Risk of Post-Polypectomy Bleeding with Prophylactic Hemoclipping

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The Investigator's Protocol

1. Title

Risk of post-polypectomy bleeding with prophylactic hemoclipping

2. Principal Investigator and Co-Investigators

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Co-investigators: Stuart Spechler, MD, William Harford, MD, Akeel Halai, MD, Suneetha Duttala, MD, Kerry Dunbar, MD PhD

Site PI (Austin): Ranjan Mascarenhas, MD

Site PI (San Antonio): Tisha Lunsford, MD

3. Sponsor of the Study

VA MERIT Award (2014-2019)

4. Investigational New Drug (IND)/Investigational Device Exemption (IDE):

None

5. Purpose of the Study, Including the Hypothesis to be Tested

The purpose of this study is to investigate whether prophylactic placement of hemoclips at the polypectomy site of large polyps (at least 1cm in size) will reduce the rates of post-polypectomy bleeding.

We hypothesize that prophylactic placement of hemoclips after removal of large polyps does not decrease the risk of delayed bleeding.

6. Background and Results of Previous Related Research

Colonoscopy with removal of polyps is recommended to reduce the risk of developing colorectal cancer. However, as with any procedure, there are complications that can be associated with colonoscopy and include bleeding after removal of a polyp. Post-polypectomy bleeding can either occur during the colonoscopy immediately after polyp removal (termed immediate bleeding) or occur at sometime after the conclusion of the colonoscopy (termed delayed bleeding). Immediate bleeding is typically handled easily during the colonoscopy by employing various techniques of hemostasis. However, delayed bleeding can sometimes necessitate hospitalization, treatment with blood transfusions, and repeat colonoscopies to treat the bleeding. A risk of post-polypectomy bleeding has been associated with polyps that are larger in size, sessile or pedunculated with a thick stalk, and co-morbid diabetes, coronary disease, lung disease, or renal disease. With the advent of hemoclips, we have often elected to place hemoclips after polypectomy, particularly in large polyps, for fear of delayed bleeding. However, there are no clear guidelines for prevention of bleeding after polypectomy and no data to support these practices.

Studies evaluating the risk of delayed bleeding after removing large polyps has ranged from 1% to 5.3% with polyp size in these studies varying from at least 1cm in size to at least 3cm in size.[1-3] In our endoscopy lab, our rates of delayed bleeding in patients with polyps removed at least 1 cm in size is 1.2%, however this includes a mixture of patients who did and did not undergo prophylactic clipping. While some have suggested that prophylactic clipping may reduce the rates of post-polypectomy bleeding[4], there has only been one study that has evaluated the rates of post-polypectomy bleeding with prophylactic placement of

hemoclips with a randomized study design. This study found no significant difference in bleed rates in those clipped and not clipped.[5] This study has been criticized, however, because the size of polyps included in the study was on average small with the average sized polyp in both the clipped and non-clipped groups being 7mm. They excluded larger polyps (>3cm) or those removed in a piecemeal fashion. Therefore, the bleeding rate after the common practice of clipping large polypectomy sites remains unclear.

7. Definition of the Population to Which the Study is Directed, with Justification

All patients scheduled for elective colonoscopy at the VA North Texas Healthcare System (specifically DVAMC and the Fort Worth Outpatient Clinic), Central Texas VA Healthcare System (specifically, Austin Outpatient clinic), or the South Texas VA Medical Center (San Antonio VA) are eligible for participation in the study.

8. Subject Selection, Inclusion and Exclusion Criteria

Inclusion criteria:

- Any patients undergoing elective colonoscopy for clinical indications where polypectomy will be considered.
- Polyps at least 1cm in size that will be removed by the endoscopist.

