COVER PAGE

Study Title: Prospective RCT Of Water Exchange (WE) vs. WE Plus Cap-Assisted Colonoscopy

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Abbreviated Protocol - Submitted To DMC

TITLE: PROSPECTIVE RCT OF WATER EXCHANGE (WE) VS. WE PLUS CAP-ASSISTED COLONOSCOPY

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PROTOCOL

I. Introduction

The purpose of this study is to compare two different, but normally, used methods of colonoscopy in patients examined by the water exchange (WE) method alone versus water exchange plus a transparent cap. This study involves the use of an FDA approved, commercially available and clinically used, transparent cap that will be fitted onto the end of the colonoscope at the tip. The aim of this study is to determine which method (with or without cap) is more effective in diminishing pain during the insertion of the colonoscope.

This will be a multi-VA site, unblinded investigators, prospective random control trial (RCT). Randomization (WE, WE + regular transparent cap) will be based on computer generated random numbers placed inside opaque sealed envelopes. The envelope (in pre-arranged order) will be opened to reveal the code when the colonoscopist is ready to insert the endoscope to begin the examination.

There are two arms or groups to this study: WE (water exchange) control group and WECAC (water exchange plus transparent cap placed at tip of the colonoscope) group which will use water plus a cap instead of air.

- Control Method (WE): This group will have the air in the colon removed and replaced with water to guide the insertion of the colonoscope.
- Study Method (WECAP): This group will use water instead of air plus the transparent cap fitted onto the end of the colonoscope.

The goals are to determine if WECAC significantly reduces real-time maximum insertion pain (RTMIP) in both genders, to identify baseline patient-and procedure characteristics that predict low RTMIP, and to assess impact of WECAC on secondary outcomes. An additional goal is to develop pilot data to assess the hypothesis that WECAC, by increasing proximal colon ADR, can reduce the occurrence of post colonoscopy colon cancer (interval cancer) particularly in the proximal colon. This long term objective in the unsedated Veterans will be facilitated by identifying the least painful insertion method.

Patients who are willing to participate will sign an informed consent before starting the colonoscopy procedure. Separate parallel randomization will be set up at each site, stratified by investigator and type of colonoscopy (screening or surveillance). All subjects will have been scheduled for unsedated colonoscopy as a result of lack of escort or personal preference.

This multi-site study is designed to enroll 256 participants in total. Up to 150 patients are anticipated to enroll from the VA Greater Los Angeles Healthcare System. The performance

site at the WLAVA will be in building 500, 5 East Clinical Procedure Center. The other study sites include: Sacramento VAMC and Palo Alto/Livermore VAMC.

This study is expected to take up to 5 years to complete. The expected duration of the patient's participation in this study is 1 hour for the colonoscopy procedure.

II. Screening Procedure

Patients will have already been scheduled for the colonoscopy procedure as part of their standard care. The patient will have received instructions for the standard preparation of the unsedated colonoscopy along with a flyer identifying and explaining the research study. The flyer will instruct the patient to call either the PI or the Study Coordinator for more information on the study if he/she is interested in participating.

If the patient is eligible, then either the PI or the Study Coordinator will ask the patient to sign the consent form. Then the patient will undergo the following assessments which can be done either at a screening visit or during the day of the procedure: a series of questionnaires, physical examination, and unsedated colonoscopy with the standard (control) or study methods. If the patient does not meet the eligibility criteria, then he/she will be offered usual unsedated colonoscopy using standard method, outside of the research study.

When the patient reports for the examination, he/she will be asked to complete a series of questionnaires related to their expectation of the examination before the actual colonoscopy procedure and after the proecedure.

III. Colonoscopy Procedure

1. The patient will have been seen scheduled for an unsedated colonoscopy (screening or surveillance) by the GI section.
2. The patient will be instructed to prepare him/her-self for the preparation of the colonoscopy procedure either by attending an educational class or choosing to receive written instructions by mail. The study information will be presented to the patient either during the instructional class or sent by mail (study flyer) with the written instructions.
3. The patient will prepare him/her-self in the standard fashion one day before the colonoscopy.
4. During the screening visit (day of procedure), the study staff will interview the patient and review their record to obtain information about social security number, address, telephone number, age, gender, and use of pain medications (Demographic Questionnaire).
5. The visit will take place in the Clinical Procedure Center located in building 500, 5East, Room 5239. The PI will ascertain eligibility from the inclusion criteria of the IRB-approved protocol. If the patient meets the inclusion criteria, he/she will be consented, enrolled, and then be randomized.
6. The control and study methods of the research study will be explained to the patient.
7. The patient will be asked to agree to allow the doctor to perform the colonoscopy by either the control or study method based on a code (prepared by the biostatistician)

inside an envelope which the doctor will pull from a box immediately before the start of the examination, scheduled after the screening visit.

8. During the colonoscopy procedure, the patient's vital signs and other procedural data (including pain scores) will be monitored and recorded.
9. After the procedure, the patient will be asked to complete two (2) questionnaires asking him/her to report on his/her experience of any abdominal discomfort, and satisfaction with the colonoscopy procedure: Patient Satisfaction and Patient Willingness to Repeat Questionnaires.
10. After the colonoscopy, the patient will be monitored in the recovery area per usual manner until discharge by the PI.
11. Polypectomy and biopsy will be performed, as usual, and all tissues will be submitted for routine histological assessment and the pathological findings will be recorded.

