NCT04281017

Effect of Anesthetic Choice in Intraocular Pressure in Robotic Gynecologic Oncology Surgeries using Steep Trendelenburg Position

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Phase:	n/a
Keywords:	Steep Trendelenburg, intraocular pressure, total intravenous anesthesia, robotic surgery, gynecological cancer

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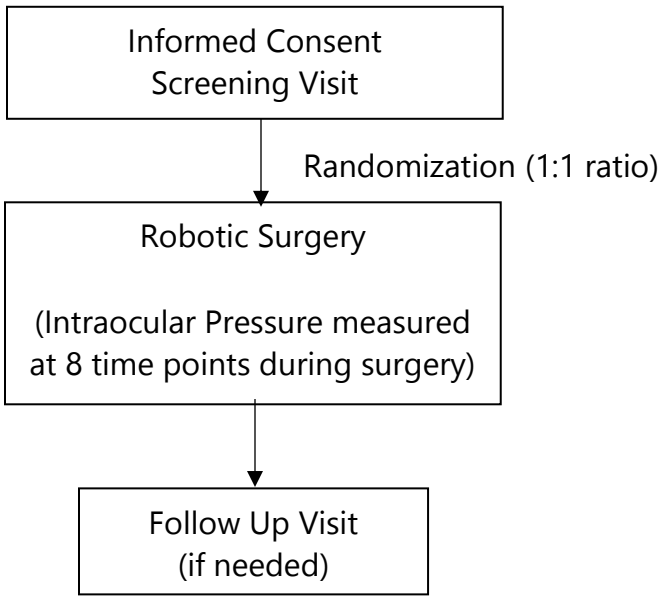
ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ASA	American Society of Anesthesiologists
CO2	carbon dioxide
CPP	cerebral perfusion pressure
CRF	case report form
CSF	cerebral spinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trials management system
CVP	central venous pressure
CRO	Clinical Research Office
CTO	Clinical Trials Office
GCP	Good Clinical Practice
HOB	head of bed
ICF	informed consent form
ICH	International Conference on Harmonization
IOP	intraocular pressure
IRB	Institutional Review Board
kg	kilogram(s)
MAP	mean arterial pressure
MMhG	millimeters of Mercury
NCI	National Cancer Institute
NSAE	non-serious adverse event
PACU	post-anesthesia care unit
PCO2	partial pressure of carbon dioxide
PI	principal investigator
SAE	serious adverse event
TIVA	total intravenous anesthesia
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
US	United States
WHO	World Health Organization



Accrual Goal: 100 (We expected to enroll around 100 patients, most of those will have a diagnosis already (60%). The remaining 40% will be suspicious but not confirmed. The rate of positive cancer is around 50% so that will account for around 20 additional patients that will be enrolled and 20 of them that will be removed.)

PROTOCOL SYNOPSIS

Title:	*NCT04281017* *Effect of Anesthetic Choice in Intraocular Pressure in Robotic Gynecologic Oncology Surgeries using Steep Trendelenburg Position*
Funding Source(s):	None
Rationale:	Steep Trendelenburg positioning and insufflation of the abdominal cavity have shown to increase intraocular pressure (IOP)[1]. Different anesthetic techniques can alter intraocular pressure and past studies have suggested a more favorable effect on IOP using intravenous anesthesia in robotic cases in the Steep Trendelenburg position (as opposed to balanced/volatile approaches that also use inhalation). It appears that a total intravenous anesthetic may have a salutatory effect on intraocular pressure while volatile agents do not[2,3]. Currently all gynecological (GYN) oncological robotic cases are performed with a mixture of volatile agents and intravenous agents at different strengths. This study aims to show whether total intravenous anesthesia shows protective effects against the increase in intraocular pressure during robotic surgery for gynecological cancer.
Objectives:	Primary: • To examine the relationship between anesthesia approach (i.e., TIVA anesthesia or balanced anesthesia) and intraocular pressure during robotic surgery for gynecological cancers Secondary: • To examine rate of abnormal intraocular pressure associated with total intravenous anesthesia as compared with a balanced approach

