A randomized, controlled study evaluating the effectiveness of the UltraVision™ visual field clearing system in laparoscopic hysterectomy and myomectomy

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Approvals	Signature & Approval Date

Compliance Statement

This study will be conducted in full accordance with this protocol, all applicable Mercy Research and Mercy Institutional Review Board policies and procedures, International Conference on Harmonization guidelines for Good Clinical Practice and all applicable Federal and state laws and regulations including 45 CFR 46 and the HIPAA Privacy Rule.

Principal Investigator: David Levine, MD
(Electronic signature to be provided in IRBNet)

CLINICAL TRIAL SUMMARY

Background

The smoke generated by electrosurgical devices in the process of dissection of tissues during laparoscopy can obscure the surgical visual field. Laparoscopic hysterectomy and laparoscopic myomectomy are procedures that produce a considerable amount of smoke, which impedes the operating surgeon. It is often necessary to suspend the surgery to allow the smoke to dissipate, or more commonly open a laparoscopic port to vent the smoke into the room, adding to the operating time. It is also common to remove the laparoscope to clean the lens because it can be soiled by the smoke as well. In order to enhance the dissipation of smoke and maintain an adequate pneumoperitoneum it is often necessary to increase the flow of carbon dioxide (CO_2) from the insufflator. Surgical smoke handling during laparoscopic surgery results in an increase of the known risks to the patient of using excessive CO_2; as well as exposing the operating room staff to the smoke which may create a potential health concern.

The electrostatic-precipitation of laparoscopic smoke is a new technique, marketed under the name Ultravision©, making it possible to precipitate the smoke as it is created, thereby actively eliminating it from the field of view. Safety and feasibility studies have been carried out allowing it to be placed on the market in Europe, Japan and the United States. A randomized study of its clinical effectiveness (ref: Ansell J. Surg, Endosc. (2014) 28: 2057-2065) showed that electrostatic-precipitation significantly improved visibility (reduction of visual impairment) and reduced surgery time in laparoscopic cholecystectomy.

Ultravision is cleared for use in all laparoscopic surgery i.e. including laparoscopic hysterectomy and myomectomy, in the United States. However, the clinical benefits arising from its use in gynaecology have not yet been quantitatively assessed and published in an independent medical journal.

Study Purpose:

There are three main study objectives

1. To evaluate the impact of use of Ultravision device during laparoscopic hysterectomy and myomectomy on the quality of visualization in the laparoscopic field
2. To evaluate the impact of use of Ultravision device during laparoscopic hysterectomy and myomectomy on procedural characteristics
3. To evaluate the impact of use of Ultravision device during laparoscopic hysterectomy and myomectomy on clinical outcomes

Primary Hypothesis

The primary hypothesis being tested in this study is that using Ultravision during laparoscopic hysterectomy and myomectomy improves visualization similar to that reported when used in laparoscopic cholecystectomy without the need for CO_2 exchange and that, by doing so, the amount of CO_2 that is utilized during the procedure and that the patient is exposed to is reduced compared to the current standard of care. Ultravision has already been shown in laparoscopic cholecystectomy to minimize the amount of CO_2 that a patient is exposed to during laparoscopic surgery because it does not rely on the process of dilution using ongoing CO_2 supply from the insufflator.

Secondary hypothesis:

There are two aspects to CO_2 exposure during laparoscopic surgery: the amount of gas used and the intra-abdominal pressure of the pneumoperitoneum. In addition to the amount of CO_2 utilized during the procedure another related factor is the intra-abdominal pressure of the pneumoperitoneum. Decreasing the intra-abdominal pressure below the conventional 12-15 mmHg during laparoscopic surgery has been shown by others to lead to improved clinical outcomes.[1]

Use of the Ultravision during laparoscopic hysterectomy and myomectomy is expected to allow for lower intrabdominal insufflation pressures. In this study, the target abdominal pressure for all procedures conducted will be 10mmHg. The ability to maintain that pressure during the procedure will be reported and compared for the randomized group. In addition to this secondary endpoint other procedure data will be collected to assess the potential impact of the Ultravision™ System on procedure characteristics such as adverse events, procedure time, patient temperature, patient end tidal CO_2 level, post-op medications for pain etc.

Study Population

The study will enroll female patients who are indicated for laparoscopic hysterectomy or myomectomy. Patients must meet all inclusion/exclusion criteria.

Study Design

This is a prospective blinded, randomized controlled study. The study will include three study arms:

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1 Yasir M, Kuldeep MS, Vigar HB, Aiman A, Masood I, Iqbal B, Evaluation of post-operative shoulder tip pain in low pressure versus standard pressure pneumoperitoneum during laparoscopic cholecystectomy, The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland, 10(2012) 71-74.

Patients undergoing laparoscopic hysterectomies will be randomized to one of either “Ultravision” (study arm 1) or “no Ultravision” (study arm 2, i.e. the current standard of care) groups. The study will be conducted blinded to the investigator during the procedure through patient discharge. The Ultravision system will be present in both, with the generator covered (not seen by user) and either on or off depending on the randomization. 30 patients will be enrolled, 15 per group.

Whilst less common, it has been reported that myomectomy is considered to be a procedure that generates a great deal of surgical smoke. Five patients undergoing myomectomy will have their procedures conducted using the Ultravision (study Arm 3). Results from this study arm will be reported and discussed. All measures conducted for the randomized study arms will be collected but no comparative statistical analysis is planned for this group.