Detailed Protocol - Originally Submitted and Approved

Research Narrative

(1) Rationale

(a) Statement of the Problem

The VA provides screening, surveillance and diagnostic colonoscopies, but many eligible *male and female* Veterans (8.8%) (14) to 10.5% (15) are underserved. *Since sedation is standard (with escort requirement and Veterans' lack of knowledge of the unsedated option*), without escort, these eligible Veterans do not participate (15). *For example, in an unpublished recent (Aug to Dec 2015) audit, 51 female Veterans at VAGLAHS were scheduled, 30 completed with sedation, 21 cancelled or were no shows, and 6 were due to lack of escorts on the day of the appointed sedated colonoscopy. Based on CPRS records, none was offered the option of scheduled unsedated colonoscopy during the scheduling process. In another set of PI's unpublished pilot data 23% of female Veterans, and in a set of PI's published observations 33% male Veterans (5) were willing to participate in scheduled unsedated colonoscopy when the option was made available.* Historically, 2% of Veterans without escort were offered unscheduled unsedated colonoscopy (6,14-22). Other Veterans prefer to avoid sedation, due to their post-traumatic stress disorders (e.g., unpleasant flashbacks triggered by sedation), or because of personal preference (e.g., watch the examination, no escort needed, save time with no recovery or activity restrictions). They request unsedated colonoscopy (23,24,13). Programs negatively affected by nursing shortage (20,21) and no shows due to no escorts (15) found an effective solution in offering the scheduled unsedated option (15,20,21). Scheduled unsedated colonoscopy permitted completion of colonoscopy in Veterans who had prior paradoxical agitation, or a history of narcotic drug use (25). An increasing number of VA (6,14-22) and non-VA (26,27) sites have reported unsedated colonoscopy *in both male and female patients*. Pain which can lead to termination of insertion indicates development of the least painful insertion technique is relevant to Veterans health (24). Water exchange (WE) is less painful (mild pain) than air insufflation (moderate pain) in the unsedated Veterans *in studies with a predominance of male Veterans* (5,6,22). *The PI's international collaborators demonstrated in RCTs that female had significantly higher insertion pain scores than male subjects, WE significantly reduced insertion pain in both gender, and WE was the least painful insertion method in both males and females (4).* An even less painful method (*converting mild to no pain in males, and moderate to mild in females*) than WE in unsedated colonoscopy will further ensure its success in a patient-centered manner (8,9,23,24,25). The costs, nursing staff for recovery and VA-sponsored transportation, can be obviated. Completion for those with a personal preference for no sedation can also be accomplished effectively. The immediate aim (investigators with varying levels of experience in WE, cap and unsedated patients at multiple sites) is to assess the generalizability of the impact of WE plus cap (WECAC), as a potentially less painful insertion technique than WE. The primary outcome of RTMIP (unblinded measure, but one on which clinical decision is made) will be compared. *Power estimates show the revised male and female sample size will permit significant differences to be demonstrated in some of the previously listed secondary outcomes. The non significant ones will be dropped. Record of these will be kept, however, to demonstrate comparability of the two groups. Furthermore, when the male and female data are combined, the sample size may reveal differences between WE and WECAC worth pursuing, thus providing pilot data for future studies (e.g. overall and segmental adenoma detection rates in scheduled unsedated Veterans). Informed/educated male and female Veterans who choose scheduled unsedated colonoscopy due to no escort or personal preference for no sedation will be considered for enrollment.*

(b) Hypotheses

Primary Hypothesis: *Real-time maximum insertion pain (RTMIP) is significantly lower in both male and female Veterans examined by WECAC compared with WE.*

Secondary Hypotheses: *WECAC will show a significantly higher proportion with no pain, shorter insertion time and higher proximal colon ADR than WE alone in both male and female Veterans.*

Exploratory hypotheses: Co-variables affect Veterans' report of RTMIP.

(c) Specific Objectives

a. To determine if WECAC significantly reduces RTMIP in both genders, to identify baseline patient- and procedure characteristics that predict low RTMIP, and to assess impact on secondary outcomes.

b. If WECAC increases *proximal colon* ADR, we will prepare for a multi-site VA cooperative study. The goal is to assess the hypothesis that WECAC, by increasing *proximal colon ADR*, can reduce the occurrence of post colonoscopy colon cancer (interval cancer) particularly *in the proximal colon*. This long term objective in the unsedated Veterans will be facilitated by identifying the least painful insertion method.

(2) Background and Significance

(a) Background

Colonoscopy with air began without sedation. Insertion pain limited success in ~20% (13,23,24). Widespread use of sedation followed (13,23,24). In for-profit settings, anesthesiologist administered propofol is a major revenue stream; but has attracted criticisms (28). The VA focus on patient-centered care, teaching, efficacy, efficiency, and research data to support the mission, underpin efforts to discover technique(s) to attenuate RTMIP in unsedated Veterans. *High quality (29) [higher proportion completing colonoscopy with no pain, shorter insertion time, proximal colon ADR] further strengthens appeal*.

Factors linked to increased pain in unsedated cases reviewed by the PI (30) include: female, low body mass index (BMI) (≤25), female with low BMI, younger age (≤40 or ≤20 years), older age (>80 years), anxiety and anticipating discomfort; history of abdominal surgery, diverticulosis, diverticulitis, incomplete colonoscopy, and irritable bowel; difficult anatomy, inflammatory bowel symptoms, technically difficult insertion, lower gastrointestinal bleeding, obstructing malignancy, and following gastroscopy.

A method for minimizing pain will improve care and ensure compliance with surveillance in unsedated patients (31). The PI (5) and collaborators (1-4,7,10) have reproducibly confirmed that RTMIP (unblinded) is uniformly higher than and significantly correlated with recalled maximum insertion pain (blinded) (32). In a RCT comparing air vs. WE, the method, but not patient characteristics, was a predictor of RTMIP (5). When insertion techniques were compared, the secondary outcome of no pain was significantly more frequent in the WE group (33) than the CO_2 group. RCT comparing WE with water immersion, air or CO_2 revealed WE as the least painful insertion method (4); CO_2 insufflation did not reduce RTMIP.

