the lesion with fluid and the excision of the lesion in one piece. This meticulous resection requires much more time (45 to 90 minutes) but offers a surgical specimen that can be oriented and evaluated for margins and depth of penetration as one complete sample. ESD is much more commonly performed in Eastern Asia (Japan) than in Europe or the United States.

O'Brien, Michael J, et. al. reported results of an analysis encompassing 8401 person-years of follow-up evaluation[3]. AT and AR measures of adenoma flatness were 95% concordant. By the AT measure, flat adenomas (n 474) represented 27% of all baseline adenomas. Flat adenomas identified in the National Polyp Study cohort at baseline were not associated with a higher risk for high-grade dysplasia initially, or for advanced adenomas at surveillance. Flat adenomas were found to be no more likely to exhibit high-grade dysplasia than sessile (polypoid) or pedunculated adenomas.

At the present time, there are 2clinical literature reports specific to the EndoRotor® System dealing with recurrent adenoma in a single center and Barret's esophagus respectively. Based on clinical and extensive pre-clinical \results in a post-market setting, the EndoRotor® has several inherent advantages over EMR and ESD techniques in the removal of scarred lesions. It is cost-

neutral with EMR and less expensive than ESD, potentially resects tissue faster than ESD, potentially affords the endoscopist more precision with resections and still allows for histological evaluation of the tissue as opposed to thermal ablative techniques. The EndoRotor® potentially presents an opportunity to evaluate an instrument that could impact incomplete resection and removal of lesions with a scarred base. According to Knabe, et al, a substantial (31.69%) proportion of piecemeal resections are incomplete and substantial numbers of inconspicuous post-resection scars harbor residual occult neoplasia that may cause late recurrences[(4)]. The authors reported on a study of 243 consecutive patients with 252 adenomas that were followed using a standardized protocol after complete endoscopic resection. After endoscopic treatment, the patients received standardized follow-up examinations after 3–6 months and 12 months. The post polypectomy scar was re-examined, assessed for residual neoplasia, and biopsied at each follow-up colonoscopy. Evident residual neoplasia was noted after 3–6 months in the majority of lesions (58 of 183 lesions totaling 31.69%). After 12 months, 126 LNLs were examined, with 19 late recurrences (16.37%). Twenty-one (6.5%) post polypectomy scars were not detected during 321 surveillance examinations. Biopsy evidence of residual/recurrent lesions was found in 16 of 228 macroscopically inconspicuous polypectomy scars (7%). All residual adenomas were treated using ER and/or argon plasma coagulation. The use of Argon plasma provides no histologic specimen in the management of post-EMR persistent lesions with a scarred base and thus precludes timely assessment of the efficacy of the resection.

1.3.2 Summary

Following a review of the published literature, the main complications found to be associated with polypectomy were bleeding/hemorrhage, perforation, and post-polypectomy syndrome, which are reported to occur in 0-10.8%, 0-2.3%, and 0.14-3.7% of patients, respectively. Deaths were reported in only 2 studies, at a rate of 0.01% and 0.1%. The greatest risk factor for an adverse event is associated with increasing polyp size. In terms of performing polypectomy, the most commonly referenced outcome measures were completeness of polyp removal or recurrence, with a range from 73-100% and 1.4-24% respectively, in the published literature. Supporting evidence of a 3-month follow up visit, as is indicated in the EndoRotor colon study, was also reported in the medical literature. Additionally, it was determined that flat adenomas are no more likely to exhibit high-grade dysplasia than sessile (polypoid) or pedunculated adenomas thereby persistent and large adenomas would demonstrate the greatest potential for persistence as supported by the literature on incomplete resection rates, and therefore provides the rationale for the inclusion criteria in the EndoRotor colon study.

1.4 Report of Prior Investigations

1.4.1 Summary of Prior Human Clinical Use

The EndoRotor® has been used to resect diseased colorectal mucosa in humans on a post-market basis commercially in over 400 procedures (100 walled off necrosis, 70 Barrett's Esophagus and over 250 colon procedures in the USA and Europe. To date there have been 3 multi-center prospective clinical studies in approximately 40 patients in colon resection and 47 patients in Barrett's Esophagus, and 30

patients in removal of walled off necrosis . In the Barrett's series 2 cases of delayed bleeding occurred and were successfully controlled endoscopically. One colon perforation was observed and closed endoscopically in this series and histo-pathological assessment provides pathologists with information over ablative techniques that eradicate pathology. EndoRotor clinical literature includes two peer review publications in addition to 3 submissions, one in colon, one in Barrett's Esophagus and one in walled off necrosis are under review.

1.4.2 Summary of Pre-Clinical (Animal) Testing

Animal testing of the EndoRotor was conducted to evaluate the overall safety and performance of the device in an animal model. A summary of the study is presented below.

The objectives of this study were to evaluate the EndoRotor system for performance of tissue resection in an animal model, with respect to safety:

- Assessment of tissue response acutely and at 2 weeks post-resection utilizing standard light microscopy
- Clinical assessment of bleeding at sites of resection

The animal study was conducted under Good Laboratory Practice (GLP) guidelines. Six Yorkshire swine were utilized. Over 120 resections were completed between the colon, stomach, and esophagus, and distributed across different sizes. The studies were conducted at CBSET Lexington, Massachusetts, USA as part of a Good Lab Practices (GLP) protocol, as well as for a preliminary research project in Germany at the Institut für Nutztiergenetik, Mariensee, Friedrich-Loeffler-Institut (FLI) Bundesforschungsinstitut für Tiergesundheitusing in live pigs[5].

Perforation and bleeding were the main safety criteria assessed. Other major endpoints were device performance/usability and histopathology. Perforation was noted in 2 (1.6%) of the resection sites, comparing favorably to the published rate of 2.3%. Bleeding was graded as mild (resolves in 2 minutes or less without intervention) in 79.5% of sites, as moderate bleeding (resolves in greater than 2 minutes without intervention) in 19.7% of sites, and one site (0.8% of sites) as severe bleeding (requires intervention to resolve the bleeding) which resolved after epinephrine administration. The bleeding rate that required intervention compares favorably to the rates for current interventional techniques published in the literature (0.8% vs. 1-16%). The study pathologist indicated that use of the EndoRotor® System for mucosal tissue resection in the porcine esophagus, stomach and colon was associated with favorable and clinically acceptable tissue responses. The EndoRotor® System received passing evaluation for all performance and intended use criteria by both physicians for the system usability assessment.
Review of multiple techniques for the removal of polyps from the gastrointestinal tract suggests that the EndoRotor® System (with or without injection) will not introduce any new or unrecognized safety risks and will have a favorable risk/benefit profile.