Primary Endpoints

Success will be based on demonstration that the procedures using Ultravision demonstrate a meaningful difference/improvement when compared to the control according to the following measures:

1. The quality of visualization in the laparoscopic field of view will be assessed by the investigator using a 5 point Visual Analog Scale (VAS). Results for the laparoscopic hysterectomy will be compared to determine if there is a significant difference between “Ultravision” and “no Ultravision” groups.
2. The amount of Carbon Dioxide (CO_2) utilization during the procedure will be measured. Results for the laparoscopic hysterectomy study arms will be compared to determine if there is a significant difference in the amount of CO_2 utilized between groups.

Secondary Endpoints:

The following data will be collected for all groups. Comparisons between the study arms 1 and 2 will be conducted. For study arm 3 the data will be reported and generally compared to study arms 1 and 2.

- From the initial 10mmHg setpoint, the time in minutes until a change /increase in the abdominal pressure is required, and the reason for the change (i.e. visualization, access).
- The number of times the laparoscope is removed in order to clean it of debris.
- The number of times a trocar valve is opened to evacuate smoke.
- The number of pauses due to a loss of sufficient visibility.
- The number of times there is a loss of pneumoperitoneum due to the evacuation of the surgical smoke.
- The maximum intra-abdominal pressure used and the duration at that pressure.
- The number of times intra-abdominal pressure required adjustment during the procedure.

- The patient's temperature during the procedure.
- The amount of pain control medicine administered to the patient prior to discharge from the hospital and reported at the two week follow-up visit.
- Adverse Events.
- End tidal CO_2 volume throughout the procedure (taken at 15-minute intervals)
- Duration of the procedure (from the time all ports are in place to completion of the colpotomy for hysterectomy and to closure of last uterine defect for myomectomy).
- Duration of post-operative hospital care (time of entry to post-operative recovery to discharge)

Pain assessments (including pain score and pain location) documented during post-operative recovery, prior to discharge and at the two week follow up visit. **Other Data Collection:**

Electrosurgical instrument(s) used.

Study Size:

30 consecutive patients undergoing laparoscopic hysterectomy randomized 1:1 to either an “Ultravision” or “No Ultravision” (control, current standard of care) group. Five consecutive patients undergoing myomectomy.

Duration of Study:

Each patient will be assessed from the start of procedure until discharge from the hospital. Routine follow-up (i.e. that normally undertaken under current standard of care) will be performed. Formal follow-up for the study is through patient discharge, however any adverse events that occur thereafter that are related to the procedure will be reported.

The target for the overall duration of the study is six months.

Data Analysis: Descriptive and comparative statistics for all endpoints will be applied to analyze the results from study arms 1 and 2. Success is dependent on a favorable comparison between Ultravision and no Ultravision groups for Primary Endpoints. 95% confidence levels are assigned. Descriptive statistics for study arm 3 with general comparisons to study arms 1 and 2. Exploratory analysis may be conducted.

1. STUDY PROTOCOL INTRODUCTION & BACKGROUND

The Ultravision™ System is a medical device that removes surgical smoke by means of electrostatic precipitation from the visual field during laparoscopic surgical procedures. “Surgical smoke” refers to the suspended particulate matter that is generated as a by-product of the combustion and other processes that are associated with the use of energy-based surgical instruments. Surgical smoke can obscure (partially or totally) the surgeon’s view of the operative field and this has obvious safety implications for the patient. In the case of laparoscopic procedures, which are increasing in popularity, the smoke is retained within the “closed abdomen” and this, coupled with the CO_2 pneumoperitoneum, presents additional challenges for the surgical team. The Ultravision™ System can therefore be considered an accessory to electrosurgical instruments that is used to clear the surgical smoke generated during their use and as such will only be used when such devices are in use.

This post-market clinical study is designed to evaluate the effectiveness of the Ultravision™ System when compared to the current standard of care (no field clearing/evacuation). Comparisons in terms of surgical field visualization, procedure times, and CO2 consumption will be conducted in order to determine whether or not any clinical benefits are derived from the use of the Ultravision™ System compared to the standard of care. In order to reduce bias, the study is being conducted using a randomized blinded design.

2. STUDY PURPOSE

There are three main study objectives

1. To evaluate the impact of use of Ultravision™ System during laparoscopic hysterectomy and myomectomy on the quality of visualization in the laparoscopic field;
2. To evaluate the impact of use of Ultravision™ System during laparoscopic hysterectomy and myomectomy on procedural characteristics; and
3. To evaluate the impact of use of Ultravision™ System during laparoscopic hysterectomy and myomectomy on clinical outcomes.

3. INTENDED USE (PER INSTRUCTIONS FOR USE)

The Ultravision™ System is indicated for the clearance of smoke and other particulate matter that is created during laparoscopic surgery.

