CMCVAMC SPECIFIC PROTOCOL SUMMARY
Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center (CMCVAMC)
Institutional Review Board (IRB)

Section 1. General Information

Protocol Title: *Comparative Effectiveness of Split-dose Colonoscopy Bowel Preparation Regimens*

CMCVAMC Protocol Version Number and Date: *Version #3 6/17/2018*

NCT number: NCT03298945

Principal Investigator (PI) Name: *Yu-Xiao Yang*

PI's Academic Degree(s): MD

Is the study funded? YES If "yes", specify funding agency: *VA*

Is a grant application requesting funds for the study currently being reviewed? NO

CMCVAMC is the only institution involved: **YES**

CMCVAMC is the coordinating center in which the PI is the lead investigator: Choose an item.
If this answer is yes, complete the next two sections:

- **List the name(s) of the other site(s) involved**.
- **Provide the FederalWide Assurance (FWA) numbers for each site**.

State name of coordinating center if this is <u>not</u> CMCVAMC.

Describe PI's qualifications to conduct this project, and attach a copy of PI's VA or NIH biosketch. Be specific in regard to PI's research experience. *NOTE: If PI does not have any prior research experience, indicate what provisions are being made to provide oversight or mentoring.* *As a staff gastroenterologist at the Corporal Michael J. Crescenz VA Medical Center for the past 10 years, Dr. Yang has intimate knowledge about the veteran population, the clinical and administrative operations of the VA and the GI endoscopy services.*

Dr. Yang is a core investigator of the VA Center for Health Equity Research and Promotion (CHERP) and a staff gastroenterologist at the Corporal Michael J. Crescenz VA Medical Center, an Associate Professor of Medicine and Epidemiology in the Gastroenterology Division and a Senior Scholar in the Center for Clinical Epidemiology and Biostatistics (CCEB) at the University of Pennsylvania. He is board-certified in Internal Medicine and in Gastroenterology. He has had extensive formal training in epidemiology and clinical research methodology and holds a Master of Science degree in Clinical Epidemiology from the University of Pennsylvania. His research program has been supported by highly competitive venues including the NIH (K08, R01), AHRQ (R01), VA (CSR&D Merit Review Award), and GI foundations.

A major theme of his highly productive and independent research program in GI epidemiology focuses on gastrointestinal epithelial cancer epidemiology, specifically colorectal cancer (CRC) prevention and risk assessment. He recently completed an AHRQ R01 project that investigated the risk of CRC following normal colonoscopies among elderly patients and those with diabetes. This project provided crucial data for determining the optimal screening colonoscopy frequency at a population level. Funded by a VA Merit review award (R01 equivalent), he is currently leading a prospective study investigating the role of insulin therapy on colorectal adenoma recurrence. The results of this study will guide the effort to optimize the CRC screening/surveillance policy in people with diabetes. This VA Merit project and his other NIH R01 project involved enrolling and following a large cohort patient both at the Corporal Michael J. Crescenz VA and the University of Pennsylvania. He has also conducted a randomized controlled trial testing the effectiveness of a physician-targeted intervention on optimizing medication prescribing in the University of Pennsylvania Health System.

Does any research staff member have an actual and/or perceived conflict of interest with this study? NO If yes, explain.

Is this study a clinical trial? YES If yes, specify the type. Phase IV

State the estimated length of time to complete enrollment of subjects. *3 years*

State the expected duration of participation by individual subjects (including any follow-up, e.g., need to re-contact subject for follow-up questions prior to closure of the study). *6 months*

Specify the projected date of completion of the study. *7/1/2021*

Section 2: Participating Site Specifications

2.1. **Where will the research project be conducted? (Check all that apply)**

- ☐ **VA Inpatient Setting**
- ☑ **VA Outpatient Clinic/Office**
- ☐ **VA Laboratories**
- ☐ **Participant Homes**
- ☐ **University of Pennsylvania**
- ☐ **Community Based Outpatient Clinics (CBOCs)**
- ☐ **Other *(Specify)*:**

2.2. **If research is conducted at a non-VA site, please specify where and how much of the project will be conducted at that location**.

Section 3: Introduction

3.1. **Provide scientific background and rationale for study. Including summary of gaps in current knowledge, relevant data, and how the study will add to existing knowledge.**

B.1 Colonoscopy and colorectal cancer risk

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the US.7 Colonoscopy is now the main tool used for CRC screening and prevention. It has been shown to effectively reduce CRC incidence and mortality.8-17 However, the effectiveness of colonoscopy in preventing CRC depends on adherence to guideline recommended colonoscopy schedules and identification and

removal of precancerous polyps at the time of the colonoscopy. Unfortunately, compliance with colonoscopy screening recommendations has been suboptimal, including in the VA population.18 Furthermore, up to 7% of CRCs are diagnosed within 3-5 years of a prior colonoscopy, with many of these being a consequence of missed lesions.19

B.2 Role of colonoscopy bowel preparation

Bowel preparation before colonoscopy is one of the most important determinants of the effectiveness of colonoscopy and is recognized as the major impediment contributing to a patient's hesitancy to accept colonoscopy as a screening examination for CRC.5 Pre-colonoscopy bowel cleansing generally involves having patients ingest a large volume of often unpalatable liquid bowel preparation agent prior to the procedure, ideally leading to effective purging of the colon to allow adequate examination. This process may cause significant disruption to the patients' daily routine (e.g., sleep disturbance, need for fasting or a restricted diet), while the large volume and unpleasant taste of the bowel preparation regimen may cause physical discomfort (e.g., nausea, vomiting, abdominal bloating/discomfort, fecal incontinence). Indeed, the bowel preparation process rather than the colonoscopy itself is the most formidable part of the colonoscopy experience from the patient's standpoint.

B.3 Adverse consequences of a poorly tolerated bowel preparation

Existing data indicate that concern over the volume and taste of the bowel preparation is the most common factor that deters patients from undergoing screening colonoscopy.5 Our pilot data also indicate that poor tolerability of bowel preparation is a leading cause of no-shows or last-minute cancellations of scheduled colonoscopies (see D.2). A substantial proportion of patients do not initiate or complete the bowel preparation secondary to the large volume and/or poor palatability of the preparation.20 The resulting cancellations, no-shows, or inadequate bowel preparation has a number of undesirable downstream consequences affecting the patients, the providers and the health system. For the patients, cancellations and no-shows represent missed opportunity to reduce CRC risk; inadequate bowel preparation is associated with reduced adenoma detection21 and increased risk of procedure-related complications,22 thus compromising the effectiveness and safety of the procedure. Poor bowel preparation often leads to aborted colonoscopy examination, necessitating a repeat colonoscopy within a few weeks to months and compounding the negative experience for the patient. From the endoscopist's standpoint, inadequate bowel preparation adds technical difficulty to the procedure and increases procedure time.23 Even in cases where the endoscopist is able to reach the cecum, suboptimal bowel preparation is a common reason for the provider to recommend an interval for the follow-up colonoscopy much shorter than suggested or recommended by current practice guidelines (e.g. 5 years for patients without polyps rather than 10 years, 3 years rather than 5-10 years for patients with low risk polyps, or 1 year rather than 3 years for patients with high risk polyps).25 For the VA health system, the need to reschedule for cancellations/no-shows and increased colonoscopy frequency for inadequate preparation quality put additional strain on service capacity (e.g., longer backlogs) and entail substantially increased health care cost.24

B.4 Bowel preparation quality in VA below benchmark

Recognizing the critical importance of bowel preparation quality, the US Multi-Society Task Force (USMSTF) on Colorectal Cancer set the minimal rate of adequate bowel preparation before colonoscopy at 85%, and recommended that improvement initiatives be undertaken for anything below that target.3 Considerable efforts have been implemented in the VA system to enhance patient compliance with bowel preparation including implementation of novel patient educational tools and

routine pre-procedure telephone call by a GI nurse. However, the rate of adequate bowel preparation within the VA is still below the acceptable benchmark based on limited published data25 and our own pilot data (see D.2). Furthermore, the colonoscopy screening uptake rate is low among VA patients, particularly among African Americans;18 the anticipated negative experience of bowel preparation associated with colonoscopy could be a contributing factor for such disparities. These observations indicate an urgent need to improve colonoscopy bowel preparation quality within the VA system.

B.5 Guideline recommendations on bowel preparation

Patient tolerability of the bowel preparation regimen is associated with the characteristics of the regimen (e.g., the chemical compound used, volume, palatability, and the timing of ingestion relative to the time of the procedure [e.g., single- versus split-dose]). Because tolerability is associated with compliance, the same variations among the existing bowel regimens also influence the quality of the bowel preparation. Based on high-quality evidence from a current systematic review, the USMSTF on Colorectal Cancer strongly recommends the split-dose preparations (i.e., roughly half of the bowel cleansing dose given on the day of colonoscopy). However, it does not make a recommendation from among the several available split-dose options.3 These split-dose regimens have substantial differences in palatability and volume (i.e., large [⩾3 liter] and low [<3 Liter]). Among these the most commonly used preparations currently in the US are 4L polyethylene glycol with balanced electrolyte solution (PEG-ELS) and 2L MiraLAX-Gatorade (M-G).

B.6 PEG

PEG is a non-absorbable solution that passes through the bowel without net absorption or secretion. Significant fluid and electrolyte balance shifts are therefore avoided. High-volume lavage solutions containing PEG-ELS such as GoLytely have been the mainstay of bowel preparation in many institutions including the VA system. However, these agents are not well-tolerated by many patients because of the large volume (4L) of solution to be consumed over a short time and its salty taste. Patient acceptance is poor.20, 26, 27 Reducing the volume and improving the taste of the preparation may be an important driving force to improved compliance.

B.7 Guideline recommendations regarding MiraLAX-Gatorade preparation

In this context, one agent that has been widely used in clinical practice in the US is MiraLAX (PEG 3350 powder) in combination with 64 oz of Gatorade sports drink. The USMSTF stated that "These OTC medications or combinations (M-G preparation included) can be recommended by physicians as part of a bowel-cleansing regimen in preparing patients for… endoscopy", but strongly recommended using the split-dose schedule to enhance tolerability and efficacy.3 A survey of a random sample of members of the American College of Gastroenterology in 2013 showed 37.4% of the gastroenterologists recommended the M-G preparation.4 Although hyponatremia is a potential risk theoretically when using a hypotonic lavage solution such as PEG powder. There have been no reports of hyponatremia with split-dose M-G regimens. In fact, based on its own review of the literature, the USMSTF concluded that "widespread use of PEG-3350 for bowel preparation seems to have been remarkably safe".3

B.7.1 Efficacy and safety data on MiraLAX-Gatorade preparation

Five small randomized controlled trials (RCTs) have compared PEG-ELS to M-G bowel preparations.28-32 However, only 3 of these compared split-dose regimens, which is the current standard.28, 29, 31 Enestvedt et al. compared split-dose 4L PEG-ELS to 2L M-G in an RCT that was terminated early. They observed that PEG-ELS was associated with a higher rate of adequate bowel

preparation (i.e., Boston Bowel Preparation score [BBPS] ⩾ 7). A higher proportion of MiraLAX users were willing to take their preparation again (P = 0.006). Hjelkrem et al. reported a prospective, randomized, single-blinded controlled trial comparing the efficacy and tolerability of a 2-L M-G preparation (with and without bisacodyl or pubiprostone) with a standard 4-L PEG-ELS preparation using split-dose administration to individuals undergoing screening colonoscopy.29 The PEG-ELS was associated with a better Ottawa Bowel Preparation Score (OBPS) than each of the M-G preparations (5.1 vs 6.3-6.9, p<0.001). However, because the OBPS downgrades the quality for retained fluids, which can be easily removed, the current USMSTF on CRC recommends against the use of this scale for assessing bowel preparation quality. Despite the difference in mean Ottawa scores, the authors did indicate that "All 4 of the bowel preparation regimens studied displayed adequate bowel cleansing". Furthermore, there was no difference in procedural time, polyp detection rate or adverse events among the 4 comparison groups. However, those in the M-G arm rated the overall experience significantly better compared to the GoLytely group (P< .001). Finally, Samarasena et al. conducted an RCT at a single VA center, comparing single-dose and split-dose 4L PEG-ELS against single-dose and split-dose 2L M-G. 31 They found that both split-dose regimens had comparably high BBPS scores (8.33 for PEG-ELS vs. 8.01for M-G, p >0.05). Bother split-dose regimens were more efficacious than the single-dose preparations. In addition, 96.8 % of the M-G group were willing to repeat the same preparation vs. 75 % in the PEG-ELS group (P < 0.01). There were no clinically significant electrolyte changes from baseline in any subject in any group after bowel preparations. A recent meta-analysis of these 3 trials showed that pooled rates for satisfactory bowel preparations were 83% for the M–G group and 89% for the PEG group, and there were no statistically significant differences between the two split-dose preparations for polyp detection.6 Overall, the published RCTs reported inconsistent results regarding the efficacy of the M-G regimen in bowel preparation quality compared to the 4L PEG-ELS preparation. However, it is worth noting that the only trial conducted among the VA population showed split-dose the M-G preparation to be at least as good as the split-dose 4L PEG-ELS preparation in bowel cleanliness.31 With regard to patient-related outcomes, M-G regimen appears strongly and consistently favored by the patients in all published studies. No safety signals with respect to electrolyte abnormalities were detected from the trials that collected data on this endpoint.30-32

B.8 Existing explanatory trial data on MiraLAX-Gatorade preparation cannot inform clinical decision

The data from the 3 existing explanatory trials cannot be used to support VA system-wide policy decisions. These 3 trials all tested how well 2L M-G and 4L PEG "can" work in narrow populations and artificial conditions. With regard to the study population, collectively the 3 explanatory trials included only 288 patients receiving split-dose M-G. In addition, these trials had extensive exclusion criteria. Most of the factors used for exclusion are associated with poor bowel preparation (e.g., non-screening indications, diabetes mellitus, constipation and narcotics use), limiting the generalizability of the findings from these trials. These data demonstrate that the results of these explanatory trials do not reflect real-world clinical practice and thus cannot be used to inform VA wide policy decisions.