Cap-assisted colonoscopy aided by air (34) reduced insertion pain, shortened cecal intubation time and increased polyp (34) or adenoma (36,37) detection. A Cochrane review recommended that RCT would provide clinically significant cap information (34). In consecutive group observational studies, the PI showed WECAC lowered insertion pain (11) and increased ADR (12,38). These findings await confirmation by RCT. Looping in the sigmoid is a cause of pain, especially in women (39). Implementation of loop reduction maneuvers consistently minimized insertion pain. Magnetic endoscopic imaging showed conflicting results (19,40). Carbon dioxide insufflation reduced pain after colonoscopy but not during colonoscopy (4).

(b) Significance

Sedation increases procedure-related costs, time and risk of cardiopulmonary complications. Some patients (preference, no escort) benefit from the unsedated option. *Maximization of tolerability is important*. *As noted by the Reviewers, WECAC adds novelty to the proposal by providing further improvement of WE technique and has the potential to provide useful information for those colonoscopists who routinely use unsedated colonoscopy. The proposal is the first to compare them against each other in a RCT. This study could provide information regarding the least painful colonoscopy technique.*

RTMIP is important because when it is excessive termination of insertion in scheduled unsedated colonoscopy is mandated. Visual analogue scale scores <2=no pain, 2 to 4=mild pain, and 4 to 7=moderate pain. A mean decrease of 1.2 [from 2.7 (mild pain) of WE to 1.5 (no pain) of WECAC (44% decrease) based on male pilot data] is clinically significant denoting improved comfort for the unsedated male Veterans.

After receipt of the critique, the PI identified 9 scheduled unsedated female Veterans (5 WE, 4 WECAC). RTMIP were WE, 6.2 (3.5) (moderate) and WECAC, 3.5 (3.7) (mild) (also 44% decrease). Female Veterans have significantly higher RTMIP than male Veterans when examined by WE, but the percent reduction of RTMIP by WECAC is equivalent (44%), and meaningful (from moderate to mild pain).

WE (being less painful) overcomes sedation as a barrier to screening. WE is used at VA (41), non-VA (42-44), and overseas (1-4,45,46) settings. The refinement will be welcome worldwide, if WECAC further reduces RTMIP (11,12, 47). Unsedated colonoscopy avoids institutional nursing and space costs, and hand injuries of assistants (with less need for abdominal compression) (48). Low ADR predicts interval cancer (49) in the proximal colon (50,51). In several RCT (1,2,52,53), WE significantly enhanced proximal (1,2) colon ADR (secondary outcome). In prospective observational studies, WECAC achieved high proximal colon ADR (11,12,47), surpassing WE. The impact of WE on ADR is being assessed by the PI and

collaborators elsewhere in the U.S. (NCT01607255), Europe (NCT02041507), Taiwan (NCT01894191) and China (NCT02135601). None overlaps with the current proposal *(focused on insertion pain).* The assessment of the impact of WE on ADR in unsedated patients in the U.S. awaits development of less painful insertion technique, e.g., WECAC, to permit large scale recruitment.

Patients requesting no sedation are educated about the option (54,55). To the PI, >30 gastroenterologists, endoscopists, Chiefs, Chairs and Deans, volunteered the information that they chose the unsedated option. Thus it is not an inferior option, when offered to underprivileged Veterans (13).

(c) Relevance to Veterans Health

Scheduled unsedated colonoscopy meets the needs of Veterans without escorts, or have a preference for no sedation. The option restored access when sedation was discontinued due to nursing shortage at one VA site (20); and significantly enhanced access for Veterans and productivity at another when no shows were due to no escorts (15). This will be the first RCT to assess efficacy of WECAC vs. WE.

(3) <u>Work Accomplished</u>

(a) Feasibility of scheduled unsedated colonoscopy and evaluations by patients

1. VA Sepulveda Ambulatory Care Center (SACC) (Participant - PD/PI)

After establishing the scheduled unsedated option at SACC (20,21 my biosketch), 25 male Veterans were surveyed (Table 1). Twelve (48%) were definitely willing to undergo repeat unsedated colonoscopy immediately after colonoscopy, and at the time of the survey. *Their mean pain score (1.26, no pain) was significantly (57%) lower than those (2.96, mild pain) who were not certain (n=9, 36%) or not willing (n=4, 16%) (Table 2).* Twenty male Veterans would still prefer the option even if escort had not been an issue, because the discomfort was only transient (lasting seconds) and outweighed by the benefits (e.g. preserved ability to communicate) (unpublished). The survey data showed reduced cost (no need to bring an escort) and absence of amnesia (able to communicate with colonoscopist) were major reasons for choosing the scheduled unsedated option. Willingness to repeat was closely associated with lower pain scores.

Table 1: Reasons for choosing unsedated colonoscopy (Total N=25, *all male, mean age 67*). Data as n (% total).			
No need to bring an escort/escort not available	21 (84%)	Short Distance from the facility	10 (40%)
Communication with the colonoscopist	18 (72%)	Concerned over sedation side effects	10 (40%)
Able to watch the procedure	16 (64%)	Return to work immediately after colonoscopy	5 (20%)
Familiarity with the doctor and facility	10 (40%)		

Table 2: Pain score (0=none, 10=most severe) - mean (SD). [*vs. Uncertain or Unwilling, $p < 0.05$, unpaired t test].				
Immediately After Colonoscopy			At time of Telephone Survey	
Uncertain or Unwilling	Definitely Willing		Uncertain or Unwilling	Definitely Willing
2.96 (2.60) (n=13)	1.26 (2.23)* (n=12)		6.04 (1.98) (n=13)	2.58 (2.13)* (n=12)

In male Veterans, an observational study showed cecal intubation rate and proportion reporting willingness to repeat (97% vs. 76%; 90% vs. 69%) were significantly higher with WE, respectively (22). In a follow up RCT (5), 82 *male* Veterans were randomized to air (n=40) or WE (n=42). Cecal intubation (78% vs. 98%, P<0.05), willingness to repeat (78% vs. 93%, P<0.05), and mean (SD) RTMIP (0=none, 10=most severe) (5.5 (3.0) vs. 3.6 (2.1), P=0.002) were significantly better with WE. Method but not patient characteristics predicted lower pain score (t=-1.99, P=0.049, R^2=0.074). WE numerically increased ADR (5).

