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RESEARCH STUDY PROTOCOL

Title: A comparison of CO2 absorption during gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 mmHg and 15 mmHg – a randomized controlled trial (AAAQ6474)

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Title: A comparison of CO2 absorption during gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 mmHg and 15 mmHg – a randomized controlled trial

Abbreviated Title: AirSeal®/CO2 absorption study

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ABSTRACT

Three main factors affect patients' cardiopulmonary status during gynecologic laparoscopy: 1) degree of Trendelenburg tilt (25 – 30°), 2) CO2 absorption and 3) increased intra-abdominal pressure (10 –20 mmHg). Slight modifications to any or all of these three factors can lead to a significant decrease in morbidity.

The AirSeal® valveless trocar system reduces CO2 absorption when compared to standard trocars during renal laparoscopy. [1] Also, use of this trocar system provides a more stable intra-abdominal pressure when compared to standard trocars, a feature that could possibly allow for laparoscopic surgery to be performed at lower intra-abdominal pressures.[2] We hypothesize that with the AirSeal® valveless trocar system, gynecologic laparoscopy can be performed at a lower intra-abdominal pressure with a possible resultant decrease in CO2 absorption, while maintaining adequate visualization of the operative field for safe completion of surgery.

The purpose of this study is to compare CO2 absorption during gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg.

1.0 STUDY PURPOSE AND RATIONALE

Conventional and robotic-assisted laparoscopic procedures have become increasingly favored by gynecologists and their patients worldwide. As these minimally invasive techniques become more widespread, the surgeon has to be aware of, and respond to, different factors that will affect a patient's cardiopulmonary status during the procedure.

Three main factors affect patients' cardiopulmonary status during gynecologic laparoscopy.
During standard gynecologic laparoscopy, a 25-30° Trendelenburg tilt is needed to visualize the pelvic anatomy. In addition, an intra-abdominal pressure (IAP) of 10 to 20 mmHg is maintained with a continuous infusion of CO2 at a flow rate of 40L/min. The Trendelenburg tilt causes cardiovascular and gas exchange impairments that are exaggerated by the CO2 pneumoperitoneum.[3] These factors affect the anesthesiologists' ability to ventilate the patient and maintain adequate end-tidal CO2 (ETCO2). Furthermore, CO2 which is the most commonly used gas for laparoscopy is absorbed transperitoneally and this absorption combined with hypercapnia and hypoventilation can lead to cardiac arrhythmias and even cardiac arrest.[4] Multiple studies have demonstrated increased systemic absorption of CO2 gas during transperitoneal and retroperitoneal laparoscopy by measuring end-tidal CO2 (ETCO2) and CO2 elimination rates.[5,6]

In attempts to minimize the effects of CO2 pneumoperitoneum, various modifications to traditional laparoscopy have been explored including gasless and/or low-pressure pneumoperitoneum, and use of alternate gases (nitrous oxide, argon, helium) for insufflation; all with varying degrees of success. [7,8,9,10,11]

The AirSeal® valveless trocar system has the potential to minimize patient complications by decreasing systemic absorption of CO2 gas.
The AirSeal® valveless trocar system was designed to provide "stable pneumoperitoneum at a CO2 flow rate of 3L/min, continuous smoke evacuation and valve free access to the abdominal cavity"[12]. Use of this system is also associated with a decrease in CO2 use, absorption and elimination when compared to standard trocars.[1] This reduction in CO2 absorption potentially makes the AirSeal ® trocar system a more attractive alternative to standard insufflation. However to date, no randomized clinical trials have been performed to demonstrate clinically or statistically significant benefits of the AirSeal® trocar system until now.