Exclusion criteria:

- Polyps that the endoscopist feels they can't completely or safely remove enodscopically
- Those unwilling to give informed consent.
- Women who are pregnant or breast feeding.
- Serious co-morbidity, as determined by the study physician, that may preclude safe participation in the study

9. Number of Subjects in the Study

Our study is an equivalence study using the TOST (two one-sided test) procedure, which is considered the simplest and most widely used approach to test equivalence. With TOST, equivalence is established at the α significance level if a $(1-2\alpha) \times 100\%$ confidence interval for the difference in efficacies (hemoclip vs. no hemoclip) is contained within the interval $(-\delta, \delta)$. The reason the confidence interval is $(1-2\alpha) \times 100\%$ [and not the usual $(1-\alpha) \times 100\%$] is because TOST is tantamount to performing two one-sided tests. Thus, our choice of a 90% confidence interval yields a 0.05 significance level for testing equivalence. In calculating the number of patients required for our two-armed study, we chose 1.5% as the expected rate of PPB (i.e. the expected rate for the "no hemoclip" group), a Type I error risk of .05, 80% power, and ±1.5% equivalence range. This equivalence range covers a bleeding risk of 0 to 3%, which falls well within the published rates of PPB (0.4 to 6%). For an equivalence study, the null hypothesis holds that there IS a difference between the two groups. The null hypothesis can only be rejected when the data indicate that outcomes for the two groups are close enough so that one cannot be considered superior or inferior to the other. Based on Blackwelder24, the sample size needed to reject this hypothesis at alpha = 0.05 and beta = 0.20, with Ps and Pn being the proportion of patients that experience PPB in the Ps (standard or "control") group and in the Pn (novel or "hemoclip") group, and D being the difference between the groups, is:$(Z\ 0.95 + Z\ 0.80)2\ [Ps(1-Ps) + Pn(1-Pn)] / (Ps-Pn-D)2$. On this basis, 1622 patients will be randomized (811 to the hemoclip arm, 811

to the no-hemoclip arm). We expect that the duration of this study will be 4-5 years.

10. Justification for the Use of Vulnerable Populations

Not applicable.

11. Study Design

- All patients who present for elective colonoscopy where polypectomy will be considered will be eligible for the study.
- Patients in whom the endoscopist encounters a polyp of at least 1cm in size will be eligible for the study. The size of the polyp will be assessed by the open jaw of a Boston Scientific maximum capacity biopsy forceps (open jaw spacing=10mm).
- If no polyp of at least 1cm in size is found on examination, the patient will be excluded from further study (and NOT randomized).
- Patients enrolled into the study will be randomized in a 1:1 fashion to either:
    - no hemoclip placement
    - prophylactic hemoclip placement with closure of the polypectomy defect
- Polypectomy will be carried out in the technique as deemed appropriate by the endoscopist (with or without saline lift, with or without epinephrine, etc).
- If the patient is randomized to the arm of the study where hemoclip placement will be performed, the goal of hemoclip placement will be for closure of the polypectomy site defect. At the completion of hemoclipping, the site will be categorized as "completely closed" or "incompletely closed". The site will be deemed completely closed if the margins of the polypectomy site are drawn together with gaps of less than 1cm between the hemoclips, otherwise it will be categorized incompletely closed.
- If the patient is randomized to the arm of the study where no hemoclip placement will be performed, the polypectomy site will be unaltered.
- If there is immediate bleeding after the polyp is removed that requires placement of a hemoclip for hemostasis, the patient will be excluded from the study arm where randomization of the polyp to be clipped or not clipped would have occurred.
- If a patient has more than one 1cm or greater polyp, the same technique will be used throughout that patient (ie if randomized to hemoclipping, then each polyp of 1cm or more in that patient will be prophylactically clipped).
- Randomization assignment and the use of hemoclips deployed solely for study purposes will not be recorded in the clinical colonoscopy report, to keep treating clinicians blinded to study treatment.
- Patients will be followed for 30 days in order to detect any delayed bleeding. They will receive phone calls from the study team at 7 days and 30 days post-procedure to assess for any bleeding.