2. West Los Angeles VAMC (Participant - PD/PI, Sul, Cohen and others)

Scheduled unsedated colonoscopy was adopted at West LA VAMC to manage inefficiency of cancellations due to lack of escorts. Veterans without escorts were offered the option (Table 3).

Table 3. The scheduled unsedated option was formally adopted on 6/3/2013, at a meeting with all the schedulers when the comparison of sedated and unsedated colonoscopy was discussed (15).		
Attributes of scheduled options	**Sedated**	**Unsedated**
Availability; cecal intubation rate	Standard in U.S.; ~90%	Not usual in U.S.; 80-90%
Sedation risks: hypotension, hypoxia, arrhythmia, etc.	Very small	No
Need to consume purge preparation; escort requirement	Yes; Mandatory	Yes; Not required
Drive after colonoscopy; discomfort reduced by medication	No; likely	Yes; not applicable

Remember discussions; need recovery; activity restriction	No; yes; yes	Yes; no; no

Excluding poor preparation and obstruction, cecal intubation was 94.6% and failure due to pain was 5.4% (Table 4). Colonoscopists were willing to perform and supervise unsedated colonoscopy. The option effectively managed last-minute cancellations by patients (3% were female Veterans) without escorts (15).

Table 4. Number of unsedated colonoscopies, no shows, and acceptance by colonoscopists. [*Fisher's exact test.]

Date	**1/1/13-6/10/13**	**6/11/13-11/22/13**	**p**
Unsedated colonoscopies	30/1073 (2.8%)	126/1203 (10.5%)	0.0001*
No shows due to lack of escorts	50/1073 (4.7%)	5/1203 (0.42%)	0.0001*
Endoscopist participation in unsedated colonoscopy	8/22 (36%)	16/21 (76%)	0.0104*

3. Sacramento VAMC (Participant - JW Leung and others)

Consecutive *male* Veterans who requested scheduled unsedated colonoscopy were randomized to WE (n=50) vs. air (n=50). 90% had no escort. WE showed lower [mean (SD)] RTMIP: 3 (3) vs. 5 (3) (p=0.0008); higher willingness to repeat: 76% vs. 48% (p<0.0007); numerically higher overall (54% vs. 48%), proximal (40% vs. 28%) and proximal <10 mm (36% vs. 28%) ADR; comparable cecal intubation rate 98% vs. 88%, and insertion times 13 (7) min vs. 12 (7) min (6).

(b) Coaching in WE by PI (Participants - Friedland, Cheung, Cohen, Sul, Yen and others)

With experienced colonoscopists, impact of coaching (by PI) was established (my biosketch) (42).

(c) WECAC, WE, RTMIP & ADR (Participant - PD/PI, JW Leung, Yen, Sul)

Five colonoscopists with experience in WE performed WECAC at 3 sites (47) (Table 5, A). In 45 male patients completing without sedation, the low mean RTMIP of WECAC observed in a published pilot study (11) was reproduced (Table 5, A vs. B). In U.S. cohorts, mean RTMIP of WECAC was lower than those of historical unsedated cohorts examined by WE (5,6) (Table 5, A vs. C-D, respectively).

Table 5: Comparison of real-time maximum insertion pain (RTMIP)

Technique		References	Study Sites	No. of Investigators (type of no sedation)	RTMIP
A	WECAC	47	2 U.S., 1 Taiwan	5 (mixed on demand & scheduled unsedated)	1.5 (1.8)
B	WECAC	11	1 U.S.	3 (Scheduled unsedated)	1.2 (1.5)
C	WE	5	1 U.S.	1 (Scheduled unsedated)	3.6 (2.1)*
D	WE	6	1 U.S.	2 (Scheduled unsedated)	3 (3.0)*

Frequency; mean (SD). A=unpublished preliminary; B=published pilot; RTMIP, real-time maximum insertion pain; VAS: 0=none, 10=most severe., *p < 0.05, vs. 1.5 (1.8), t test.

Table 6 shows comparable intubation rates. Trends favored WECAC in intubation time WECAC (18-20 min) vs. WE (13-34 min), right colon preparation WECAC (3.1-3.3) vs. WE (2.3-3.0), painless insertion WECAC (41-51%) vs. WE (10-28%); overall ADR (56% vs. 46%), and proximal colon ADR (46% vs. 40%).

Table 6: Demographics and procedural outcomes

Technique		n	Age (yrs)	BMI	PAS	Cecal Intubation		Proximal Bowel Prep Score	Painless insertion	Overall ADR	Proximal Colon ADR
					Yes	Time	Rate (%)				
A	WECAC	45	62 (10)	29 (4)	34%	20 (14)	96	3.1 (0.5)	51%	Combined 40/72 (56%)	Combined 33/72 (46%)
B	WECAC	26	64 (8)	31 (5)	-	18 (12)	96	3.3 (0.5)	41%		
C	WE	42	66 (9)	32 (7)	-	34 (3)	97.6	3.0 (0.7)	10%	Combined 42/92 (46%)	Combined 37/92 (40%)
D	WE	50	61 (7)	30 (7)	30%	13 (7)	96	2.3 (0.5)	28%		

PAS, prior abdominal surgery. Bowel prep score: 4=excellent; 3= good; 2= fair; 1= poor. Data, mean (SD); % total.