The AirSeal® valveless trocar system has the potential to minimize patient complications by decreasing the intra-abdominal pressure needed to safely complete a laparoscopic gynecologic surgery.
There is scant evidence regarding the effect of low-pressure pneumoperitoneum on cardiopulmonary function during gynecologic laparoscopy. An increased intra-abdominal pressure during laparoscopic surgery reduces lung volume, increases peak airway pressure and decreases pulmonary compliance. In addition, this elevated pressure reduces diaphragmatic excursion and shifts the diaphragm cephalad, collapsing smaller airways and causing intraoperative atelectasis, which in turn decreases functional residual capacity.[13] It therefore makes sense that, in the event of refractory hypoxemia, high peak pressures or hypercapnia, the recommendation by anesthesia is to release pneumoperitoneum and re-insufflate slowly using a lower intra-abdominal pressure.[14] A recent systematic review of the use of low-pressure pneumoperitoneum revealed decreased pulmonary compliance in low-pressure vs. standard pressure pneumoperitoneum but showed comparable end tidal CO2, pCO2, oxygen saturation, pO2 and blood gas analyses.[15] However, only one study in this review involved pelvic surgery and so the generalizability of these conclusions to gynecology is limited.

AirSeal ® /CO2 absorption study protocol

Use of the AirSeal® trocar system provides a more stable intra-abdominal pressure when compared to standard trocars; a feature that could possibly allow for laparoscopic surgery to be performed at lower intra-abdominal pressures. We hypothesize that with the AirSeal® valveless trocar system, gynecologic laparoscopy can be performed at a lower intra-abdominal pressure with a possible resultant decrease in CO2 absorption, while maintaining adequate visualization of the operative field for safe completion of surgery. The purpose of this study

is to compare CO2 absorption during gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg.

2.0 STUDY DESIGN AND STATISTICAL PROCEDURES

2.1 Overall design

Type of study: A randomized controlled trial

Randomization and blinding: Simple randomization

Single vs. multi-center: Single center

2.2 Study objectives

2.2.1 Primary objective: To compare CO2 absorption during gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15mmHg

2.2.2 Secondary objectives:

a) To evaluate the anesthesiologists' perception of difficulty in maintaining adequate ETCO2 during laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15mmHg

b) To evaluate the surgeon's visualization of the operative field during laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg

c) To compare post-operative shoulder-tip pain when using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg

2.3 Aims & Hypotheses

2.3a Specific Aim 1

To determine if there is a difference in CO2 absorption when gynecologic laparoscopy is performed using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15mmHg

2.3a.1a Hypothesis 1a

CO2 absorption is decreased when gynecologic laparoscopy is performed using the AirSeal® valveless trocar system versus standard insufflation trocars

2.3a.1b Hypothesis 1b

CO2 absorption is decreased when gynecologic laparoscopy is performed at an intra-abdominal pressure of 10 versus 15 mmHg

2.3b Specific Aim 2

To determine if the anesthesiologists' perception of difficulty in maintaining adequate ETCO2 during gynecologic laparoscopy as measured on a 3-point likert scale differs using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15mmHg

2.3b.1 Hypothesis 2

Maintaining adequate ETCO2 is less challenging when using the AirSeal® valveless trocar system versus standard insufflation trocars for gynecologic laparoscopy at intra-abdominal pressures of 10 and 15 mmHg

2.3c Specific Aim 3

To determine if the surgeon's visualization of the operative field during gynecologic laparoscopy as measured on a visual analog scale (VAS) differs when using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg

2.3c.1 Hypothesis 3

Visualization of the operative field is improved when using the AirSeal® valveless trocar system versus standard insufflation trocars for gynecologic laparoscopy at intra-abdominal pressures of 10 and 15 mmHg

2.3d Specific Aim 4

To determine if post-operative shoulder pain as measured on a VAS pain scale differs following gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg

2.3d.1 Hypothesis 4

Post-operative shoulder pain is improved following gynecologic laparoscopy using the AirSeal® valveless trocar system versus standard insufflation trocars at intra-abdominal pressures of 10 and 15 mmHg

2.4 Data Management and Analysis

In this study, the primary objective is to analyze the effect of two independent factors: 1. Type of trocar system (AirSeal® trocar vs. standard trocars) 2. Intra-abdominal pressure (IAP: 10 vs. 15 mmHg) on the dependent factor: CO2 absorption. This will result in four (4) study arms. CO2 absorption in each arm will be compared at 15 and 60 minutes.