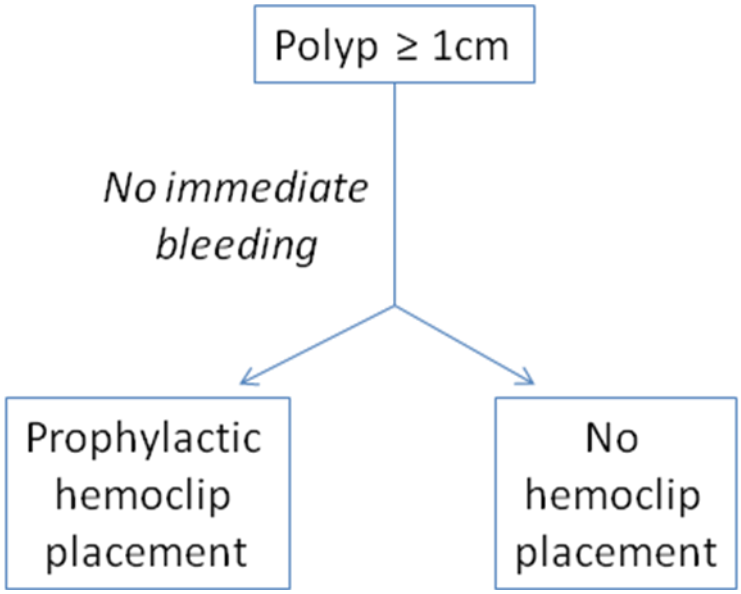

Figure 1: randomization algorithm

Definitions:

Immediate post-polypectomy bleeding: persistent bleeding at the polypectomy site that is deemed by the endoscopist to require endoscopic treatment and that is noted during the initial colonoscopy during which the polypectomy is performed (i.e. before completion of the procedure); bleeding will be further categorized as spurting or oozing.

Clinically important delayed post-polypectomy bleeding: rectal bleeding occurring within 30 days of polypectomy and beginning after the completion of the colonoscopy that results in 1 of the following: 1) blood transfusion, 2) hemodynamic instability (orthostasis with fall in systolic blood pressure >10mm Hg or increase in heart rate at least 20 beats/minute OR systolic blood pressure < 100 and/or heart rate >100), 3) fall in hemoglobin by at least 2 grams per deciliter from previous baseline. When colonoscopy is performed for the post-polypectomy bleeding, the bleeding site will be categorized as either 1) active spurting, 2) oozing, 3) presence of adherent clot, 4) visible vessel, 5) flat pigmented spots, or 6) clean based ulcer. The time to bleeding (measured from the day of initial colonoscopy) will be noted.

The *primary end-point* is clinically significant delayed bleeding. Delayed bleeding will be defined as any patients who have rectal bleeding within 30 days of their procedure. Clinically significant delayed bleeding will be defined as bleeding requiring admission to the hospital, transfusions, hemodynamic instability, or Hb drop more than 2 units.

Patients who experience clinically important post-polypectomy bleeding will be treated as per the standard of care. This typically includes hospitalization, volume resuscitation with intravenous fluids or blood, if necessary, and repeat colonoscopy with an attempt to treat the bleeding polypectomy site. In the large majority of cases, colonoscopy with hemostasis is sufficient treatment. However, if this is unsuccessful, patients will be considered for angiography or surgical treatment.

12. Description of Procedures to be Performed

Randomization:

A computer-generated randomization schedule will be used to assign patients to one of the two study groups. Randomization will be 1:1 with variable block sizes. To ensure equal distribution of patients using anticoagulants (warfarin, thienopyridines, heparin), the randomization will be stratified by whether or not patients are taking these agents. Randomization assignments will be placed in opaque envelopes by study team personnel not involved in the study procedure, numbered sequentially, and used in chronological order. The randomization envelope will be opened by the endoscopy team only at the time of randomization, when a 1cm or larger polyp is discovered during colonoscopy. More specifically, the randomization assignment will not be revealed until after the endoscopist has completed the polypectomy, so as not to bias the choice of removal technique.