Table 7: Procedural details

Technique	Screening/ Surveillance/	Position Change (%)	Abdominal Compression (%)	Water Volume on Arrival to Cecum (L)	Withdrawal Time (min)

		Diagnostic	Yes	Combined	Yes	Combined	Infused	Suctioned	
A	WECAC	19/15/11	29	25%	44		1.6 (0.8)	1.9 (1.4)	21 (11)
B	WECAC	17/10/0	19		30		1.3 (1.2)	1.4 (1.6)	23 (13)
C	WE	17/17/8	64	34%	57	40%	1.8 (0.7)		22 (13)
D	WE	36/14/0	8		26		1.5 (0.7)		19 (11)
Frequency count; (%), % of total; mean (SD); L, liters; blank cell=data not listed in reports.									

Table 7 shows that indications were variable. WECAC required 1-2 L infusion; equivalent volume suctioned upon cecal arrival, confirming infused water suctioned mostly during insertion. Position change (25% vs. 34%) and abdominal pressure (37% vs. 40%) were needed less often with WECAC than in WE.

4. VA Palo Alto Healthcare System (Participant - Friedland and others)

In 229 male Veterans successful minimal-sedation was 51% (water immersion) vs. 28% (air), P=0.0004, less pain (4.1±2.7 vs. 5.3±2.7; P=0.001) (56). PI's coaching (42) led Dr. Friedland to use WE (57). After coaching (42) co-investigator Dr. Cheung has adopted WE (no formal published data).

(e) *Significant correlation between RTMIP and recalled maximum insertion pain (PD/PI, Cadoni)*

The PI (5) and collaborators (3,4) have reproducibly confirmed that RTMIP (unblinded) is uniformly higher than recalled maximum insertion pain (blinded) and the 2 measures are significantly correlated (26).

(4) Work Proposed

(a) Study type descriptor. Prospective, multisite, multi-investigator, RCT, single (patient) blinded.

Sites (no. investigators). VA: VAGLAHS (n=3); VAPAHCS (n=2); VANCHCS (n=2).

(b) Research design, methods and procedures to be used to accomplish the specific aims.

The investigators will describe the study at local lectures. The research coordinators will distribute flyers about the RCT to practitioners in primary care clinics, and will work closely with the colonoscopy schedulers to identify potential candidates (no escort, preference for no sedation). For scheduled unsedated Veterans, the coordinator will send each patient material (e.g. summary description, consent form) related to the RCT, with a follow up phone call to address questions that the Veterans may have. *At all sites, Women's Health Clinics will assist the coordinators, to inform female Veterans of the scheduled unsedated option.*

Inclusion criteria. *Informed/educated (about pros and cons of the unsedated option)* male and female *Veterans* (18-80 years old) undergoing diagnostic (positive stool occult blood test in the context of screening), surveillance (follow up of polyps) or screening (first-time) colonoscopy at participating sites, choosing scheduled unsedated colonoscopy for any reason (lack of escort, personal preference).

Exclusion criteria. Decline to be randomized**,** unable to give consent or respond to questionnaires, history of colon surgery, active inflammatory bowel disease, lower gastrointestinal bleeding (except for occult blood or FIT positive in the context of colon cancer screening)**,** therapeutic colonoscopy (e.g., hemostasis, removal of large polyp)**,** proctosigmoidoscopy**,** bidirectional endoscopy**,** inadequate consumption of bowel preparation**,** known history of severe diverticulosis or diverticulitis**,** history of abdominal surgery previously requiring sedation for colonoscopy**,** current narcotic/anxiolytic medication use**,** prior unsuccessful experience with unsedated colonoscopy**,** emergent colonoscopy, evidence of colonic obstruction based on pre-colonoscopy clinical evaluation, current participation in other studies, medical condition that could increase the risk associated with colonoscopy (e.g., active cardiac or pulmonary disease or other serious disease), medical condition that would preclude a benefit from colonoscopic screening (e.g., cancer or any terminal illness), prosthetic heart valve, anticoagulant therapy, nonmedical problems (e.g., psychiatric disorders, excessive use of alcohol), need for special precautions in performing colonoscopy (e.g. antibiotic prophylaxis), and request of on demand sedation.

Primary outcome measure (for male and female subjects).

Real time maximum insertion pain (RTMIP) (unblinded) score (validation by correlation with recalled pain described below)	Pain during insertion reported to the unblinded assisting nurse, visual analogue scale, VAS: 0=none, 10=most severe. The highest pain score will be tabulated for analysis. Timing of data collection will be at the discretion of the nurse to minimize bias by colonoscopist behavior.

Secondary outcome measures (for male and female subjects).

Proportion with no insertion pain	Proportion report no pain during insertion of the colonoscope. Quality marker.

Insertion time	Time to cecum (clock display on monitor). Faster insertion is a quality marker
Proximal colon ADR	ADR from cecum to splenic flexure. Measure of high quality colonoscopy

Method of randomization. After signing informed consent patients will be randomized to WE or WECAC, based on computer generated random numbers accessible using the web-based randomization application set up by the Data Curation Center (DCC) programmer. The code will be revealed when the colonoscopist is ready to insert the endoscope to begin the examination. Randomization will be carried out by the method of random permuted block design with variable block sizes of 4 and 6. Gender will be used as a stratification factor. The 7 VA investigators will be a blocking factor for the randomization to obtain treatment balance across investigators, however in the analytical phase the data from these investigators will be combined for the analysis of the primary endpoint.