	• To build a model to examine rate of abnormal intraocular pressure in subjects with different pre-existing conditions and surgical variables, including length of procedure, pre-existing conditions and anesthesia type
Study Design:	This is a randomized, non-blinded study between two standard of care methods of anesthesia delivery during robotic surgery.
Accrual Goal:	Up to 100 subjects
Inclusion Criteria:	Individuals eligible for study participation must meet the following criteria: A. Females ≥ eighteen years of age B. Written informed consent obtained from the subject and the subject agrees to comply with all the study-related procedures C. Subjects must be planning to receive robotic surgery for gynecological cancer or high suspicion of cancer (these subject will be withdrawn if it his proven they don't have cancer) D. Subjects must be cleared for surgery by the pre-anesthesia clinic
Exclusion Criteria:	Subjects with any of the following will not be eligible for study participation: A. Subjects with a previous treatment of diagnosis of increased intraocular pressure B. Subjects who have undergone eye surgery in the 30 days prior to consent C. Subjects for whom an ophthalmologist has determined cannot undergo intraocular pressure measurement
Assessments:	Intraocular pressure (IOP) will be measured at up to seven (7) timepoints during robotic surgery. IOP will be measured using a tonometer (Tono-Pen XL Medtronic Solan, Jacksonville, FL).

Statistical Considerations:	We will use a series of ANCOVAs to evaluate the relationship between the independent variable of anesthesia approach (i.e., TIVA anesthesia or balanced anesthesia) and the dependent variables of intraocular pressure measured at Time 2 – Time 6 (and possibly Time 7). The Time 1 (subject's baseline) measure of intraocular pressure will be included in the model as a covariate. Other covariates will be considered for the model after investigating the success of randomization on the distribution of baseline demographic and health history variables.
Estimated Enrollment Period:	36 months
Estimated Study Duration:	48 months

1. BACKGROUND

1.1 Potential Risk

The measurement of IOP is commonly done in the outpatient setting without any sedation. Patients will undergo measurements of intraocular pressure after the eye is anesthetized with a drop. We anticipate having minimal discomfort other than having eye drops in both eyes. The drops may burn a little when applied. The measurement itself is painless and the potential risk is infection, which will be mitigated by using standard sterilization procedures. There are no rules for stopping the study unless an untoward event occurs. If any untoward event occurs the research team will review all protocols and perform an assessment with the chief of quality of the department of anesthesiology.

1.2 Potential Benefits

Knowing the pressure in patient eyes is always a positive piece of information for patients. Early detection and treatment of increased intraocular pressure (IOP) can save vision or be beneficial for preventing future eye disease.

1.3 Anesthesia for Robotic Surgery for Gyncological Cancer

The Steep Trendelenburg positioning of patients, which is defined as 20-30 degrees in the head down position, is often used during camera-assisted gynecological surgery (see Figure 1).

Figure 1. Patient in the Steep Trendelenburg position (source: https://www.alimed.com/trendelenburg-patient-positioning-blog/)

This position allows some displacement of intra-abdominal organs, in order to better visualize the pelvic structures. Visualization and ease of manipulation by instruments is further aided by the insufflation of carbon dioxide (CO2) into the peritoneum. The Steep Trendelenburg position causes many physiological changes in pulmonary and hemodynamic functions as well as alteration in the kidneys and the eyes, and increases intracranial pressure[5,6] Since the early days of robotic surgery, anesthesiologists have studied and developed ways to manage the hemodynamic and pulmonary changes associated with this procedure to maintain homeostasis. The increase in intracranial pressure seen in the Steep Trendelenburg position poses a risk to patients with poor intracerebral compliance and those with CSF (cerebral spinal fluid) shunting devices. In the brain, regional blood flow increases due to changes in PCO2 (partial pressure of carbon dioxide) is related to the infusion of CO2 to maintain pneumoperitoneum[6,7,8]. The anesthesiologist manages those changes to maintain adequate cerebral perfusion pressure (CPP) with increases in central venous pressures (CVP) and maintenance of adequate mean arterial pressure (MAP).

