NCT01936948

Safety of endoscopic resection of large colorectal polyps: A randomized trial.

Sponsor Protocol – version 9

September 13, 2019

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1. ABSTRACT

Background: The effectiveness of colonoscopy in reducing colorectal cancer mortality relies on the detection and removal of neoplastic polyps. Because the risk of prevalent cancer and of transition to cancer increases with polyp size, effective and safe resection of large polyps is particularly important. Large polyps ≥20mm are removed by so-called endoscopic mucosal resection (EMR) using electrocautery snares. Resection of these large polyps is associated with a risk of severe complications that may require hospitalization and additional interventions. The most common risk is delayed bleeding which is observed in approximately 2-9% of patients. A recent retrospective study suggests that closure of the large mucosal defect after resection may decrease the risk of delayed bleeding. However, significant uncertainty remains about the polypectomy techniques to optimizing resection and minimizing risk. Important aspects that may affect risk include clipping of the mucosal defect and electrocautery setting.

Aims/Hypothesis: Our primary aim is to examine whether clip closure of the mucosal defect after endoscopic mucosal resection (EMR) of large polyps (≥20mm) will reduce the risk of delayed bleeding in a prospective randomized trial. In secondary analysis we will explore, whether electrocautery settings affect the risk of complications. We hypothesize that clip closure will reduce the risk of delayed bleeding.

Methods: The study will include patients with a polyp ≥20 mm in size. Experienced endoscopists will follow a standardized resection protocol. Patients will be randomized in a 2x2 factorial design to one of two electrocautery settings (Endocut versus low power coagulation; secondary comparison) and to either undergo or not undergo closing of the mucosal resection defect after resection. For the primary comparison (clip vs. no clip) the primary outcome will be incidence of delayed bleeding complications within 30 days following the procedure. We further plan to identify factors that may be associated with delayed bleeding. We are also interested in understanding recurrence of neoplastic polyps at first and second follow-up colonoscopy, defined as the presence of biopsy proven neoplastic tissue.

Anticipated Results: The results of the study will help to determine whether clip closure of the mucosal defect after resection of large polyps is associated with a decreased delayed bleeding risk. The results will further help to understand whether there is a preferred electrocautery setting with a lower complication risk. The findings may therefore help to identify a safe resection practice and contribute to the development of resection standards for polypectomy.

2. SPECIFIC AIMS

Aim 1. The primary aim of the study is to compare the rate of delayed bleeding complications in patients undergoing endoscopic resection of large polyps between:

A) Closing the mucosal defect after resection (Clip group) and
B) Not closing the mucosal defect after resection (No clip group).

Aim 2. The secondary aim of the study is to compare the rate of overall complications in patients undergoing endoscopic resection of large polyps between two cautery settings:

A) Low power coagulation and
B) Endocut.

Hypothesis: Specific endoscopic techniques are associated with a lower complication rate of endoscopic mucosal resection of large colorectal polyps.

Additional secondary aims: The study further examines the rate of complete polyp resection, polyp recurrence, and factors that are associated with complete resection and recurrence during 5 years of follow-up.

3. RESEARCH PLAN

3.1. Background and Significance

Colorectal cancer is the second most common cause of cancer death in the United States[1]. The effectiveness of colonoscopy in reducing the risk of dying from colorectal cancer relies on the detection and safe resection of neoplastic polyps to prevent incident cancers. Most polyps are small and can be easily removed using snare with or without electrocautery. Because the risk of prevalent cancer or transition to cancer increases with polyp size, effective and safe resection of large polyps is particularly important.
Endoscopic mucosal resection (EMR) is evolving as the primary endoscopic technique to remove large non-pedunculated polyps. These flat or sessile polyps are defined as lateral spreading tumors with a low vertical axis that extend laterally along the luminal wall. Several mostly retrospective studies from Europe, the U.S. and Japan, have demonstrated a high "cure" rate, with results lending credence to the shift from surgical resection to endoscopic management of these lesions. Of concern, however, is 1) a fairly high overall complication rate of 8-26% in prospective studies[2-6], and 2) the persistence of residual neoplasia on follow-up endoscopy ranging from 16% to 46%[2, 5, 7].

3.1.1. Complications of endoscopic mucosal resection of large polyps

Severe complications that are associated with a standard screening colonoscopy, which may include resection of predominantly smaller polyps, are uncommon. Significant bleeding occurs in 0.2 to 0.5% of patients (defined as a 2gm drop in Hemoglobin), perforation of the colon in 0.05-0.10%, and post polypectomy syndrome in <0.5%[8, 9].
The risk of severe complications increases with polyp size. The incidences of complications associated with resection of large polyps are summarized in table 1. The most common complication is bleeding reported in 2 to 24% of polyp resections. Perforation occurred in approximately 1% of resections and postpolypectomy syndrome in 1-4% of patients. Postpolypectomy syndrome is caused by focal inflammation as a result of deep cautery injury to the serosal surface when resecting a polyp. Patients typically present with abdominal pain, fever, and leukocytosis.
In addition to size, other factors that may affect complications. These include type of resection (piecemeal versus en-bloc), polyp location (right colon with a thinner wall than the left colon), age and comorbidities, especially those that affect clotting abilities (e.g. renal insufficiency, liver disease, use of anticoagulation). Studies that have examined variables, which may directly decrease the risk of complications associated with large polyp resection, are limited.

Table 1. Studies that examined complications related to EMR of large colon polyps.

Study	Design	Patients n	Size	Electro-cautery	Compli-cations, overall	Blee-ding	Perfo-ration	PPS
Walsh 1992[10]	Retrospective	108	≥10mm	Unclear	**10.2%**	9.3%	0.9%	-
Brooker 2002[2]	Prospective	34	≥15mm	Low power coag	**26.5%**	23.5%	0	-
Ahmad 2002[11]	Retrospective	29	8-30mm	Unclear	**24.1%**	24.1%	0	0
Conio 2004[3]	Prospective	136	≥ 20mm	Blended	**14.7%**	-	0	3.7%
Kaltenbach 2007[12]	Retrospective	125	≥ 10mm	Blended	**1.8%**	1.8%	0	0
Arebi 2007[7]	Retrospective	161	≥ 20mm	Blended	**8.2%**	5.7%	0	-
Luigiano 2009[13]	Retrospective	148	≥ 20mm	Unclear	**12.2%**	10.1%	0.7%	1.4%
Swan 2009[6]	Prospective	174	≥ 10mm	Blended	**16.2%**	9.8%	0	-
Ferrara 2010[4]	Prospective	152	≥15mm	Blended	**18.4**	14.5%	1.3%	2.6%
Moss 2011[5]	Prospective	464	≥ 20mm	Blended	**7.7%**	2.9%	1.3%	1.5%
Gimeno-Garcia 2012[14]	Retrospective	1894	≥ 10mm	Unclear	**Na**	9.1%	Na	Na
Buchner 2012 [15]	Retrospective	249	8-100mm	Low power coag	**11.6%**	10.0%	0.4%	1.2%
Qumseya & Wallace 2012[16]	Retrospective	525	≥ 20mm	Low power coag	**Na**	7.0%	Na	Na
Liaquat & Rex 2013[17]	Retrospective	420	≥ 20mm	Low power coag	Clip: **5.8%** No clip: **12%**	3.1% 8.8%	0.5%	1.2%