Most importantly, the published explanatory trials narrowly focused solely on preparation quality among patients who actually consumed the bowel preparation and showed up for a colonoscopy. However, poor tolerability of bowel preparation has been reported by patients (both those who have [57%] and have not [66%] undergone screening) as the most important factor that deters them from undergoing screening colonoscopy.7 The majority of patients (59% of those having and 69% of those not having undergone screening) also indicated that a smaller volume bowel preparation was the most preferred

solution to improve their chance of undergoing screening colonoscopy.5 Indeed, our pilot data (See Section D.2) indicated that with the current VA standard split-dose 4L PEG, 44% of the scheduled colonoscopies were not completed due to cancellations, no-shows and inadequate preparation quality. Furthermore, poor tolerability and non-compliance of the current standard preparation was a leading determinant of incompletion of scheduled colonoscopies which adds substantial financial and logistical strain on endoscopy services in the VA. Therefore, in addition to preparation quality, a comparison of the existing bowel preparation options intended to inform policy decisions must also evaluate the effect of bowel preparation regimen on the rate of non-compliance and no-shows among all scheduled colonoscopies. Based on these considerations, there is no adequate comparative effectiveness data currently regarding the relative advantage of the split-dose low volume M-G versus the current VA-standard of split-dose high volume PEG-ELS that can be used to inform real-world clinical and policy decisions regarding the optimal bowel preparation regimen in the VA system.

B.9 Rationale for the proposed pragmatic clinical trial design

The overarching goal of the proposed project is to address this critical knowledge gap. Specifically, we propose to conduct a pragmatic point-of-care (POC) clinical trial to generate the necessary comparative effectiveness data to directly inform policy and clinical decision-making regarding the optimal choice of standard colonoscopy bowel preparation in real-world VA clinical practice. This trial will answer novel questions not addressed by any of the prior trials – whether completion rates of scheduled colonoscopy and population-level adenoma detection rate differ between these two strategies when used in routine clinical practice. We hypothesize that owing to its superior tolerability and solid efficacy in producing adequate bowel preparations, the split-dose 2L M-G regimen is a better option than the current standard split-dose 4L PEG-ELS regimen in the VA population. To maximize pragmatism of the trial, key design features of the study will include direct comparison against current VA standard bowel preparation and broad patient inclusion criteria such that the study population offers the maximum opportunity for generalization of study results to the general VA population. Most importantly, by focusing on the overall completion rate of scheduled colonoscopy and population-level ADR as the primary endpoints, the proposed study will be the first to determine the full spectrum of downstream impact of a lower-volume and better-tolerated bowel preparation on the efficiency and effectiveness of colonoscopy. Furthermore, all the study procedures including enrollment, randomization, and administration of the treatments and data collection will be seamlessly integrated into the point of care with virtually no interference to the flow of usual clinical care. Also, the implementation of these procedures will take advantage of the existing VA electronic medical records system to maximize efficiency and minimize cost. These innovative design features will reduce study costs, enhance external validity of the study and accelerate the translation of research findings to practice. They are consistent with the VA's commitment to learning through the integration of research and practice.

C. Significance

The poor tolerability of the current standard colonoscopy bowel preparation is contributing to the unacceptably low colonoscopy uptake and completion rate within the VA population. Split-dose M-G preparation is a lower-volume and more palatable alternative which has been widely used in non-VA clinical settings with better patient acceptance than the current VA standard and a good safety profile. The few small and narrowly focused explanatory RCTs comparing the two regimens cannot be used to support policy and clinical decisions. The proposed pragmatic clinical trial will fill this critical evidence gap by generating comparative effectiveness data in the real-world VA setting regarding the

effectiveness of the split-dose M-G regimen in maximizing the overall effectiveness of VA colonoscopy services. If the M-G bowel preparation regimen is found to be the superior option compared to the current standard, it would improve patient satisfaction, reduce CRC risk and promote more efficient use of VA endoscopy resources. This innovative study leverages the existing features of the VA electronic medical records system to seamlessly integrate the research procedure into the routine clinical care activity, minimizing cost and intrusiveness to routine care while maximizing the efficiency and pragmatism of the study. As such, the proposed project will contribute to the current mission to transition the VA into a learning health care system in which research and practice are intertwined to enable systematic learning from ongoing clinical care that will constantly improve clinical practice.

Section 4: Objectives Section

4.1. **Describe the study's purpose, specific aims, or objectives.**

Primary Aim: To compare split-dose 4L PEG to split-dose 2L MiraLAX/Gatorade bowel preparation regimen with respect to the rate of completion of scheduled colonoscopy and population-level adenoma detection rate (ADR) among veterans scheduled for colonoscopies.

Hypothesis: the 2L split-dose Miralax/Gatorade is better than 4L split-dose PEG with regard to completion of scheduled colonoscopy and adenoma detection.

Secondary Aim #1: To compare split-dose 4L PEG to split-dose 2L MiraLAX/Gatorade bowel preparation regimen with respect to cancellation/no-show rate, the bowel preparation quality and patient willingness to repeat the bowel preparation among veterans undergoing colonoscopies.

Hypothesis: the 2L split-dose Miralax/Gatorade is better than 4L split-dose PEG with regard to bowel cleanliness and patient preference.

Secondary Aim #2: To compare split-dose 4L PEG to split-dose 2L MiraLAX/Gatorade bowel preparation regimen with respect to the rate of completion of scheduled colonoscopy, population-level ADR, bowel cleanliness and willingness to repeat the bowel preparation in subgroups defined by sex, diabetes status, history of constipation and age (≥65 and <65), indication of colonoscopy, timing of colonoscopy (AM vs. PM).

Hypothesis: the 2L split-dose Miralax/Gatorade is better than 4L split-dose PEG with regard to completion of scheduled colonoscopy, ADR, bowel cleanliness and patient preference regardless of sex, age, diabetes status, timing of colonoscopy, indication of colonoscopy or constipation.

Exploratory Aim: To quantify and compare the average staff/physician time and cost spent on completing a round of colorectal examination per patient using split-dose 4L PEG versus split-dose 2L MiraLAX/Gatorade.
Hypothesis: the 2L split-dose Miralax/Gatorade is associated with lower average staff/physician time and cost spent on completing a round of colonoscopy examination per patient than split-dose 4 L PEG.

4.2. **State the hypotheses to be tested.**

See above

Section 5: Study Procedures

5.1. Study Design

5.1.1. Describe in detail the experimental design, i.e. from recruitment procedures to study closure.

E.1 Overview The proposed study will be a pragmatic, open-label, randomized trial comparing 4L split-dose PEG to 2L split-dose M-G bowel preparation regimen among veterans scheduled to undergo a colonoscopy at the CMCVAMC. The colonoscopy bowel preparation ordering workflow in the VA computerized patient record system (CPRS) will be slightly modified to allow the ordering provider to give permission for the patient to be enrolled into the trial. The study will be conducted with a waiver of documentation of informed consent. Enrolled patients will be randomized in the CPRS at the point of care to one of the two bowel preparations, and the order for the assigned preparation will be generated automatically for provider signature. Study patients will undergo the colonoscopy as usual. The providers performing the colonoscopy are requested to document in their routine pre-procedure note the patients' willingness to repeat the bowel preparation regimen they received as well as their assessment of the clarity and completeness of the bowel preparation instructions. There are no study-related diagnostic procedures and no study-specific follow-up events required. Outcomes and covariate data will be collected directly from the CPRS. The primary endpoints are completion rate of scheduled colonoscopy and population-level ADR, and the secondary endpoints are cancelation/no-show rate, bowel preparation quality and patient-oriented outcomes (e.g., willingness to repeat). Analysis will be based on intention-to-treat (ITT).

E.2. Study Site and Data Source

The proposed project will be performed at the CMCVAMC. CMCVAMC is the largest VA facility in the southeastern Pennsylvania, New Jersey and Delaware Tri-state area, providing comprehensive care for nearly 40,000 patients annually. The facility is staffed by more than 1,500 employees and supports more than 150 acute beds and a 240-bed Nursing Home Care Unit. The CMCVAMC houses a number of primary care and subspecialty clinics. About 16,000 patients are seen annually in primary care clinics. CPRS is a comprehensive electronic medical record system that has been implemented since 1998 at all VA medical centers nationwide and at VA outpatient clinics, nursing homes, and other sites of care. It is well integrated with other Veterans Health Information System and Technology Architecture (VistA) applications, such as pharmacy, radiology, laboratory and histologic data, inpatient and outpatient progress notes, discharge summary, consult notes, all endoscopic procedure notes, problem list, VistA imaging, billing, and patient administration. Information in the CPRS is retrievable through database query of the VISN 4 data warehouse on a large scale or by individual chart review when more detailed or comprehensive information in a specific patient is needed.

E.3 Study Population

Our goal in selecting study patients for this pragmatic trial is to enroll all patients who meet the basic entry criteria and reflect the full range of patients undergoing bowel preparation for colonoscopies found in regular VA clinical practice. The study population will consist of all veterans seeking healthcare at the CMCVAMC.

E.3.1. Inclusion criteria

The inclusion criteria for potentially eligible subjects are:

1. > 18 years of age, and

2. being scheduled for outpatient elective screening, surveillance or diagnostic colonoscopies, and

3. the provider ordering the colonoscopy giving permission to enroll the patient.

E.3.2. Exclusion criteria

Patients who are <18 years, undergoing inpatient colonoscopy, those with contra-indications to receiving the standard 4L PEG-ELS colonoscopy bowel preparation (e.g., allergy to PEG) will be excluded. We are excluding inpatient colonoscopies because they account for a very small fraction of the total colonoscopies performed. Also, inpatient colonoscopies are often performed for urgent reasons such that rapid bowel preparation procedures are followed. In addition, because the objective of inpatient colonoscopy is often not to look for small polyps, the threshold for "adequate" bowel preparation quality might be different from that for outpatient procedures. In addition, for patients undergoing more than 1 colonoscopy during the study period, only their first colonoscopy will be included in the primary analysis. Patients who are undergoing a repeat colonoscopy for to a recent inadequate colonoscopy examination with poor bowel preparation will be excluded.