Control technique (WE) (Table 8). (5,8,9,23,41) Complete exclusion of air (air pump off) minimizes colon distention and elongation. Water will be infused via the accessory channel intermittently during insertion using a peristaltic pump. Turbid water due to residual feces will be suctioned and replaced by clean water to ensure visualization of the lumen. Suction of infused water and all residual air will be implemented. Infused water will be removed predominantly during insertion (checked by the volume infused and suctioned being comparable upon arrival to the cecum). Adjunct maneuvers will be used as described later. Cecal intubation is confirmed by touching the floor of the cecum, and viewing the medial aspect of the cecum between the appendix orifice and ileocecal valve. Mucosal inspection, biopsy or polypectomy will be performed in the air filled colon during withdrawal using withdrawal time >6 min.

Study technique (WECAC) (Table 8). (11,12,47) A FDA approved, commercially available transparent cap (Olympus) will be fitted to the colonoscope tip. The usual and adjunct maneuvers otherwise are similar to those of WE described above. Sporadic reports suggested the cap reduced insertion pain when air was used (58-61). The effect of the cap plus WE on pain has not been reported in RCT. The pilot (11) and preliminary data (12,47) of the current team do indicate WECAC reduces RTMIP compared to historical cohorts. The possible mechanism of further reduction of insertion pain is not known. The cap may ease the pinpointing of the correct location of the collapsed lumen (22) by maintaining separation of the mucosa from the lens of the colonoscope, improving visualization in a non-distended colon. The cap is particularly helpful at acute bends in the air filled lumen (62-65).

Table 8: Content of colonoscopy insertion techniques	WE	WECAC
Cap attached to tip of colonoscope		✓
Split-dose bowel preparation, begin without medication, air pump off before start of examination, small towel cover eyes during insertion for blinding patient to the technique used, air pocket and residual feces suctioned during insertion, infused water suctioned predominantly during insertion, frequent loop reduction, change position if scope tip does not advance despite loop reduction, abdominal compression if scope tip does not advance despite above maneuvers	✓	✓

Patient and procedure factors affect insertion pain. Proper randomization will distribute these factors evenly amongst the groups. Change in the subject pool over time may occur as the trial may extend over years. The types of patients attending the clinic may change. Block randomization ensure that comparable numbers of subjects are assigned to each arm at each period of the study.

Standard tools will be used to ensure as far as possible that all patients are prepared and examined similarly, with only the dependent variables varying systematically between groups.

Bowel preparation. Standardized split dose minimizes differences in bowel preparation quality. Trained support staff will provide the instructions to minimize variations in patient compliance. Efforts will be made (e.g., telephone reminders by research coordinator) to encourage proper compliance. The most up-to-date purge preparation will be used. Standard instructions will be provided by the schedulers. There are variations in the bowel regimen at participating sites at present. The preparation will be standardized during the start-up period. Veterans with diabetes, chronic constipation, or known history of poor bowel preparation will be asked to refrain from solid food intake for an extra day before colonoscopy.

Patient blinding. An air filled surrounding results in unblinding of the cap (rim around the tip). Several measures will be used to blind the patients. 1. The patients will not be informed of the technique (with or without cap), and what the cap at the tip looks like. 2. The colonoscope will be set up in the absence of the patient. 2. Before the start, a small towel will cover the eyes of the patients, and care will be taken not to

uncover the eyes when the patient is moved. Upon confirmation of arrival to the water-filled cecum (passing ileocecal valve, viewing the appendix opening and touching the cecal floor, or intubation of the terminal ileum), the patient will be asked to guess which technique has been used. If the correct guesses are <60%, adequate blinding during insertion will be assumed (3,4). As an accepted benefit of unsedated colonoscopy, the patient can observe and ask questions during the withdrawal phase. Air will be used to distend the lumen for inspection, and biopsy or polypectomy during withdrawal in all patients.

Adjunct maneuvers. These will include loop reduction, patient position change and abdominal compression. They will be employed in the order as listed to minimize assistant hand/wrist injury. Loop reduction will be applied whenever insertion is not associated with advancement of the tip of the colonoscope in the lumen. Position change will be employed whenever the tip of the colonoscope fails to advance despite loop reduction. Abdominal compression will be employed when both of the above fail to permit advancement of the colonoscope. The number of times application of these maneuvers is employed will be recorded for analysis.

Management of polyps. To optimize insertion time, all polyps will be managed during withdrawal. Small polyps (size <7 mm) will be removed by standard cold snare or biopsy forceps. Larger polyps (size >7 mm) will be removed by hot snare. Very large polyps with features suggestive of malignancy will be biopsied for diagnosis, with removal in the same session or referral to local interventional colonoscopist, at the discretion of the colonoscopist. The research coordinator will add pathology results to the database.

Management of adverse events. Colonoscopy-related adverse events (AE) (e.g., persistent abdominal pain immediately after colonoscopy, fecal incontinence), and severe adverse events (SAE) (e.g., severe bleeding requiring interventions and blood transfusion, perforation, cardiovascular events during and immediately after colonoscopy) will be monitored by assisting nurse, and research coordinator, and appropriately managed by the investigators. Subjects will also be instructed to return to the emergency department if AE persists or SAE develops. The subjects will be contacted by the research coordinator by phone at 24 hours, weekly until 30 days after colonoscopy. All AE and SAE will be recorded by the research coordinator and reported to the investigators, PD/PI, data safety and monitoring board and local IRB.

(c) Subject recruitment.

Subject availability (scheduled unsedated colonoscopy).