Justification of sample size: An effect size of 0.46 was calculated based on average CO2 absorption rates in a study comparing CO2 absorption when using the AirSeal® trocar versus standard trocars for laparoscopic renal surgery.[1] 30 patients per arm would be needed to detect an effect size of 0.46 or greater, with 80% power and a two-tailed alpha of 0.01. In order to allow for a possible 10% drop out, 132 patients will be enrolled in the study.

CO2 absorption calculation:

CO2 elimination rate = CO[2][3] absorption rate in order to keep patient metabolically constant.

[1] Wolf JS Jr., Monk TG, McDougall EM, et al. The extraperitoneal approach and subcutaneous emphysema are associated with greater absorption of carbon dioxide during laparoscopic renal surgery. J Urol. 1995;154:959-963.

[2] Ng CS, Gill IS, Sung GT, et al. Retroperitoneoscopic surgery is not associated with increased carbon dioxide absorption. J Urol.
[3] ;162:1268-1272

Carbon dioxide elimination rate [1,2] $= \frac{ETCO_2 \times Vt \times RR}{(P_B - P_{H2O}) \times Wt}$

$ETCO_2$: end-tidal carbon-dioxide pressure, Vt: expired tidal volume, RR: respiratory rate, P_B: barometric pressure (760 mmHg), P_{H2O}: partial pressure of water (13 mmHg), Wt: patient's weight in kilograms

General Analyses

Continuous variables will be summarized using means, standard deviations, medians, and ranges. If normally distributed, they will be analyzed using parametric tests such as T-test and analysis of variance. To find associations between continuous variables and to control by relevant covariates we will use multiple regressions. If the normality assumption is violated we will use non-parametric tests such as Mann-Whitney or Kruskal-Wallis.

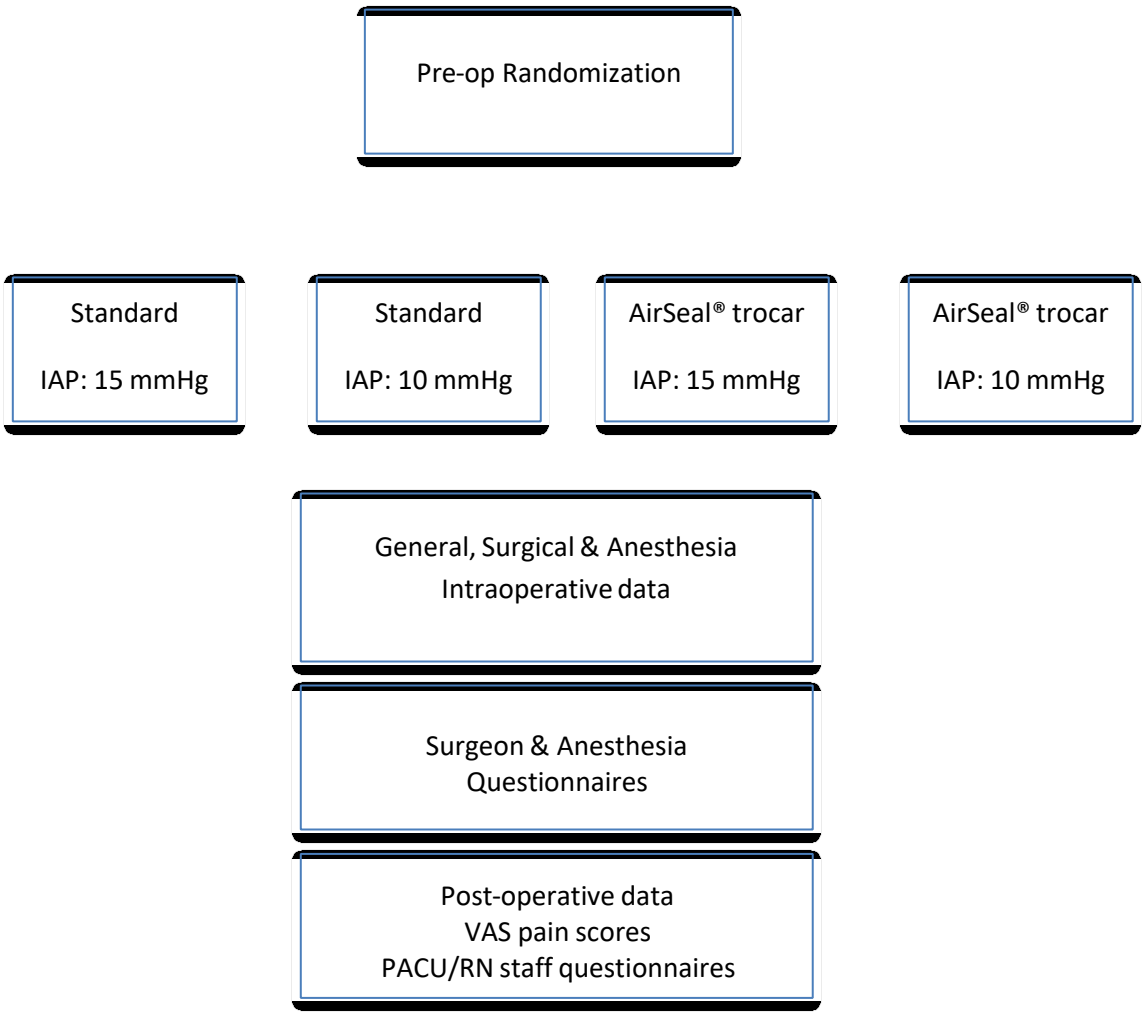
Categorical variables will be summarized with frequencies and percentages and analyzed with logistic regression or categorical response models.