PPS = postpolypectomy syndrome (synonymous for transmural burn syndrome)

3.1.2. Limitations of prior studies

Prior studies (table 1)	**Proposed study**
• Studies often included polyps of <20mm. Because of the association between size and complications, results from these studies do not reflect complications with resection of ≥20mm polyps.	The study will only include patients with non-pedunculated ≥20mm polyps.
• Most studies were retrospective. Complications following within a 30-day window may go unnoticed (selection bias). There are few larger studies that evaluated complications prospectively. The risk of overall complications varied between 8% and 18%, with a bleeding risk between 3% and 14%.	The design will be a prospective RCT.

• The follow-up interval was not always clear, which may also lead to underreporting of delayed complications.	Complications will be assessed within 30 days following the procedure.
• The definition of what was considered a complication was not always provided.	Complications will be defined as clinical events following polyp resection, which require a visit to the ED, admission, or additional tests or procedures (see outcome measures).
• The denominator of how complications were measured was not always clear. The incidence could be related to number of polyps or number of patients (a patient could have more than one polyp).	We will calculate the incidence of complications per polyp and per patient.

3.1.3. Electrocautery and complication risk

Electrocautery snare resection represents the standard approach to resecting larger polyps. The principle of electrocautery snare resection relies on the application of an electrical current to the snare while closing the snare around the base of the polyp. Electrical energy is converted to heat energy by changing from a low frequency current (60Hz) to a high frequency current (>300,000Hz).
Two types of currents can generally be distinguished, cutting current and coagulation current. Cutting current delivers a high frequency (density) and low voltage current, which results in high-energy intensity and allows swift “cuts” through tissue without deep thermal tissue injury. The flip side is that it does not provide sufficient cautery time to seal cut blood vessels and bleeding is therefore a concern.
In contrast, coagulation current delivers a lower frequency (density) current. This current allows “sealing” of cut vessels and may prevent bleeding, but may cause deeper tissue injury and increase the risk for postpolypectomy syndrome and perforation. For polyp resection the so-called *low power coagulation* is used to resect polyps.
Two minimize risk, cautery units provide a setting of cutting current alternating with coagulation current, also called blended current. Realizing that heat production is dependent on tissue resistance, some cautery units provide a special type of blended cautery setting (also called “Endocut” when used with the ERBE cautery unit, which will be used in the study). Endocut is a microprocessor-controlled current alternating between coagulation and cutting adjusted for tissue resistance.
The rationale for assessing electrocautery current is very strong. It is a fundamental aspect of polypectomy and not a single randomized trial has been done to address its effect on complications. Endoscopists do polypectomy the way they were trained to do it. It is not an issue that is settled. In the 2004 a survey by Singh et al found that 46% of US endoscopists used blended current and 46% use low power coagulation[18]. Two retrospective studies found that low power coagulation causes delayed bleeding and blended current causes immediate bleeding[19, 20]. Thus the type of current used for polyp resection remains an important clinical question.

3.1.4. Clipping and complication risk

It is apparent that resection of a large polyp leaves behind a large mucosal defect. The mucosal ulcer that forms after polyp resection can take several weeks to heal. Bleeding complication typically occur within 7 to 10 days, requiring often admission, a repeat

colonoscopy to stop bleeding, and possible blood transfusions. To reduce the risk of bleeding it has been proposed to close the mucosal defect after polyp resection.

To date, no randomized trial has examined whether clip application affects complications after large polyp resection. One recent study did not show a benefit[21]. Bleeding occurred in 2% in either group. However, the study included patients with smaller polyps (mean size 8mm) with a low expected bleeding risk. A recent retrospective study by Liaquat et al. showed that clip closure was associated with a significantly reduced risk of delayed bleeding (2% vs. 10%), and a reduced risk of overall complications (4% vs. 12%), when compared to historical controls[22]. Main limitations of the study include unmeasured factors that may have affected the outcome and performance of all resections by one expert colonoscopist. However, a third very recent retrospective study by Qumseya et al. reviewed their experience with 525 large colon polyp resection and did not find that clip closure was associated with delayed bleeding complications[16].

In clinical practice use of clips after polyp resection is largely dependent on endoscopist preference and availability. In preparation for this study informal evaluation of polyp resection practice showed that some endoscopists use clips, and others do not. The unclear benefit with using clips, the required technical skills to achieve clip closure of the mucosal defect, and the additional cost may prevent some from using clips routinely.

Whether clip application prevents bleeding and other complications following resection of large polyps and may reduce overall cost of care remains an important clinical question: there is no established superior method, the issue arises daily, the potential impact on clinical practice from a definitive trial would be significant, both to establish an optimal approach and in terms of patient benefits.

3.2. Research Design and Methods

3.2.1. Design and patients

General study design: The study will be designed as a multicenter multi-endoscopist randomized trial.

A schematic diagram of the study design, procedures and stages is detailed in Figure 1, Appendix 3.

Study participants: Potential study participants will include patients with a colonic non-pedunculated polyp ≥ 20mm in size considered for endoscopic resection (see inclusion and exclusion criteria).

Anticipated number of research subjects (see also sample size calculation)**:**

- Estimated number of participants for duration of entire study: Female: 470, Male: 550 (several sites are VA Medical Centers)
- Estimated total number at each site: ≥20

3.2.2. Inclusion and Exclusion criteria

Inclusion criteria:

- Any patient ≥18 and ≤89 who presents for a colonoscopy and who does not have criteria for exclusion
- Patients with a ≥20mm colon non-pedunculated polyp

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
- Pregnancy

We will document patients who were referred for a resection of a large polyp, but were not consented. For these patients (not study subjects) we will record the reason for not consenting (e.g. did not elected to participate, patient met exclusion criteria, etc.), the patient's age and gender.

Similarly, we will collect information on reasons for exclusion of polyps (including size, morphology, and location).

3.2.3. Study screening procedures

To determine patient eligibility:

- Review of the patient's personal medical history
- Review of medical records to verify patient inclusion and exclusion criteria (age, comorbid conditions, anticoagulation).