4. DEVICE DESCRIPTION

The Ultravision™ System is an accessory to electrosurgical instruments that is used to clear the surgical smoke generated during their use and as such will only be used when such devices are in use. An example of

the effect of the Ultravision™ System during use to improve the visualization of the field of view is demonstrated in Figures 2 and 3 below:

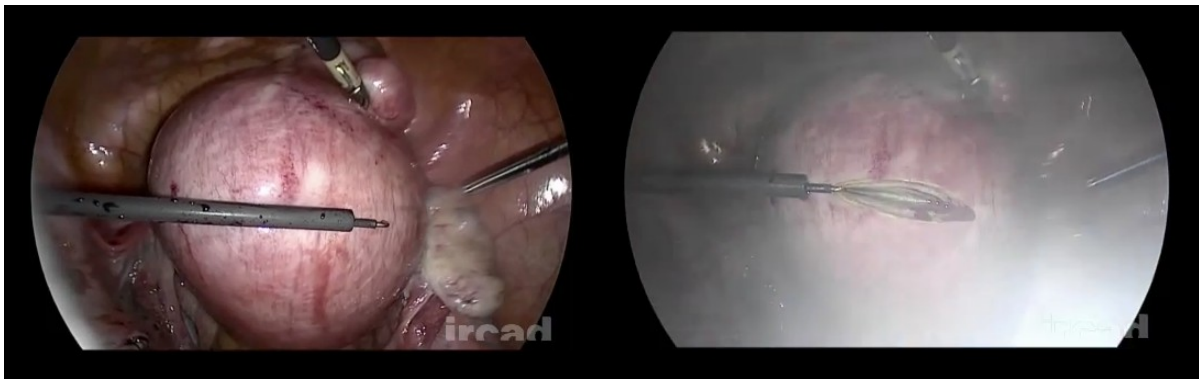

Figure 1 View before and during cutting with an electrosurgical instrument

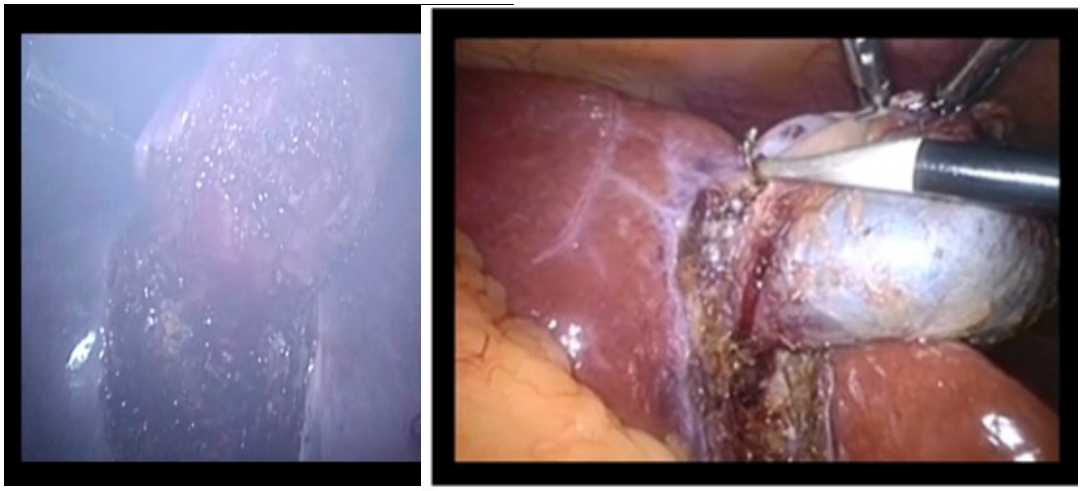

Figure 2 Electrosurgical smoke without Ultravision Figure 3 Electrosurgical smoke cleared with Ultravision

The system includes the following elements:

Standalone battery-operated generator unit

Figure 4 Ultravision Generator with battery pack

Ionwand™, which is introduced into the abdomen of the patient through either the Ultravision™ 5mm Trocar or a 2.5mm percutaneous catheter and provides the source of the electrons that create the negative ions that transiently charge the surgical smoke particles.

Figure 5 Ionwand, sterile assembly in package (top), 5mm Trocar (bottom)

Other accessories include a patient return adaptor and battery recharging station.

5. US REGULATORY STATUS

The Ultravision™ System obtained regulatory clearance through US FDA's De Novo Classification Process (DEN 150022). The system has been in distribution in Europe since January 2014 and in the US since December of 2016, over 250 systems are currently in use. To date there have been no incident or medical device reports (patient injury reports) and there have been no product recalls. The Ultravision™ System and consumable items are being provided for this study free of charge.

6. STUDY DESIGN

This is a prospective blinded, randomized controlled study.

Arms 1 and 2: Patients enrolling in study arms 1 and 2 who are undergoing laparoscopic hysterectomy will be randomized to either the Ultravision™ System (Arm 1) or Standard of Care/no Ultravision (Arm 2) study arms.

Arm 3: Patients enrolling in study arm 3 who are undergoing a laparoscopic myomectomy will have their procedure conducted with the Ultravision™ System. The procedure is purported to generate the greatest smoke and therefore constitutes a worst-case challenge for the system.

All prescribed evaluations will be performed for all study arms.

7. STUDY SIZE

Arms 1 and 2 (randomized) will enroll 15 patients each. Arm 3 will enroll an additional 5 patients.

8. DURATION

The total duration of the study is expected to be approximately 6 months.