95% confidence intervals will be provided for descriptive statistics, as warranted.

Subject characteristics are assumed to be comparable at the start of the study (randomization design) and so no formal statistical group comparisons will be conducted on the subject characteristics.

An overall alpha-level of 0.01 will be used as a cut-point for statistical significance and all statistical tests will be two-sided. All data will be analyzed by the Columbia University Mailman School of Public Health Biostatistics team.

2.5 Graphical schema of study



3.0 STUDY PROCEDURES

./ In the pre-operative area, subjects will be randomized via sealed, opaque envelopes containing a simple randomization scheme to one of the four groups:
Group A: Standard trocar/IAP 15 mmHg
Group B: Standard trocar/IAP 10 mmHg
Group C: AirSeal® trocar /IAP 15 mmHg
Group D: AirSeal® trocar /IAP 10 mmHg

./ All intraoperative staff assigned to the patient will be made aware of her participation in the study. The delegated research staff will fill out all pre-operative data. (CRF1)

./ Once in the operating room, standard surgical positioning, prepping and draping will be performed.

./ The patient's randomization group will be stated at the surgical TIME OUT.

./ Proposed surgery will commence using the AirSeal® or standard trocar at IAP of either 10 or 15 mmHg.

./ All cases will be performed with routine general endotracheal anesthesia. Ventilatory parameters and settings will be at the discretion of the anesthesiologists.

./ Pneumoperitoneum will be established using the Veress needle and trocar insertion performed at 20 mmHg.

./ Immediately following trocar insertion/port placement, pressure will be decreased to 10 or 15 mmHg.

./ If at any point the surgeon or anesthesiologist feels that the patient's safety is in question, necessary changes, including increasing the intra-abdominal pressure or switching between trocars, will be made expeditiously, and recorded.

./ During surgery, "surgical data" and "anesthesia data" variables will be filled. (CRF 3 & 4)

./ Following surgery 'General intraoperative data' variables listed below will be collected. (CRF 2)

./ At the end of the case, the surgeon and the anesthesiologist will complete questionnaires (CRF 3 & 4)

./ Post-operatively, the patient will fill out Visual Analog Scale pain scores at specified time periods. (CRF 5)

./ PACU/nursing staff will fill out a questionnaire indicating pain medication used during recovery and post-operative recovery time (CRF 6