To determine polyp eligibility:

- Examining eligibility of a potential study polyp during the colonoscopy with respect to polyp inclusion and exclusion criteria (size, morphology).

Potential study participants include patients with a ≥ 20mm non-pedunculated colorectal polyp (= study polyp).

Identification of study participants:

- Patients with a known ≥ 20mm polyp detected at a prior colonoscopy and referred for resection of this polyp.
  Patient characteristics (age), comorbidities (see exclusion criteria), and medications (exclusion of coagulopathy) will be reviewed prior to the procedure. The patient will be informed about potential study participation. If the patient agrees to participate and after informed consent is provided, the colonoscopy will be performed. Whether a polyp will meet inclusion criteria (size and morphology) will be determined during the colonoscopy. If the patient does not have a polyp that meets the inclusion criteria, the patient will not be included and considered a screen failure.

An alternative subject identification may be applied at some centers with fewer referrals for polyp resection. Any patient who is scheduled for an elective colonoscopy will be provided with an information sheet that allows him/her to opt out to be considered for study enrollment. If the patient does not opt out and if an eligible study polyp is detected during the colonoscopy, the patient may be randomized to one of the four protocol arms (only if patient and polyp inclusion/exclusion criteria are met). The Polyp resection will be performed as determined by randomization. Following the procedure the patient will be informed about the

randomized approach to polyp resection and informed about potential participation in the study. Only after the patient provides informed consent, he/she will be included in the study (see Alternative Consent Process).

3.2.4. Patients on anticoagulation

Patients on anticoagulation medications will be managed according to the ASGE guideline[23]. According to the guideline, polypectomy is considered a high-risk procedure. All study procedures are elective procedures. In accordance with the guideline, the type of anticoagulation and the patient risk for a thromboembolic event will determine the decision on managing periprocedural anticoagulation.

3.2.5. Allocation to treatment (Randomization process)

Randomized will occur at the time of colonoscopy when a polyp has been identified as a study polyp using computer generated randomization. Patients will be randomized following a 2 x 2 factorial design to: (i) Endocut vs. low power coagulation after inspection of the polyp and decision to resect the polyp, and (i) clipping vs. no clipping of the mucosal defect after resection.

Patients will hence be randomized to one of four groups:

A) Endocut and clipping,

B) Endocut and no clipping,

C) Low power coagulation and clipping, and

D) Low power coagulation and no clipping.

Should a patient have more than one study polyp, all polyps will be resected in the same way (per patient randomization). The primary comparison will be between clip and no clip application. The comparison between cautery currents is secondary and exploratory.

Breaking the blind: The study is not blinded.

Treatment adherence/study compliance: The primary intervention (one-time clip placement) does not require adherence to the intervention. Participants will therefore not be excluded because of non-compliance.

The major outcome of interest will be assessed after 30 days following the intervention by a phone call. We expect that such short interval will allow an almost complete follow-up.

Secondary outcomes of interests include polyp recurrence during longer-term follow-up. We will collect data on all follow-up procedures that are performed as per standard of care (not as a study intervention).

3.2.6. Colonoscopy and endoscopic mucosal resection (EMR)

Patients will have undergone colonoscopy prep as it is standard at each center, typically a polyethylene glycol lavage with 4–6 L until clear rectal fluid is evacuated. Periprocedural antithrombotic mediations will be managed according to ASGE guidelines[23]. All exams will be performed using high-definition colonoscopes with digital chromoendoscopy capability (e.g. Olympus 180 or 190 series or Pentax). Sedation will be provided as per standard of

care, typically moderate sedation using intravenous midazolam and a narcotic analgesic, or sedation per anesthesia if required.

Lesions will be identified using conventional colonoscopic views and further characterized using digital chromoendoscopy (e.g. narrow band imaging or i-Scan). Digital chromoendoscopy utilizes integrated electronically activated filters or electronic post-image processing techniques to enhance mucosal architecture and microvasculature. It allows detailed examination of polyp morphology and delineation of the lesion. Polyp characteristics will be recorded (see outcome measures).

Complete polyp resection during the first colonoscopy is intended. Endoscopic mucosal resection (EMR) using the strip biopsy method, as described by Karita et al[24], will be used for all resections.

This study will include the following standard steps (all considered standard of care):

1. The polyp will be submucosally injected, so that the lesion will lift and demarcate from the submucosal layer.
2. Polyp margins will be identified.
3. The polyp will be resected with electrocautery snare using one of two electrocautery settings (as per randomization).

Submucosal injectate: 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 and a contrast agent. The lifting agent will be at the discretion of the endoscopist (e.g. NaCl or hydroxyethyl starch). The recommended preferred lifting agent will consist of a small amount of NaCl followed by an injection of a mixture of Hydroxyethyl starch (HES). In one recent study from Australia a HES equivalent (Gelufusin) had a similar rate of complications than NaCl, but a nonsignificant lower risk of adenoma recurrence (8 vs. 12 %)[25]. Independent on the lifting agent used, it will be mixed with a contrast agent as typically used with EMR. The recommended preferred contrast agent will be Indigo carmine 0.4% at a ratio of approximately 100:1 (i.e. 0.1ml Indigo carmine and 10ml of HES). Indigo carmine is a contrast dye that has been routinely used for submucosal injection and for chromoendoscopy to enhance contrast between polyp and surrounding normal mucosa to delineate the margin of the polyp and to define the submucosal plane[26]. Recent studies have used a modified EMR without using submucosal injection. Submucosal injection may make it more difficult to grasp polyp tissue of some polyps (e.g. flat sessile serrated adenomas/polyps). Similarly, immersing the polyp area in water (underwater EMR) may enhance engagement of the snare with the polyp and facilitate EMR[27]. Endoscopists may not perform submucosal injection if they consider that it might make resection more difficult.

Snares: Various resection snares are available that differ in size, shape, and stiffness. During a polyp resection, different snares may be used dependent on size and morphology of polyp tissue. There are no data on the effect of snares on complications or on completeness of polyp resection. Preliminary assessment of resection practice showed that individual endoscopists at different study centers use different snares. The type of snare used is dependent on prior experience and availability at individual centers. We will therefore leave snare selection at the discretion of the endoscopist, document what snares were used, and examine whether snare selection had an effect on outcome.

Following resection, the endoscopist will confirm that the polyp appears to be completely resected macroscopically by detailed examination of the resection margin. Visible remaining polyp tissue should be resected or ablated (typically using argon plasma coagulation [APC]). Once resection is considered complete the mucosal defect will be either closed or not closed with clips, as determined per randomization protocol. After resection, the site will

be marked with spot injection to identify the polyp site at a future endoscopy (standard of care).