9. HYPOTHESES

Primary hypothesis:

The primary hypothesis being tested in this study is that using the Ultravision™ System during laparoscopic hysterectomy and myomectomy improves visualization similar to that reported when used in laparoscopic cholecystectomy and that the amount of carbon dioxide (CO_2) utilized is reduced as CO_2 is deemed related to complications such as tissue desiccation and postoperative pain.[2]

Secondary hypothesis:

In addition to the amount of CO_2 utilized during the procedure another related factor is the intra-abdominal pressure of the pneumoperitoneum. Decreasing the intra-abdominal pressure below the conventional 12-15 mmHg during laparoscopic surgery has been shown by others to lead to improved clinical outcomes.[3]

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2 Veekash G, Wei LX, Su M, Carbon dioxide pneumoperitoneum, physiologic changes and anesthetic concerns, Ambulatory Surgery, 162 July 2010.

3 Yasir M, Kuldeep MS, Vigar HB, Aiman A, Masood I, Iqbal B, Evaluation of post-operative shoulder tip pain in low pressure versus standard pressure pneumoperitoneum during laparoscopic cholecystectomy, The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland, 10(2012) 71-74.

Use of the Ultravision during laparoscopic hysterectomy and myomectomy is expected to allow for lower intrabdominal insufflation pressures. In this study, the target abdominal pressure for all procedures conducted will be 10mmHg. The ability to maintain that pressure during the procedure will be reported and compared for the randomized group. In addition to this secondary endpoint other procedure data will be collected to assess the potential impact of the Ultravision™ System on procedure characteristics such as adverse events, procedure time, patient temperature, patient end tidal CO_2 level, post-op medications for pain etc.

10. STUDY ENDPOINTS

10.1. PRIMARY ENDPOINTS

Success will be based on demonstration that the procedures using the Ultravision™ System show a meaningful difference/improvement when compared to the control according to the following measures:

1. The quality of visualization in the laparoscopic field of view will be assessed by the investigator using a 5 point Visual Analog Scale (VAS). Results for the laparoscopic hysterectomy will be compared to determine if there is a significant difference between Arm 1 (Ultravision) and Arm 2 (no Ultravision).
2. The amount of Carbon Dioxide (CO_2) utilized during the procedure will be monitored. Results for the laparoscopic hysterectomy study arms (randomized cohort) will be compared to determine if there is a significant difference in the amount of CO_2 utilized between groups.

10.2. SECONDARY ENDPOINTS

The following data will be collected for all groups. Comparisons between the study arms 1 and 2 will be conducted. For study arm 3 the data will be reported and generally compared to study arms 1 and 2.

- From the initial 10mmHg setpoint, the time in minutes until a change /increase in the abdominal pressure is required, and the reason for the change (i.e. visualization, access).
- The number of times the laparoscope is removed in order to clean it of debris.
- The number of times a trocar valve is opened to evacuate smoke.
- The number of pauses due to a loss of sufficient visibility.
- The number of times there is a loss of pneumoperitoneum due to the evacuation of the operating smoke.
- The maximum intra-abdominal pressure used and the duration at that pressure.
- The number of times intra-abdominal pressure required adjustment during the procedure
- The patient's temperature during the procedure.

- The amount of pain control medicine administered to the patient prior to discharge from the hospital and reported at the two week follow-up visit.
- Adverse Events.
- End tidal CO_2 volume (etCO2) throughout the procedure (15 minute intervals).
- Duration of the procedure (from the time all ports are in place to completion of the colpotomy for hysterectomy and to closure of the last uterine defect for myomectomy).
- Duration of post-operative hospital care (time of entry to post-operative recover to discharge).
- Pain assessments (including pain score[4] and pain location) documented during post-operative recovery, prior to discharge and at the two week follow up visit.
    - An attempt will be made to assess pain scores in different areas of the body, specifically abdominal pain and referred ("shoulder tip") pain.

10.3. OTHER DATA COLLECTION

List of the electrosurgical instrument(s) used.

11. SUBJECT IDENTIFICATION & SELECTION

Potential subjects will be identified from the clinical practice of the participating investigator or by their respective research staff.

Patients presenting to the clinical practice of the participating investigator for diagnosis or treatment consistent with the inclusion criteria will be informed about the study.

With referral from the treating physician/provider, patients scheduled for surgery prior to the start of the study may be contacted via telephone by a study team member to inform them of the study, assess their interest and assess their eligibility to participate. An IRB approved script will be used for such calls. For interested patients, a copy of the informed consent can be mailed or emailed to the patient for their review and consideration prior to their next clinic visit or the scheduled procedure.

Each new subject presenting for evaluation or inclusion is to be assessed for adherence to the following inclusion/exclusion criteria. Determination of whether subjects satisfy the criteria may be established by review of medical records, subject interview, physical examination, or testing as appropriate. A baseline form

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4 Dworkan et al, Core outcome measures for chronic pain clinical trials:IMMPACT recommendations, Pain 113 (**2005**) 9–1

is used to collect subject screening information and baseline assessments. Patients are considered enrolled once it has been demonstrated that the inclusion/exclusion criteria have been met and the patient signs the informed consent.

11.1.INCLUSION CRITERIA

Subjects MUST meet all the following:

I1	Is 21 years or older.
I2	Provide written informed consent prior to trial procedures after studies indicate that the patient needs the prescribed procedure.
I3	Agrees to attend all follow-up assessments.
I4	Is clinically indicated to undergo laparoscopic hysterectomy (with or without unilateral or bilateral oophorectomy or salpingo-oophorectomy) or myomectomy.