4.0 STUDY DRUGS OR DEVICES

The AirSeal® trocar is a valveless trocar that has been designed to replace the "trap door" and silicone valve of standard trocars with a curtain of forced CO_2 gas (Fig. 1)[1]. With the AirSeal® trocar, escaping gas is collected at the proximal end of the trocar, filtered, and redirected into the peritoneal cavity to maintain the pressure differential. The result is an invisible barrier that instantaneously responds to changes in intra-abdominal

pressure, either by allowing more CO2 inflow with pressure drops or by serving as a pressure relief valve during pressure spikes.[12]

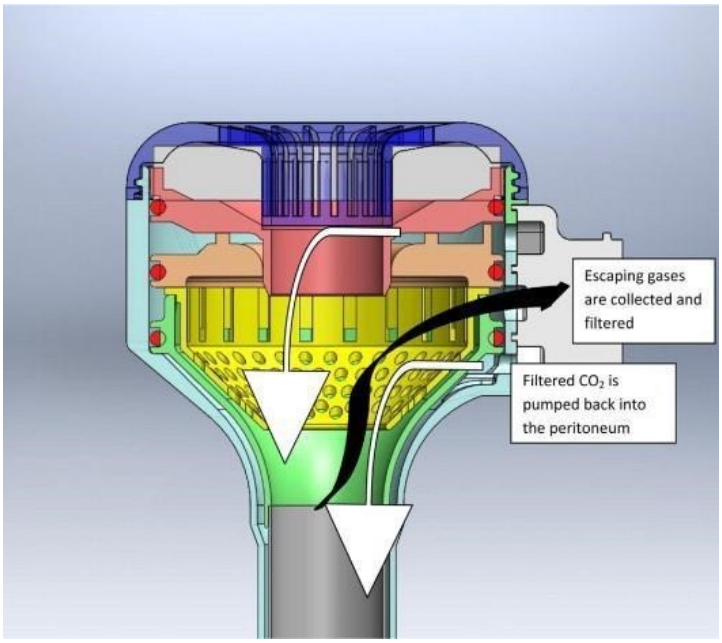


Figure 1.Schematic diagram of the AirSeal® valveless trocar

5.0 STUDY INSTRUMENTS: Questionnaires (See Appendix)

6.0 STUDY SUBJECTS

Any woman ≥ 18 years of age undergoing gynecologic laparoscopy with or without robotic assistance

6.1 Inclusion criteria:

Y Any woman ≥ 18 years of age undergoing a gynecologic laparoscopic procedure Y
Able to understand the consenting process and willing to participate in study

6.2 Exclusion criteria:

Y Patient unable to undergo laparoscopic procedure due to size of pathology or medical comorbidities Y
Emergent surgery

7.0 RECRUITMENT

All potential study participants are patients scheduled to undergo laparoscopic surgery with a GSS (gynecology specialty surgery) provider. All GSS providers are co-investigators for this study and will be responsible for recruiting eligible patients. Patients will be approached and recruited during their pre-operative visits at any of

the clinic sites. Once a GSS provider has identified a potential study participant, the informed consent process will be completed as detailed in the 'Informed Consent Process' section.

8.0 INFORMED CONSENT PROCESS

After the provider determines eligibility of study participants, the informed consent process will be completed in 2 possible ways as listed/explained below by the PI or research staff (Co-investigator or other delegated study staff):

Option 1:

- ./ Patient will be offered participation in the study at their pre-operative visit
- ./ During this visit, the informed consent and HIPAA form will be explained and all questions answered
- ./ The provider will inform the patient that participation in the study will be contingent on availability of the medical device on the day of the procedure
- ./ The informed consent and HIPAA form will be signed by the patient and a copy given to them for their personal records
- ./ The original 'wet-ink' signed consent and HIPAA form will be stored in the patient's chart
- ./ On the procedure day, when the patient is in the pre-operative area, availability of the medical device will be confirmed and then the patient will be randomized into 1 of 4 groups
- ./ Patients who are consented but not randomized will not be considered 'drop outs'

Option 2:

- ./ At the time of the pre-operative visit, if time does not permit for consent to be obtained, the provider will obtain permission from the patient to allow a member of research team contact them about an ongoing research study – if the provider is not a Co-I in the study, he/she will document permission for the research team to contact the subject
- ./ The patient will be given a copy of the informed consent and HIPAA form with their pre-operative packet and asked to review it in anticipation of a call (if they have agreed to this).
- ./ A member of the research team will contact the patient to review the informed consent and HIPAA form and answer all questions
- ./ Patient will be informed that participation in study will be contingent on availability of the medical device on the day of the procedure
- ./ At the end of the phone conversation patient consent (or denial of consent) will be obtained and documented in patient's chart
- ./ If the patient consents to participate by telephone, their signature will be obtained on the consent form in the preoperative area
- ./ A copy of the signed form will be given to the patient and the original 'wet-ink' copy will be stored in the patient's chart
- ./ When availability of the medical device is confirmed the patient will be randomized into 1 of 4 groups
- ./ Patients who are consented but not randomized will not be considered 'drop outs'

With both options of the informed consent process, when participation is offered to the patient, the informed consent and HIPAA form will be explained in detail along with the study design, procedures, inclusion/exclusion

criteria, risks and benefits, and study requirement. It will be emphasized that participation is completely voluntary and that she may revoke her participation at any time. There will be no further documentation of the informed consent process.

9.0 CONFIDENTIALITY OF STUDY DATA

To ensure confidentiality of medical information, each patient will be assigned a unique identifier in the database that can be linked to the medical record number. The database will be password-protected, encrypted and stored on a secure server (system 3959) accessible only from computers in the Gynecologic Specialty Surgery division. Subject demographics and date will be entered into REDCap (system 4283). REDCap is a mature and secure web application for building and managing online surveys and databases. It allows data to be exported to Excel and SPSS.

10.0 PRIVACY PROTECTIONS

The Principal Investigator and study staff will assure that the subject's privacy will be strictly maintained and that their identities are protected from unauthorized parties. This will be accomplished by securing all study documents and subject information. These files will be accessible to study staff only and maintained in a secure study office. The study staff will assign a code number and/or letters to the subject for data analysis. Documents that contain identifiers will be kept in a locked research office and/or stored within computers with password protection and encryption. We will safeguard patients' expectation that the information they offer will be held in confidence. We will protect each participant's information as prescribed by the University and Hospital police and relevant Federal law.

11.0 POTENTIAL RISKS

Participation in this study will incur no additional surgical risks to the patient. If at any point the surgeon or anesthesiologist feels that the patient's safety is in question, necessary changes, including increasing the intra-abdominal pressure or switching between trocars, will be made expeditiously.

The patients' privacy will be protected with the highest level of security however potential for breaches in security must always be considered.

12.0 DATA AND SAFETY MONITORING

All subjects will be evaluated prior to, during and following surgery. All charts will be carefully reviewed prior to and following surgery up until patient is discharged from the hospital. Adverse events will be recorded. See Clinical Research Forms attached in the rascal documents section.

13.0 POTENTIAL BENEFITS

There are no potential benefits to participants of this study. However, knowledge gained from the study may benefit patients in the future.

14.0 ALTERNATIVES

The alternative to this study is not to participate

15.0 RESEARCH AT EXTERNAL SITES

Not Applicable

16.0 COLUMBIA AS LEAD INSTITUTION

This is a single center study, with recruitment from Columbia University Medical Center and a few satellite sites:

Locations: The study patients will be recruited from outpatient settings of Columbia University Medical Center:

Columbia Ob/Gyn Uptown: 161 Fort Washington Ave, New York NY 10032
Columbia Ob/Gyn Midtown: 51 W 51st street, New York, NY 10019
Columbia Ob/Gyn Columbus Circle: 1790 Broadway, New York, NY 10019
Columbia Ob/Gyn Rockland: 516 Route 303 in Orangeburg, New York, NY 10962
Columbia GYN surgery clinic: 21 Audobon Clinic, New York, NY 10032
Columbia Ob/Gyn Scarsdale: 696 White Plains Road, Scarsdale, NY 10583

Proposed Timeline

Overall timelines: (1)
Date of initiation of study: first patient could be treated 2/1/16
Date of study enrollment completion: 2/1/17
Follow up of last patient: 2/10/17
Date of completion of analysis and submission of publication: 5/1/17

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