In some circumstances the endoscopist may consider it as clinically appropriate to place a clip, even if the patient was randomized to the non-clipping group. Such situations may include, but are not limited to placing a clip to control bleeding during the polyp resection. In these situations the endoscopist will be asked to document the reason for clip placement.

Following the procedure patients will be observed in recovery as per standard of care at each institution.

3.2.7. Follow-up procedures

The primary aim of the study is to assess whether clip closure of the mucosal defect after large polyp resection will reduce the risk of delayed bleeding complications. Secondary aims include to examine whether clip closure reduces the incidence of complications overall. Clip closure can therefore be considered effective if the risk of complications is reduced.

Follow-up:

- Patients will be contacted within 1-3 days to assess for any possible complications as per standard of care at each institution.
- Patients will be contacted after 30 days to inquire about possible adverse events.
- Per guideline patients with large polyps that are resected piecemeal should have a follow up colonoscopy within 3 to 6 months[28]. The study will aim to schedule the recommended follow-up colonoscopies between 3 to 4 months.
- Assuming complete polyp resection a second follow-up colonoscopy will be scheduled one year following the first follow-up exam (within standard of care). Additional surveillance colonoscopies will be based on findings (third colonoscopy typically three years following the second colonoscopy). At follow-up the prior polypectomy site will be inspected for macroscopic residual polyp or recurrence and biopsies obtained from the site. We will collect information on colonoscopies and clinical course (i.e. need for surgery) up to five years after initial polyp resection.

3.2.8. Schedule of activities (Study table)

Schedule of activities is detailed in Figure 2, Appendix 4.

3.2.9. Study outcome evaluation

The *primary aim* of the study is to compare the incidence of delayed bleeding complications between patients after the resection of large ≥20mm polyps who underwent clip application to those who did not.

The *secondary aim* is to compare the incidence of overall complications between patients after the resection of large ≥20mm polyps with Endocut vs. low power coagulation.

3.2.9.1. Outcome measures

Primary Outcome Measure:

- Delayed bleeding complications [Time Frame: 30 days].

Assessment: Patient contact, if severe adverse event, review of medical records, to obtain details on complication, treatment and outcome.

Secondary Outcome Measures:

- Overall complications [Time Frame: 30 days]
  Assessment: Patient contact, if severe adverse event, review of medical records, to obtain details on complication, treatment and outcome.

- Factors associated with complications [Time Frame: 30 days].
  Assessment: Using patient and polyp characteristics, and procedural data, obtained at the time of study polyp resection.

- Complete polyp resection [Time Frame: 6 months]
  Assessment: a) immediately after polyp resection, based on evaluation of the endoscopist. b) at first follow-up endoscopy, based on results of biopsies from the resection site.

- Polyp recurrence [Time Frame: 3 months to 5 years].
  Assessment: at follow-up endoscopies after complete resection was achieved.

- Factors associated with incomplete resection or recurrence [Time Frame: 5 years].
  Assessment: Using patient and polyp characteristics, and procedural data, obtained at the time of study polyp resection.

Procedures to assess safety of clip use

- Clip complications [Time Frame: 30 days].
  Assessment: Patient contact, if severe adverse event, review of medical records, to obtain details on complication, treatment and outcome.

3.2.9.2. Study endpoints

Endpoints of primary analysis (*Comparison between clip group versus no-clip group within 30 days of follow-up):*

Primary endpoint:

• *Delayed bleeding complications:*

Delayed bleeding is a serious adverse event that is defined as a patient who left the endoscopy unit and subsequently had to return to any health care facility for evaluation of rectal bleeding AND who required either hospitalization, transfusion, a repeat colonoscopy or sigmoidoscopy for examination of the polypectomy site or control of bleeding, or surgery within 30 days after completion of the colonoscopy.

Secondary endpoint:

• *Complications overall:* Overall complications will be defined as an aggregate of all complications that occur at the time of the procedure (immediate complications) or during 30 days of follow-up. They include bleeding complications as defined above, perforation, postpolypectomy syndrome, and clinical events that require an ED visit, admission to the hospital, or additional testing or intervention.

Explorative:

• *Immediate and delayed complications:* Immediate complications are considered all complications at the time of polyp resection. They include bleeding that cannot be controlled by endoscopic intervention, perforation, or clinical events that require abortion of the procedure. Delayed complications are complications that occur following the completion of the colonoscopy within 30 days of the procedure.

• *Complete and partial clip closure:* Degree of closure of the resection defect will be categorized as completely closed, partially closed, and not closed. Complete closure is defined if opposing resection margins are drawn together by clips from one side to the other, with gaps of less than 1cm between the clips. A site is considered partially clipped if only a portion of the defect could be closed[17].

• *Factors associated with complications:* Factors that may be associated with complications, including polyp size, location of the polyp in the colon (right, left, rectum), histology, polyp morphology, time required for resection.

Endpoints of secondary analysis *(entire study cohort):*

- *Complete polyp resection:* Rate of complete study polyp resection a) at the initial colonoscopy and b) at first follow-up endoscopy

- *Polyp recurrence:* Rate of recurrent polyp at the resection site after complete polyp resection.

- *Factors associated with incomplete resection or recurrence:* Factors that may be associated with incomplete resection include prior attempts of removal, use of adjunctive argon plasma coagulation for residual polyp removal, polyp size, location, and histology.

3.2.9.3. Data collection

We will collect the following data:

- Patient characteristics, including date of birth, gender, body mass index, ASA classification.
- General procedure details, including date of procedure, endoscopist, indication, and immediate complications.
- Polyp resection method, including prior biopsy, prior attempt of resection, perceived difficulty of positioning the endoscope, use of cap, submucosal injection, cautery current, type of snare, resection pieces, use of adjunct resection or cautery measures, number of clips placed, retrieval method, polypectomy time, clipping time, method of assessment of resection margins (e.g. NBI)
- Polyp characteristics, including polyp size, polyp site, histology polyp morphology (e.g. Paris classification), lifting sign, and supplemental methods.
- Follow-up data, including results of histopathology of the removed polyp, delayed complications.
- Follow-up procedure, including interval events (e.g. need for surgery), findings, presence of polyp/neoplasia at 4-6 months follow-up and within 5 years,
- Endoscopist characteristics include annual endoscopy procedure volume, years since training, average number of large polyp resections per year.
- Information on possible complications will be obtained at the time of the procedure, and identified based on the subjects' self-report at the post-procedure follow-up

phone call within 24-72 hours, at a phone call at least 30 days following the colonoscopy. Medical records will be reviewed for serious complications.

Image and video recording

Mandatory images will be taken during each polyp resection. These include an image before resection to verify the polyp size (adjacent snare with standardized size), and image after complete resection, and an image after clip closure if applicable. Further polyps that were not considered resectable will also be photographed.