E.4 Recruitment Strategies

The CAC at CMCVAMC will change the existing CMCVAMC colonoscopy bowel preparation order workflow in CPRS slightly to incorporate an option for the ordering provider to allow the patient to be enrolled into the proposed trial. Specifically, the only difference is that after the provider submits the colonoscopy consult request, a pop-up CPRS window (Step B) will briefly introduce the proposed trial to the providers (who should already be aware of the study because the study team will present the study to all PCPs before the enrollment initiation) and ask if they believe the patient would be appropriate for consideration of enrollment. If they believe it is, they will ask the patient whether he/she would like to opt out of being approached for consideration of enrollment in the trial (see script template). Those who do not opt out will be given an information sheet (see letter template). If either the provider or the patient does not agree to having the patient approached for the study, the provider will document this by clicking a

radio button in the window indicating "No. The patient may not be approached. Proceed with usual care" and s/he will continue with the current workflow proceeding with ordering the default 4L Golytely (PEG). A health factor is automatically created to allow the study team to track the number of refusals generated at this stage in the process. If both the provider and the patient agree that the patient may be contacted for consideration of enrollment in the trial, the provider will select the radio button indicating "Yes. Patient agreed to be contacted. The research team may approach this patient for consideration of enrolment". Selecting that the patient may be approached will automatically prepopulate and send a research consult to the study staff. The provider is then directed back to the order entry menu to place an order for 4L Golytely (PEG) until the patient can be consented and randomly assigned. This "holding order" ensures that care is not disrupted in the event that the study nurse is unavailable. On receiving the research consult, the study staff calls the patient and explains the study to the patient and obtains verbal informed consent. If the patient consents to the study, the study staff will discontinue the "holding order" and activate the randomization procedure built in the prepopulated reminder dialog progress note, which will return the randomization assignment instantaneously. This reminder dialog progress note will also serve the purpose of documenting the participant's consent, as well as date, and the name of the person conducting consent in the EMR. If the patient declines to participate in the study, a pre-populated progress note is automatically entered into the EMR, which is forwarded to the colonoscopy ordering clinician, along with prepopulated order for Golytely (the current standard prep), for review and signature. Progress notes for both patients accepting and declining participation are automatically created for and forwarded to the provider ordering colonoscopy. Medication orders are prepopulated according to treatment assignment and must be signed by clinicians. A CPRS/VISTA alert is therefore used to prompt the provider to sign and complete the randomized order. The study staff also verifies that the order has been 'released' by the provider and contacts the provider directly if necessary. Finally, a health factor is created that documents which of the two arms the patient is randomly assigned to. This allows the study team to identify subjects and their interventions quickly in the CPRS/VISTA database.

HIPAA authorization will be obtained in subjects who present to CMCVAMC GI endoscopy suite to have a colonoscopy to be performed by Dr. Yang. Dr. Yang will routinely check CPRS notes before every outpatient colonoscopy procedure to determine whether his patient is enrolled in the current study. We will request a HIPAA waiver for all other patients who will have no face-to-face interaction with the study team.

The proposed project meets the requirements for a waiver of documentation of informed consent. The oral consent will be read to the subject. The research presents no more than minimal risk of harm to participants and involves no

procedure for which written consent is normally required outside of research context. Existing literature suggests that extensive disclosure in pragmatic trials that compare low-risk standard-of-care interventions may confuse potential subjects into thinking that the research differs substantially from standard care and that they face a critical decision.33 Furthermore, such unnecessary disclosure can be associated with low satisfaction and increased anxiety and may introduce substantial selection bias and clinical disruption.33

E.4.1 Measures to ensure high referral rate for providers

We expect that VA PCPs will be responsible for the vast majority of the referrals and will thus implement multiple measures to ensure a high referral rate. First, the Chief of Primary Care will serve as a consultant for the proposed study and meet with the PI at least monthly. He will champion the study among the PCPs, actively solicit their concerns and feedback regarding the study implementation and communicate these to the PI, and help the PI develop strategies to address any concerns. Second, prior to the start of the study, the PI will give in-person presentations to all PCPs and GI providers during monthly faculty meetings regarding the purpose and the details about the study, particularly those aspects relevant to the providers work flow (e.g., the one choice they need to make, etc.). He will also answer any questions about the M-G prep option with which some VA providers might not be familiar. The PI will also contact individual providers who cannot attend the faculty meetings to set up one-on-one meetings. The goal will be to proactively convey the importance of the study, explain the specific actions required of the PCPs and resolve any questions and concerns from the PCPs. The PI will also regularly attend the faculty meetings after the implementation of the trial to address any new concerns. Third, any planned changes in the CPRS study-flow and order menu change will first be piloted among a sample of PCPs and Dr. Tzanis to ensure readability and usability and modified based on their feedback. Further modifications will also be performed based on feedback solicited after the initiation of the trial. Fourth, the design and the implementation of the study procedures will benefit from the expertise of Charlene Weir, PhD from the Salt Lake VA IDEAS COIN who will serve as a consultant on this project. Dr. Weir is a renowned expert on real-world implementation and formative evaluation of EMR-based interventions in VA practices. Of particular relevance to the proposed trial, she led the only study that assessed VA providers' beliefs and attitudes toward pragmatic trials embedded at the point of care. 34 She will ensure that the study-related procedures are responsive to these provider factors.

E.7 Study procedure

E.7.1 Randomization

The randomization procedure will be carried out based on an approach recently developed in the VA CPRS system.2 This method takes advantage of a random number generator ($RANDOM) feature of CPRS/VISTA to generate a random

integer between 0 and 999. The returned integer is used by a CPRS feature called "computed finding" to randomly generate a bowel preparation order for each patient. Patients will be randomly assigned to the 4L PEG-ELS or 2L M-G regimen at a 1:1 ratio. A template progress note activated by the study coordinator will document randomization.32 This template progress note will generate 'health factors' in CPRS that will serve to identify patients as subjects in the trial for tracking purposes in VISTA.

E.7.2. Bowel preparation regimens

The bowel preparation regimens being compared are split-dose 4L PEG-ELS, which is the current standard bowel preparation regimen within the VA system, and split-dose 2L MiraLAX-Gatorade preparation. We will use a treatment schedule that mirrors real-world practice. To that end, the patients will receive either regimen (i.e., GoLytely or GlycoLAX [generic of MiraLAX]) from the VA central pharmacy via postal mail. The currently-used instructions for the 4L PEG-ELS will be used (see Appendix 1). The instructions for the 2L M-G preparation will be adapted from the one used at the University of Pennsylvania Health System (where it is the standard colonoscopy bowel preparation) or other premier academic medical centers. The patients in the M-G preparation arm will be instructed to mix the entire 238g bottle of the generic form GlycoLAX in 32 ounces of Gatorade or any other clear non-carbonated liquid. Patient with diabetes will be instructed to use sugar-free Crystal Lite solution instead of Gatorade. Those who are randomized to the M-G preparation arm will need to purchase 64 oz. of Gatorade (~$2) or Crystal Lite on their own. Based on our consultation with VA PBM leadership as well as local and central VA pharmacy, VA is unlikely to provide Gatorade as a VA pharmacy item even if the M-G bowel preparation becomes the standard bowel preparation. Therefore, we designed the M-G arm of our trial to reflect how the intervention would eventually be implemented in real-life practice. This is consistent with the pragmatic nature of the trial.

The 4L PEG and 2L M-G regimens are the two dominant forms of bowel preparation regimen used in the US. Although there are other formulations, their use is limited in clinical practice due to potential safety issues (e.g., sodium phosphate, picosulfate), limited supporting evidence (e.g., picosulfate, oral sodium sulfate), or high cost (e.g., 2L PEG preparation such as MoviePrep). Therefore, we chose not to include these regimens.

E.7.3 Follow-up

Since information regarding main outcomes will be collected via VA administrative records (e.g., cancelations/no-shows) and VA electronic medical records, there will be no need for any patient follow-up.

E.7.4 Blinding

Blinding of the patients is impossible in this trial. Since endoscopists routinely ask the patient about their experience with bowel cleansing in usual practice, blinding of the endoscopists would also be difficult and more importantly would not reflect usual practice. Therefore, to maximize pragmatism in the trial design, no blinding will be implemented.

E.7.5 Outcomes

E.7.5.1. Primary Outcomes

Because the objective of the proposed pragmatic trial is to generate data that can directly inform system-wide policy decision regarding the optimal bowel preparation choice, it is critical that the primary outcomes capture the full-spectrum of the down-stream effects of bowel preparation. Published evidence indicates that the tolerability of the bowel preparation is regarded by patients (both those who have and have not undergone CRC screening) as the most important factor that deters them from undergoing colonoscopy.5 Therefore, poorly tolerated bowel preparation can not only compromise patient compliance with bowel preparation instructions, but also their likelihood of undergoing scheduled colonoscopies. For these reasons, our primary outcomes will be the completion rate of scheduled colonoscopy and population-level ADR. The completion rate of scheduled colonoscopy will be defined as the proportion of patients who show up for their scheduled colonoscopy and have endoscopist-rated "adequate" bowel preparation quality, among those scheduled for a colonoscopy. The colonoscopy reporting software from Endosoft® allows documentation of the following ratings for quality of bowel preparation: poor, fair, good and excellent. We will consider a rating of "good" or "excellent" as adequate preparation quality. We recognize the 4-category rating scale is an imperfect instrument, but elect to use it to define our outcome measure for several reasons. The 4-category rating scale is the most commonly used rating scale in clinical practice both within and outside of the VA. In this scheme, excellent and good are widely viewed as adequate.3 VA endoscopists use this scale to make clinical decisions regarding need for repeat colonoscopy or follow-up intervals. We recognize that there are three other commonly used bowel preparation quality rating scales (OBPS, BBPS and Aronchick). However, based on its review of these scales, the USMSTF recommends against the use of Aronchick or Ottawa scales because they downgrade the score for retained fluids.3 It further concluded that none of the existing scales satisfactorily captures the operational definition of adequate preparation (i.e., the one in which the colonoscopist can and does recommend a follow-up screening or surveillance interval for the next colonoscopy that is appropriate for the examination findings), although the USMSTF regarded BBPS as being closer to this concept compared to the other scales. BBPS is an available option in the Endosoft® colonoscopy procedure note template. However, to implement this scale would necessitate education and training of the endoscopists and impose substantial additional documentation burden on the

providers which is outside of usual clinical care, and would compromise the "pragmatic" nature of the study design.

The population-level ADR in this trial will be calculated as the proportion of patients who are found to have at least 1 adenoma, among those scheduled for a colonoscopy. This definition of ADR differs from the conventional concept of ADR which is calculated among those having undergone colonoscopies. While poor bowel preparation quality may decrease the probability of polyp detection among patients having undergone colonoscopies, patients who cancel or fail to show up for their scheduled colonoscopies because they do not want to go through with the poorly tolerated bowel preparation will have zero probability of having his/her polyp(s) detected. Therefore, it is imperative that we examine the ADR among all patients scheduled for a colonoscopy so that we can capture the full effect of bowel preparation on the overall effectiveness of colonoscopy service.

E.7.5.2. Secondary Outcomes

Our secondary outcomes will be the rate of cancellations/no-shows, the proportion of patients with endoscopist-rated "adequate" (i.e., Excellent or Good) bowel preparation quality among patients who show up for their colonoscopy, which reflects the immediate effect of bowel preparation and patient-reported outcomes: patient's self-reported willingness to repeat the bowel preparation and patients reported clarity and completeness of the bowel preparation instructions. The patient's self-reported willingness to repeat the bowel preparation is an established patient-reported outcome measures to assess patient preference in this setting.

The patient-reported endpoints will be defined dichotomously based on the patient's response (i.e., Yes/No) to the following questions immediately before the colonoscopy: 1). If you had a choice of products, would you be willing to repeat the same bowel preparation in the future? 2). Were the bowel preparation instructions written in a way that is clear to you? and 3). Did the bowel preparation instructions fail to include any relevant information? For quality improvement purposes, those patients answering "No" to the latter two questions will be asked to elaborate on which aspect(s) of the instructions is(are) unclear or missing. In order to obtain information for these outcomes, we will add the above questions to the mandatory pre-procedure note by the endoscopist immediately before each colonoscopy (see example in Appendix) and request the endoscopists to ask the patients these questions and document the responses in the routine mandatory pre-procedure note. Since the endoscopists are already required to document several related data elements in the pre-procedure note including last per oral take of clears and food of any form, adding these simple yes/no questions should not lead to excessive burden to the endoscopists.

As an exploratory endpoint, we will also determine the proportion of patients with inadequate bowel preparation who are recommended to have earlier-than-usual

follow-up colonoscopy. This is a clinical outcome with resource utilization implications. It is consistent with the USMSTF operational definition of adequate preparation quality. Ideally, the endoscopist who performed the procedure should provide this information in each case. However, requiring the endoscopists to uniformly and consistently provide written justification of all their recommendations and document the impact of bowel preparation on each of their follow-up recommendations is outside the standard practice and may represent undue burden. More importantly, such burden might alter their behavior in grading or documenting the bowel preparation quality (e.g., they may upgrade the preparation quality to avoid such burden). For these reasons, the information for this outcome will be assessed by the PI and the co-investigator (Dr. Khan) by reviewing CPRS. Any disagreement between the PI and co-investigator (Dr. Khan) will be resolved by a discussion between the two to reach a consensus. It is expected that endoscopists deviate from guideline recommended follow-up colonoscopy intervals for a variety of reasons other than the quality of bowel preparation. Such reasons may not be apparent based on a chart review even by an expert gastroenterologist. Given the potential for misclassification for this outcome, we will include it as an exploratory outcome.