Experience of scheduled unsedated colonoscopy in recent years	No. of male Veterans	*No. of female Veterans*
VA Greater Los Angeles Healthcare System	1 to 2/month	*1 Veteran/month*
VA Northern California Healthcare System	1 to 2/month	*1 Veteran/month*
VA Palo Alto Healthcare System	1 to 2/month	*1 Veteran/month*

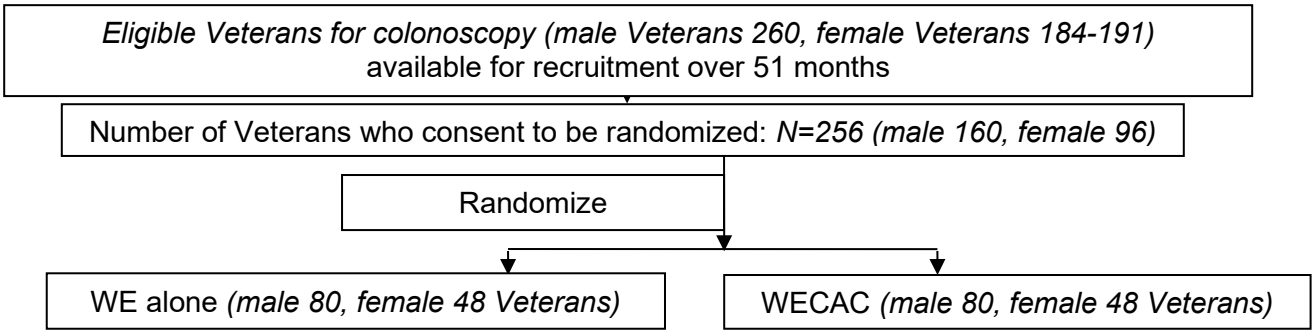
When ~2200 colonoscopies were offered at VAGLAHS, updated pilot data showed the PI performed 30 (1.36%) scheduled unsedated colonoscopy in male Veterans in one year. At participating sites, a total of ~9000 colonoscopies (VAGLAHS 2200, VANCHCS 3300, VAPAHCS 3500) will be performed each year. For conservative estimation, 1/2 of 1.36% (0.68%) of all colonoscopies will be presumed to be in scheduled unsedated male Veterans when the option is made available. In 51 month (4.25 year) enrollment period, a total of 38520 colonoscopies will be performed. 260 (0.68% of 38520) male Veterans will receive scheduled unsedated colonoscopy, making target enrollment of 160 achievable (only 62% enrollment rate needed).

Additional unpublished pilot data showed that of 400 consecutive colonoscopies performed by the PI, 17 were in females, of whom 4 (1% of 400) requested no sedation (personal preference or no escort). I'll assume 1/2 of 1% (0.5%) of all colonoscopies will be in scheduled unsedated female Veterans when the option is presented up front. In 51 month (4.25 year), 191 (0.5% of 38250) will choose the option and available for recruitment. A recruitment rate of 50% (96/191) will be needed. We observed that when female Veterans lacked knowledge of unsedated colonoscopy, and if the option was not offered, 100% would be scheduled sedated and asked to bring escorts; those without escorts were left out (e.g., in a recent 5 month audit conducted by the PI at VAGLAHS, 6 of 51 scheduled female Veterans had last minute cancellations due to no escorts). These missed opportunities will be a source that the research coordinators will focus on. At each site we'll request VA Women's Health Clinics to assist the coordinators, to inform female Veterans of the scheduled unsedated option. As pointed out by Women's Health Directors, VA statistics indicate that nationwide, female Veterans, 11.6% of all Veterans in 2013, are projected to increase to 13% in 2020. With post-deployment chronic diarrhea, abdominal pain, 35% have digestive system diagnosis; and after

exclusion of Giardia and Amoebiasis, colonoscopy is frequently used in further assessment. The increase over time will further enrich the pool of available female subjects. If 6 female Veterans in 5 months at one site were limited by no escorts, the total number during the study period will be 6/5 months x 51 months x 3 sites = 184; they will be targeted by the research coordinators for enrollment into the study. The concordance between the number (191 and 184) of available female Veterans based on estimates using two different approaches is remarkable and will enhance our confidence in recruitment. Since there will be a sufficient number of female Veterans available for recruitment, we'll drop other previously described approaches that will require additional expenses to recruit non Veteran females (e.g., radio advertising).

Timeline. A 6 month startup is anticipated to put all procedures in place (e.g. hire/train part-time coordinators, obtain local committee approval, prepare mailed material for patients. 51 months will be devoted to recruitment of subjects and performance of scheduled unsedated colonoscopy using WE or WECAC. The last three months will be devoted to data analysis and preparation of reports.

Flow Chart Based on CONSORT Guideline



(d) Description of base population and groups to be studied.

Base Population. Patients without escorts or with a personal preference for no sedation will be given a standard description (Table 3) of the scheduled unsedated option by the research coordinator (15). Veterans who accept the option will receive standardized verbal and written description of the RCT. Those interested in participation will be given a description of the study and consent form will be mailed for review. Prior to the start of colonoscopy, any further questions will be addressed. The patients will be informed that the endoscopist will use maneuvers (e.g., loop reduction, removal of colonic luminal content, position change, abdominal compression) to minimize insertion pain. These will be recorded by the assistant. Topical lidocaine (2%) will be applied to the anal canal to minimize purge or hemorrhoid-related anal discomfort. All subjects will be informed that the colon will likely react to the presence of the colonsocope to "push it back out". This translates into a sensation of an urge to have a bowel movement. The reaction is normal and natural. More severe pain will be reported to the colonoscopist who will employ maneuvers to minimize the pain. During the examination if implemented maneuvers fail to keep pain at a tolerable level, insertion will be halted. Enrolled patients will sign informed consent before start of colonoscopy to agree to be randomized, to allow the colonoscopy examination be recorded for analysis, to respond to questionnaires before, immediately after and at 24 hours, weekly thereafter until 30 days after colonoscopy. *Subjects who fail cecal intubation due to pain have the option to reschedule for a repeat colonoscopy under sedation (with usual escort requirement).*

(e) Justification of endpoints, procedures and links between questions, data, and endpoints.