1.4.3 Summary of Design Verification and Validation Testing

The Interscope EndoRotor® System has undergone extensive design verification and validation testing consistent with the Essential Requirements of the Medical Device Directive, applicable ISO standards, and applicable test methods. The EndoRotor® has been tested and has successfully passed the acceptance criteria for the following:

- Biocompatibility
- Functional Performance
- Sterilization
- Shelf Life
- Electromagnetic Compatibility
- Software Verification
- Usability
- Package Integrity

2.0 DEVICE DESCRIPTION

The EndoRotor® System performs both tissue dissection and resection with a single device. The EndoRotor® System allows a gastroenterologist to access and remove polypoid or abnormal mucosa through an endoscope's instrument biopsy channel without removing and re-inserting the scope and without having to use multiple instruments. A motorized, rotating, cutting tool driven by an electronically controlled console performs tissue resection. Resected tissue is immediately aspirated away from the resection site and collected onto a micron filter. Tissue collected on the filters can be used for pathological examination using standard methods. The device is not user programmable - it utilizes an off the shelf Maxon® electric motor built in the console and cannot be adjusted by the user

The EndoRotor® System is comprised of the following core components:

- EndoRotor Console®: The system control unit housing the motor drive, peristaltic pump and pinch valve to provide rotation, irrigation, and vacuum regulation respectively. (Figure 1).
- EndoRotor Foot Control®: Activates/deactivates cutter rotation/lavage and aspiration (suction).
- EndoRotor Catheter®: The outer jacket of the cutter catheter serves as the delivery vehicle for the irrigation fluid that flows between the inner wall of the braid and outer wall of the torque coil. It also allows for outer cutter repositioning. The outer braided sheath is attached to the distal cutter at the end of the catheter. The torque coil transmits internal rotation to the inner cutter and is sealed with a shrink sleeve to contain aspiration. The rotation motion cuts tissue, which is simultaneously removed from the resection site by suction. The distal ends of the lavage and aspiration tubing are permanently affixed to the catheter (Figures 2-4).

- Collection Device: EndoRotor Specimen Trap® with pre-loaded micron filter. This custom trap is designed specifically to capture EndoRotor® specimen.
- Polyp Filter: The EndoRotor Filter Set® includes 200 replacement filters that can be exchanged and placed within the EndoRotor Specimen Trap® to ensure collection of resected tissue.

Figure 1. EndoRotor Console®

Figure 2. Tubing and Resecting Cutter Components

Figure 3. Disposable Resecting Cutter

Figure 4. Drawing of Resecting Cutter Deployed in Endoscope Working Channel

2.1 Indication for Use

The EndoRotor® is intended for use in endoscopic procedures by a trained gastroenterologist to resect and remove tissue, not intended for biopsy, of the gastrointestinal (GI) system including post-endoscopic mucosal resection (EMR) tissue persistence with a scarred base and residual tissue from the peripheral margins following EMR. The EndoRotor® System resects and removes mucosal tissue simultaneously through a catheter inserted into the working channel of a flexible endoscope. The EndoRotor® System will be used for removal of mucosal/sub-mucosal

tissue in the colon within the 510(k) clearance indications and according to the Instructions for Use.

2.2 Contraindications

The EndoRotor® should not be used for the primary resection of lesions or for tissues intended for biopsy.

2.3 Device Use in Clinical Study

Devices will be used in the study whenever an Investigator decides to use the EndoRotor® System for standard of care removal of mucosal/sub-mucosal tissue in the colon.

3.0 POST-MARKET STUDY PLAN

3.1 Study Objective

This study is being conducted as a post-market 510(k) study to collect data in support of the safety and performance of the Interscope EndoRotor® Endoscopic Mucosal Resection System. The study will demonstrate that EndoRotor® resections are safe and effective and support market adoption efforts.

3.1.1 Study Design

This study has been designed as a prospective, non-randomized, multi-center, observational study for the treatment of subjects with the need for resection of recurrent, flat or sessile dysplastic/adenomatous rectal/colonic mucosa where EndoRotor is the primary resection modality.

3.1.2 Enrollment

Total enrollment is 60 evaluable subjects at up to 15 clinical sites in the United States and Europe. Each site may enroll a minimum of one (1) subject and a maximum of 8 subjects until a maximum of 60 evaluable subjects are enrolled.

3.1.3 Study Population

Adult (>18 years to ≤85 years) subjects who have at least one recurrent flat or sessile rectal/colon mucosal polyp up to 6 cm in diameter and/or length.

3.2 Study Duration & Follow-Up

It is anticipated that the study will begin enrollment in June 2019. Enrollment is expected to continue until December 2019. Study subjects shall return for clinic visits in 90 days (+/- 14 days) post-procedure; data from these visits shall be collected. Primary and other endpoints will be assessed. All subjects will be treated per this protocol, the Instructions for Use, and as per standard of care, as indicated. The last follow-up visit is expected to be completed by March 2020 at the last subject's 90-day (+/- 14 days) follow-up visit. The study is complete following the collection of all study data and all final site visits have been completed in June 2020.

4.0 STUDY ENDPOINTS AND SUBJECT POPULATION

4.1 Primary Endpoints

Primary Effectiveness Endpoint (Performance):

Technical Success, defined as the ability of the EndoRotor device to resect recurrent flat or sessile colorectal lesions without concomitant use of other resection modalities for mucosectomy and no definitely or probably device-related serious adverse events (SAEs) throughout the 90-day follow-up period.

Primary Safety Endpoint:

Assessment of Serious Adverse Events (incidence, relationship to device and severity) at index procedure and at 90 days, post-procedure.

4.2 Secondary Endpoints

The following is a list of other secondary endpoints to be explored:

1. Completeness, in percentage, of resection based on endoscopy film and/or photographs in addition to diagnostic assessment of specimen by the independent pathologist.
2. Presence of colon stenosis based on endoscopy film and/or photographs.
3. Rate of persistence of disease at the location of resection at 90 days.
4. Histologic assessment of the diagnostic value of the collected specimens.

4.3 Inclusion Criteria

Subjects are required to meet **ALL** the following inclusion criteria in order to be included in this clinical study:

1. Subjects aged ≥18 to ≤85 years.
2. At least one recurrent flat or sessile colorectal lesion up to 6 cm in diameter and/or length.
3. Presence of lesion where the EndoRotor® may be used to resect recurrent neoplasia.
4. Favorable anatomy that allows the investigator to access the lesion.
5. Subject is able and willing to comply with site standard medical follow-up, including a 90-day follow-up visit.
6. Subject has been informed of the nature of the study, agrees to participate and has signed the consent form.