Although the primary focus of the trial is to evaluate the impact of bowel preparation on colonoscopy completion, the trial presents an opportunity to collect information on all health factors that could affect the outcome. Such data would help us interpret the findings of the main trial and inform the design of future trials by identifying potentially modifiable factors. Therefore, we will collect information on the reasons for non-shows/cancellations among a sample (e.g., all non-shows/cancellations in the first month of each quarter during the study) of eligible patients.

Although hyponatremia has not been associated with split-dose M-G regimen, as an exploratory safety endpoint, we will track incident cases of hyponatremia or renal failure over the 6 month period following the ingestion of the bowel preparation within among our study patients. In order to efficiently collect such data, the CHERP programmer will perform electronic query within VISN 4 data warehouse using ICD-9 codes for these two diagnoses within the 6-month time frame.

E.8 Data Collection

We will collect all study data regarding baseline characteristics or covariates (i.e., sex, age, race, DM status, history of renal failure, history of heart failure, history of hyponatremia, history of constipation or current use of laxatives, history of colon resection, history of inflammatory allergy history, history of mental health issues, use of narcotics, indication for colonoscopy, baseline creatinine level, total procedure time, timing of procedure [AM/PM], colonoscopy examination aborted [yes/no], cecal intubation [yes/no]) and all outcomes (i.e., colonoscopy completion

rate, bowel preparation quality rating by endoscopist, patient willingness to repeat, number of polyps removed and the corresponding pathology report, endoscopist recommended timing of next colonoscopy, incident renal failure and hyponatremia within 6 months after the bowel preparation).

Information on scheduled colonoscopies as well as procedure cancellations/no-shows is routinely collected by the GI section nurse manager on a daily basis for administrative purpose and will be used for this study. To minimize interference with routine care, we will first search for reasons for cancellations/no-shows in CPRS because this information is usually documented for cancellations based on our pilot data. If the underlying reason cannot be identified in CPRS, we will conduct a telephone survey of the patients to collect such data. In order to encourage honest answers, the survey will be conducted as a part of an on-going QI initiative in the GI section of CMCVAMC, analogous to the survey described in D.2.

Information on all other variables is expected to be available for all patients in CPRS. As described above, the information on baseline comorbidity status and incident cases of hyponatremia and renal failure will be collected through electronic query of the VISN 4 data warehouse using ICD-9 codes on structured fields including all visit-associated diagnoses and problem list. Medication use at baseline will be collected by VISN 4 warehouse query for the corresponding drug class. Information from colonoscopy report and associated pathology report will be collected by manual chart review of the CPRS. Finally, endoscopist recommendations regarding timing of next colonoscopy and the impact of bowel preparation on such recommendation will be collected by manual chart review by the PI and co-investigator.

E.9.4 Exploratory Cost Analysis

A dedicated full economic analysis would be necessary to comprehensively quantify the short-term and long-term financial impact of adopting the superior regimen in the VA. Given the complexity of such a dedicated economic analysis (e.g., the need for extensive modeling of long-term health utility, etc.), it would be beyond the scope of the current project. We intend to apply for addition funding to perform such an analysis as a future step. Nevertheless, along side of the proposed trial, we will conduct an exploratory economic evaluation prospectively. Our exploratory economic analysis will focus on quantifying staff/physician time and cost for the completion of the scheduled colonoscopies associated with each of the two bowel preparation options during the 3 years of follow-up and compare these costs between the two options.

Counts of the four possible outcomes for scheduled colonoscopies -- cancellations, no-shows, colonoscopies with inadequate bowel prep, and colonoscopies with adequate bowel prep -- will be derived from the clinical data collected during the trial. For the patients included in the economic analysis, we

will collect additional information from CPRS to take into account repeated cancellations, no-shows, and colonoscopies with inadequate bowel prep for the same round of colorectal examination over the period of follow-up. Per-patient counts of outcomes will be multiplied by estimates of the average cost per outcome and the sum of these costs will represent the per-patient cost devoted to completion of a scheduled colonoscopy. The cost of these outcomes will be derived from either self-timing/self-report35 (cancellations and no shows) or direct observation time-and-motion estimation35 (colonoscopies with inadequate bowel prep, and colonoscopies with adequate bowel prep) of the average staff/physician time required for each of these outcomes and staff/physician wages (including benefits).

For the cancellation and no-show outcomes, we will collect data on the time GI staff spend contacting the patients and rescheduling colonoscopies (staff self-report)as well as the time a GI nurse spends providing bowel prep instructions for the rescheduled colonoscopy (Staff self-report). Because our pilot data suggest that cancellations and no-shows occur on the day of the procedure and because colonoscopy requires specific bowel preparation with dietary restrictions as well as arrangement for an escort ahead of the procedure, the vacated colonoscopy slots can rarely be filled by another patient, We thus conservatively assume that the idle resources from a cancellation or no-show will be equivalent to that for a colonoscopy with adequate bowel prep (see below). In a separate sensitivity analysis we will exclude the costs of the staff/physician time due to a vacated and unfilled colonoscopy slot.

For the 2 colonoscopy outcomes, staff/physician time will include bowel prep instructions (staff self-report), for colonoscopies with inadequate bowel prep it will include time spent rescheduling repeat colonoscopy (staff self-report), plus staff/physician time spent performing the colonoscopy (direct observation, time-and-motion study). Separate time estimates will be developed for colonoscopies with and without adequate bowel prep.

In performing the time and motion study, each of the services provided to perform a colonoscopy will be enumerated. The average time needed to perform these services will be estimated by use of direct observation. Separate estimates will be made for colonoscopies with and without adequate bowel prep. We will perform direct observation in a random sample of at least 100 scheduled colonoscopies in each of three years of the trial. Assuming that 20-25% of colonoscopies performed are associated with inadequate bowel prep, we anticipate observing 20 such colonoscopies per year for a total of 60 colonoscopies. If in any year we fail to observe 20 colonoscopies with inadequate bowel prep, we will continue to directly observe a random sample of colonoscopies until 20 colonoscopies with inadequate bowl prep have been observed.

Data on the average annual salary plus benefits (by grade and step) for personnel like the ones who are observed will be obtained from the GI section nurse manager and the section Director. Issues of confidentiality will be minimized by working with average wages and benefits by grade and step rather than by use of wages and benefits for individual VA staff/physicians.

In addition to estimating the average cost per patient in each arm of the trial, we will also estimate the average cost saving per annum by multiplying the average cost saving per scheduled colonoscopy completed by the total number of colonoscopies scheduled per year at CMCVAMC. We will also incorporate the cost difference between the preparations in calculating the net savings. One potential issue is that the cost of MiraLAX may decrease if it becomes a part of the standard preparation at the VA. We will perform the analysis using its current price. If the cost of MiraLAX tips the balance in the overall cost comparison, then we will calculate the threshold price that would make the M-G preparation cost-saving.

We will be tracking costs over multiple years of the study. To avoid having to inflation-adjust the annual cost data, we will use salary, benefits, and preparation costs that are appropriate for the last year of follow-up. Some patients may have repeated scheduled exams over a period of time that exceeds 1 year. In these cases we will discount follow-up costs at 3% per year.

E.10 Logistics

E.10.1. Dissemination of research findings

Dissemination activities will be coordinated through the VA CHERP program. The CHERP Dissemination and Communication Core supports CHERP investigators in disseminating research results, developing policy recommendations, and delivering information to target audiences. CHERP will regularly update VA HSRD about opportunities to disseminate appropriate updates about the progress and findings of the study on their Web site and through their other communications vehicles, including cyber seminars for VA clinicians. In Year 4, CHERP will produce a Research Bulletin summarizing the project and its findings. It will be distributed electronically to Office of Quality and Performance leaders, VISN Network and Primary Care Service Line directors at all VA medical centers. Furthermore, as the chairperson for the Medical Advisory Panel for Pharmacy Benefits Management for VA and the Co-Director of the VA Center for Medication Safety, the consultant for the project, Dr. Chester B. Good, will help facilitate the implementation and dissemination of the study findings within the VA system.

This research has potential for application outside the VA. The progress and findings will be presented at national meetings and published in peer-reviewed medical journals. In Year 4, Dr. Yang and designated members of the investigative team will apply to HSRD for travel funds to present the project's

findings at the national conferences of scientific societies, including the annual HSRD conference.

E.11.2.Project Management Plan

We have assembled an outstanding multi-disciplinary team.

Principal Investigator: Dr. Yang is a Core Investigator with the Center for Health Equity Research and Promotion (CHERP), a VA HSR&D Center of Innovation (COIN) with offices in Philadelphia and Pittsburgh. He has extensive experience conducting VA and non-VA clinical research studies. He will be responsible for the completion of all aspects of the study aims. He will also be responsible for the fiscal, administrative and regulatory aspects of the study, including all regulatory affairs, data collection and management, adherence to all policies and procedures, coordinating meetings and email/telephone communications among the contracted Divisions, consultants and the primary team at the CMCVAMC, and maintenance of study protocol to ensure that the specific aims of the study are being met. Dr. Yang will develop Manual of Procedures.

Co-investigators and supporting staff at CMCVAMC: Dr. Khan is the Director of the GI section at the CMCVAMC. He is a clinical gastroenterologist with extensive experience conducting clinical research including clinical trial within the VA system. He will provide support to all aspects of the study. Dr. Hubbard, a biostatistician in the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania, will provide statistical support. Dr. Glick is an expert in performing economic analysis embedded in clinical trials and will oversee all aspects of the prospective economic evaluation.

Consultant: As the chairperson for the Medical Advisory Panel for Pharmacy Benefits Management for VA, and as the Co-Director of the VA Center for Medication Safety, Dr. Chester B. Good will share his experience in national formulary issues, drug safety issues and optimizing prescribing practice within the VA. He will help with design of the intervention and facilitate the implementation and dissemination of the study findings within the VA. Dr. James Lewis, Professor of Medicine and Epidemiology at the University of Pennsylvania, is a board certified gastroenterologist and prolific clinical investigators. He has been the PI for 4 NIH funded clinical trials and is on the steering committee for a 5th NIH funded trial. These studies have used a variety of designs to facilitate recruitment, data collection, and retention while not altering practice patterns in real world settings. We will adapt these methods for this trial given the importance of studying the different regimens as practiced in usual care. Dr. Charlene Weir will provide her expertise to help ensure the study procedures are acceptable to VA providers.

The entire project will require 4 years to complete.

5.1.2. **What research methods will be used in the project*? Check all that apply.***

☐ **Surveys/Questionnaires** ☐ **Interviews** ☐ **Audio Taping**

☐ **Behavioral Observations** ☐ **Chart Reviews** ☐ **Video Taping**

☐ **Focus Groups** ☑ **Randomization** ☐ **Double-Blind**

☐ **Control Group** ☐ **Placebo** ☐ **Withhold/Delay Treatment**

☐ **Specimen Collection** ☐ **Deception** ☐ **Telephone Survey**

☑ **Other (Describe)** *time-in-motion study for exploratory cost analysis*

5.1.3. **Provide description of the study population (delineate all categories of subjects – male, female, inpatients, outpatients, providers, family members, employees, etc.). Include anticipated initial enrollment numbers (and number of subjects anticipated to complete all aspects of the protocol).**

Our goal in selecting study patients for this pragmatic trial is to enroll all patients who meet the basic entry criteria and reflect the full range of patients undergoing bowel preparation for colonoscopies found in regular VA clinical practice. The study population will consist of all veterans seeking healthcare at the CMCVAMC.

E.3.1. Inclusion criteria

The inclusion criteria for potentially eligible subjects are:

1. > 18 years of age, and

2. being scheduled for outpatient elective screening, surveillance or diagnostic colonoscopies, and

3. the provider ordering the colonoscopy giving permission to enroll the patient.