Primary outcome. Patient with insertion pain that cannot be brought to a tolerable level by colonoscopist implemented maneuvers will be considered failure of cecal intubation and the insertion will be discontinued. The pain level at the time of discontinuation will be noted for analysis.

Standardized validated instruments.

Proportion with no insertion pain, insertion time, proximal colon ADR (secondary outcomes in males) have been defined above; demographic data, co-morbidities, prior history and additional procedure based and patient level parameters will be analyzed as covariables (Tables 9 and 10).

Table 9: Demographic variables, co-morbidities and prior history				
Age	In years		Hemorrhoids	0=no, 1=yes
Gender	Male, female		Chronic pain treatments	0=no, 1=yes

Education	Elementary, high, college, graduate		Substance abuse	0=no, 1=yes
Ethnicity	White, Black, Hispanic, Asian, other		Prior abdominal surgery	0=no, 1=Yes (type)
BMI	Weight/height^2		Prior sedation colonoscopy	0=no, 1=yes
Indication	Screening, surveillance, diagnostic, pain		Prior unsedated colonoscopy	0=no, 1=yes

Table 10: Additional procedure based and patient level covariates

Recalled maximum insertion pain score (blinded data)	*Maximum pain during insertion reported to a blinded observer after colonoscopy before discharge, VAS: 0=none, 10=most severe. Correlation with RTMIP.*
Overall ADR - entire colon	*Proportion of patients with at least one adenoma of any size.*
Right colon ADR	*ADR from cecum to hepatic flexure*
Adequacy of patient blinding	Patient guesses which method is used (<60% correct=adequate).
Successful cecal intubation	0=no, 1=yes
Current abdominal discomfort	Abdominal pain prior to start of colonoscopy: 0, none to 3, severe (recorded before examination)
Loop reduction maneuvers	Number of times used, recorded by nurse assistant
Position change	Start with left lateral, change as needed to supine, right lateral, prone.
Abdominal compression	0=no, 1=Yes (sigmoid, transverse, hepatic, right side)
Need to change technique	0=no, 1=yes (to air insufflation)
Water volumes (insertion)	Volume of water (infused and suctioned) upon arrival to the cecum, equivalent volumes confirm appropriate application of water exchange
Water volumes (total)	Volume of water (infused and suctioned) at the end of colonoscopy
Quality of bowel preparation	Documented during withdrawal (4=excellent, no residual stool; 3=good, small amount of residual stool; 2=fair, moderate amount of residual stool; 1=poor, large amount of residual stool) (5)
Failed (poor prep)	No. of patients in whom the cecum is not reached due to poor prep
Video data	Based on playback review of recorded procedure by blinded observer and tabulation of pertinent variables described above. Insertion and withdrawal phase will be separately coded for blinded review
Patient satisfaction	0=not satisfied, 10=very satisfied
Willing to repeat same in future	*0=not willing, 10=willing. Recorded by blinded observer prior to discharge.*
Recommend to family/friends	0=not willing, 10=willing. Recorded by blinded observer prior to discharge.
Participant satisfaction	0=Not satisfied, 10=satisfied
Reason for choice of unsedated	No ride, personal preference, other
Abdominal discomfort today	0=none to 3=severe (recorded before examination)
Expectation today	0=poor to 4=excellent (recorded before examination)
Previous endoscopy experience	0=poor to 4=excellent (recorded before examination)
Pain tolerance (patient reported)	0=poor to 4=excellent (recorded before examination)
Subjective anxiety	0=none to 3=high (recorded before examination)
Objective anxiety	0=none to 3=high (assessed by endoscopist before examination)

Record keeping: A digital video recorder will be used to record the procedure to document procedure times (insertion, arrival in the cecal, biopsy, polypectomy, end of examination), cecal intubation (touching cecal floor) and the findings during the withdrawal phase. The digital images will bear no personal identifier.

Links. Enrolled patients will be randomized to 2 groups for examination. We can determine if WECAC will be superior to WE alone in providing low insertion pain. The influence of covariables on results of treatment can also be determined. The CONSORT guideline will be followed in reporting the data.

Standardization: During the start-up period, the PI will re-visit each site to facilitate standardization of WE and WECAC, and use of loop reduction, position change and abdominal compression maneuvers.

(f) Data collection methods, intervals, and follow-up procedures:

Prospective data gathering. Table 11 shows measures, their purposes, timing of data collection.

Table 11: Data to be monitored[a]	Baseline	During or after Colonoscopy	Up to 1 month follow up[b]
Co-variables: Demographic data interview & record review, detailed medical and surgical history, physical examination, e.g. anal rectal pain	X		
Procedural data, primary outcome: RTMIP (unblinded); patient guesses which method has been used, recalled maximum insertion pain score (blinded) [validates primary] [c]		X	
AE, adverse events; SAE, serious adverse events.		X	X
[a]Data obtained by investigators, nurse assistants or coordinators at visits; [b]Data obtained by mailed questionnaires and follow up telephone calls; [c]Questionnaires will be completed not in the presence of the therapist(s).			

Training and quality control measures to assure accuracy, precision and validity of the data

Throughout the 6-month start-up period, training of study personnel will take place by way of conference calls by all participating investigators, site research coordinators and statistic core personnel. Case report forms will be finalized and a detailed manual of study operations will be written and circulated. This manual will serve as the training manual for the meetings and as a reference document following the meetings. The PI's office and the data coordinating team will provide the training.

The general training will include the study treatment, patient screening and consent, baseline evaluation, follow-up procedures, and proper entry and maintenance of data (assisted by statistics core personnel). Research coordinators from all participating sites will be trained in the administration of a variety of state-of-the-art assessment instruments to insure accuracy and precision of administration of the instruments to maximize inter-rater reliability.