4.4 Exclusion Criteria

Subjects are required to meet **NONE** of the following exclusion criteria to be included in this clinical study:

1. Inability to give informed consent.
2. Subject age is <18 or >85 years of age.
3. Presence of a lesion that represents cancer or has a high chance of harboring submucosal invasive cancer.
4. Presence of synchronous lesions intended for resection that would necessitate use of a concomitant resection modality
5. Medical reasons the procedure cannot be performed (i.e. labile blood pressure, anticoagulation laboratory levels that are too high and risk excessive bleeding, systemic infection etc.)
6. Active antiplatelet therapy (Plavix®, 325mg aspirin therapy, etc.) where subject cannot be off treatment for at least 1 week prior to index procedure.
7. Inability to undergo a procedure under Propofol sedation or general anesthesia.
8. Female patients known to be pregnant.
9. Co-morbid conditions that, in the opinion of the investigator, place the subject at an unacceptable surgical risk (e.g., severe chronic obstructive pulmonary disease, hepatic failure, cardiac disease, autoimmune disorders or conditions of severe immunosuppression).
10. Any clinical evidence that the investigator feels would place the subject at increased risk with the deployment of the device.
11. Subject is participating in another study of a device, medication, biologic, or other agent within 30 days of enrollment and could, in the opinion of the investigator, impact the results of this study.
12. Subject has other medical, social or psychological problems that in the opinion of the investigator would preclude them from receiving this treatment and the procedures and participating in evaluations pre- and post-treatment.

5.0 STUDY PROCEDURES

5.1 Subject Screening

All subjects presenting to the institution who are scheduled to undergo flexible interventional colonoscopy for colon polyps will be informed of the study and offered enrollment if they meet the inclusion/exclusion criteria.

A member of the study team shall perform a preliminary evaluation of the potential participant's medical history and previously performed examinations to assess for initial eligibility. If the subject is willing to participate in the study, a written consent will be obtained. All subjects that have consented to participate in the study will be entered into the Enrollment / Screening Log.

Any subject that fails the screening process after providing consent will be considered a screen failure; the reason for failing the screen will be recorded on the log.

5.2 Informed Consent

Written Informed Consent, with the IRB approved consent form, will be obtained for all subjects **prior** to any data collection for the study in accordance with 21 CFR 50.20. The subject shall be given adequate time to read the informed consent form and will have the study process explained to them prior to signing the Informed Consent document. All subjects are to receive copies of their signed informed consent documentation.

5.3 Subject Enrollment and Withdrawal

All subjects requiring interventional colonoscopy for colon polyps are potential study candidates and will be screened for eligibility. Every effort will be made to ensure eligibility of the participants prior to study procedure. Actual enrollment in the study occurs at the time of informed consent.

Subjects who do not meet all inclusion / exclusion criteria (e.g., including inability to reach the target area or colon anatomy not conducive to tissue resection) will be considered a screen failure and will not be followed in the study (no data will be collected on these subjects). Subjects in whom the Interscope EndoRotor® is inserted into the colon and resection is attempted, but the procedure is aborted without resection of tissue, will be followed through discharge for safety. At discharge, the subject will be assessed for safety only and the subject will be allowed to exit the study.

Subjects may withdraw at any time from the clinical study without jeopardy or prejudice. If a subject prematurely terminates from the study, the reason for study termination will be recorded and the results will be tabulated by number and percent for each category. If termination is the result of an adverse event or death, an Adverse Event Form will also be completed. Subjects who withdraw consent after treatment will have their data evaluated until the time of their withdrawal.

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing medical observations will occur due to loss to follow-up, withdrawal, or non-adherence with required assessments. If a subject cannot be located, they will be considered lost to follow-up. If they are contacted but refuse to return for visits or they actively request to withdraw from the study, they will be considered withdrawals. Data collected up to the time of lost to follow-up, and withdrawal of consent will be maintained in the study database and used for analysis purposes, as appropriate. These subjects will not be replaced.

Subjects who are enrolled and treated, but who are later discovered to not meet all of the study eligibility criteria will remain in the study and follow-up data will be collected. A protocol deviation will be completed for study subjects who are found to be ineligible after enrollment.

5.4 Anticipated Total Enrollment

It is anticipated that sixty (60) evaluable patients will be enrolled. Loss to follow-up is anticipated to be no more than 10%.

5.5 Schedule of Events

A summary schedule of the study assessments is provided in **Appendix 1**.

5.6 Baseline Evaluation, not greater than 14 days prior to the Index Procedure

Baseline data will be collected after the subject signs the informed consent form in order to confirm **all** inclusion and **no** exclusion criteria are met. All assessments must be completed within the 14 days prior to undergoing the study procedure, with the exception of the pregnancy test. A negative pregnancy test within 1 day before the study procedure is required for women of childbearing potential.

The following baseline evaluations will be assessed and recorded on all patients who provide written informed consent:

- Demographic information
- Medical and surgical history, including risk factors
- Pregnancy test results (completed within 1 day before the study procedure)
- Physical examination
    - Vital signs
    - Height and weight
    - Target review of symptoms
- Assessment against I/E criteria

5.6.1 Baseline Demographics and Relevant Medical History

The subject's demographic information and relevant medical history will be documented in the subject's source medical record and on the appropriate case report form (CRF). This will include the subject's:

- Age
- Gender
- Height
- Weight
- Race and Ethnicity Information

- Relevant medical history
- Physical Examination

5.7 Index Procedure

All patients will receive the EndoRotor® treatment following the technique described by Interscope's Instructions for Use.

The mucosal resections are performed during standard flexible colonoscopy procedures. All medications given, pre- and post-procedure precautions and follow-up assessments are part of routine standard of care. This protocol concerns itself with the actual removal of the mucosal lesion once the abnormal area is identified using the colonoscope.

- Patients will be prepped in the usual manner for lower GI endoscopy prior to their interventional visit.
- The procedures will be performed with either Propofol sedation or under general anesthesia.
- When a mucosal lesion is found, the EndoRotor® system will be prepared by attaching the EndoRotor® catheter, foot pedal and the calibrated suction to the Control Unit, ensuring there is a filter in the collection unit (specimen trap), and then priming the catheter with 0.9% normal saline.
- Lesions will be injected using saline solution with dye such as Indigo carmine or Methylene Blue. Indelible ink (such as SPOT) will be injected into the region of the resection to identify the site after resection.
- The EndoRotor® catheter will be inserted through the working channel of the endoscope until it is in proper cutting position with the cutting surface oriented towards the mucosal lesion and the catheter no more than 3cm out of the scope. The physician will turn the motor on by depressing the blue pedal and engage cutting by holding the orange pedal for as long as he/she wishes to cut tissue.
- Cutting should be performed while moving the EndoRotor® catheter. The endoscopist will take care to not keep the suction activated when he/she is not intending to cut mucosa and when stopped for more than 1 second while apposed to tissue to not risk creating a perforation.
- Various techniques can be used to remove the lesion. Recurrent, flat or sessile lesions will be attempted to be removed entirely with the EndoRotor® with no other treatment modalities. The physician will utilize the recommended technique appropriate to the lesion until there is no longer visible evidence of mucosal lesion. The intent of the protocol is to complete lesion resection using the EndoRotor as the only treatment modality. However, should it prove not feasible to complete the resection with the EndoRotor, the investigator may convert to the use of an alternative resection modality.