Data collection:

Data for the study will be collected using the data collection sheet. First, data will be collected in regards to the patient's demographic and clinical characteristics including age, race, sex, co-morbid illnesses, smoking history, family history of colon cancer, indication for colonoscopy, current medications, specifically including use of aspirin, non-steroidal anti-inflammatory drugs, thienopyridines, warfarin, DOAC, or heparin, with dosages used and day of last dose taken in relation to day of colonoscopy, and Body Mass Index. Second, during the colonoscopy, data will be collected in regards to polyp characteristics including size, morphology (sessile or pedunculated), diameter and length of stalk (if applicable), location of stalk resection (near polyp, near colon wall, or in the middle), location (cecum, ascending, transverse, descending, sigmoid, rectum), technique of polyp removal (cold biopsy, cold snare, hot snare, inject and lift, use of epinephrine, piecemeal technique, fulgaration), number of hemoclips placed after removal (if applicable), immediate bleeding (that requires treatment) after polypectomy, type of bleeding (oozing or spurting), and modality used to stop the bleeding. In addition, for patients randomized to hemoclipping after polypectomy, we will record whether the endoscopist was able to completely close the defect with hemoclips or if the defect was only able to be partially closed. After the completion of the procedure, the pathology of each polyp, once available, will be reviewed and recorded (normal, hyperplastic, tubular adenoma, sessile serrated adenoma, tubulovillous adenoma, dysplasia, cancer, other). The occurrence of post-polypectomy hemorrhage will be assessed by phone calls to the patient at both 7 days and 30 days after the procedure. The patients are also given the contact information for the VA and the study team and are encouraged to report any bleeding symptoms. During this same contact, the patient will also be questioned about any other complications after polypectomy during follow-up period (perforation, post-polypectomy syndrome, cardiopulmonary complications, etc) as well as dates of restarting any antiplatelets or anticoagulants that may have been held in the periprocedural period. If patients do experience a post-polypectomy bleed, they will be directed to come to the hospital for evaluation, if they have not already done so on their own. If they have been evaluated at an outside facility, the outside treating facility and treating doctor will be contacted to collect further information about their bleeding and evaluation in regard to cause and necessary treatment. The determination of a PPB will be made by the final diagnosis of the treating (non-study) team, who will be blinded regarding the treatment assignment (clip or no clip placement). For patient safety reasons, if the treating physician determines that there is a PPB, these data will be provided to that physician if he/she deems it clinically pertinent. The study team will collect data in regards to days in hospital, transfusion requirements, endoscopic treatment required for treatment of the bleeding, and any need for surgical or angiographic intervention to stop bleeding. Once the data collection is complete, the data will be entered into an electronic Access database for analysis.

Study procedure:

The procedure to be performed is a colonoscopy with polypectomy. Colonoscopy is the gold-standard at this time for detecting colon cancer and precursors of colon cancer (i.e. polyps). This is the test that is routinely recommended for colon cancer screening and subsequent surveillance once a history of polyps has been

established. Endoscopic polypectomy is the treatment of choice for polyps detected by any of the means of screening (i.e colonoscopy, barium enema, CT colonography). Polypectomy can be performed by several techniques, most commonly cold biopsy or hot snare. Cold biopsy is where the endoscopist removes the polyp by "biting" or "pinching" it off with a device placed into the colon through the colonoscope. This method is typically used for smaller polyps (less than 5mm in size). Hot snaring, typically reserved for larger polyps, is performed by inserting a device through the colonoscope that has a noose, or "snare", that is placed around the polyp base and electric cautery is used to burn though it. The cautery is also helpful to stop bleeding after the polyp is removed. Immediate bleeding after polypectomy can almost always be controlled endoscopically with use of cautery, hemoclips (devices that pinch the colon lining together and apply pressure), or endoloops (loops, like a snare, that can be tightened around a polyp base to stop bleeding).

figure 2: A hemoclip (Boston scientific resolution clip)

A B C

The patients enrolled in the study will be undergoing elective colonoscopy that was already clinically indicated. It will be performed per routine, as above, except for the randomization of post-polypectomy site treatment.