Transient and total visual loss has been described in the literature following robotic surgery in the Steep Trendelenburg position[9,10]. We do not know the increase in IOP and the duration of the events for the patient with transient or permanent damage. Borahay et al[1] studied changes associated with the Steep Trendelenburg position during minimally invasive (non-robotic) gynecological surgery. A significant increase in IOP from baseline was noted after 1 hour and 2 hours of Steep Trendelenburg positioning. Interestingly, the IOP remained significantly elevated once the patient was returned to the supine position when compared with the baseline IOP.

The largest database on post-operative vision loss maintained by the ASA (American Society of Anesthesiologists) suggests that the Steep Trendelenburg position is a risk factor for post-operative vision loss. The exact mechanism of visual loss is not well described, but a “second hit phenomenon” may be involved whereby there is cumulative effect of sequential ocular insults. Patients who have a latent non-apparent eye disease or intrinsic anatomical variation may be at higher risk to develop decrease or loss of vision.

Thus, we know that there is a significant increase in intraocular pressure during robotic surgery in the Steep Trendelenburg position. In efforts to learn more about how to mitigate this undesirable effect in IOP, a number of small studies have been reported examining the effects of total intravenous anesthesia vs balanced or volatile modes. Total intravenous anesthesia (TIVA) involves administration of anesthetic agents solely via infusion. Balanced anesthesia includes a lower dose administration of 2 or more agents rather than one large dose of one single agent. Volatile anesthetics are liquid at room temperature, but evaporate easily for inhaled administration. Most recent research has suggested a more favorable effect in intraocular pressure with the use of total intravenous anesthesia.

Kim et al[2] studied the effect of adding an infusion of dexmedetomidine to a standard anesthetic that included volatile (inhaled) agents to determine differences in IOP in males undergoing prostate surgery. Results showed significant differences in IOP between the two groups favoring the group receiving intravenous dexmedetomidine.

Another study by Yoo et al[3] studied 66 male subjects undergoing robotic prostatectomy in Steep Trendelenburg position at 30 degrees. Nine measurements were performed before, during and after the surgery. One group was given standard anesthetic care using a volatile agent and the control group received only intravenous anesthetic agents (TIVA). Results indicated showed that intraocular pressure differed between the two groups, again favoring the intravenous approach.

We do not know whether increases in IOP portent visual compromised or early glaucoma that should be followed up. We maintain that possibly saving the vision of just one patient is worth the investment in this effort and this protocol aims to examine two different routine modes of anesthesia delivery to assess whether they result in differential effects in intraocular pressure of patients will undergoing robotic surgery.

1.4 Rationale for Current Study

It is known that Steep Trendelenberg position is associated with increased visual problems. However, it is an ideal position for camera-assisted gynecological surgery because it allows some displacement of intra-abdominal organs, in order to better visualize the pelvic structures. Visualization and ease of manipulation by instruments is further aided by the insufflation of carbon dioxide (CO2) into the peritoneum. The primary interest of this protocol is to learn more about the potential negative effects this position may have on vision and whether adjusting the anesthetic plan can help mitigate some of the risk.

There is no study, to our knowledge, on female endometrial cancer patients undergoing robotic surgery for cancer treatment. There is a possibility that preexisting conditions may predispose this group to IOP and eye injury during robotic surgery. Many of the patients present with known risk factors for open and close angle glaucoma that can lead to optic nerve damage and blindness: Age over 40, diabetes, Hypertension, myopia, previous eye surgery, steroids used in chemotherapy, and cardiovascular disease. Therefore, this group is of particular interest.

The current study will examine the relative degree of increased intraocular pressure for subjects receiving **balanced** (intravenous with the use of inhalation agents) or **TIVA** (total intravenous without the use of inhalation agents) anesthesia during gynecological cancer robotic surgery. Additionally, the current study will add to the current literature by including a larger cohort in a randomized fashion with the goal of determining incidence and identifying possible risk factors for increases in intraocular pressure during surgery utilizing Steep Trendelenberg position.