Video recordings of all available EMR procedures will be collected from each participating endoscopist to understand not yet identified or possible non-measurable technical differences between endoscopists that might affect outcomes of interest.

All images and videos will be recorded without any patient identifier and stored at the coordinating site based on the patient, endoscopist, and center identification numbers.

3.2.10. Statistical analysis

3.2.10.1. Primary analysis: Comparison between clip group vs. no-clip group, 30 day follow-up)

Primary endpoint: Delayed bleeding complication.
We will assess the null hypothesis that clipping has no effect on delayed bleeding complications using a chi-square test to compare the two study arms (as randomized, intention-to-treat), or a Fisher's exact test if appropriate with a 5% significance level.

Secondary endpoint: Overall complications.
The secondary endpoint will be compared between the clip and no-clip arms using a chi-square test (or Fisher's exact test if appropriate) with a 5% significance level.

The primary endpoint (delayed bleeding complication) and secondary endpoint (overall complications) are planned to be used to support clip-labeling plans.

The main analyses of the primary and secondary endpoints will be done on a per subject basis. Additional analysis will be conducted at the unit per polyp. Clustering of polyps within patients (estimated to occur in approximately 5%) will be accounted for by using the method generalized estimating equations as well as mixed-effects-analysis with a random intercept for patient.

Subgroup Analyses: While the study is not powered to look at subgroups we will conduct exploratory analyses to determine if any difference in the clip and no-clip arms is modified by characteristics such as time of occurrence (immediate vs. delayed) and by etiology (bleeding, perforation, etc.). This examination will be descriptive because the study will unlikely be sufficiently powered for identifying differences as significant.

Explorative analysis of the effect of electrocautery setting: The comparison between the two electrocautery settings (low power coagulation vs. Endocut) will be explorative. Pilot data show that one third of participating endoscopists typically use low power coagulation and two thirds use Endocut. Acknowledging a possible effect of cautery on the incidence of complications there is a need to standardizing the cautery setting for the EMR procedure. Rather than using one cautery setting for all procedures, the cautery setting will be standardized by randomizing patients to one or the other setting. At the same time this randomization will allow an explorative analysis of the effect of cautery on complications. This

information, although descriptive, would provide valuable guidance to develop resection standards.

3.2.10.2. Secondary analysis: Entire study cohort

In secondary analysis we will further describe the rate of complete polyp resection and rate of neoplasia recurrence in all patients within 5 years, independent of their randomization. These endpoints will be calculated as proportion with 95% confidence interval. We will explore what factors might be associated with incomplete resection using logistic regression analysis.

All data collected will be summarized descriptively, overall, and by subgroups. Means will be compared using the student test if normally distributed and the Mann-Whitney test if not normally distributed.

3.2.10.3. Interim Analysis

An interim analysis will be conducted when we have enrolled 50% of the targeted 1020 patients, and completed 30-day follow-up on them. We will conduct an efficacy and futility analyses. For efficacy of clipping we will stop the trial if the two-sided p-value is less than 0.01. This alpha spending means that at the final analysis, a two-sided p-value less than 0.044 will be consider significant. At the interim look we will calculate the conditional power and terminate the study for futility if the conditional power is less than 20%. If the study will be continued, we will not modify the sample size based on the results of the interim analysis.

Because higher risk lesions may be more likely to benefit from clip closure the study should not continue to enroll patients if such benefit is apparent before study completion. We will therefore perform an interim safety sub-analysis for two groups of patients:

(a) Patients with study polyps >4cm, and

(b) Patients who are on anticoagulation or resume anticoagulation within 14 days of the polyp resection.

We assume that either group will contribute 10 to 20% to the study. We plan to conduct this safety analysis for each of these subgroups after 60 patients have been enrolled into either of the two subgroups (i.e. after enrollment of 60 patients with a >4cm study polyp and separately after enrollment of 60 patients who resumed anticoagulation after polyp resection). For example, the safety analysis would detect the occurrence of 2 vs. 9 delayed bleeding complications in the non-clip vs. the clip group as a significant difference (RR 4.5, 95% CI 1.01, 19.96). The study should cease to enroll these patients if the interim safety analysis shows a significantly increased relative risk in delayed bleeding complications in the non-clip group compared to the clip-group (see also Section on Monitoring).

A second safety analysis for these two groups will be part of the interim analysis after enrollment of 50% of patients (see above). Similarly, should this analysis show a significant difference in delayed bleeding complications, these patients should not be further enrolled.

3.2.10.4. Sample Size Determination

Our sample size calculation is based on the primary aim. We hypothesize that polyp resection with clip closure of the mucosal defect will reduce the incidence of delayed bleeding complications. Prior studies have reported an overall bleeding incidence between 2 and 24% (table 1). We consider an absolute difference of 5% in delayed bleeding incidence (e.g. 8% and 3%) as clinically important. Assuming a two-sided alpha of 0.05 and a power of 80%, the study will need to include a total of 730 subjects (365 subjects into each group) to show such difference as significant. We assume that for approximately 20% of patients clip

closure will not be considered possible. Therefore a approximately 920 patients will need to be included. However, approximately 10% of potential study polyps of referred patients will not meet inclusion criteria (screen failures). We estimate therefore that we need to enroll (=consent) a total of 1,020 patients for 920 patients to undergo the study intervention.

Because the primary outcome measure (delayed bleeding) will be assessed after 30 days of the colonoscopy we do not expect any dropouts.

3.2.11. Timetables

We expect to complete enrollment within two and a half years. The main outcome measure will assessed between 30 and 45 days for each enrolled patient. The duration of the study to obtain information on the major outcome of interest is expected to be completed within three years.

a) Length of participant involvement in the study: 5 years

b) Estimated time to enroll enough participants to complete this study: 2.5 years

c) Estimated time to achieve primary objective of the study: 3 years

3.2.12. Research setting

This is a multicenter study. The WRJ VAMC/Dartmouth will be the coordinating center. The centers listed below intent to participate in this study. Additional sites may plan to participate. These will be added to the research plan when appropriate. The local IRB will review the study protocol at individual sites. We are offering participation to centers outside the US.