13. Anticipated Data and Data Analysis

Data to be collected in regards to patient characteristics:

1) Age, race, sex, smoking history
2) Family history of colon cancer
3) Indication for colonoscopy
4) Current medications, specifically including use of aspirin or nonsteroidal anti-inflammatory drugs, with dosages used and day of last dose taken in relation to day of colonoscopy
5) Body Mass Index

Data to be collected from colonoscopy:

1) Polyp characteristics
    a. Size
    b. Morphology (sessile, pedunculated)
    c. Location (cecum, ascending, transverse, descending, sigmoid, rectum)
    d. Technique of polyp removal (cold biopsy, hot snare, inject and lift, use of epinephrine)
    e. Number of hemoclips placed after removal (if done)
    f. Immediate bleeding after polypectomy and modality used to stop the bleeding
2) Pathology of each polyp (normal, benign, dysplasia, cancer)
3) Hemorrhage (delayed) after polypectomy within 30-day follow-up period

4) Any other complications after polypectomy during follow-up period (perforation, post-polypectomy syndrome, etc)
5) Whether the procedure was performed with the assistance of a fellow

Data to be collected after colonoscopy:

1) 7 day and 30 day follow-up in regards to bleeding (blood in stool, abdominal pain or discomfort, need for hospitalization, days in hospital, units of blood transfused)
2) Other post-colonoscopy complications (perforation, post-polypectomy syndrome, etc)

Primary end-point: delayed post-polypectomy bleeding (within 30 days)

Secondary end-points:

1) Delayed bleeding after endoscopic treatment for immediate post-polypectomy bleeding
2) days in hospital
3) transfusion requirements if hospitalized for post-polypectomy bleed
4) need for surgical or angiographic intervention to stop bleeding
5) other post-polypectomy complications (perforation, post-polypectomy syndrome, etc)
6) procedure duration
7) multivariate analysis to look at other factors that may contribute to risk of bleeding (polyp number, characteristics, type, co-morbidities, ASA or NSAID use, BMI, age, race, sex, tobacco use)

Statistical analysis:

Primary objective: To compare the proportion of patients with important delayed PPB between the two treatment arms: no hemoclip placement and prophylactic hemoclip placement.

Secondary objectives: To compare the proportion of patients with unimportant delayed PPB between the two treatment arms: no hemoclip placement and prophylactic hemoclip placement. Next, to compare the proportion of patients with perforation between the two treatment arms: no hemoclip placement and prophylactic hemoclip placement.

Intention to treat analysis: To ensure patient safety and to ensure that patients are treated according to accepted standards of clinical care, patients who have immediate PPB or who exhibit visible vessels or signs of perforation after endoscopy will have hemoclips placed if the colonoscopist deems this appropriate for clinical purposes, regardless of the patient's randomization status. However, if, for any reason, a study colonoscopist places hemoclips in a patient randomized to the "no hemoclips" group, or does not place them according to protocol in a patient randomized to the "hemoclips" group, the reason for the practice will be recorded and these patients will be considered deviated from the protocol.

Per protocol analysis: The patients randomized into the study and treated per the randomization schema will be analyzed in the per-protocol analysis. We will exclude the patients who had to be treated outside of the study randomization due to safety issues (immediate bleeding, visible vessels, or concern for perforation in the patients randomized to no hemoclip or inability to place a hemoclip in the group randomized to hemoclip placement). This will give the clearest analysis of the true effect of prophylactic hemoclipping. Moreover, we expect that this analysis will include the majority of our randomized patients, as patient safety issues, like immediate post-polypectomy bleeding, occur in a minority of patients (1-2% in prior studies and 4-5% in our preliminary data).