2. OBJECTIVES

2.1 Primary

2.1.1 Primary Objective

- To examine the relationship between anesthesia approach (i.e., TIVA anesthesia or balanced anesthesia) and intraocular pressure during robotic surgery for gynecological cancers

2.1.2 Primary Endpoint

- Intraocular pressure at up to 8 time points during surgery

2.2 Secondary

2.2.1 Secondary Objectives

- To examine rate of abnormal intraocular pressure associated with total intravenous anesthesia as compared with a balanced approach
- To build a model to examine rate of abnormal intraocular pressure in subjects with different pre-existing conditions and surgical variables, including length of procedure, pre-existing conditions and anesthesia type

2.2.2 Secondary Endpoint

- Rate of abnormal intraocular pressure (IOP) (defined as greater than 25 mm/Hg)

3. STUDY DESIGN

3.1 Study Overview

This is a single center, randomized, non-blinded trial. 100 subjects are planned. Each subject will undergo up to seven (7) measurements of intraocular pressure while receiving either balanced anesthesia or TIVA during robotic surgery for gynecologic cancer while in Steep Trendelenburg position of approximately 20-30 (+/- 10) degrees, to provide information about whether there are differential effects on IOP associated with each mode of anesthesia. All subjects will undergo a similar surgery (robotic surgery for gynecologic cancer) with the same surgeon, in order to control for variations in surgical time and surgical protocols. Intraocular pressure will be measured using a tonometer.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Total duration of subject participation will be about 60 days post-surgery (+/- 7 days). Total duration of the study is expected to be 48 months (36 months of enrolling).

4. SELECTION OF SUBJECTS

Subjects with a diagnosis of gynecological cancer who meet the following inclusion and exclusion criteria will be eligible for participation in this study. **Per UFHCC guidelines, exceptions to inclusion and exclusion criteria are not permitted.**

4.1 Number of Subjects

Up to 100 subjects are expected to participate in this study.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

A. Females ≥ eighteen years of age
B. Written informed consent obtained from the subject and the subject agrees to comply with all the study-related procedures
C. Subjects must be planning to receive robotic surgery for gynecological cancer or high suspicion of cancer (these subjects will be withdrawn if it is proven that they don't have cancer), to be performed in the Steep Trendelenburg position
D. Subjects must be cleared for surgery by the pre-anesthesia clinic

4.3 Exclusion Criteria

Subjects with any of the following will not be eligible for study participation:

A. Subjects with a previous treatment or diagnosis of increased intraocular pressure
B. Subjects who have undergone eye surgery in the 30 days prior to consent
C. Subjects for whom an ophthalmologist has determined cannot undergo intraocular pressure measurement

Members of all races and ethnic groups are eligible for this trial.

5. REGISTRATION PROCEDURES

All consented subjects must be entered into the University of Florida's Clinical Trial Management System (OnCore) prior to assignment of a subject identification number. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial.

All eligible and enrolled subjects will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

6. STUDY PROCEDURES

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated. Screening measurements will be obtained within 30 days prior to registration into the study. After registering a subject into this study, study procedures must begin within 30 days.

All patients scheduled for gynecological oncology resective surgery will be approached for possible participation in the study. All patients will be under the direct care of the study team members, i.e., as physicians/surgeons. These patients will be scheduled for surgery as deemed appropriate by, and per standard protocol including review by, the University of Florida GYN Tumor Board. Medical clearance for surgery as deemed appropriate by the attending surgeon and preoperative anesthesia clinic will be required.

The day of surgery after confirming consent, the patient will be randomized to **TIVA** (total intravenous) anesthesia or **balanced anesthesia** including a volatile agent, both of which are standards of care. Randomization will be performed using a block randomized design put in place by the study statistician, in a 1:1 allocation ratio, to ensure a balance in sample size across groups over time.

During the day of surgery, the intraocular pressure (IOP) for both eyes will be measured by the anesthesiologist at eight time points using a tonometer over the course of course of a 4-5-hour surgery, within 60 days of follow-up (see section 6.2):

- Time 0 – Baseline
- Time 1- Induction
- Time 2- Post-induction with table at 0 degrees
- Time 3- Supine after pneumoperitoneum with 14 mmHg pressure
- Time 4- After docking robot at correct Steep Trendelenburg position of 20-30 (+/- 10) degrees (measured by a level)
- Time 5- After undocking and before moving supine
- Time 6- Supine and before extubation. If the intraocular pressure remains elevated above 19 mmHg, subject will require a 7th measurement in the post-anesthesia care unit (PACU) with the head of the bed (HOB) at 20-30 (+/- 10) degrees.
- Time 7- if needed, see Time 6 description above. If the intraocular pressure is still at or above 19 mmHg, an ophthalmology consult will be triggered.