- For synchronous lesion interventions, respective lesion specimens should be isolated and separately collected to avoid confounding results.
- APC or similar techniques used for hemostasis on a resected lesion is not considered an alternative resection modality.
- Treat with EndoRotor, assess percentage of tissue removed with EndoRotor followed by photograph from region at equidistant location.
- Photo-document the region following EndoRotor treatment.
- If the complete lesion cannot be removed in a single treatment visit, a second visit can be scheduled to complete the removal in advance of the 90 day visit.

5.7.1 Index Procedure Details

Refer to the Instructions for Use for a description of the procedure. The following data will be collected on all subjects during the index procedure and prior to discharge on the Index Procedure case report form:

- Summary of symptoms from physical examination
- Endoscopic imaging study
- The EndoRotor® achieved the attempted resection of the targeted lesion(s).
- The EndoRotor® pathological specimens were able to be interpreted by GI pathologists and enabled the rendering of clinical diagnoses.
- The total number of recurrent lesions treated with the EndoRotor.
- Time from scope insertion to scope removal.
- EndoRotor time from resection start to resection end.
- Adverse event assessment and treatment (i.e. delayed bleeding, presence of perforations). Note: Typical and routine steps (endoscopic clipping/mucosal apposition) will be taken to close perforations if they are discovered.
- Ease of use and overall satisfaction with the EndoRotor® System.
- Identification of technical difficulties and device malfunction, if any.
- Photographs post-EndoRotor treatment.

Current standard of care does not guarantee pathology in recurrent lesion procedures due to the difficulty to remove they often are treated with avulsion or Argon Plasma Coagulation. Since the EndoRotor retrieves specimen it can be sent for histopathological review. Although the EndoRotor is not intended for biopsy in this study pathologist will also be able to evaluate specimen that would normally be ablated. Resected tissue collected in the Specimen Trap will be placed in 10% Formalin and sent to the resident pathologist for histological evaluation. The

following steps will be taken for the review and interpretation of the specimens from the Specimen Trap following the procedure:

1. The resident pathologist shall be responsible for the preparation of the histology slides and the review and interpretation of the slides per hospital standard operating procedures.

2. The prepared specimen will be de-identified per hospital procedure and shipped by courier to an independent pathologist.

3. An independent pathologist selected by the Sponsor will prepare histology slides to assess the quality of the specimens.

4. The independent pathologist will document his/her assessment of the quality of the specimens.

5. Results of the independent pathologist's assessment will be documented on the Histopathology Log within **30 days** of receiving the specimens and uploaded to the Sponsor's secure web server. The table will include site number, patient number, date of receipt, date of analysis, the analysis result, and the date the specimen was returned to the research center.

6. The slides will be shipped back to the hospital pathologist by courier for retention per hospital procedures.

5.8 90-Day Follow-Up (+/- 14 days)

- Assessment of symptoms and adverse events
- Using standard of care endoscopy, record the presence of persistent lesions. Determine % of tissue persistence of EndoRotor cases.
- Using standard of care endoscopy, record resection-associated stenosis.
- Assessment of the presence of post polypectomy syndrome.
- Independent quality assessment of pathology specimens by independent pathologist.

6.0 ADVERSE EVENTS

Adverse events will be recorded and documented throughout the duration of the study. In this study, adverse events related to the device or procedure, serious adverse events and Unanticipated Adverse Device Effects will be recorded. Adverse events (AE) unrelated to the device will not be documented on the CRF.

The Investigator at each participating center is ultimately responsible for reporting applicable adverse events to the Sponsor. The adverse event case report form (CRF) will be used to record

adverse event data. The adverse event CRF for a given visit must report all device-related and procedure-related adverse events that have occurred since the last documented visit.

The Sponsor shall review all adverse events for their severity, relationship to the study device(s) and comparative anticipated safety event rates. The Sponsor will conduct evaluations of any unanticipated device-related event per standard operating procedures.

6.1 Adverse Event (AE)

Adverse Events (AEs) are clinical findings that result in an untoward medical event, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, regardless of whether or not it is related to the investigational medical device. Adverse events will be classified as to severity (mild, moderate, severe), Anticipated (anticipated, not anticipated) and device and procedure relationships. Adverse events will further be categorized as either serious or non-serious.

The following definitions for rating severity of adverse events will be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

AEs or SAEs will also be classified as to their relationship to the device and procedure as follows:

Not Related: The event is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the investigational device, procedure or general surgery.

Possible: The event has a strong temporal relationship to the use of the investigational device, procedure or general surgery, and an alternative etiology is equally or less likely.

Probable: The event has a strong temporal relationship to the use of the investigational device, procedure or general surgery and another etiology is unlikely or significantly less likely.

Definite: An event that can only be attributed to the use of the

investigational device, procedure or general surgery.

Not Assessable: The event's relationship to the use of the investigational device, procedure or general surgery cannot be assessed.

For purposes of this study, the following events are not considered adverse events because they are normally expected to occur in conjunction with endoscopic procedures / post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-procedural pain (within 24 hours post-study procedure) related to the procedure or position on procedure table
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-study procedure)
- Low grade temperature increase (≤38°C/≤101.4°F)
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Any pre-planned surgical procedures

This listing of events is intended to provide guidance to the study sites for purposes of adverse event reporting. The Investigator at the study site should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above events should be reported as adverse events.

6.1.1 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an adverse event that:

- Is life threatening or fatal;
- Results in permanent impairment of a body structure or function;
- Results in congenital anomalies/birth defects
- Requires or prolongs hospitalization; or
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Delayed bleeding and perforations are the most serious adverse events associated with the resection of mucosal lesions, regardless of technique employed. Each requires the physician to identify it (the source of bleeding or the perforation) and swiftly act in a clinically appropriate manner to rectify the situation. Severe bleeding requires finding the source of bleeding and either using hemoclips or electrocautery to stop the flow of blood. Perforations, once identified

as such, can be treated using specialized endoscopic clips to approximate the edges and eliminate the perforation. Unidentified severe bleeding can result in anemia (decrease in the Hemoglobin and Hematocrit blood counts) with confusion, lethargy, and irritability, as well as hematemesis and hematochezia (bloody stools). Unidentified colon perforations can result in free air within the peritoneum causing compression of vascular structures (vena cava), abdominal distention, discomfort and pain, as well as sepsis and decreased cardiac output and death. Patients need to be made aware of the seriousness of not feeling well after resection of tissue and encouraged to immediately return to the hospital for evaluation.