E.3.2. Exclusion criteria

Patients who are <18 years, undergoing inpatient colonoscopy, those with contra-indications to receiving the standard 4L PEG-ELS colonoscopy bowel preparation (e.g., allergy to PEG) will be excluded. We are excluding inpatient colonoscopies because they account for a very small fraction of the total colonoscopies performed. Also, inpatient colonoscopies are often performed for urgent reasons such that rapid bowel preparation procedures are followed. In addition, because the objective of inpatient colonoscopy is often not to look for small polyps, the threshold for "adequate" bowel preparation quality might be different from that for outpatient procedures. In addition, for patients undergoing more than 1 colonoscopy during the study period, only their first colonoscopy will be included in the primary analysis. Patients who are undergoing a repeat colonoscopy for to a recent inadequate colonoscopy examination with poor bowel preparation will be excluded. We project to randomize 10,000 eligible patients with scheduled colonoscopy. We expect all 10,000 eligible patients to complete the study (i.e, allow us to determine primary outcome of completion of scheduled colonoscopy).

5.1.4. **As applicable, provide rationale and information on any added protections and safeguards for vulnerable populations (children, prisoners, pregnant women, physically or mentally-disabled persons, and economically or educationally disadvantaged persons).**

N/A

5.1.5. Does this project target a specific race or ethnic group as participants? **NOT APPLICABLE** **If yes, check all that apply.**

Race	**Ethnicity**
☐ **American Indian or Alaska Native**	☐ **Hispanic or Latino**
☐ **Asian**	☐ **Not Hispanic or Latino**
☐ **Black or African American**	
☐ **Native Hawaiian or other Pacific Islander**	
☐ **White**	
☐ **Other**	

5.1.6. Will this study bank data and/or specimens? **NO**

5.1.6.1. **If yes, include information on data and specimen banking.**

5.1.6.2. ***IF BANKING SPECIMENS, IT MUST BE AT A VA APPROVED FACILITY*. *(For additional information, go to the following website http://www.research.va.gov/programs/tissue_banking/, or contact the IRB office.)***

5.1.6.3. **If specimens will be banked, specify banking location**.

5.1.6.4. **If the location is a non-VA site, has the mandatory approval from VA Central Office been obtained through submission of a tissue banking application? Choose an item.**

5.1.6.4.1. **If yes, provide a copy of the response from VA Central Office.**

5.1.6.5. **If applicable, explain how destruction of banked samples will be substantiated.**

5.1.6.6. **Do you anticipate using the banked specimens for other studies beyond the defined study period and defined study parameters? Choose an item.**

5.1.6.6.1. **If yes, will you need to re-contact subjects? How will this be done?**

5.2. **Participant Recruitment Methods**

5.2.1. **State how many subjects will be needed**.

10,000

5.2.2. **Who will be responsible for recruiting potential participants**? **Provide titles of individuals.**

PI, research coordinator, research assistant

5.2.3. **How will initial contact with potential participants be made? (*e.g., local clinics, physician referrals, letters to prospective participants)*** *NOTE: VA*

policy prohibits "cold calls" to potential VA research participants. Provide an introductory letter and telephone script.

The providers who order the colonoscopy will introduce to the patient the opportunity to be considered for enrollment and an information sheet will be presented to them so there will be no cold calling. The study team will only contact the patient after the primary care providers indicate that patient agrees to be approached for consideration of enrolment in the study.

5.2.4. **Will you be using any of the following methods to recruit participants? (Check all that apply.)**

- ☐ **N/A**
- ☐ **Local database for which participants have NOT given prior permission to be contacted for Research.** *NOTE: If this option is checked, please submit a Waiver of Individual Authorization for Disclosure of Protected Health Information.*
- ☐ **Personal contact with patients over whom you have direct/indirect oversight**
- ☑ **Provider (Clinician) Referrals of potential participants**

5.2.5. **Indicate the types of recruitment/advertisement materials that will be used: Check all that apply. Submit copies of recruitment materials, for IRB review**.

☐**Not applicable; none to be used**

☐**Fliers** ☐**Newspapers** ☑**Letters** ☐**Websites** ☐**Television**

☐**Radio** ☐**Audio** ☐**Video** ☐**Surveys**

☑**Other (Specify, e.g. employee newsletters**) Information Sheet

5.2.6. **Participants will be given a copy of the Notice of Privacy Practice. NOT APPLICABLE**

5.3. **Compensation for Participation - NOT APPLICABLE If yes, complete the following**.

5.3.1. **Summarize any financial compensation that will be offered to subjects**.

5.3.2. **Provide the schedule for compensation**.

5.3.2.1. **Per study visit or session.**

5.3.2.2. **Total amount for entire participation.**

5.3.3. **State how compensation will be provided: Choose an item.**

5.4. **Informed Consent Procedures**

5.4.1. **Indicate if informed consent will be obtained and/or if you are requesting a waiver of informed consent or waiver of documentation of informed consent. Because the research presents no more than minimal risk and involves no procedures for which written consent is required, we are requesting Waiver to Obtain Documentation of Informed Consent**

5.4.2. **If the research involves multiple phases, specify for which phases of the research the waiver(s) is/are being requested.**

n/a

5.4.3. **Describe circumstances, if any, that may need to be addressed in seeking informed consent (e.g., subjects with impaired decision making ability and the use of a legally authorized representative, etc.)**

Because we only approach patients deemed suitable for consent by their primary care providers, we do not expect such special needs. Regardless, we will ensure that consents are obtained only from an adult capable of providing consent.

5.4.4. **If applicable, indicate how study personnel will be trained regarding human subjects protections requirements and how to obtain and document informed consent.**

All study personnel will receive annual VA Privacy and HIPAA training as well as Collaborative Institutional Training Initiative training. Study personnel will be required to follow the consent document, explain the details such a way that the patient or representative can understand, invite and answer patient/representative's questions.

5.4.5. **Inclusion/Exclusion Criteria: Describe the criteria that determine who will be included in or excluded from the study.**

5.4.5.1. **Inclusion Criteria**

The inclusion criteria for potentially eligible subjects are:

1. > 18 years of age, and

2. being scheduled for outpatient elective screening, surveillance or diagnostic colonoscopies, and

3. the provider ordering the colonoscopy giving permission to enroll the patient.

5.4.5.2. **Exclusion Criteria**

Patients who are <18 years, undergoing inpatient colonoscopy, those with contra-indications to receiving the standard 4L PEG-ELS colonoscopy bowel preparation (e.g., allergy to PEG) will be excluded. We are excluding inpatient colonoscopies because they account for a very small fraction of the total colonoscopies performed. Also, inpatient colonoscopies are often performed for urgent reasons such that rapid bowel preparation procedures are followed. In addition, because the objective of inpatient colonoscopy is often not to look for small polyps, the threshold for "adequate" bowel preparation quality might be different from that for outpatient procedures. In addition, for patients undergoing more than 1 colonoscopy during the study period, only their first colonoscopy will be included in the primary analysis. Patients who are undergoing a repeat colonoscopy for to a recent inadequate colonoscopy examination with poor bowel preparation will be excluded.

5.5. **Withdrawal of Subjects**

5.5.1. **Describe how a subject can withdraw from the study**.

n/a

5.5.2. **Describe any anticipated circumstances under which subjects will be withdrawn from the research without their consent**.

n/a

5.5.3. **Describe the consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the**

subject (e.g., the subject contacting the investigator for an end-of-study visit).

n/a

5.6. **Potential Risk/Benefit Analysis**

5.6.1. **Potential Study Risks**

5.6.1.1. **Describe and assess all of the following risks that may be associated with the research**:

5.6.1.2. **Physical (***Physical risks include physical discomfort, pain, injury, illness or disease brought about by the methods and procedures of the research. A physical risk may result from the involvement of physical stimuli such as noise, electric shock, heat, cold, electric magnetic or gravitational fields, etc. Engaging a subject in a social situation which could involve violence may also create a physical risk***.)**

The risks associated with participating in the study are less than minimal to the patients involved in the project.

Other than being randomized to one of the two bowel preparation regimens, there is no change in the care the patients receive. In addition, the two bowel preparation regimens used represent the most commonly used split-dose bowel regimens in routine clinical practice in the US. No clinically significant adverse effects have been reported to be associated with their extensive use. They are recommended by the current US Multi-Society Task Force (USMSTF). The 4L split-dose PEG group is the current standard bowel preparation in the VA. The 2L split-dose MiraLax/Gatorade preparation is the standard bowel preparation in many if not the majority of GI practices in the US (including the University of Pennsylvania Health System) and has been used by millions of patients worldwide. MiraLax is available over-the-counter, and Gatorade is a common sports drink. In addition, patients with diabetes are instructed to use Crystal Lite instead of Gatorade. Like any colonoscopy bowel preparations, these preparations would lead to diarrhea, urgency and bloating, but these should not be more than what the patient would have experienced with the usual preparation regimen and should not lead to clinically important adverse effects. Of course, allergic reactions can occur to any medication but are extremely rare.

5.6.1.3. **Psychological (***Psychological risks include the production of negative affective states such as anxiety, depression, guilt, shock and loss of self-esteem and altered behavior. Sensory deprivation, sleep deprivation, use of hypnosis, deception or mental stresses are examples of psychological risks.)*

None

5.6.1.4. **Social/Economic (***Social/Economic risks include alterations in relationships with others that are to the disadvantage of the subject, including embarrassment, loss of respect of others, labeling a subject in a way that will have negative consequences, or in some way diminishing those opportunities and powers a person has by virtue of relationships with others. Economic risks include payment by subjects for procedures not otherwise required, loss of wages or other income and any other financial costs, such as damage to a subject's employability, as a consequence of participation in the research.)*

Those randomized to the MG prep will need to purchase 2L of Gatorade because it is a sports drink .

5.6.1.5. **Legal (***Legal risks exist when the research methods are such that the subject or others will be liable for a violation of the law, either by revealing that the subject or others have engaged, or will engage, in conduct for which the subject or others may be criminally or civilly liable, or by requiring activities for which the subject or others may be criminally or civilly liable.)*

none

5.6.1.6. **Loss of Confidentiality** *(In all research involving human subjects, confidentiality of identifiable information is presumed and must be maintained unless the investigator obtains the express permission of the subject to do otherwise. Subjects have the right to be protected against injury or illegal invasions of their privacy and to preservation of their personal dignity. The more sensitive the research material, the greater the care that must be exercised in obtaining, handling, and storing data. In order to minimize the risk for loss of confidentiality, investigators should only collect personal information that is absolutely essential to the research activity. If personal data must be collected, it should be coded as early in the activity as possible and securely stored so that only the investigator and authorized staff may access it. Identities of individual subjects must never be released without the express consent of the subject. In addition, if an investigator wishes to use data for a purpose other than the one for which it was originally collected and the data are still identifiable (e.g., a code list for the data still exists), the investigator may need to obtain consent from the subjects for the new use of the data.)*

Every effort will be made to reduce the risk of loss of confidentiality in this study. Research files containing confidential material will be stored in a locked file cabinet in the PI's locked office at the Philadelphia VA Medical Center. Security during data extraction and management will follow the standard operating procedure of the CHERP. Specifically, data obtained to fulfill the information needs of IRB-approved studies or QI efforts are housed on a secure server physically located within the FITS computer room of the Philadelphia VA Medical Center and networked within the VA Intranet. As a result, the servers have the same degree of physical and electronic protection afforded other VA computer systems, including antiviral protection and routine back-ups. FITS is responsible for managing the server hardware and software, including its physical and network security and connectivity, backup processes, operating system patches, and application management. Study data will be stored in one of two places – either within tables on a Philadelphia VAMC SQL Server (the CHERP4 machine), or in data files stored within protected directories on the server (CHERP NAS). CHERP file folders will be created by the CHERP Dataset Administrator (DSA) and stored on the CHERPNAS server with read and write access to study files restricted by the operating system to authorized persons only for the time-frame designated during the IRB and R&D approval. At the end of the timeframe the folders will be locked. By using this approach, access to the data will be under the strict surveillance and control of the CHERP data administrator (Christopher Roberts or a CHERP assigned programmer with equivalent experience).

To ensure subject confidentiality and comply with HIPAA regulations, none of the 18 HIPAA identifiers will be stored in the database, e.g.no personal information, such as names, dates, contact information, social security/medical record numbers, etc. All

research files containing protected health information will be stored in a locked file cabinet in a locked office or on a secure VA server on a password protected computer in a locked office at Philadelphia VA Medical Center. All VA data will be appropriately kept behind the VA firewall and in compliance with all VA data security guidelines. All members of the research team will maintain up-to-date training on HIPAA, patient oriented research, and data security measures at the VA.