Potential study sites:

Beth Israel Deaconess, MA
Brigham and Women's Hospital, MA
Dartmouth-Hitchcock Medical Center, NH
Georgetown University, Washington D.C.
Indiana University, IN
Johns Hopkins Hospital, MD
Kansas City Veterans Affairs Medical Center, Kansas City, MO
Mayo Clinic, Jacksonville, FL
Mayo Clinic, Rochester, MN
Roudebush VA Medical Center in Indianapolis, IN
University of Alabama, AL
University of Chicago, IL
University of Iowa, IA
University of Maryland, MD
University of Michigan, MI
University of North Carolina, NC
University of Texas, TX
University of Vermont, VT
University of Washington, WA
VA Detroit, MI.
VA Maryland, MD
VA Oklahoma City, OK
VA Palo Alto, CA
VA Seattle, WA
VA West Haven (Yale)
VA White River Junction, VT
Yale University Medical Center, CT
Montreal University Hospital (CHUM), St. Luc Hospital, Montreal, Canada
University Medical Center, Utrecht, Netherlands

Update on currently enrolling sites and those with interest/under IRB review (June 22, 2016)

Beth Israel Deaconess, MA
Dartmouth-Hitchcock Medical Center, NH
Indiana University, IN
Johns Hopkins Hospital, Baltimore, MD
Sibley Memorial Hospital, DC
University of Kansas, Kansas City, MO
University of Chicago, IL
University of Michigan, MI
Hershey Medical Center, Hershey, PA
Medical University of SC, Charleston, SC
University of North Carolina, NC
VA Detroit, MI.
VA West Haven (Yale)
VA White River Junction, VT
VA Tampa, FL
Yale University Medical Center, CT
Gastroenterology Associates, Asheville, NC
Florida Hospital, Orlando, FL
Montreal University Hospital (CHUM), St.
Hospital Clinic de Barcelona, Spain

3.3. Data and Safety Monitoring Plan

Appropriate consent documentation and clinical study documentation, progress of the trial, including assessments of data quality and timeliness, participant recruitment, and participant risk versus benefit will be monitored monthly by the principal investigator.

The DSMP includes the following:

- Use of standard procedures and precautions for colonoscopy with polyp resection.
- Post-procedure telephone follow-up call within 24 to 72 hours with an appropriate plan of action should any clinical signs suggesting complications occur.
- All patients will be asked to contact the endoscopist/or representative, their health care provider, or present to the local emergency room, should they experience any problems after the colonoscopy (i.e. abdominal pain, bleeding) (see methods section).
- Approximately 3-4 month call-back for follow-up colonoscopy.
- All serious adverse events will be reviewed by the principal and co-investigators to assess whether this complication was related to study participation following the event and by the DSMB. In addition, procedural complications will be reviewed at individual sites per local standard. These reviews will assure additional independent assessment and evaluation of possible adverse events.
    - For VA sites: All patients from the WRJ VA are subject to independent review for serious adverse events by the local complication board, which meets every three months. All serious adverse events that occurred during any endoscopy procedure are reviewed by the committee and graded according to the severity of the event.
    - For VA sites: The VHA information security officer will be solicited to review any potential security violations of the network protected study database.

3.3.1. Monitoring Plan

The main goals of monitoring the use of the clip as a nonsignificant risk device include

1) To secure compliance, and
2) To allow immediate evaluation of an unanticipated adverse device event (FDA, 21CFR 812.46)

The purpose of the monitoring plan is to outline the approach to monitoring this clinical trial. The plan is based upon verification of compliance with FDA regulations and guidelines and Good Clinical Practice (GCP) guidelines, which require monitor verification that:

a) The rights and well-being of human subjects are protected
b) The reported data are accurate, complete, and verifiable from source documents
c) The conduct of the trial is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

The monitoring focuses on the primary aim of the study and the safety of the Resolution Clip in its off label use as a non-significant risk as a non-significant risk device. Considering the safety profile of the clip and the potential that the clip will reduce complications, we plan off site monitoring where appropriate. This will include conference calls and upon request sending de-identified CRFs for review to the monitor according to the following time plan:

- The study will only commence at individual sites if all requirements as outlined in the monitoring plan are met.
- After 5 to 10 patients were enrolled at a site, the site will be monitored to assure adherence to the study protocol, especially with respect to eligibility, consent process, and completeness of data collection.
- Repeat monitoring will be conducted after 20 to 30 patients have been enrolled at a site.
- A final monitoring of each site will be performed after enrollment is complete.

On-site visits may be conducted based on individual performance criteria, especially with respect to adverse event reporting (e.g. sites with the highest or lowest reports of adverse events), and enrollment (i.e. sites that are far above or below target).

3.3.2. Data Safety Monitoring Board

- The DSMB consists of three independent gastroenterologists who are considered experts with respect to large polyp resection, and one statistician. After half of planned participating patients have been enrolled, the members of the DSMB will review all serious adverse events and review recruitment based on the proposed timeline.
- The study will be stopped should there be serious adverse events (bleeding, requiring additional interventions following the colonoscopy, perforation) related to study participation beyond what would be expected with respect to frequency or severity. The decision to stop the study will be made by the DSMB. The following stopping rules apply:
    - The study will be stopped should the interim analysis show a substantial difference between the clipping and non-clipping group of $p<0.01$ (see Interim Analysis).
    - Patients with >4cm polyps will no longer be enrolled should the interim safety subanalysis show a significant absolute difference in delayed bleeding complications between the clip and the non-clip group of at least 30% (see Interim Analysis).
    - Patients who are on anticoagulation or scheduled to resume anticoagulation within 14 days of a study polyp resection will no longer be enrolled should the interim safety subanalysis show a significant difference in delayed bleeding complications between the clip and the non-clip group (see Interim Analysis).

Research Materials. Data will be collected only if the subjects participate in the study. Data will be obtained only for research purposes.

Protection. Subjects will be afforded a variety of protections. First, all protocols will be IRB approved and subject to oversight by the local IRB. Second, once the data are collected they will be dealt with in an anonymous manner with adherence to HIPAA guidelines.

4. GENDER/MINORITY MIX

We expect approximately 45% of the patients to be women. Because several participating centers will be VA Medical Centers, the majority of enrolled patients will be men. We will make every effort to recruit a diverse group of subjects, but there are no race or ethnic-based questions to this protocol.

5. RISK ANALYSIS

5.1. Anticipated Risks

There are no risks incurred with the study that are beyond those associated with the clinically warranted procedure (colonoscopy with EMR, see background section). In theory there is a minimal risk associated with an increased time needed to apply clips for closure of the mucosal defect. Dependent on the size of the lesion endoscopic clipping may take 5 to 10 additional minutes. Considering that an EMR of large polyps often takes more than 60 minutes, the additional relative increase in procedure time would be low. Furthermore, there has been no study to show that a small proportional increase in procedure time is associated with an increased risk. Should there be any concern regarding the safety of the patient related to prolonged procedure time when applying clips, the procedure will be aborted.

Risk/Benefit analysis. It is unknown whether the patient will benefit from the proposed study.