NOTE: Planned hospitalization for a pre-existing condition or a procedure required by the study plan, without serious deterioration in health, is not considered a serious adverse event.

NOTE: Hospitalization is defined as any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

6.1.2 Unanticipated Adverse Device Effects (UADE)

If an SAE is determined to be probably or definitely related to the investigational device and has not been previously anticipated, the clinical finding would further be classified as an unanticipated adverse device effect (UADE). A UADE is defined as "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 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."

All SAE/UADEs must be reported to the IRB in accordance with institutional policies. The Investigator will note whether the adverse event was device-related or procedure-related and the severity of the event. All SAE/UADEs must be reported to Interscope within 24 hours of knowledge of the event.
Any Device Malfunction and/or Failure shall be documented in the CRFs.

6.2 Adverse Event Reporting Requirements

6.2.1 General Reporting Requirements

For the purposes of this study, only device-related and procedure-related serious adverse events, including unanticipated, will be recorded and documented on the Adverse Event CRF throughout the duration of the study. The report should include, but not limited to: severity, duration, action

taken, treatment outcome, seriousness, concomitant medications, pre-existing conditions and relationship of the adverse experience to the study device and procedure.

All AE's should be followed until the event is resolved or judged to be clinically stable. The clinical site should plan to provide additional, relevant AE follow-up information to the Sponsor upon request.

6.2.2 Reporting Requirements for Serious Adverse Events

All serious adverse events must be reported by the Investigator (or designee) to the Sponsor, within **24 hours** of becoming aware of the event.

The Investigator (or designee) must complete the Serious Adverse Event CRF within seven (7) working days of the initial report. The minimum required data to be recorded for an SAE includes: date of event, type of event, duration of event, severity, seriousness, action taken, outcome and, if appropriate, causality and possible relationship to the Interscope EndoRotor® System. In the case of a USADE, when possible, the device involved in the failure or malfunction is to be returned to the Sponsor for analysis.
All SAE's should be followed until the event is resolved or judged to be chronically stable. The clinical site should plan to provide relevant AE follow-up information to the Sponsor upon request.

In the case of serious adverse events, procedure and / or device observations, malfunctions or failures medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) must be provided to Interscope or its designee.

It is the responsibility of the Investigator to inform the IRB of serious adverse events as required by the IRB policies and in conformance with local regulatory requirements. Any serious adverse device effects and all deaths regardless of cause must also be reported to the IRB per local IRB requirements, and documentation of the report sent to Interscope or its designee.

The Sponsor or its designee will report all applicable serious adverse events and device incidents as post-market vigilance reports per FDA Regulations. The Sponsor will decide whether all of the local Investigators need to be informed immediately of an SAE or SADE, or whether this can be postponed until the next regularly scheduled study update.

6.2.3 Treatment Failure & Device Malfunction Reporting

All reported device observations, malfunctions or failures of the Interscope EndoRotor® System are required to be documented in the Case Report Form. In the event of a suspected observation or device problem, the study device shall be returned to the Sponsor for analysis via Interscope's

Complaint System. Instructions for returning the study device shall be provided to the Investigator.

7.0 RISK/BENEFIT ASSESSMENT

The Interscope EndoRotor® System has been cleared under the Pre-Market program as a 510(K) and certified with the CE Mark and is approved for commercial use wherever the CE Mark is recognized. The device's safety and performance have been established through extensive design verification and validation testing, including prior human use, and through a detailed risk analysis process per 21 CFR Part 803. Interscope does not anticipate new risks to be identified through this clinical study. A summary of the benefits and risks identified are provided below.

The main complications found to be associated with polypectomy appear to be bleeding/hemorrhage, perforation, and post-polypectomy syndrome, which are reported to occur in 0-10.8%, 0-2.3%, and 0.14-3.7% of patients, respectively. Deaths have been reported in only 2 studies, at a rate of 0.01% and 0.1%. The greatest risk factor for an adverse event is associated with increasing polyp size.

The EndoRotor® holds the promise to improve the resection of mucosal-based lesions in the GI tract (stomach, small and large intestines) by making the resections more precise, quicker and more comprehensive. Because of its design, the EndoRotor® suctions in mucosa and then cuts it (about 1750 times a minute) to quickly remove mucosal disease. This quick cutting action allows the user to precisely define the resection margins, allowing all gross visible disease to be removed. User errors tend to increase when fatigue increases. Reducing the procedure time from an hour to several minutes can help to reduce the fatigue associated with mucosal resections. There is the potential that we could see a reduction in persistent lesions (meaning better initial comprehensive removal of disease) when the EndoRotor® is used as the resection tool, meaning that in the future the necessity for second-look procedures could be reduced or eliminated, further decreasing patient morbidity. Because the EndoRotor® was engineered to be a simple device (it only resects mucosa), most users feel comfortable after a few attempts, narrowing the performance gap between an expert endoscopic proceduralist and one who is still in training. The ease with which physicians learn to use the EndoRotor® could also result in less patient morbidity.

7.1.1 Risk Minimization

As with any endoscopic procedure, appropriate safety precautions will be followed. In addition, this protocol provides additional steps to minimize risk to study subjects. These include the following:

- **Investigator Selection**: The Investigators in this study are selected based on their experience in performing endoscopic treatment procedures, including resection of mucosal tissue.
- **Investigator Training**: All investigators shall be trained on the use of the EndoRotor® to develop a base level of proficiency prior to the execution of the protocol.

- **Subject Screening**: Careful subject selection as per device Instructions for Use and per study selection criteria.
- **Objection by minors or incapacitated subjects**: Minors or those patients who are incapacitated and cannot consent for themselves are not included in this study.

7.2 Justification for the Study

This study is justified because additional safety and performance data on the Interscope device is desirable on a larger number of subjects for comparison to other commercially available devices. Risks have been minimized through previous clinical experience in humans on a post-market basis, through device safety and performance testing, Investigator training, and through closely controlled conditions under this study.

7.4 Incentives (if applicable)

Subjects will not be offered any incentives to participate in this study.

8.0 STATISTICAL ANALYSIS PLAN

The analysis of the data from this study will be primarily descriptive. Continuous endpoints will be summarized by N, mean, standard deviation, median, minimum, and maximum. Categorical or binary endpoints will be summarized by N and percentage with confidence intervals as appropriate.

8.1 Population Demographics

The demographics and medical history will be presented in tabular form for all subjects enrolled in this study. Means, standard deviations, and Ns will be used to summarize continuous characteristics such as age. Percentages and counts of subjects exhibiting a characteristic will be used to summarize categorical characteristics such as gender.