5.6.1.7. **Other, e.g. radiation, placebo, washout of medications**

none

5.6.1.8. **Assess the likelihood and seriousness of such risks**.

The likelihood of the risks described above is extremely. Also, the risks are not serious.

5.6.2. **Include a description of how anticipated risk will be minimized and include an analysis of risk vs. potential benefit.**

Every effort will be made to reduce the risk of loss of confidentiality in this study. Research files containing confidential material will be stored in a locked file cabinet in the PI's locked office at the Philadelphia VA Medical Center. Security during data extraction and management will follow the standard operating procedure of the CHERP. Specifically, data obtained to fulfill the information needs of IRB-approved studies or QI efforts are housed on a secure server physically located within the FITS computer room of the Philadelphia VA Medical Center and networked within the VA Intranet. As a result, the servers have the same degree of physical and electronic protection afforded other VA computer systems, including antiviral protection and routine back-ups. FITS is responsible for managing the server hardware and software, including its physical and network security and connectivity, backup processes, operating system patches, and application management. Study data will be stored in one of two places – either within tables on a Philadelphia VAMC SQL Server (the CHERP4 machine), or in data files stored within protected directories on the server (CHERP NAS). CHERP file folders will be created by the CHERP Dataset Administrator (DSA) and stored on the CHERPNAS server with read and write access to study files restricted by the operating system to authorized persons only for the time-frame designated during the IRB and R&D approval. At the end of the timeframe the folders will be locked. By using this approach, access to the data will be under the strict surveillance and control of the CHERP data administrator (Christopher Roberts or a CHERP assigned programmer with equivalent experience). To ensure subject confidentiality and comply with HIPAA regulations, none of the 18 HIPAA identifiers will be stored in the database, e.g.no personal information, such as names, dates, contact information, social security/medical record numbers, etc. All research files containing protected health information will be stored in a locked file cabinet in a locked office or on a secure VA server on a password

protected computer in a locked office at Philadelphia VA Medical Center. All VA data will be appropriately kept behind the VA firewall and in compliance with all VA data security guidelines. All members of the research team will maintain up-to-date training on HIPAA, patient oriented research, and data security measures at the VA.

5.6.3. **Potential Study Benefits**

5.6.3.1. **Indicate potential benefits to be gained by the individual subjects, as well as benefit(s) that may accrue to society in general as a result of the planned work. If the subject will not receive any direct benefit, this fact must be stated here and in the consent form.**

According to VHA Handbook 1108.04 (research): 12. CO-PAYMENTS, item a. Title 38 U.S.C. 1722A, Co-Payment for Medications, and 38 CFR § 17.110, Co-Payment for Medications, VA medication co-payments must be waived if the medication is provided to the subject as part of a VHA-approved research protocol. This waiver applies whether or not the sponsor of the investigational study provides the medication. This benefit applies to all patients who would be responsible for co-pay for the 4L PEG regimen. Finding an effective and better tolerated bowel preparation could benefit all future VA patients undergoing colonoscopies. Overall, the minimal risks to the study patients and providers are reasonable in relation to the anticipated benefit.

5.6.4. **Alternative Treatments Outside the Study**

5.6.4.1. **Describe alternatives available to the subject outside the research context. If there are no such alternatives, state that the alternative is not to participate in the research study**.

Alternative is not to participate in the study

5.7. **Data Monitoring (***Monitoring plans describe how a monitor, independent of the study team, regularly inspects study records to ensure the study is adhering to the study protocol and applicable research regulations and CMCVAMC requirements. Monitoring plans do not necessarily require the use of an independent Data and Safety Monitoring Board (DSMB). Such independent boards are usually reserved for high-risk phase I studies, or large, multi-center phase III trials. Federally funded studies may require the use of an independent DSMB.)*

5.7.1. **Will a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) oversee the project? NO**

5.7.1.1. **If yes, provide contact information for the DSMB or DMC representative**.

5.7.1.2. **If the project will not be overseen by a DSMB or DMC, describe the data and safety monitoring plan to be followed.**

A data and safety monitoring plan will be implemented to ensure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. Investigators and personnel involved in the study will meet twice annually to discuss the study (e.g., study goals, progress, modifications, documentation, recruitment, data analysis and confidentiality). Minutes will be kept for these meetings and will be on file. These meetings will be overseen by the PI, Dr. Yang. The PI will meet with individual study team members as needed in order to address specific issues and concerns in the

team members' area of expertise. Any instances of adverse events, protocol deviations, or other problems identified will be reported within the required reporting time-frames using standard forms and/or procedures set forth by the IRB. In addition, clinical research coordinators may review study documentation to ensure that participants' confidentiality is maintained.

This minimal risk study does not warrant the establishment of a Data Safety Monitoring Board.

5.8. **Reporting of Protocol Deviations, Adverse Events (AEs), Serious Adverse Events (SAEs), Breaches of Confidentiality, Unanticipated Adverse Device Effects (UADEs), and Unanticipated/Unexpected Problems**

5.8.1. **Include procedures for reporting these events to the CMCVAMC IRB and sponsor**. (*Note: Except for AEs, all other events must be reported to the CMCVAMC IRB within 5 business days of discovery. Use the CMCVAMC Serious-Adverse Event form for reporting SAEs, UADEs, and unanticipated/unexpected problems. Use the CMCVAMC Protocol Deviation form for reporting protocol deviations. On-site AEs should be reported at the time of continuing review.)*

The primary potential adverse events associated with this study would be due to breach of confidentiality. Such events will be reported to the PVAMC IRB within 24 hours in writing. In addition, any protocol deviation will also be reported to the PVAMC IRB in writing. Except for AEs, all other events will be reported to the CMCVAMC IRB within 5 business days of discovery. We will use the CMCVAMC Serious-Adverse Event form for reporting SAEs, UADEs, and unanticipated/unexpected problems. We will use the CMCVAMC Protocol Deviation form for reporting protocol deviations. On-site AEs will be reported at the time of continuing review.

5.9. **Privacy and Confidentiality**

5.9.1. **Describe whether the study will use or disclose subjects' Protected Health Information (PHI).**

The study will use PHI.

5.9.2. **Check the PHI to be collected on all subjects for this research protocol.**

☑ **Name**

☑ **All geographic subdivisions smaller than a State, including street address, city, county, precinct, ZIP code, and their equivalent geographical codes, except for the initial three digits of a ZIP code if, according to the current publicly available data from the Bureau of the Census:**

a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people; and

b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.

☑ **All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.**

☐ **Telephone numbers** ☐ **Fax numbers**

☐ **Electronic mail addresses** ☑ **Social Security/Medical Record Number**

☐ **Health plan beneficiary numbers** ☐ **Account Numbers**

☐ **Certificate/license numbers**

☐ **Vehicle identifiers and serial numbers, including license plate numbers**

☐ **Device identifiers and serial numbers**

☐ **Web universal resource locators (URLS)**

☐ **Internet protocol (IP) address numbers**

☐ **Biometric identifiers, including fingerprints and voiceprints**

☐ **Full-face photographic images and any comparable images**

☐ **Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.**

☐ **HIV (testing or infectious disease) records** ☐ **Sickle cell anemia**

☑ **Drug Abuse Information** ☑ **Alcoholism or Alcohol Use**

5.10. **Information Security** (*Contact the Information Security Officer for additional assistance regarding confidentiality (storage/security) of research data.)*

5.10.1. **List the data/information that will be stored (including signed, original informed consent and HIPAA authorization forms, if applicable, case report forms, etc.)**

We will use electronic case report forms to collect information regarding patient demographics, comorbidity information, as well as study outcomes (e.g., colonoscopy prep quality , completion rate and colorectal adenoma detection rate).

5.10.2. **Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data)**.

Every effort will be made to reduce the risk of loss of confidentiality in this study. Research files containing confidential material will be stored in a locked file cabinet in the PI's locked office at the Philadelphia VA Medical Center. Security during data extraction and management will follow the standard operating procedure of the CHERP. Specifically, data obtained to fulfill the information needs of IRB-approved studies or QI efforts are housed on a secure server physically located within the FITS computer room of the Philadelphia VA Medical Center and networked within the VA Intranet. As a result, the servers have the same degree of physical and electronic protection afforded other VA computer systems, including antiviral protection and routine back-ups. FITS is responsible for managing the server hardware and software, including its physical and network security and connectivity, backup processes, operating system patches, and application management. Study data will be stored in one of two places – either within tables on a Philadelphia VAMC SQL Server (the CHERP4 machine), or in data files

stored within protected directories on the server (CHERP NAS). CHERP file folders will be created by the CHERP Dataset Administrator (DSA) and stored on the CHERPNAS server with read and write access to study files restricted by the operating system to authorized persons only for the time-frame designated during the IRB and R&D approval. At the end of the timeframe the folders will be locked. By using this approach, access to the data will be under the strict surveillance and control of the CHERP data administrator (Christopher Roberts or a CHERP assigned programmer with equivalent experience).

To ensure subject confidentiality and comply with HIPAA regulations, none of the 18 HIPAA identifiers will be stored in the database, e.g.no personal information, such as names, dates, contact information, social security/medical record numbers, etc. All research files containing protected health information will be stored in a locked file cabinet in a locked office or on a secure VA server on a password protected computer in a locked office at Philadelphia VA Medical Center. All VA data will be appropriately kept behind the VA firewall and in compliance with all VA data security guidelines. All members of the research team will maintain up-to-date training on HIPAA, patient oriented research, and data security measures at the VA.

5.10.3. **Indicate how and where data/information will be stored, and specify pertinent security systems**.

Every effort will be made to reduce the risk of loss of confidentiality in this study. Research files containing confidential material will be stored in a locked file cabinet in the PI's locked office at the Philadelphia VA Medical Center. Security during data extraction and management will follow the standard operating procedure of the CHERP. Specifically, data obtained to fulfill the information needs of IRB-approved studies or QI efforts are housed on a secure server physically located within the FITS computer room of the Philadelphia VA Medical Center and networked within the VA Intranet. As a result, the servers have the same degree of physical and electronic protection afforded other VA computer systems, including antiviral protection and routine back-ups. FITS is responsible for managing the server hardware and software, including its physical and network security and connectivity, backup processes, operating system patches, and application management. Study data will be stored in one of two places – either within tables on a Philadelphia VAMC SQL Server (the CHERP4 machine), or in data files stored within protected directories on the server (\\vhaphicherpnas). CHERP file folders will be created by the CHERP Dataset Administrator (DSA) and stored on the CHERPNAS server with read and write access to study files restricted by the operating system to authorized persons only for the time-frame designated during the IRB and R&D approval. At the end of the timeframe the folders will be locked. By using this approach, access to the data will be under the strict surveillance and control of the CHERP data administrator (Christopher Roberts or a CHERP assigned programmer with equivalent experience).

To ensure subject confidentiality and comply with HIPAA regulations, none of the 18 HIPAA identifiers will be stored in the database, e.g.no personal information, such as names, dates, contact information, social security/medical record numbers, etc. All research files containing protected health information will be stored in a locked file cabinet in a locked office or on a

secure VA server on a password protected computer in a locked office at Philadelphia VA Medical Center. All VA data will be appropriately kept behind the VA firewall and in compliance with all VA data security guidelines. All members of the research team will maintain up-to-date training on HIPAA, patient oriented research, and data security measures at the VA.

5.10.4. **Will PHI be transmitted or transported outside of CMCVAMC? NOT APPLICABLE If yes, complete sections 5.10.4.1 through 5.10.4.4. If no, go directly to section 5.11.**

5.10.4.1. **Does the informed consent document and Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research form disclose entities/individuals to which/whom PHI will be transported or transmitted? Choose an item.**

5.10.4.2. **Specify entities/individuals outside CMCVAMC to which/whom data will be disclosed, the justification for such disclosure and the authority, and how they will access it**.

5.10.4.3. **List the data/information that will be transmitted or transported, and specify how data will be transported or transmitted from one location to another and how it will be protected during transmission or transportation outside of CMCVAMC.**

5.11. **Communication Plan**

5.11.1. **Include plan for ensuring that the study is conducted according to the IRB-approved protocol.**

We will ensure all members of the study team are up-to-date on clinical research conduct training. We will develop a manual of operations according the IRB approved study protocol. The study team will promptly report any AEs, SAEs, and unanticipated problems, protocol violations to the IRB according to IRB guidelines.