11.2.EXCLUSION CRITERIA

Subjects MUST not have any of the following:

E1	Existing comorbidities that would contraindicate them for laparoscopic surgery.
E2	Be pregnant.

12. SUBJECT INFORMED CONSENT AND HIPAA AUTHORIZATION

A partial waiver of HIPAA Authorization is being requested for the purposes of initial screening for study eligibility and recruitment purposes. Identifiable health information to be accessed under this waiver will include contact information, demographics, and medical history. Only study team members will have access to this information. Safeguards to maintain privacy and confidentiality of information will be taken as described in the data collection and management section of the protocol. Patient inclusion could be substantially hindered without the ability to review patients' records for eligibility and recruitment purposes, particularly for patients who may have already been scheduled for surgery at the time the study begins.

Referred patients presenting for diagnosis or treatment consistent with the inclusion criteria will undergo the informed consent process to authorize the gathering of data recorded on the Subject Screening & Enrollment Form.

The study investigator will administer informed consent or may delegate the responsibility to a qualified individual as long as it is defined on the study responsibility log. When administering consent, it must be evident that the participant comprehends the nature of the study and the risks and benefits. Evidence is the patient is able to verbalize these topics in sufficient detail to confirm comprehension.

Completion of the informed consent does not constitute enrollment. Enrollment occurs once screening is complete and all criteria for participation have been met.

Subjects must document their consent for study participation by signing the Institutional Review Board approved Informed Consent Form. The informed consent process must be consistent with the Declaration of Helsinki. The subject must be given the opportunity to ask questions of, and receive answers from, study personnel prior to a request to sign the Informed Consent Form. This form is to be co-signed by the investigator. Failure to obtain consent prior to subject participation is considered a protocol deviation and must be reported to the Institutional Review Board.

Note that subjects will be asked to provide consent so that data related to their eligibility status data can be gathered.

After the subject and investigator sign the Informed Consent Form, the original is to be filed in the subject's study binder. Copies will be filed in the subject's medical record and the subject is also to be given a copy.

13. **SCREENING & ENROLLMENT**

Patient demographics and other baseline information will be collected to establish whether the patient meets the requirements for the study. Each patient will be assigned a unique study number. Baseline information will be collected, consistent with the standard of care.

Table 1
Baseline Form Information

Type of Information	Data Sources	Time Frame
Date of Evaluation	Investigator	NA
Subject Age	Subject interview	NA
Ethnicity	Subject interview & medical record	NA
Medicinal allergies or intolerance	Subject interview & medical record	Within one month prior to surgery
Physical Exam	Investigator Report	Within one month prior to surgery
Prior/Existing Medical Conditions	Subject interview & medical record	Within one month prior to surgery
Prior/Existing Medical Interventions	Subject interview & medical record	Within one month prior to surgery
Diagnosis indicating surgical intervention	Investigator Report	Within one month prior to surgery
Current Drug Therapies	Subject interview & medical record	Within one month prior

Table 1 Baseline Form Information		
Type of Information	**Data Sources**	**Time Frame**
		to surgery
Diagnostic Tests and Exams		
Abdominal ultrasound	Investigator Report	Within one month prior to surgery
Labs – as normally prescribed Pregnancy test (if child-bearing age)	Hospital laboratory	Within 3 months prior to surgery

13.1. RANDOMIZATION AND BLINDING

For study arms 1 and 2 patients will be randomized using a paper envelope system. Randomization shall occur just prior to surgery. The investigator will not be informed of the randomization assignment until after the surgical intervention for a patient is completed. For randomization, a simple envelope system will be used. Pre-made study arm assignment envelopes of the study quantity will be created. 30 envelopes – 15 containing “Ultravision” cards and 15 containing “Non-Ultravision” cards - will be opened by the Lead Study Coordinator just prior to the procedure. For patients randomized and withdrawn prior to the procedure or converted to open procedure, replacement envelopes will be added to the envelope pool.

To preserve blinding of the investigator/surgeon during the procedure, the Ultravision™ System consumable will be introduced into the patient and the generator will appear operational during all procedures. The display will be covered during use so that the investigator is not aware of whether the system is on or off. If for any reason unblinding occurs accidentally or the Principal Investigator deems it necessary to unblind a particular patient, it will be recorded by notifying the Lead Study Coordinator and recording the reason for this unblinding on the narrative CRF in the relevant section. Study assessments will be collected per protocol, but the data will not be pooled with blinded data for analysis.

13.2. PREOPERATIVE PROTOCOL

Patients will be assessed preoperatively in accordance with the current standard of care.

Table 2 Preoperative Assessments Conducted within 24 hours of surgery	
Type of Information *Collected within 24 hours of surgery*	**Data Sources**
Patients general wellbeing (illness such as flu, cold etc.…)	Investigator Report
Changes since baseline assessment • Medical conditions • Drug therapy • Medical interventions	Medical Record/Patient Report

Table 2 **Preoperative Assessments** **Conducted within 24 hours of surgery**	
Type of Information *Collected within 24 hours of surgery*	**Data Sources**
Laboratory Panel – as normally prescribed Pregnancy test (if child bearing age)	Medical Record

13.3. PROCEDURE PROTOCOL

The Ultravision™ System will be set up in the OR for all cases. For randomized study arms 1 and 2, the system will be covered such that the electronic display is not visible to the investigator. The system will be turned off for all non-Ultravision procedures. For all procedures, the Ionwand will be inserted/introduced as described in the Instructions for Use.