The planned interventions are variations of standard of care and the study compares different approaches representing a comparative effectiveness study. While the risk of added time in the clip group may be minimal (if present at all), it is plausible that clip application will decrease bleeding risk and may improve polyp resection. If so, fewer follow-up procedures (either colonoscopy or surgery) would be needed, which might lower the future overall risk. Whether clip application is truly a helpful modification of the EMR resection practice is not known, hence the study.

As for the comparison of cautery settings (Endocut vs. lower power coagulation), it is unclear, which mode is associated with fewer complications. It is the purpose of this study to explore whether one choice of cautery setting may be associated with a lower risk. This understanding may ultimately contribute to an improved polyp resection practice.

5.2. Adverse Event Recording and Reporting

5.2.1. Adverse event definitions

Adverse effect: Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the investigational device.

Associated with the investigational device: There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect: Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect: Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Hospitalization shall include 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.

Unexpected adverse effect: Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol.

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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5.2.2 Eliciting adverse effect information

Clinical study subjects will be routinely questioned about adverse effects at study visits. See section "Follow-up Procedures".

5.2.3 Recording and assessment of adverse effects

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device.

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequalae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

5.2.3.1 Abnormal test findings:

An abnormal test finding will be classified as an *adverse effect* 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 or other therapy.
- The test finding leads to a change in discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse effect by the investigator-sponsor.

5.2.3.2. Causality and severity assessment:

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device; and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device* for reporting purposes. If the investigator-sponsor's final determination of causality is unknown but not related to the investigational device, this determination and the rationale for the determination will be documented in the respective subject's case history.

5.2.4. Reporting of adverse effects to the responsible IRB

In accordance with applicable IRB policies, the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) *associated with the investigational device or, if applicable, other study treatment or diagnostic product(s)*; 2) *a serious adverse effect*; and 3) an *unexpected adverse effect*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) *associated with the investigational device*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

5.3. Withdrawal of subjects due to adverse effects

The study intervention will only applied once after a study polyp resection. The clip will typically fall of within 1-2 weeks and excreted with a bowel movement, which is usually not noticed by the patient. A continued exposure to the study intervention is therefore not given.
Should the patient have the wish to withdraw from the study, no he/she will no longer be followed as part of the study.

6. FDA RISK DETERMINATION

The study will use the Resolution clip, which was approved by the FDA primarily for hemostasis (treatment of intestinal bleeding) and closure of perforations (FDA-K122660; December 3, 2012). Closure of a mucosal defect after polyp resection was not an FDA approved indication at the time of study commencement. The FDA reviewed the study protocol, and determined in its response from the clip to be a non-significant risk device (March 5, 2014; Q131671,*(Appendix 3).*

The FDA has recently revisited indications for the Resolution clip and determined (based on the retrospective study by Liaquat[17], table 1) that the clip can be used for "Prophylactic clipping to reduce the risk of delayed bleeding post lesion resection" (Appendix 501K, December 1,2014). Clip closure (study intervention) is therefore now an FDA approved clip application.

7. CONSENT PROCESS

Standard Consent Process

Potential study participants include patients between 18 and 89 years of age who are scheduled for a colonoscopy and for a resection of a large (≥20mm polyp).
According to the requirements of local IRBs, patients will be informed about the study within appropriate time prior to the study.
According to the local requirements some site investigators will send out a letter to potential participants to inform about the study and include a consent form for review (i.e. VA White River junction and Dartmouth-Hitchcock Medical Center). The letter will also contain contact information for questions to allow the patient to call the study investigator or coordinator directly with questions. The letter will also allow the study investigator/coordinator to contact a potential study participant, after they have received the letter, to discuss their interest in participating. Upon arrival for the scheduled colonoscopy patient's record will be reviewed to determine eligibility. Patients will be informed about the nature of the study and the possibility to enroll in the study. The individual, who obtains the consent, will answer possible questions. The consent will be obtained at the same time as the consent for the colonoscopy prior to the procedure.

Alternative Consent Process

In addition to the standard of consenting we request the study allows an alteration of the regular consent process for patients who are found to have a large (≥20mm) non-pedunculated polyp at the time of the colonoscopy.

Any patient who presents for a colonoscopy between the ages of 18 and 89 and who does not meet exclusion criteria, an information sheet about potential study participation will be mailed prior to the schedule colonoscopy, and also given to the patient upon arrival for the scheduled colonoscopy. This information sheet contains information about possible enrollment into a study, if a large ≥20mm polyp is found along with assurance that any approach follows standard of care. If the patient does not agree to be considered for the study, he/she can actively opt out by initialing the appropriate box at the information sheet. In that case a polyp will be resected per endoscopist preference.

If the patient does not opt out and a large polyp is found the standardized resection protocol (as detailed above) will be followed and patients will be randomized accordingly. Following the procedure the patient/accompanying person will be informed about the findings, the polyp resection, and the possibility to participate in the study. The patient will be given a consent form to be read at home and contacted following the procedure (but more than 24 hours) to discuss

the consent form. If the patient wishes to participate he/she may then sign the consent form and send it to the study coordinator or bring it at his/her next appointment. Only then and if the patient signs the consent, he/she will be enrolled into the study. Telephone consent will be documented in the patient's records.

We believe that such approach is responsible for two reasons – first the studied resection methods are all considered standard of care, and it is unclear which one is superior; and second, large polyps (≥20mm) are very uncommon (approximately 1-2%), and it would be impractical to consent each person who presents for a colonoscopy prior to the procedure just in case a large polyp is found.

Privacy and Confidentiality

All patient information will be kept confidential and only information relevant to the study will be recorded. Each site, each patient, and each endoscopist will be given a unique identification number and all study data will be recorded on a case report form. Each form will be kept as a hard copy and stored in a locked cabinet. Collected data will be transferred from each form to an electronic database for further analysis. Data that will be sent to the coordinating center will only contain event dates (including procedure dates, surgery dates, and patient contact dates) as the only patient identifier. Only dates and no other identifiers will leave each site. Patients will be asked in the consent form, whether they agree to share dates with the coordinating center. Each site research team will have access to their data, however, only the primary investigator and the team at the coordinating center will have access to the entire data set. For de-identification purposes each site will keep a separate de-identification log (matching name with assigned ID). This list will be kept separately at each center in a locked cabinet.

8. ADDITIONAL RECORDS AND REPORTS

8.1. Data handling and record-keeping

Data will be entered on case report forms (CRF) and transferred into an electronic database after establishing a web based data entry. Once established data may be entered directly into the data entry site. The site investigator is responsible for complete data ascertainment at the site and entry into the database. Data will be collected centrally at the coordinating center. Each site will maintain a hard copy of completed CRFs and a de-identification list.