5.11.2. **If a multi-site study, include information on**

- **ensuring that all required local site approvals are obtained and notifying the Director of any facility where the research is being conducted but the facility is not engaged, and**
- **keeping all engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization**, and
- **informing local sites of any Serious Adverse Events, Unanticipated Problems, or interim results that may impact conduct of the study**, and
- **notifying all local facility directors and local site investigators (LSI) when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).**

5.12. **Investigational Drug NO If yes, complete the rest of this section. If no, go directly to section 6.** *NOTE: If this study involves an investigational drug, investigator must contact the Pharmacy and Therapeutics (P&T) Committee and provide its approval to IRB.*

5.12.1. **Specify if the drug or biological agent is:**

5.12.1.1. **FDA approved: Choose an item.**

5.12.1.2. **Used for off-label purposes: Choose an item.**

5.12.2. **Include the FDA Investigational New Drug (IND) number for all non-FDA approved and off-label drugs, biological agents or nutritional supplements. If not applicable state, "Not Applicable."**

5.12.3. **Provide all relevant information about the drug, including pre-clinical data.**

5.12.4. **Explain any wash-out periods, rescue medications permitted and any type of medications not permitted while enrolled in the study.**

5.12.5. **Describe blinding and un-blinding procedures.**

5.12.6. **Include the dosage, route of administration, previous use, and the safety and efficacy information on any drug used for research purposes.**

5.12.7. **Describe rationale for the dosage in this study.**

5.12.8. **Justify why the risks are reasonable in relation to anticipated benefits and/or knowledge.**

5.12.9. **Describe where drug preparation will be done.**

5.12.10. **All drugs for CMCVAMC subjects must be dispensed through the VA investigational pharmacy.**

5.12.11. **Describe where the study treatment will be administered.**

5.12.12. **Describe plan for tracking a non-compliant treatment study subject.**

5.12.13. **Describe the process for the storage, security, dispensing and return of an investigational drug.**

5.13. **Investigational Device - NOT APPLICABLE If yes, complete the rest of this section.**

5.13.1. **The Investigational Device Exemption (IDE) number must be submitted for all significant risk devices and if an IDE exists for a non-significant risk device.**

5.13.2. **Significant Risk or Non-significant Risk - If a device is not approved by the FDA, specify whether or not the sponsor has determined this device to be a "significant risk" or "non-significant risk" as defined by the FDA.**

5.13.3. **Provide all relevant information about the device.**

5.13.4. **Describe blinding and un-blinding procedures.**

5.13.5. **Specify if device is:**

5.13.5.1. **FDA approved: Choose an item.**

5.13.5.2. **Used for off-label purposes: Choose an item.**

5.13.6. **Explain if the investigational device will be delivered and/or stored by the Principal Investigator or Pharmacy Service.**

5.13.7. **Describe the process for the storage, security, dispensing and return of an investigational device.**

5.13.8. **For research involving an investigational device, describe the SOP or plan for device control.**

5.13.9. **Address how the device will be stored in such a way that only research staff associated with the protocol will have access to the device.**

5.13.10. **Describe measures that will be put into place to ensure that the device will only be used in subjects of this research protocol.**

Section 6: Resources and Personnel

6.1. **Include where and by whom the research will be conducted**.

The entire study will be conducted at the CMCVAMC. We have assembled an outstanding multi-disciplinary team.

Principal Investigator: Dr. Yang is a Core Investigator with the Center for Health Equity Research and Promotion (CHERP), a VA HSR&D Center of Innovation (COIN) with offices in Philadelphia and Pittsburgh. He has extensive experience conducting VA and non-VA clinical research studies. He will be responsible for the completion of all aspects of the study aims. He will also be responsible for the fiscal, administrative and regulatory aspects of the study, including all regulatory affairs, data collection and management, adherence to all policies and procedures, coordinating meetings and email/telephone communications among the contracted Divisions, consultants and the primary team at the CMCVAMC, and maintenance of study protocol to ensure that the specific aims of the study are being met. Dr. Yang will develop Manual of Procedures.

Co-investigators and supporting staff at CMCVAMC: Dr. Khan is the Director of the GI section at the CMCVAMC. He is a clinical gastroenterologist with extensive experience conducting clinical research including clinical trial within the VA system. He will provide support to all aspects of the study. Dr. Hubbard, a biostatistician in the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania, will provide statistical support. Dr. Glick is an expert in performing economic analysis embedded in clinical trials and will oversee all aspects of the prospective economic evaluation.

Consultant: As the chairperson for the Medical Advisory Panel for Pharmacy Benefits Management for VA, and as the Co-Director of the VA Center for Medication Safety, Dr. Chester B. Good will share his experience in national formulary issues, drug safety issues and optimizing prescribing practice within the VA. He will help with design of the intervention and facilitate the implementation and dissemination of the study findings within the VA. Dr. James Lewis, Professor of Medicine and Epidemiology at the University of Pennsylvania, is a board certified gastroenterologist and prolific clinical investigators. He has been the PI for 4 NIH funded clinical trials and is on the steering committee for a 5th NIH funded trial. These studies

have used a variety of designs to facilitate recruitment, data collection, and retention while not altering practice patterns in real world settings. We will adapt these methods for this trial given the importance of studying the different regimens as practiced in usual care. Dr. Charlene Weir will provide her expertise to help ensure the study procedures are acceptable to VA providers.

Joyce Askew (Clinical Applications Coordinator/Program analyst)

Ms. Askew is a full-time health informatics specialist at the Corporal Michael J. Crescenz VA Medical Center. Ms. Askew is familiar with the functionality of clinical and administrative applications and the interrelationships of those applications to the operations of clinical services, particularly with regard to Veterans Health Information Systems and Technology Architecture (VistA) and the Computerized Patient Record System (CPRS). Using her expert knowledge for the VA electronic health record and associated clinical software applications, she routines provides technical support to develop, generate, deploy, validate, maintain and modify major CPRS clinical application components including Order Entry/Results Reporting, TIU documents, Consult Request Tracking, Health Summary, Problem List, Care Management, VISTA Web and Clinical Reminders. She routinely engages in projects in process improvement and reengineering business process for clinical efficiency and documentation, including several changes to the GI endoscopy consultation and the colonoscopy bowel preparation ordering menu. In preparation for the current project, she has obtained from her counterpart from Boston VA Medical Center the programming codes for the implementation of linking the ordering menu change with study randomization procedure and tested these in a pilot environment in CPRS. If the grant is funded, she will be responsible for modifying the colonoscopy bowel preparation menu, linking the ordering menu to implementation of study randomization procedure as well as auto-population of associated progress notes, health alerts and consultations in CPRS. She will also be responsible for maintaining this system in CPRS and troubleshooting during the study period. Her responsibility in the proposed project will be a part of her formal job responsibilities, and no additional salary support is requested.

Roberts, Christopher B. (Dataset Administrator non-2210).

Christopher B. Roberts MPH, is a Dataset Administrator for CHERP and will assume the Dataset Administrator position for the project, a non-2210 position. His Salary totals reflects 2% COLA and anticipated step increases during each project year The Dataset Administrator will establish a study folder for the proposed project on a secure CHERP server. He will be responsible for developing electronic query algorithms for extracting patient lists and other study participant data such as patient demographics and all the other baseline characteristics from the VISN4 regional data warehouse. He will set up prospective execution of the queries and store the collected data in a secure and accessible manner for the PI and the study coordinators. In concert with the Sr. Research Coordinator and the PI, he will develop the electronic CRFs, project database and will interface for data entry and project tracking/report generation. Working closely with the biostatistician and the PI, he will develop, test, and implement data cleaning, data quality monitoring procedures and will be responsible for creation of analytic databases for all data analyses. The Dataset Administrator will have

oversight responsibility for data storage on the secure research data server and will maintain documentation of IRB approval to support data use and access by study staff.

TBN (Sr. Research Coordinator)

We are requesting funds for a full-time MS- level senior clinical research coordinator for each of the 4 years of the project. He/she will be responsible for the following: working with the CHERP dataset programmer to setup study database for collection of study data; creating a manual of operation procedures for the study; performing EHR chart review for initial screening; contacting patients, obtaining consent, and obtaining patient procedure cancellation/no-show data; forwarding procedure ordering request to the PI; supervising the abstraction of patient randomization data and progress notes from CPRS, recording and entering the study data into the study database, ensuring that subject data are secure and kept confidential; assisting the CHERP programmer with setting up and updating patient tracking spreadsheet, monitoring study financial expenditures, ordering supplies/subject recruitment materials, troubleshooting study data collection and/or study participant-related issues.

The senior research coordinator will also support the activities of the investigators including conducting library and computer searches for relevant study literature; assisting with document and correspondence production; creating, updating and maintaining project files in a confidential manner. In addition, he/she will assist Dr. Yang with preparation of progress and study milestone reports and publications, adverse event tracking and reporting, IRB correspondence and renewals and regulatory auditing of the study. He/she will document proceedings of team meetings and teleconferences and process project-related forms. This senior research coordinator will have the added the responsibility of supervising the junior research assistant.

TBN (Research Assistant)

We are requesting funds for a full-time research assistant for each of the 4 years of the project. Given the large sample size (10,000 patients) and the need to complete the study procedures and data collection in a timely manner, a second junior level research assistant will be required to complete study tasks. He/she will be responsible for the following: documentation in CPRS, ensuring patient follow-up and retention, and preparation of data for analysis at the CMCVAMC/Philadelphia site. The research assistant will also assist the senior research coordinator in the preparation of data for reports and IRB submissions. The junior research assistant will work under the supervision of the Sr. Research Coordinator to maintain study database for collection of study data; assist with creating a manual of operation procedures for the study; assist with EHR chart review for initial screening; contact patients, obtain consent, and collect patient procedure cancellation/no-show data; forward ordering request to the PI; collecting randomization data and progress notes from the CPRS, recording and entering the study data into a study database, ensure that subject data are secure and kept confidential;

assist the Sr. Research Coordinator with updating patient tracking spreadsheet. The research assistant will also support the activities of the investigators including assisting with document and correspondence production; creating, updating and maintaining project files in a confidential manner.

Carson Clark 8/8th (Dissemination Manager) (CHERP Communications Coordinator)

Ms. Clark has over 20 years of experience in public relations, marketing, advertising and publication. She has led the communications activities on numerous prior studies conducted by researchers at CHERP. Ms. Clark will have primary responsibility for all strategic communication and public relations activities related to the dissemination of study findings to VA and non-VA researchers and policymakers, the media and the general public. She will handle the development of all electronic and print communications for the study. This project will require 5% effort of Carson Clark's time in year 4 of the project only.

6.2. **Provide a brief description of each individual's role in the study. Indicate who will have access to protected health information and who will be involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis**.

See above section. The PI, the research coordinators and the dataset administrator will have access to PHI

6.3. **If applicable, provide information on any services that will be performed by contractors, including what is being contracted out and with whom**.

None

6.4. **If applicable, provide information on any Memoranda of Understanding (MOUs) or Data Use Agreements (DUAs) that are being entered into, including with whom and for what reason**.

n/a

Section 7: Genetic Testing

7.1. **Does the project involve genetic testing?** **Not Applicable, SKIP TO SECTION 8**

7.2. **Will specimens be kept for future, unspecified use? Choose an item.**

7.3. **Will samples be made anonymous to maintain confidentiality? Choose an item.** (*If there is a link, it is not anonymous. Coding is not anonymous.)*

7.4. **Will specimens be destroyed after the project-specific use is completed? Choose an item.**

7.5. **Will specimens be sold in the future? Choose an item.**

7.6. **Will subjects be paid for their specimens now or in the future? Choose an item.**

7.7. **Will subjects be informed of the results of the specimen testing? Choose an item.**

7.8. **Are there any implications for family members based on specimen testing results? Choose an item.**

7.8.1. I**f answer to section 7.8 is yes, they may be participants**.

7.9. **Will subjects be informed of results obtained from their DNA? Choose an item.**

7.10. **Explain if the study is looking for an association between a genetic marker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value**.