Table 3 **Intraoperative/Procedure Information**		
Type of Information	**Time Point**	**Data Sources**
Date of Procedure	Before opening	Patient Medical Record
Anesthesia	Before opening	Investigator Report
Procedure to be performed	Before opening	Investigator Report
Pneumoperitoneum pressure after camera trocar is inserted	Intraoperative	Investigator Report
The From the initial 10mmHg setpoint, the time in minutes to a change /increase in the abdominal pressure and the reason for the change i.e. visualization, access.	Intraoperative	Investigator Report
The maximum intra-abdominal pressure used and duration at that pressure, using a stop watch that is reset each time the pressure is increased.	Intraoperative	Investigator Report
The number of times intra-abdominal pressure required adjustment during the procedure	Intraoperative	Investigator Report
The number of pauses due to a loss of	Intraoperative	Investigator Report

Table 3 Intraoperative/Procedure Information		
Type of Information	**Time Point**	**Data Sources**
sufficient visibility		
The number of times there is a loss of pneumoperitoneum due to the evacuation of the operating smoke	Intraoperative	Investigator Report
The number of times the laparoscope is removed in order to clean it of debris	Intraoperative	Investigator Report
The number of times a trocar valve is opened to evacuate smoke.	Intraoperative	Investigator Report
The patient's temperature at 15-minute intervals during the procedure.	Intraoperative	Investigator Report
Adverse Events	Intraoperative	Investigator Report
Planned concomitant interventions (bilateral or unilateral oophorectomy or salpingo-oophorectomy)	Intraoperative	Investigator Report
Unplanned concomitant interventions or procedures	NA	Investigator Report
End tidal volume of CO_2 (etCO2), recorded at 15-minute intervals during the procedure	Intraoperative	Investigator Report
Number of CO_2 liters consumed during the procedure	Intra-operative	Investigator Report
Overall procedure time* –	NA	Investigator Report
Surgeon Survey on Quality of Visualization	Immediately Post-operative	Investigator Report
Electrosurgical devices used	NA	Investigator Report
The amount of pain control medicine administered to the patient during recovery, prior to discharge from the hospital, and at 2-week follow-up	Post-operative	Investigator Report
The time from entry to post-operative recovery to discharge	Post-operative	Investigator Report
Pain Assessments (including pain score and pain location) documented during post-operative recovery and prior to discharge	Post-Operative	Patient Report (0-10 Numerical Rating Scale)
Pain Assessment at two week follow-up visit	2 week follow up visit	

Table 3 Intraoperative/Procedure Information		
Type of Information	**Time Point**	**Data Sources**
Device used (lot# and model #)	NA	Investigator Report
Device malfunction	NA	Investigator Report

* Overall procedure time is defined as the time from when all ports are in place to the time when colpotomy is performed for hysterectomy procedures or when the last uterine defect is closed for myomectomy procedures.

14. SURGEON VISUALIZATION SURVEY

Immediately post procedure the investigator will be asked three questions:

1. Proportion of operating time with effective visibility?
   A 1-100 numerical rating scale will be used to estimate the time proportion.
2. What is the overall rating of visibility?
   The following scoring scheme will be applied:

Score	Impairment Scale Impairments are:	Quality
1	Imperceptible	Excellent
2	Perceptible (but not interfering)	Good
3	Slightly interfering	Fair
4	Interfering	Poor
5	Highly interfering	Bad

3. For randomized study arms do you know if the patient was in the Ultravision group?
   A yes or no, or don’t know answer and the information that influenced the answer is recorded.

15. POST PROCEDURE FOLLOW-UP PROTOCOL

Post procedure follow-up assessments include discharge and 2-week follow-up, which is the current standard of care, as prescribed Attachment 4.

16. ADVERSE EVENTS

16.1. ADVERSE EVENT CATEGORIES

For purposes of this protocol the adverse event definitions are derived from GCP standards and FDA Guidance.[5]

Table 4
Adverse Event Definitions

Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device. Includes events related to the study device or comparator device, or the procedures involved.
Serious Adverse Event (SAE)	Adverse event that: ▪ Led to death ▪ Led to serious deterioration in the health of the subject, that: o Resulted in a life-threatening illness or injury, or o Resulted in a permanent impairment of a body structure or a body function, or o Required in-patient hospitalization or prolongation of existing hospitalization, or o Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function o Led to fetal distress, fetal death, or a congenital abnormality or birth defect Planned hospitalization for a pre-existing condition without serious deterioration in health, is not considered a serious adverse event. Hospitalization is defined as an admission greater than 24 hours
Adverse Device Effect (ADE)	Untoward and unintended response to a medical device or as a consequence of inadequate labeling and includes any event that is a result of user error.
Serious Adverse Device Effect (SADE)	Untoward medical occurrence that happens in a subject or other person, is related to the study device, comparator, or procedure, and is serious, but is not unanticipated
Unanticipated Serious Adverse Device Effect (USADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, procedure, or comparator device if that incidence effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the risk analysis report of the plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5 Clinical Investigation of Medical Devices for Human Subjects - Part 1: General Requirements. ISO 14155-1. International Organization for Standardization. 2011.

The signs, symptoms, and sequelae of an underlying adverse event (linked pathophysiologically to the AE) should not be reported as separate adverse events.