The electronic system includes safeguards to ensure complete data entry and minimizing erroneous entries. The investigator-sponsor is responsible for assuring complete data collection, especially with respect to adverse events. If needed, missing or additional information will be obtained from local site investigators.

Web based data entry, recording and analysis of clinical and laboratory data related to the safety and/or efficacy of the investigational device, will be in compliance with the FDA's electronic records and electronic signatures regulations as detailed in 21 CFR Part 11.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*. All relevant clinical study data will be recorded on CRF or directly entered into the data collection site. These include patient characteristics, procedure data, and clinical events, particularly complications. For details see "Data Collection" and "Data Analysis". Therefore CRF data or those directly entered into the data collection site are considered Source Data.

8.2. Record maintenance and retention

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the risk determination application and Investigational Plan;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Master randomization list (incorporate only if applicable);
- Monitoring reports;
- Copies of investigator-sponsor correspondence to sub-investigators, including notifications of adverse effect information;
- Subject screening and enrollment logs;
- Investigational device accountability records, including documentation of device disposal;
- Interim data analysis report(s); and the
- Final clinical study report.

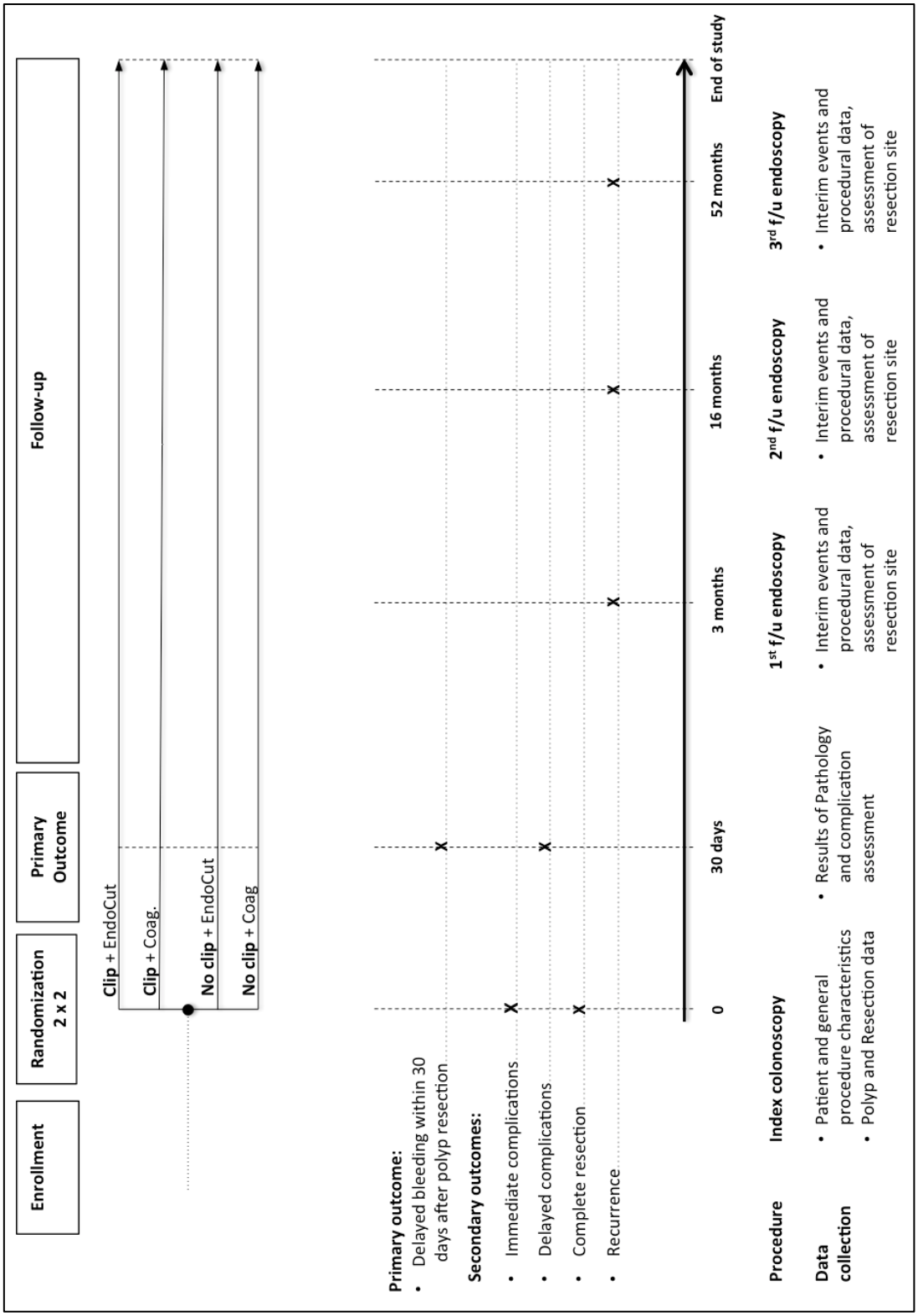
9. FUNDING

The study received funding support from Boston Scientific Corporation (BSC). BSC does not take the responsibility as a sponsor. Sponsor responsibilities will stay with the primary investigator. The study is therefore not an industry-sponsored study, and continues to be an investigator-initiated study.

Veterans Education and Research Association of Northern New England, Inc. (VERANNE) will administer the funds (office located at White River Junction VA Medical Center). VERANNE and BSC have signed a CRADA (cooperative research and development agreement). In addition to monetary funds to create a web-based data entry site and financial aid for participating centers, BSC also provides study clips.

Appendix 1. STUDY DESIGN

Figure 1. Schematic diagram of the study design, procedures and stages



Appendix 2. STUDY TABLE

TABLE 1. **Summary of procedures performed at screening, for treatment, and at follow-up.**

	Screening	**Treatment**			**Follow-up**			
Time	Before index colonoscopy	During index colonoscopy		1-3 days	≥30 days	3-4 months	+ 1 year	+ 3 years
Procedures & activities	-Assess patient eligibility from medical records and patients interview prior to the colonoscopy	-Assess polyp eligibility -Decide whether to resect or not -Randomize patient	-Resect polyp -Clip closure (or no closure) after polyp resection	Follow-up phone call.	-Phone call to patient to assess whether complications occurred	At the time of 1st f/u endoscopy: -Assessment of interim events -Assessment of resection site	At the time of 2nd f/u endoscopy: -Assessment of interim events -Assessment of resection site	At the time of 3rd f/u endoscopy: -Assessment of interim events -Assessment of resection site
Data collection	-Patient characteristics	-Polyp data	-Procedure characteristics -Resection data	-Complications	-Results of pathology -Complications	-Interim events -Procedure data (Resection site)	-Interim events -Procedure data (Resection site)	-Interim events -Procedure data (Resection site)

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