7.11. **Describe if the study is based on the premise that a link between a genetic marker and a specific disease or condition is such that the marker is clinically useful in predicting the development of that specific disease or condition.**

7.12. **Will the subject be notified of the results and the provision for genetic counseling? Choose an item.**

Section 8: International Research

8.1. **Does this study involve international research? NOT APPLICABLE If no, go directly to section 9.**

8.1.1. ***For further instructions, refer to VHA Directive 2005-050, Requirements for Conducting VA-Approved International Research Involving Human Subjects, Human Biological Specimens, or Human Data***

8.1.2. ***VHA Handbook 1200.05 definition of international research - VA international research is any VA-approved research conducted at international sites (not within the United States (U.S.), its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research sending such specimens or data out of the U.S. NOTE: For the purposes of the VHA Handbook 1200.05, research conducted at U.S. military bases, ships, or embassies is not considered international research.***

Section 9: Statistical Analysis

9.1. Include statistical power calculations and the assumptions made in making these calculations.

The GI section is expected to perform 10,500 colonoscopies over the 3-year recruitment period. Based on our pilot data, the 10,500 colonoscopies performed will entail approximately 15,000 colonoscopies scheduled during the same period. Again based on our preliminary data, 11% of the scheduled colonoscopies during the period will be expected to represent repeat examinations for the same patients during the 3-year period and will thus be excluded. Due to the low risk of the intervention and minimal burden on the provider and participant, we expect to have very high enrolment rates among eligible patients. We therefore project to randomize 10,000 eligible patients with scheduled colonoscopy. Following the ITT analysis design, all 10,000 randomized patients will be included in the primary analysis with 5,000 allocated to each treatment arm. Based on preliminary data, we anticipate that in the 4L PEG-ELS arm 74% of patients will show up for their scheduled colonoscopy and undergo the examination, and 75% will have adequate bowel preparation. We therefore anticipate that 56% will satisfy our composite primary outcome of colonoscopy completion. At α=0.025, we will have 99.8% power to detect a 5% improvement, or 90.3% power to detect a 3.5% improvement in the colonoscopy completion rate. Assuming an ADR of 28% in the 4L PEG-ELS arm, we will have in excess of 99.9% power to detect a 5% improvement in ADR at the □ = 0.025 level in the 2L M-G arm. Analyses of cancellation/no-show rate will be similar to the analyses for primary outcomes. At α=0.017, we will have 95.4% power to detect a 3.5% difference in cancellation/no-show rate. The analyses of other secondary outcomes will be conducted in the sub-group of patients who show up for their scheduled colonoscopy. We thus anticipate a sample size of 7,400 for these secondary analyses. Assuming 3,700 patients in each arm, we anticipate that in the 4L PEG-ELS arm 75% will have adequate bowel preparation. At α=0.017, we will have in excess of 99.7% power to detect a 5% improvement in the rate of adequate bowel preparation in the 2L M-G arm.

Assuming the proportion of patients in the 4L PEG-ELS arm willing to repeat the preparation is 66.7%,6 we will have 98.8% power to detect a 5% improvement in the rate of patients willing to repeat their bowel preparation regimen at the □ = 0.017 level in the 2L M-G arm.

We have designed our study to be overpowered for the primary comparisons in order to improve power for subgroup analyses. For instance, in a sub-group consisting of 10% of the total sample (N = 1,000 patients) we will have 80% power to detect a difference between treatment arms at the □ = 0.05 level of 8.7% in the completion rate, 8.3% in ADR, and 9.3% in the proportion willing to repeat their bowel preparation regimen. Note that we have used an □-level of 0.05 in exploratory analyses in order to maximize power, as exploratory analyses are fundamentally hypothesis-generating. We thus deem type II errors more severe in exploratory analyses than type I errors and accordingly set a less conservative □ level. Results of such hypothesis-generating analyses must be confirmed, however, in subsequent studies.

Within-endoscopist correlation in our outcomes of interest will result in decreased power relative to the nominal power computed above under independence. Although we anticipate that within-endoscopist correlation will be minimal due to the largely patient-oriented nature of our outcomes, we have designed our study to have sufficient power under a moderate level of within-endoscopist correlation. Specifically, as correlation among observations increases, the effective sample size decreases according to the relationship Neff = N/(1+□(b-1)), where N is the total number of patients sampled, b is the average number of patients per endoscopist, and □ is the intraclass correlation coefficient. In primary analyses in which the nominal sample size is 10,000, our study will have 80% power to detect a 5% difference in the colonoscopy completion rate at the □ = 0.025 level for effective sample sizes as small as 3,703 and a 5% difference in ADR at the □ = 0.025 level for effective sample sizes as small as 3,222. For our secondary analysis of the cancellation/no-show rate with nominal sample size of 10,000, our study will have 80% power to detect a 5% difference at the □ = 0.017 level for effective sample sizes as small as 3,009. For secondary analyses in which the nominal sample size is 7,400, our study will have 80% power to detect a 5% difference in the adequate bowel preparation rate at the □ = 0.017 level for effective sample sizes as small as 2,919 and a 5% difference in the rate of willingness to repeat the regimen at the □ = 0.017 level for effective sample sizes as small as 3,567. Across all primary and secondary outcomes, we will thus have at least 80% power as long as our effective sample size is 48.2% (3,568/7,400) of the nominal sample size or larger.

9.2. Define plans for data and statistical analysis, including key elements of the statistical plan, stopping rules and endpoints.

E.9.2.1 Descriptive statistics

The initial analyses will utilize descriptive statistics to describe the characteristics of the study cohort. Continuous variables will be described as medians and interquartile ranges. Categorical variables will be described using proportions. Formal statistical comparisons of these descriptive variables between study arms will be performed comparing the two arms of the study using the Wilcoxon rank sum test for continuous variables and the chi squared or Fisher's exact test for categorical variables. Because any imbalance in the two groups is by definition a chance occurrence, these analyses will be used to highlight areas of substantial imbalance between the study arms.

E.9.2.2 Primary Effectiveness Analysis

Our study will have two primary effectiveness outcomes. The first primary outcome is the colonoscopy completion rate, a composite binary indictor based on patient attendance at scheduled colonoscopy and having adequate (i.e., excellent or good) quality bowel preparation as rated by the endoscopist. The corresponding parameter of interest is the proportion of patients in each arm of the trial who both show up for their colonoscopy and are rated as having adequate bowel preparation. The second primary outcome is the ADR estimated as the proportion of patients with at least one adenoma detected among all patients scheduled for colonoscopy. We hypothesize that patients using the 2L M-G regimen will have a higher colonoscopy completion rate and higher ADR than patients using the 4L PEG-ELS regimen. Analyses will be based on intention-to-treat (ITT) principles, with all randomized patients included in the primary analysis and analyzed according to the regimen to which they were randomly allocated. At the conclusion of the trial we will report the primary outcome measures (i.e., colonoscopy completion rate and ADR) for each preparation regimen group with 95% confidence intervals as well as the difference in outcome rates between arms with their 95% confidence intervals. Because of the very large sample size and fixed-design 1:1 randomization, we anticipate minimal imbalance in baseline characteristics between study arms. Adjustment for baseline patient characteristics is therefore not anticipated to be necessary in the primary analysis. Treatment arms will be compared using two-sample tests of proportions. To account for the multiple primary outcomes, hypothesis tests will be conducted at the 2-sided □ = 0.025 level in order to control the type I error rate at the family-wise 0.05-level using a Bonferroni correction to account for the two hypothesis tests.

E.9.2.2 Secondary Effectiveness Analysis

Our study will have three secondary effectiveness outcomes. The first secondary outcome is the rate of cancellation or no-show in each bowel prep arm. The second secondary outcome is adequate bowel preparation, a binary indictor based on endoscopist rating of excellent or good quality bowel preparation. The corresponding parameter of interest is the proportion of patients in each arm of the trial rated as having excellent or good quality bowel preparation, computed among the subset of patients in whom the colonoscopy examination was started regardless of the extent of the examination. The third secondary outcome is a binary outcome based on patients' self-reported willingness to repeat the bowel preparation regimen among patients attending their scheduled colonoscopy. The corresponding parameter of interest is the proportion of patients reporting willingness to repeat the bowel preparation regimen in each arm of the study, computed from among those patients in whom the colonoscopy examination was attempted regardless of the extent of the examination. We hypothesize that patients using the 2L M-G regimen will have lower cancellation/no-show rate, higher adequate bowel preparation rates and a higher proportion willing to repeat the regimen than patients using the 4L PEG-ELS regimen.

Analyses for cancellation/no-show rate will mirror those for the primary outcomes. However, since the other two secondary outcomes will be estimated among the subset of patients in whom the colonoscopy was performed, we will exclude all patients not attending their scheduled procedure or the few patients who showed up but do not undergo the colonoscopy (e.g., having fever, non-compliance with dietary instruction, etc.). At the conclusion of the trial we will report the secondary outcome measures (i.e., cancellation/no show rate, adequate bowel preparation

rate and proportion willing to repeat the regimen) for each preparation regimen group with 95% confidence intervals as well as the difference in outcome rates between arms with their 95% confidence intervals among patients attending their colonoscopy. Treatment arms will be compared using two-sample tests of proportions. To account for the multiple secondary outcomes, hypothesis tests will be conducted at the two-sided = 0.017 level in order to control the type I error rate at the family-wise 0.05-level using a Bonferroni correction to account for the three hypothesis tests.

E.9.2.3 Exploratory Sub-group Analyses

We will conduct additional exploratory analyses to examine the comparative effectiveness of the two bowel prep regimens within subgroups of trial participants. We will compare three effectiveness outcomes, colonoscopy completion rate, ADR, and proportion willing to repeat the regimen, in pre-specified sub-groups defined by patient gender, advanced age (≥ 65 or <65), DM, timing of colonoscopy (AM vs. PM), and history of constipation, narcotic use or laxative use. These factors have been associated with bowel preparation quality. Within strata defined by each sub-group, we will compute outcome measures as described above and compare treatment arms using two-sample tests of proportions. Because of the potentially limited sample size within some patient sub-groups, this analysis will be primarily descriptive. However, we believe it will provide useful information to inform the design of future studies including implementation of primary trial results.

E.9.2.4 Safety Analysis

To ensure safety of the 2L M-G regimen, we will evaluate one safety outcome, incidence of hyponatremia or renal failure in the 6-month period following colonoscopy. We will report the number and proportion, with 95% confidence intervals, in each treatment arm experiencing hyponatremia or renal failure in the 6-month period following the colonoscopy.

E.9.2.5 Accounting for Within Endoscopist Correlation

While some of our outcomes are largely dependent on patient behavior and preferences, provider-specific ADR and rate of adequate bowel preparation may potentially exhibit some within-endoscopist correlation. Correlation within clusters defined by endoscopists will tend to decrease the effective sample size and power of our study. Because we anticipate that variability attributable to endoscopist will constitute a small proportion of the overall variability, our primary analyses will be conducted at the patient-level without accounting for endoscopist. However, we will conduct sensitivity analyses to ensure that within-endoscopist correlation does not affect our inference. Because of the small number of endoscopists included in this trial (an estimated n = 8 endoscopists), we will use fixed effects logistic regression models including terms for treatment arm and a separate fixed effect for each endoscopist to account for this source of correlation. By conditioning on endoscopist, the resultant fixed effects regression model satisfies the assumption of conditional independence among observations from the same cluster. We have selected this approach because alternative approaches to accounting for within-cluster correlation, including generalized estimating equations and mixed effects models, are unsuitable in the context of small numbers of clusters. We will compare the statistical significance of the treatment arm term in these regression models to the significance from our primary and secondary analyses using two-sample tests of proportions to ensure that within-cluster correlation does not affect our inference.

9.3. Provide sample size determination and analysis (include anticipated rate of screen failures, study discontinuations, lost to follow-up, etc.)

The GI section is expected to perform 10,500 colonoscopies over the 3-year recruitment period. Based on our pilot data, the 10,500 colonoscopies performed will entail approximately 15,000 colonoscopies scheduled during the same period. Again based on our preliminary data, 11% of the scheduled colonoscopies during the period will be expected to represent repeat examinations for the same patients during the 3-year period and will thus be excluded. Due to the low risk of the intervention and minimal burden on the provider and participant, we expect to have very high enrolment rates among eligible patients. We therefore project to randomize 10,000 eligible patients with scheduled colonoscopy. Following the ITT analysis design, all 10,000 randomized patients will be included in the primary analysis with 5,000 allocated to each treatment arm. Based on preliminary data, we anticipate that in the 4L PEG-ELS arm 74% of patients will show up for their scheduled colonoscopy and undergo the examination, and 75% will have adequate bowel preparation. We therefore anticipate that 56% will satisfy our composite primary outcome of colonoscopy completion.

9.4. Describe how, where and by whom the data will be analyzed.

The data analysis for the primary and secondary aims will be performed by the biostatistician (Dr. Hubbard) and the PI. The exploratory cost analysis data will be analyzed by Dr. Glick and the PI.

Section 10: References - Bibliography of cited literature