6.1 Anesthesia protocol

The anesthesia protocol for both balanced anesthesia and TIVA will consist of induction with 1% propofol (2–3 mg/kg), fentanyl (1–3 mg/kg), and Rocuronium 1-1.5 mg/kg. Before the injection of propofol, 5 mL 1% lidocaine (50 mg) will be administered to limit any discomfort associated with the propofol injection. Then, anesthesia will proceed as below as described in 6.1.1 and 6.1.2, depending on randomization arm.

For all subjects, throughout the procedure, muscle relaxation will be maintained using aliquots of Rocuronium to 0-to-1 train-of-4 twitch response of adductor pollicis. During the surgery, all subjects will be mechanically ventilated using pressure-controlled mode (peak inspiratory pressure 30cm H2O). We aim for tidal volume of 5-7 ml/Kg of ideal body weight with a positive end-expiratory pressure of 5 cm H2O, and a respiratory rate to maintain end-tidal carbon dioxide between 30 to 40 mmHg.

If the patient has any increased readings at the end of the procedure, the attending anesthesiologist in the post-operative recovery area / PACU will do a Time 7 post-op IOP measurement prior to discharge. Any abnormal readings will prompt an ophthalmology consult and follow up with ophthalmology department.

6.1.1 Balanced Anesthesia Arm:

After endotracheal intubation, the depth of anesthesia will be **maintained at a minimum alveolar concentration of 1 to 1.25 using isoflurane in oxygen and air mixture (50%/50%) and titrated to keep the mean arterial pressure within 20% of its pre-induction value.**

6.1.2 TIVA Arm:

After endotracheal intubation, the depth of anesthesia will be with **intravenous infusion of propofol, lidocaine, ketamine or narcotic as deemed appropriate by the attending anesthesiologist. There will be no inhalation anesthetic used at all. Ventilation will be maintained with oxygen and air mixture (50%/50%) and titrated to keep the mean arterial pressure within 20% of its pre-induction value.**

6.2 Measurement of Intraocular Pressure (IOP)

Prior to the first measurement, both eyes of the patient will be anesthetized using topical proparacaine hydrochloride ophthalmic solution 0.5%.

The anesthesiologist, trained by an ophthalmologist prior to subject enrollment, will measure each eye's IOP using a tonometer (Tono-Pen XL Medtronic Solan, Jacksonville, FL). A tonometer is a mobile, electronic, handheld instrument that measures the resistance of the cornea when pressed. To obtain a measurement (reported as mmHg, or millimeters of Mercury), the tonometer is gently and quickly applied to the cornea for less than a few seconds. The instrument will indicate a measurement of how much the cornea presses back. Typically, this procedure is painless and the main potential risk is infection, which will be mitigated using standard sterilization procedures. Normal intraocular pressure is usually between 12-22mmHg. Individuals with glaucoma typically have IOP over 20mmHg.


Medtronic
TOKO-PEN XL

6.3 Schedule of Events

Visit: / Procedure:	Screening (≤ 30 days prior to Robotic Surgery)	Robotic Surgery Visit								Follow up (after surgery) (within 60 +/- 7 days)
		Anesthesia Administration	Time 0	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6	Time 7[5]	
Informed Consent	X										
Demographic Information[1]	X										
Medical History, including ophthalmologic and cancer history	X										
Randomization		X									
Administration of anesthesia		X									
Intraocular Pressure (IOP) Measurement[2]			X	X	X	X	X	X	X	X	
Adverse Event Review	X	X		X	X	X	X	X	X	X	X
Pre-anesthesia screening	X										
Surgical Data[3]				X	X	X	X	X	X	X	
Cancer Staging[4]	X										X
Ophthalmology Consult[6]											X