Analysis of primary outcome: Given our study design, we will test for equivalence with the TOST procedure, at significance level α, with the $(1-2\alpha) \times 100\%$ confidence interval (CI). Therefore, our a priori equivalence margin is ± 1.5% around the difference between the two groups of zero. Once the study is completed and the CIs calculated, if the lower CI limit around the difference between the groups is less than -1.5% or greater than 1.5%, then we must accept the null hypothesis that the groups are different. Similarly, if the upper CI limit around the difference between the groups is less than -1.5% or greater than 1.5%, then we must accept the null hypothesis that the groups are different. We will calculate the confidence interval for the difference in proportions using the method described by Gart and Nam (1990)26, which will be

computed with NCSS 9.0 statistical software (Hintze, 2013).
Logistic regression analysis: If we find significant differences in baseline characteristics, we will do stratified analysis to assess impact on risk of PPB. To assess impact of other potential covariates (polyp characteristics and histology and removal techniques; number clips used, age, BMI, race), we will apply the SAS macro by Bursac and colleagues (2008), which applies an algorithm that automates the variable selection process for logistic regression analysis. The macro iteratively identifies predictors of the outcome variable. Any variable having a significant univariate association at an alpha of .25 is selected as a candidate for the multivariate analysis. In the iterative process of variable selection, covariates are removed from the model if they are non-significant and not a confounder. Significance is then evaluated at a 0.1 alpha level and variables are considered confounders if their removal results in a change in any parameter estimate greater than 20%.
Subgroup analyses: To investigate for potential subgroups that may have benefitted from prophylactic hemoclipping, we will perform subgroup analyses. Because we are looking for differences, subgroup analyses will be performed using the Pearson chi-square test. Subgroups that will be analyzed include those on anticoagulation (none, aspirin, non-steroidal anti-inflammatory drugs, thienopyridines, warfarin, heparin, and combinations of therapy). Other subgroup analyses will include polyp size, polyp morphology (sessile versus pedunculated), and polyp removal techniques. We will perform subgroup analysis for delayed PPB in the patients who were treated for immediate bleeding after polypectomy and were not included in the per-protocol analysis for delayed bleeding. If differences are found, we will calculate absolute and/or relative risks and associated 95% confidence intervals for these groups.
Interim analysis: An interim analysis will be performed primarily to identify unanticipated patient safety issues after enrollment of half of the proposed patients (i.e. after enrollment of 811 patients – approximately 405 in each group). Interim analysis will be performed with a Fisher's exact test (not TOST testing), because the primary concern of the interim analysis is to identify a significantly higher bleeding rate in one of the two study arms. If the bleeding rate for either group is significantly higher than the other, then we will terminate the study early.

14. Provisions for Managing Adverse Reactions

Any emergency adverse event resulting from participation in the study will be treated at the Dallas VA Medical Center. One of the study doctors, Drs. Feagins, Harford, Spechler, Cryer, Davila, Dunbar or Halai will evaluate all adverse events and determine the appropriate course of action.

15. Risk/Benefit Assessment

There is no risk involved in physical, psychological, social, economic, or legal terms. The risks to study patients are those associated with standard colonoscopy and biopsy. Serious complications of colonoscopy in patients who have no serious comorbidities (a requirement for study entry) are rare and include aspiration, perforation and bleeding. The colonoscopy for all patients will be indicated for clinical purposes, and the study procedures are not expected to increase the risk of adverse events. Overall the risk of participating in this study is minimal.