8.2 Analysis Populations

Two analysis populations are defined for this protocol, Intent to Treat and Per Protocol.
Intent to Treat Population: All subjects in whom the EndoRotor was used for any resection of a lesion. This includes those subjects that were either treated with the EndoRotor alone or with another adjunctive modality.

Per Protocol (PP): Subset of the Intent to Treat population including those subjects who had complete lesion resection with the EndoRotor alone without any adjunctive modality resection, did not have inclusion/exclusion protocol deviations and completed the 90 day follow up visit. The effectiveness analyses will be conducted on the per protocol population.

Safety Population: Defined as all subjects who were treated with the device.

8.3 Interim Analysis

No interim analyses are planned. The study data will be analyzed when the sample size requirements are met.

8.4 Primary Endpoint Analysis

The primary analysis will be completed on the Per Protocol population and will consist of all evaluable subjects enrolled in the study who have documented recurrent flat or sessile colorectal lesions up to 6 cm in diameter and/or length and are treated with the Interscope device without adjunctive modality. The analysis will be conducted on the percent of lesions with persistent disease. The primary endpoint is:

Technical Success, defined as the ability of the EndoRotor device to resect recurrent flat or sessile colorectal lesions without concomitant use of other resection modalities for mucosectomy and no definitely and probably device-related serious adverse events (SAEs) throughout the 90-day follow-up period.

This analysis population will be used to describe the primary effectiveness and the secondary endpoints. A confidence interval for the successful removal of all lesions will be calculated by Clopper-Pearson exact methods[6] if all subjects are treated for one lesion. In the event that one or more subjects are treated for multiple lesions, then a generalized estimating equation with a logistic link function will be used to estimate the 95% confidence interval of the success rate.

8.5 Safety Analysis

The safety population will include all subjects in the Intent to Treat Population treated with the Interscope EndoRotor® device. Only monitored data, including safety data confirmed by review of source documents, will be entered into the database for statistical analysis. All serious adverse events will be adjudicated by an Independent Physician Adjudicator serving as the Data Monitoring Committee for safety. Reports of SAE adjudication will be included in the final analysis and clinical report.

8.6 Secondary Endpoint Analysis

The secondary endpoints will be characterized using descriptive statistics.

8.7 Site Poolability

Due to the small number of subjects anticipated to be enrolled at each site, which would result in underpowered testing of site differences, poolability over site will not be tested. Data will be pooled over sites for analysis.

8.8 Sample Size

With a sample size of 60 and a success rate of 0.85, we can expect the 95% exact confidence interval to be between 0.782 and 0.967. Our goal is to achieve a confidence interval half width of our point estimate that is not greater than 0.10. The proposed sample size of 60 will provide a

confidence interval half width 0.0972, and so will meet the targeted precision for our point estimate. Further, because this study is a post-market, confirmatory, observational study, the sample size identified is consistent with post-market studies of similar devices.

8.9 Handling of Missing Data

Missing data for the primary effectiveness endpoint will be dropped from the analysis of that endpoint. Safety endpoints, as is standard, will not be imputed.

9.0 INVESTIGATOR RESPONSIBILITIES, RECORDS & REPORTS

The Investigators are responsible for signing the Investigator agreement prior to the commencement of the study and for ensuring that this study is conducted according to this clinical protocol, the Declaration of Helsinki, US FDA requirements and any other local, national or IRB requirements that apply to post-market clinical studies at their center.

It is also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this study have the appropriate qualifications and that they complete training on the study device and study procedures, as required to fulfill their roles in the study, as well as ensuring subject confidentiality is respected.

9.1 Institutional Review Board (IRB) Approval

Because this study is collecting medical data from subjects providing written informed consent, the Investigator at each site is responsible for securing IRB approval for this study protocol and the Informed Consent documents. The local IRB for each specific institution (or Western Institutional Review Board (WIRB), as applicable for central IRB sites) must review and approve this study protocol and the specific Informed Consent form to be used at that site **prior** to study procedure of the first subject. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a copy of any IRB correspondence as well as the final approval letter and the final approved Informed Consent from the IRB.

The Investigator or clinical site staff will not make amendments to this protocol or the Informed Consent form without **PRIOR** written approval from the Sponsor. All approved amendments must then be submitted to the IRB, as appropriate for approval.

9.2 Withdrawal of Approval

If the Investigator's IRB withdraws their approval to conduct this study for any reason, the Investigator **must** notify the Sponsor as soon as possible, but in no event later than **five working days** after the withdrawal of the approval.

9.3 Amendments

All substantial amendments will be notified to the IRB. Non-substantial amendments will not be notified to the approving IRB but will be recorded and filed by the sponsor. The Investigator or clinical site staff will not make amendments to this protocol or the Informed Consent form without **PRIOR** written approval from the Sponsor.

9.4 Informed Consent

The Investigator is responsible for ensuring that all applicable local, national, GCP, Declaration of Helsinki, and US FDA guidelines and regulations are met when completing the informed consent process. Written informed consent is to be obtained for all subjects **prior** to treatment.

9.5 Clinical Data Collection

Standardized CRFs will be used to collect complete and accurate records of the clinical data from this study according to the Good Clinical Practice (GCP) requirements. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study and **submitting it to the Sponsor in a timely manner**.

9.6 Device Accountability

The Sponsor will ship devices intended for this study to the designated Investigators participating in this study following IRB. All Investigators will be responsible for providing a secure storage location for the devices, supervising device use, and the disposal and/or return of the devices as instructed by the Sponsor. These devices are the same as the commercial devices but will be kept separate for the purposes of this study; therefore, all Investigators will maintain records to document the receipt, use and disposition of all devices received by their site intended for this study. The Sponsor will also maintain records of all shipments and disposition of the devices. The Sponsor and/or their authorized CRO will routinely inspect the clinical site inventory records for device accountability at the clinical sites participating in this study. At the conclusion of the study (study enrollment complete), all remaining study devices will be returned to the sponsor.

9.7 Investigator Reports

9.7.1 Serious Adverse Events (SAEs) & Unanticipated Adverse Device Effects (UADEs)

The Investigator shall report any SAEs or UADEs as soon as possible, (e.g., within 24 hours of the Investigator becoming aware of the event) to the Sponsor. Additionally, SAEs and UADEs should be reported to the IRB, as required per their local requirements. The Adverse Event electronic CRF is to be fully completed within seven working days of the event. The contact information for reporting SAEs and UADEs is provided in the study contact section of this protocol.

9.7.2 Device Performance Issues

The Investigators shall report to Interscope (and/or designee) any Device Performance issues (e.g., device malfunction or failure) that occur to as soon as possible, e.g., 24 hours of the Investigator becoming aware of the event. The report may be made via telephone, email or fax. The Investigator or study staff is to return the devices per the Instructions for Use for investigation via Interscope's complaint handling system, if applicable.