1. Demographic data will include date of birth, ethnicity, race, zip code, and body mass index (BMI)
2. Intraocular pressure measurements will be performed using a tonometer
3. Surgical data will include vital signs and all medications, fluids and outputs, description of surgery, and length of procedure
4. Cancer staging will be collected before and at 60 days (+/- 7 days) after surgery
5. Only required if triggered if the intraocular pressure remains elevated above 19 mmHg at Time 6
6. Only required if triggered by abnormal intraocular pressure readings at Time 7. The consult will occur within 1 day of surgery

7. STUDY DISCONTINUATION

7.1 Screen Failures

Subjects who sign informed consent, but do not meet eligibility criteria, or withdraw prior to eligibility being verified, and undergo at least some of the screening procedures will be considered screening failures. Subjects who sign informed consent and are verified as eligible, but do not proceed to formal registration will be considered "unregistered." A record of screen failures and unregistered subjects will be maintained by the study site.

7.2 Lost to Follow Up

If a subject becomes unreachable during the course of the study, the investigator or study team will make a reasonable effort to contact the subject and document each attempt (in accordance with Section 4.3.4 of the ICH E-6 GCP). If these attempts are not successful, the subject may be declared "lost to follow up." For subjects lost to follow-up, the termination date will be the date of last contact with the subject.

7.3 Criteria For Study Treatment Discontinuation

Subjects who discontinue participation in the study on their own or subjects who are withdrawn by the investigator prior to completing the End of Study Visit will be defined as premature withdrawals. Any data captured up until the date of withdrawal may be included in study results.

A subject will be discontinued from the study under the following circumstances:

- Any adverse event which, in the Investigator's opinion, requires termination of the study.
- The subject takes part in activities that may, in the opinion of the Investigator, have a reasonable chance of interfering with results.
- The subject is lost to follow-up.
- The subject withdraws consent to continue in the study.
- If the subject is enrolled under suspicion of cancer and then is proven to be cancer free.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF).

7.4 Replacement of Subjects

Subjects will be considered for replacement if they cannot provide data for analysis of the primary endpoint due to premature study withdrawal or any intraoperative adverse event that precludes IOP data collection.

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event

The term "adverse event" (AE) includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). An AE is therefore any unfavorable and unintended symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

Adverse events fall into the categories "serious" and "non-serious." The Investigator or

his/her designee will probe, via discussion with the subject, for the occurrence of AEs during each subject visit.

8.1.2 Serious Adverse Event

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s). When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded rather than the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the event.

NOTE: The following hospitalizations are not considered SAEs in UFHCC clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

8.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria and will not be recorded.

8.2 Period of Observation

Following the subject's written consent to participate in the study, all SAEs must be collected through the Follow Up Visit, including those thought to be associated with protocol-specified procedures.

8.3 Documenting and Reporting of Serious Adverse Events by Investigator

All serious adverse events must be fully recorded in the subject's case record form and the site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE and all follow-up information as per local requirements.

Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, relationship to the study procedure(s), action taken and outcome.

Every attempt should be made to describe the event in terms of a diagnosis that

encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have serious adverse events, whether considered associated with the study procedure(s) or not, must be monitored to determine the outcome. The clinical course of the event will be followed according to accepted standards of medical practice.

8.3.1 Assessment of Causal Relationship with Study Procedure(s)

The Investigator will provide an assessment of the potential causal relationship between serious adverse events and study procedure(s) by determining whether or not there is a reasonable possibility that the event was caused by the study procedure(s). The relationship or association of the event to the study procedure(s) will be characterized as not related, unlikely related, possibly related, probably related, or related:

Not Related: There is not a temporal relationship to the study procedure(s) or the event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.

Unlikely Related: There is little or no chance that the study procedure(s) caused the event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

Possibly Related: The association of the adverse event with the study procedure(s) is unknown; however, the event is not reasonably attributed to any other condition.

Probably Related: When a reasonable temporal relationship exists between the event and the study procedure(s); significant symptoms abate upon discontinuation of the study procedure(s) and there is a reasonable explanation based on known characteristics of the study procedure(s) and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).

Related: When the event is a known side effect of the study procedure(s) or there is a temporal relationship to the study procedure(s); or the event reappears upon re-administration of the study procedure(s); or the significant symptoms of the event abate upon discontinuation of the study procedure(s).