All adverse events, of any type, are to be recorded on an "Adverse Event Form". Adverse events are to be characterized by their severity, relatedness the implant procedure, need for therapy, and resolution status.

Adverse events will initially be characterized as "serious" or "non-serious" by the study investigator.

16.2. ADVERSE EVENT ADJUDICATION

Events are to be initially judged by the investigator as to their relatedness to the study device, implant procedure, or "other etiology". The classifications will be "not related", "probably not related", "undetermined", "probably related", or "related".

16.3. REPORTING OF ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

Serious adverse events and Unanticipated Problems related to the research will be reported to the Mercy Institutional Review Board.

16.4. SUBSEQUENT SURGICAL INTERVENTIONS

Some complications may lead to a subsequent surgical intervention. The reason for each subsequent surgical intervention and the action taken is recorded on the case report form, along with the identification of the type subsequent surgical interventions according. The exact type of intervention must be specified.

17. PATIENT WITHDRAWAL

A patient may choose to withdraw from participation in the study at any time without penalty. If a patient chooses to withdraw they will still receive medical care consistent with the standard of care. The investigator may at their discretion withdraw a patient from participation. Examples include if the procedure necessitates conversion from laparoscopic to open technique, lack of adherence to visit schedule, adverse events, or safety concerns. For all withdrawals the date, point in the study, and reason for withdrawal will be recorded.

18. STUDY SUSPENSION/TERMINATION

If for any reason the principle investigator chooses to suspend or terminate the study, the IRB shall be informed of the decision and the basis of the decision.

19. STUDY MATERIALS

The Investigator is responsible for assuring that routine medical supplies, equipment, personnel, and facilities are available to successfully implement this study plan in a timely and efficient manner. Provisions should be made for research and medical staff to sufficiently accomplish:

- Screening of subjects to identify suitable study subjects,
- Conducting and obtaining informed consent,
- Scheduling for examinations and procedures,
- Coordination, monitoring, and source data verification,
- Case Report Forms,
- Investigational devices and
- Clinical study Plan and supporting study documentation.

20. PROVISION AND INVENTORY OF STUDY DEVICES

The device and required materials will be provided to the Investigator by Alesi Surgical Ltd.

21. DATA COLLECTION AND MANAGEMENT

The investigator and study team members as delegated are responsible for collecting the data from the study. Copies of all imaging documentation files will be collected and retained by the study team.

Case Report Forms (CRF) specifically created for this study will be used to collect all data. Case Report Forms shall reflect the contents of this study plan. The CRF and any amendment to it shall bear a version number and each page shall be identifiable by the number and identification of the subject whose data the CRF pertains. If/when it is necessary to amend the CRFs, the investigator shall review the IP to determine if an amendment to this IP is necessary.

Manually entered information on any paper study documents must be legibly written in black ink only. If changes are required, a single line must be drawn through the incorrect information, the correct information written in, and the changes initialed and dated. The reason for the correction should be noted, unless obvious. Use of white-out, obscuring incorrect data (scribbling-out), and additional comments written on the documents is prohibited.

The investigator must review sign and date each CRF or document review on a CRF review log; these responsibilities cannot be delegated to another person. The investigator is responsible for the accuracy and completeness of all study data.

All original imaging, laboratory, and procedural reports, etc., are considered source documents and will also be retained at the investigational site.

For analysis data may be extracted from case report forms and entered into spreadsheets or local computerized systems.

Study subjects will be identified by unique study identification numbers. The identification number is the 3-digit study number and the patients three initials. A master key will contain the study identification number

and patient identifier (as defined by the Study number, the patient ID number and the patient's initials). The master key will be stored in the study binder and kept in a secure, locked location in the Principal Investigator's office.

Study binders containing study data will be collected and stored in a secure, locked location in the Principal Investigator's office. Access to the records will be limited to the Lead Study Coordinator and the Principal Investigator only.

Study data will not be removed from the site listed above at any time during the course of this study. Data extracted into spreadsheets or computer files may be shared outside of the facility for data analysis purposes. Such data extractions will be transmitted to the Biostatistician by the Mercy Secure File Transfer System for data analysis. All shared data will be de-identified.

22. IMAGING DIAGNOSTICS

All imaging performed for patients is considered consistent with standard of care.

23. DATA ANALYSIS PLAN

23.1. SAMPLE SIZE JUSTIFICATION

The sample size selected (15) per group is considered to be a number to allow for a meaningful comparison between the study arms conducted by a single investigator. As a post-market study intended to evaluate user satisfaction and relative impact the Ultravision™ System has on the procedure as opposed to demonstrating safety and efficacy, the sample size is considered to be sufficient for that purpose. This essential information is identified in the primary and secondary endpoints.

23.2. DATA ANALYSIS

Data collected will be summarized using descriptive statistics. For study success results must demonstrate a clinical benefit for the randomized Ultravision group compared to the no Ultravision group based upon the primary endpoint analysis. Additional exploratory analysis may be conducted during data analysis. Because the study is not statistically powered, analysis for primary and secondary endpoints will be conducted using comparative statistics with the caveat understood regarding the relatively small sample sizes for each group.

24. TRAINING PROCEDURES

Specific training of trial personnel is the responsibility of the Investigator. Training will occur before the first device use. To ensure compliance with the study plan and regulatory requirements as well as accurate data

collection, site training will include a detailed review of this Investigational Plan, case report form (CRF) completion instructions, adverse event reporting, device handling and inventory, monitoring logistics, and regulatory requirements.