9.7.3 Deviations from the Study Plan

The Investigator must notify the Sponsor of any deviation from the protocol. The Investigator should also notify the IRB as required per their local requirements. This notice must occur as soon as possible, but in no case longer than five working days after the Investigator becomes aware of a major deviation. **Major deviations include those that involve the informed consent process, or any deviation that involves or leads to a serious adverse event in a study participant.**

9.7.4 Investigator Final Report

The Investigator shall provide a final study report that summarizes their enrollment and study participation. This report should include a summary of enrollment, SAEs, UADEs and Device Performance issues. This report will be forwarded to the IRB and the Sponsor after all of the enrolled subjects have completed their final follow-up visit or have exited the study and the study close-out visit has been completed, but no later than 3 months following completion of the last follow-up visit.

Table 2: Investigator Report Submission Summary

Form/Report	Required and Suggested Submission Timeframes
Enrollment Notification	Complete Study Entry CRF **within 48 hours** of enrollment.
CRFs	Complete **within 7 days** of visit completion.
Procedure Images	Upload to the Sponsor's secure web server within **7 working days** of completion. Images shall be de-identified prior to submission.
Device malfunction / Failure	Notify Sponsor via email within 48 hours of knowledge. Complete CRF within 48 hours of knowledge.
SAEs & UADEs	Complete CRF **within 24 hours** of the Investigator becoming aware of the event; submit to the IRB as required or as directed by the Sponsor.
Deviations from the CIP	Complete CRF **within 7 days** of knowledge.
Study Progress Reports	As required by the IRB; submit to the IRB as required or as directed by the Sponsor.
Final Report to the IRB	**Within 3 months** of study completion.

10.0 SPONSOR RESPONSIBILITIES

As the study Sponsor, Interscope is responsible for the overall conduct and quality of the study, including the assurance that the study complies with the appropriate international standards and regulations that apply to medical device post-market studies. Interscope will also ensure adherence to the Sponsor general duties as outlined by GCP standards and the applicable FDA regulations. Additionally, Interscope will ensure that qualified monitors and designated personnel are monitoring the study according to the pre-determined monitoring plan and that the Informed Consent process is followed per each site's local and national requirements.

10.1 Selection of Clinical Sites & Investigators

Interscope will select qualified clinical sites and Investigators who are experienced with endoscopic procedures and resection of the mucosa. The Investigator must work with a qualified IRB to oversee the rights, safety and welfare of the study participants. The clinical site must also have an adequate subject population and the appropriate staffing and equipment to meet the requirements of the study protocol and the expected enrollment time frames.

10.2 Investigator & Staff Training

Training of the Investigators and clinical study staff is the responsibility of the Sponsor and their designee. Training may be conducted during a site initiation visit or appropriate training venues if the investigator has not used the device for commercial cases prior to the study. Investigator(s) have received training in proper device operation. Investigators and study staff will undergo training on the study protocol, safety, compliance, eligibility criteria, device accountability, and proper storage of the equipment and supplies, prior to participating in the study. Training may encompass didactic information regarding the study device and system, as well as hands-on practice with the device. Procedural technique and experience with the Interscope device may be assessed by clinical/engineering personnel. Observations during the cases will also be discussed with the Investigator and study staff.

10.3 Monitoring

The assigned CRO will monitor the study and will select or designate clinical monitors who are qualified by training and experience, to monitor and oversee the conduct of the ENDOROTOR study. The clinical monitors will follow the Sponsor's standard operating procedure for monitoring and the Monitoring Plan to be written on a risk-based approach for this study. The Monitoring Plan will require evaluation of compliance with the protocol, GCP compliance, FDA regulations, and any specific recommendations made by the site's IRB and the signed Investigator and Study Agreements. Periodic phone contacts, site visits, and intermittent remote visits will be conducted to ensure that the protocol is being followed. The clinical monitor(s) will also verify that the electronic Case Report Forms (eCRFs) are in agreement with the source documentation and other records.

For record verification purposes, the clinical monitor and/or authorized Sponsor representative will be provided access to hospital records, original laboratory data, and other records and data

as they relate to the study and as agreed to with the Investigator prior to the initiation of the study. The Investigator will also make available to the clinical monitor all regulatory documents, all CRFs, informed consent documents, source documentation and other relevant records for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representative become aware that an Investigator is not complying with the study protocol, the Investigator Agreement, the Declaration of Helsinki, GCP Guidelines, FDA Regulations, applicable privacy standards, or any condition of the study imposed by the IRB, the Sponsor or their authorized representative shall immediately secure compliance. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the Investigator's termination from the study by the Sponsor.

Study close-out visits will be conducted after the final follow-up visit is completed at each site and following the resolution of any outstanding data discrepancies and adverse events. A final study report will be generated and submitted to the Investigator and the appropriate study oversight authorities. Study document retention requirements will be reviewed with each site during the close-out visit.

10.4 On-Site Audits

In accordance with GCP and FDA requirements, the Sponsor or CRO representative may request access to all study records, including source documents, for inspection and duplication. In the event that an Investigator is contacted by a local IRB in relation to this study, the Investigator will notify the Sponsor as soon as possible.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e., Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits. Confidentiality of study patients will be maintained consistently as described in Section 11.4.

10.5 Records & Record Retention

The Sponsor and/or their designated CRO shall maintain copies of correspondence, data, device shipments, clinical events (AEs, SAEs) and supporting documentation and other records and reports related to this clinical study on a secure web server.

The Sponsor and clinical sites will maintain the study records until two (2) years after the final study report is completed, or longer if required by local, national or international regulatory

agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

10.6 Study Data Reports

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

10.7 Publication Policies

At the conclusion of the study, a multi-center manuscript may be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of Interscope, Inc. The analysis of other pre-specified and non-pre-specified endpoints will be performed by Interscope and will require pre-approval by Interscope. For the purposes of timely abstract presentation and publication, such secondary publications shall be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data and/or single-center experience reports will require approval from Interscope.

This study will be registered with www.clinicaltrials.gov.

10.8 Supplemental Applications

As appropriate, the Sponsor will submit changes to the study protocol to the Investigators and obtain IRB approval.

10.9 Coverage of Subject Expenses

The treated subjects will not be compensated for their time during the study.

11.0 QUALITY ASSURANCE & ETHICAL STANDARDS

The study will be conducted according to the Declaration of Helsinki, Good Clinical Practice Guidelines (GCP), FDA Regulations and any additional IRB requirements and local and/or national requirements that apply to post-market clinical studies of medical devices. As the study Sponsor, Interscope, Inc. has the overall responsibility for the conduct of the study, including the assurance that the study is in compliance with these guidelines, standards and requirements.