8.3.2 Action Taken with Study Participation

The action the Investigator took with study participation as a result of the event should be recorded as one of the following:

None – No action was taken with regard to study participation as a result of the adverse event.

Interrupted – Study participation was stopped due to the adverse event, but was later resumed.

Permanently discontinued – The subject was withdrawn from the study due to the event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry: permanently discontinued > interrupted.

8.3.3 Definition of Outcome

The outcome of the SAE should be recorded as one of the following:

Resolved without sequelae – The subject fully recovered from the event with no observable residual effects.

Resolved with sequelae – The subject recovered from the event with observable residual effects.

Not resolved – The event was present at the time of last observation.

Death – The subject died as a result of the event.

9. UNANTICIPATED PROBLEMS

Unanticipated problems include risks to subjects or others to generally include any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures described in the protocol and informed consent document and/or the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

All unanticipated problems must be fully recorded in the subject's case record form and the site investigator is responsible for reporting to the IRB, as per local requirements.

10. STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

10.1 Data Collection Plan

Data to be collected: Demographic data, including age, race, body mass index (BMI), comorbidities, and ophthalmologic history. We will collect all intraoperative anesthesia data, including vital signs and all medications, fluids and outputs. Post-surgical data will include pain scores, nausea, pain and nausea treatment, vital signs and laboratory values. We will collect surgical data including name, description and length of procedure. We will collect diagnosis and staging of the cancer before and approximately 60 days after surgery.

10.2 Data Safety and Monitoring Plan

Data will be stored on University of Florida computers that are protected according to institutional requirements for password and encryption standards. Any paper

documentation (i.e. consent forms, etc.) will be stored in locked offices in the Department of Anesthesiology. Data will be de-identified at the time of collection and subjects assigned a non-identifiable record number. Stored data/documents will have no HIPAA identifiers.

The procedures outlined in this protocol are all routine, and there are no pre-specified rules for stopping the study. If any untoward event occurs that is deemed related to the study, the Principal Investigator and the research team will review all protocols and perform an assessment with the chief of quality of the department of anesthesiology to determine whether stopping rules are appropriate. Untoward ophthalmological events include eye pain, change of vision or drainage. Any patient with persistent elevated IOP will be seen by ophthalmology in the recovery area and followed afterwards.

10.3 Sample Size Justification

A total of 100 participants will be enrolled in this study,most of those will have a diagnosis already (60%). The remaining 40% will be suspicious but not confirmed. The rate of positive cancer is around 50% so that accounts for around 20 patients that will be enrolled and 20 of them that will be removed.

The probability is more than 80% that the study will detect a medium effect size of 0.50 at a 0.01 significance level (the 0.01 level was selected to adjust for multiple testing in the application of 5 ANCOVAS), with an assumed R2 value of 0.40 or greater between baseline IOP value and IOP value at each subsequent time point, and with 57 participants completing the study. An additional 10 participants will be recruited to account for screen failures or withdrawals. We used the sample size formula given by Borm et al. for our power analysis calculations.[11]

10.4 Analysis of Primary Endpoint

The primary objective of this study is to examine the relationship between anesthesia approach (i.e., TIVA anesthesia or balanced anesthesia) and intraocular pressure during robotic surgery for gynecological cancers. The hypothesis is that total intravenous anesthesia will have a protective effect in the increase in intraocular pressure during robotic gynecological cancer surgery, a series of independent ANCOVAs will be performed. These ANCOVAS will model the relationship between the independent variable of anesthesia approach (i.e., TIVA anesthesia or balanced anesthesia) and the endpoint of intraocular pressure measured at Time 2 – Time 6 (and possibly Time 7). The Time 1 (subject's baseline) measure of intraocular pressure will be included in the model as a covariate. Other covariates will be considered for the model after investigating the success of randomization on the distribution of baseline demographic and health history variables.