16. Data Safety Monitoring Plan

Does this study have a Data Safety Monitoring Board (DSMB)? ☒ YES ☐ NO

17. Process for Obtaining Informed Consent and Protecting Patient Privacy

All subjects will be recruited from the patients already scheduled to undergo a colonoscopy in the at the VA North Texas (Dallas or Fort Worth) or one of the other participating VA sites (Austin or San Antonio). The PI

or one of the study team meambers will screen the study subjects and each subject who appears to be eligible will be given a description of the study, and asked if he/she would like to participate. If interested, the patient will be given all of the details in regards to the study, including possible risks and benefits. Discussions with the patient during recruitment and the consent process will be conducted in the GI lab and held in a private location to assure patient confidentiality. After informed consent is obtained, the patient will receive a copy of his or her consent forms. All consent forms will be maintained in binders which will be kept in locked cabinets in the PI's office or at the respective local site PI's office at all times.

For patients to decline to participate in the study, we will keep a list of these patients so that we do not again ask them to participate. These lists will only contain names and SSN of the patients and will be kept on a password-protected document on the VA server in the Feagins research folder (for VA North Texas participants or a similar folder at the respective VAs).

18. Documentation of Informed Consent

All eligible recruits will have the full informed consent presented to them by the study team, with all risks and inconveniences identified. Subjects must be able to demonstrate the ability to provide informed consent by showing a clear understanding of their role in the research study (able to describe back for us in their words the goals of the study, their role, and the risks/benefits of study participation). They will be allowed and encouraged at any needed time to discuss their participation in the study with their family or friends prior to signing the consent forms. Patients will not receive any premedication prior to discussions of the study protocol and consent. The patient will be given a copy of his or her consent forms. The appropriate research enrollment accept or decline notes will be recorded in CPRS.

19. Payment to Subjects for Their Participation

None

20. Provisions for Data Storage and Confidentiality

All paper records will be maintained in a locked cabinet in the PI's office at the Dallas VA Medical Center or at the local VA site-PIs office. Computerized data will be de-identified, stored separately from the key code, and stored on the VA secured network that is accessible from a password protected computer in the PI's locked office. No persons, including study personnel, will be allowed to view the study data without specific cause. In accordance with HIPAA, the consent form describes to the subject what protected health information (PHI) will be obtained and/or stored and for what purpose, as well as a list of who may have access to this data, including outside agencies. In accordance with VA guidelines, all records of this research study will continue to be securely maintained in accordance with VHA Record Control Schedule. The records will be kept in a locked file cabinet or locked room with limited access. If the PI leaves the VA facility, the original research records will be retained by the institution.

21. Provisions for storage/analysis of research specimens:

Not applicable.

22. Dissemination of Research Results

We plan for the results of this study to be published in a peer-reviewed journal (s). The results may also be presented in the form of an abstract at national meetings, for example DDW (Digestive Disease Week). The multi-site PI, Dr. Linda A. Feagins, will take the lead in writing up the results of this project. All patient information will be de-identified prior to any publications.

23. Multi-Center Research

This is a multi-center study and the Dallas VA is the coordinating site.
Participating sites (all VA facilities) and site PI's are:

1) Austin Outpatient VA Endoscopy Center
   IRB: Central Texas VA
   FWA00001125
   Ranjan Mascarenhas, MD; Cell: 405-613-2486 Office (512) 823-4023; ranjan.mascarenhas@va.gov
2) San Antonio VA
   IRB: UT San Antonio Health Science Center
   FWA00001220
   Tisha Lunsford, MD; 210-567-4872; LunsfordT@uthscsa.edu

- Protocol changes/amendments: The participating sites will be given an updated protocol within 1 week for any changes made to the protocol. Once the limited access shared folder is created, this will facilitate sharing these documents even more easily.
- Adverse Events: Serious adverse events at sub-sites will be required to be reported to the coordinating site within 48 hours. Adverse events or unanticipated problems will be required to be reported to the coordinating site within 5 days. These will be able to be shared via the limited access data folder. The study team at each site will be asked to alert the Dallas team when these events occur so the data can be reviewed.
- The study teams will have periodic meetings (every 4 months at least or more often as needed) to review any available interim data, discuss issues with recruitment or other study related problems/concerns.

References:

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