11.1 Data Monitoring Committee for Adverse Event Adjudication

To meet the ethical responsibilities and standards for study subjects, at a minimum, an Independent Physician Adjudicator (IPA) will serve as the Data Monitoring Committee to the

Sponsor. In order to enhance objectivity and reduce the potential for bias, the IPA shall be independent of the Sponsor as well as the study sites / investigators.

The IPA shall serve in the following capacities throughout the course of the study: a) adjudicator of all reported serious adverse events, device-related adverse events, and procedure-related adverse events; and b) assessor for severity and causality of all reviewed events to ensure the safety of study subjects. In addition, the IPA shall serve to assist the sponsor in reviewing technical events (e.g., device malfunctions and reported failures) specifically for reporting within the study. Vigilance assessment and reporting will be completed per the sponsor's Complaint Handling and Vigilance Reporting systems for determining device technical events.

The methodology for performing these responsibilities shall be developed and outlined in the Safety Adjudication Charter. The Safety Adjudication Charter shall include study-defined stopping rules. Operational provisions shall be established to minimize potential bias (i.e., the physician serving as IPA shall be blinded to the clinical site to the extent possible during adverse event review and adjudication). In the case of an SAE with associated imaging, the IPA may review imaging assessments to assess the reported event. The Safety Adjudication Charter shall be available upon request.

11.2 Compliance Monitoring & Study Termination

The Sponsor reserves the right to terminate a site from the study for any of the following reasons:

- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events within 48 hours of knowledge
- Loss of or unaccountable device inventory
- Repeated protocol violations or safety concerns
- Repeated failure to complete Case Report Forms
- Failure to enroll an adequate number of subjects

11.3 Data Management

Standardized Case Report Forms will be used to collect clinical data during this study. Investigators are responsible for the accurate completion and timely submission of the data collected during this study. The Case Report Forms will be completed on the Sponsor's secure web server.

11.4 Confidentiality

The personal data obtained in the course of the study, in accordance with the informed consent, and in particular clinical findings are subject to confidentiality. A unique identification code will be assigned to each subject participating in this study. A log will be provided to the investigator to enable identification of the patient's name to the patient number assigned which will be

available and maintained only at the investigational site. The dissemination of the collected data is carried out within the framework of the study in an anonymized form.

Access to the subject's medical records will be limited to authorized personnel of the Sponsor, their designated monitors, clinical site study staff and authorized regulatory authorities as required by the IRB. Any data that may be published in abstracts or scientific journals and/or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the study.

12.0 LIST OF RELEVANT DEFINITIONS

Adverse Device Effect (ADE): An adverse device effect is defined as any untoward adverse event related to the use of an investigational device or unintended response to a medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device or any event that is a result of user error.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 30%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Bleeding Complication at Index Procedure: Bleeding is considered an adverse event if additional measures such as endoscopic salvage methods (i.e. OTSC clipping, hemospray) or surgery become necessary.

Death: (divided into 2 categories)

A. Cardiac death is death due to any of the following:

1. Acute myocardial infarction.
2. Cardiac perforation/pericardial tamponade.
3. Arrhythmia or conduction abnormality.
4. Stroke within 30 days of the procedure or stroke suspected of being related to the procedure.
5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
6. Any death for which a cardiac cause cannot be excluded.

B. Non-cardiac death is a death not due to cardiac causes (as defined immediately above).

Delayed Bleeding: Bleeding that occurs post-procedure requiring intervention.

Device Failure: A device that is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance. Includes damage, stress fracture or other failure as observed at the procedure.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Perforation: Puncture of the alimentary tract.

Serious Adverse Event (SAE): A serious adverse event (SAE) is defined an adverse event that:

- led to death,
- led to a serious deterioration in the health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- resulted in a permanent impairment of a body structure or a body function, or
- required in-patient hospitalization or prolongation of existing hospitalization, or
- resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study plan without serious deterioration in health, is not considered a serious adverse event.

Unanticipated Adverse Device Effect (UADE): A UADE is an event that occurs that has not been expected to occur with the device or during the course of the study procedures and has not otherwise been identified as a possible risk in the clinical investigations.

13.0 BIBLIOGRAPHY

1. Repici A Hassan C, Vitetta E, Ferrara E, Manes G, Gulloti G et al (2012) Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. Endoscopy 44(1):27-31.
2. Bretagne J-F, Manfredi S, Piette C, Hamonic S, Durand G, Riou F (2010) Yield of high-grade dysplasia based on polyp size detected at colonoscopy: a series of 2295 examinations following a positive fecal occult blood test in a population-based study. Dis Colon Rectum 53(3):339-345.
3. O'Brien, Michael J, et. al. Flat Adenomas in the National Polyp Study: Is There Increased Risk for High-Grade Dysplasia Initially or During Surveillance?; Clinical Gastroenterology and Hepatology: 2004;2:905–911.
4. Knabe M, Pohl J, Gerges C et al (2013) Standardized Long-Term Follow-Up After Endoscopic Resection of Large, Nonpedunculated Colorectal Lesions: A Prospective Two-Center Study. American J of Gastroenterology 2014; 109:183–189; doi:10.1038/ajg.2013.419; published online 17 December 2013
5. Hollerbach S. Meier P. Wellman A. et al. The EndoRotor®: endoscopic mucosal resection system for non-thermal and rapid removal of esophageal, gastric, and colonic lesions: initial experience in live animals. Endosc Int Open. 2016 Apr;4(4):E475-9. doi: 10.1055/s-0042-105207. Epub 2016 Mar 30.
6. Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika. 26: 404–413. doi:10.1093/biomet/26.4.404.

PPENDIX 1 – SCHEDULE OF EVENTS

Assessment	Baseline[1]	Procedure[7]	Discharge	90 Days (+/- 14 Days)
Informed Consent	X[2]			
Medical History	X			
Physical Examination[3]	X			
Pregnancy Test[6]	X			
Endoscopy	X[4]	X[4]		X[4]
Procedural Data		X[3]		
Adverse Event Assessment		X	X	X
Assessment of presence of colon stenosis and rate of persistence of disease at the resection location				X
Ability to interpret the pathology samples retrieved during resection.[5]				X

[1] Baseline evaluations may be done up to 14 days before the procedure.
[2] Consent to be obtained within 14 days prior to study procedure.
[3] Refer to protocol section for comprehensive list of physical exam & procedural data collection needs.
[4] Standard of care assessments
[5] Independent pathologist review of quality of specimens following resident pathologist's interpretation of specimens and quality assessment. Resident pathologist's reports shall be submitted to the Sponsor within 30 days of their receipt.
[6] Pregnancy test for female subjects of child bearing potential within 1 day of procedure.
[7] Second procedure can be completed if complete resection was not achieved during initial procedure