10.5 Analysis of Secondary Endpoints

Also of interest is the rate of abnormal intraocular pressure associated with total intravenous anesthesia as compared with a balanced approach, in addition to building a model to investigate factors associated with an unacceptable increase of IOP (defined as an increase in IOP above 25mmHg). We will use logistic regression with baseline demographic, health history variables, and perioperative variables (e.g. demographic data including age, race, body mass index (BMI), comorbidities, and ophthalmologic history, intraoperative anesthesia data including vital signs and all medications, fluids and outputs, post-surgical data including pain scores, nausea, pain and nausea treatment, vital signs and laboratory values, surgical data including name, description and length of procedure, and diagnosis and staging of the cancer before and after surgery) as predictors in this analysis of the secondary endpoint of unacceptable increase of IOP.

10.6 Principal Investigator Responsibilities

Per UF IRB requirements, the PI is personally responsible for conducting and supervising the conduct of human subjects research by "protecting the rights, safety, and welfare of subjects under the investigator's care." The PI also must ensure that all the research

conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB.

Oversight is defined as "management by overseeing the performance or operation of a person or group; watchful care, superintendence, general supervision". Any person serving as a PI has voluntarily accepted these responsibilities and is expected to fully comply with these requirements, as outlined in the UFHCC Guidance: *Principal Investigator Responsibilities and Oversight.*

The PI will be primarily responsible for continuous monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper forms, CRFs, and Informed Consent forms.

11. EMERGENCY PROCEDURES

11.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

11.2 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

12. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

All potential serious breaches must be reported immediately per local guidelines. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

12.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

12.3 Compliance with Laws and Regulations

It is intended that the proposed study be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Please refer to the International Conference on Harmonization and GCP:

http://www.fda.gov/oc/gcp/guidance.html; Declaration of Helsinki: http://www.fda.gov/oc/health/helsinki89.html; Code of Federal Regulations, Title 21:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch. cfm]

All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov. All studies must be registered prior to enrollment of the first participant. The investigator will maintain the responsibility of updating trials registered with ClinicalTrials.gov. Per FDA requirement, information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study.

12.4 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom (s)he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

12.5 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by

the personally dated signature of the person conducting the informed consent discussions and a copy of the consent form (preferably signed) must be given to the subject for their records.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

12.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, or other regulatory authorities, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

12.7 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments will not be implemented without prior written IRB approval. All amendments will be submitted to the IRB and SRMC (as applicable), and written verification that the amendment was submitted and subsequently approved is to be obtained, and notification will sent out to the applicable study teams, prior to implementing the amendment.

On an emergency-basis, to eliminate an immediate safety hazard to a subject, a protocol deviation may be implemented immediately, provided the IRB and UFHCC CRO PMO (pmo@cancer.ufl.edu) are notified within **5** business days with a full justification and description of the event.

12.8 Case Report Forms

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document protocol-required outcomes for safety monitoring and data analysis. All study data will be entered electronically in an Electronic Data Capture system in accordance with the protocol schedule of events and guidelines developed in the Data Management Plan for the study, using a secure access account.

All protocol data is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.

12.9 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

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13. APPENDICES

Appendix A: PROTOCOL VERSION HISTORY / SUMMARY OF CHANGES

Protocol Version Number	Protocol Version Date	Affected Section(s)	Summary of Revisions Made
1.0		N/A- Initial protocol	
1.1	*8/21/2020*	IRB approval contingencies requested adding risk and benefit sections on page 11.	
2.0	*12/04/2020*	Updates to the inclusion criteria, the degree of Trendelenburg, and withdrawal criteria.	
2.1	*12/04/2020*	**Updates to headers and footers for consistency based on DISC audit.**	
3.0	*04/13/2021*	Updating phase of the study from III to N/A	
4.0	*02/06/2022*	PI Change	
5.0	*03/14/2023*	1. Minor edits made to header and footer regarding protocol number and version # and date 2. Add baseline IOP collection	
5.1	*3/25/2024*	1. The subscript in the schedule of events is misformatted. This has been corrected so subscripts match in the table and the description. 2. Removal of the protocol signature page 3. With a change in surgeons the degree of Trendelenburg is being revised. They normally shoot for 30 degrees but it can vary. Updating range in protocol from 15-20 (+/- 5 degrees) to 20-30 (+/- 10 degrees).	

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