25. ADMINISTRATION

This study is being conducted as an "Investigator Sponsored" post-market study. The Investigator holds ultimate responsibility for the design, conduct, analysis, and reporting of the results from this study and is the primary contact for all matters related to this investigational plan. The Primary Investigator is also accountable for monitoring this investigation and performing those actions necessary to protect the scientific credibility of the way this study is conducted.

26. REGULATORY COMPLIANCE

The investigators and all research staff participating in this investigation are expected to adhere to this investigational plan, Good Clinical Practices, applicable privacy laws, the Declaration of Helsinki, and any approval requirements imposed by an Institutional Review Board. The study will be submitted for review and approval by the Mercy Institutional Review Board.

26.1. INSTITUTIONAL REVIEW BOARD

Subjects may not be enrolled into this study until legal authority to do so has been granted by the authorizing Institutional Review Board. A copy of all approval letters must be maintained in the site file.

26.2. GOOD CLINICAL PRACTICES

The principles of Good Clinical Practices defined in ISO 14155:2011-1 Clinical investigation of medical devices for human subjects – Part 1: General Requirements, Part 2: Clinical investigation plans will be adhered to in the design, conduct, analysis, and reporting of results of this investigation.

27. PRIVACY AND CONFIDENTIALITY

This study is to be performed in accordance with all applicable privacy laws. All data and information concerning subjects and their participation in this trial are considered confidential. Only authorized investigators and approved study personnel will have access to some portions of these confidential files. Institutional Review Boards and other regulatory authorities also have the right to inspect and copy records pertinent to this trial. All public reporting of the results of this study will eliminate identifiable references to the subjects.

28. RECORDS AND REPORTS

The following records and reports must be created and/or maintained by the parties as specified below.

28.1. INVESTIGATOR RECORDS

Records to be maintained by the investigator in a designated study file include:

- Site information
    - Site signature log
    - Responsibility log
    - CVs of all study personnel
    - Training records for all study personnel
- Clinical study Plan/Protocol
    - plan and all amendments
    - Blank sets of each version of CRFs and Consent Forms
- Institutional Review Boards Records
    - Institutional Review Board Membership List
    - Submission to Institutional Review Boards
    - Approval letters
    - Notification of serious and unanticipated adverse device events
    - updates/reports
    - Any other communication
- Screening and enrollment form
- Consent Form
    - Institutional Review Boards approved copy
    - Revised approved, consent forms
- CRFs
    - Annotated CRF, CRF worksheets, and/or CRF instructions
    - Blank CRFs
- Correspondence

- All correspondence of material concern relating to the trial between the investigator and other parties (e.g. IRB).

The following records must be maintained for each subject enrolled in the trial:

- Signed Consent Form
- Completed CRFs
- Protocol Deviation Forms
- Complete medical records, including procedure reports, lab reports, professional notes, etc. for participating subjects.
- Records pertaining to subject death during the investigation (including death records, death certificate, and autopsy report, if performed)

28.2. INVESTIGATOR REPORTS

Traditional Investigator Reports such as progress reports are not applicable due to the acute nature of the investigation. The investigator shall be required to complete a summary report to Alesi Surgical, Ltd capturing their general observations.

28.3. RECORD RETENTION

Subject records, correspondence files, all supporting documentation, and reports must remain on file at the investigational site for a minimum of three years or in line with the Mercy document retention policy (if longer) after the completion/termination of this or when it is no longer needed to support a marketing application, whichever is later.

29. RISK/BENEFIT ASSESSMENT

As a surgical accessory device, the Ultravision™ System does not administer any medical treatment. The risks associated with its use are consistent with other surgical accessories used in laparoscopic surgery. The device has been tested for sterility, biocompatibility, and electrical safety demonstrating that such risks have been mitigated to acceptable levels. The benefits that are being evaluated in this study are improved visualization, lower pressure of pneumoperitoneum, and CO_2 consumption have the potential to favorably impact patient outcomes.

30. RELATED DOCUMENTS

The following documents are related to the proper execution of this protocol. They include the following document types:

A1. Subject Informed Consent

A2. Case Report Forms

A3. Instructions for Use Labeling

A4. Study Visit Schedule

Study Phase	***Baseline***	***Pre-operative Visit***	***Procedure***	***Post Procedure – prior to discharge assessment***	***Discharge Assessment***	***2-week Post-discharge follow up***
Visit Number						
Study Day						
Procedures:						
Informed Consent	*X*					
Eligibility Criteria	*X*					
Medications and Allergies	*X*	*X*		*X*	*X*	*X*
Medical Record Review	*X*	*X*				
Vital Signs	*X*	*X*				
Physical Exam	*X*	*X*				
Lab Test	*X*	*X*				
Pregnancy Test	*X*	*X*				
Abdominal Ultrasound	*X*					
Randomization			*X*			
Procedure: Laparoscopic Hysterectomy OR Laparoscopic myomectomy			*X*			
Visual Analog Scale			*X*			
Adverse Event Assessment			*X*	*X*	*X*	*X*
*Pain Assessment**				*X*	*X*	*X*

*Pain Assessments (including pain score and pain location) documented during post-operative recovery and prior to discharge will be recorded