The ULTRA Study:
Uterine Leiomyoma Treatment with Radiofrequency Ablation

University of California Fibroid Network
PI: Vanessa Jacoby, MD, MAS
University of California, San Francisco
Department of Obstetrics, Gynecology, and Reproductive Sciences

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1.0 BACKGROUND

Uterine leiomyoma, or fibroids, are benign smooth muscle tumors that occur in 25% of premenopausal women and cause heavy bleeding, pelvic discomfort, urinary and bowel dysfunction, and adverse pregnancy outcomes. Hysterectomy and myomectomy are the mainstay treatments for fibroids. However, many women seek minimally invasive, uterine-preserving therapy to avoid overnight hospitalization and allow for a rapid return to their usual activities.

The Radiofrequency ablation device is a new FDA approved surgical procedure that aims to effectively treat fibroids with a minimally invasive outpatient procedure. Radiofrequency ablation uses radiofrequency energy to heat fibroid tissue and cause instantaneous cell death. The necrotic cells are then reabsorbed by the lymphatic system resulting in decreased fibroid size and improved symptoms. The Radiofrequency ablation device is placed within the fibroid under ultrasound guidance during a standard outpatient pelvic laparoscopy.

There is limited outcome data on Radiofrequency ablation.[1,2] In the pivotal trial for FDA approval of 135 women, fibroid symptoms decreased by 52% and fibroid volume decreased an average of 40% within 3 months of treatment.[3] These therapeutic effects were persistent through 12 months of follow-up with 56% decrease in symptoms and 45% decrease in fibroid volume from pre-procedure values. Sixty one percent of study participants were very satisfied with treatment and 80% reported they would definitely recommend the treatment to a friend. One study participant required re-intervention for persistent or recurrent fibroid symptoms following Radiofrequency ablation treatment. The Radiofrequency ablation procedure resulted in minimal blood loss (median 33cc) and an average return to normal activities of 9 days. Therefore, Radiofrequency ablation treatment may result in decreased pain, less blood loss, faster return to normal activities, and lower rates of re-operation compared with either abdominal *or* laparoscopic myomectomy.

2.0 STUDY RATIONALE

The Radiofrequency ablation procedure offers women a new approach to fibroid treatment that improves bothersome symptoms with the potential for significantly less morbidity compared with current fibroid surgery. The existing studies of Radiofrequency ablation are all uncontrolled trials that demonstrate subjective and objective improvement in fibroid-related symptoms. However, no trials have been conducted to examine the benefit of Radiofrequency ablation in comparison with other surgical fibroid treatments. Our ultimate goal is to conduct a multi-centered, randomized, noninferiority trial of Radiofrequency ablation versus myomectomy (laparoscopic or abdominal) among women with symptomatic fibroids. This trial will provide gold standard evidence to determine if Radiofrequency ablation results in similar symptom improvement as myomectomy but offers the advantages of less operative morbidity and lower rates of re-operation for recurrent fibroid symptoms.

To prepare for a future multi-centered comparative trial of Radiofrequency ablation, we will first conduct an uncontrolled pilot study (the ULTRA study). The pilot will allow us to assess the feasibility of recruiting and retaining study participants to this surgical trial, and establish effective communication and organizational tools among the five study sites. We will also complete essential preparatory work for a future randomized trial; we will create and test study forms, a manual of operations, and a study database that can be easily adapted for a

comparative trial. The ULTRA pilot study will lay the foundation for a successful future comparative study of Radiofrequency ablation.

The ULTRA study will also provide preliminary data on the efficacy of Radiofrequency ablation in a "post-market" setting. This is the first Radiofrequency ablation trial after FDA approval in November 2012. Previous studies have enrolled a highly symptomatic patient population with a minimum menstrual blood loss of 200cc (normal is <80cc) to adhere to the requirements for FDA approval. However, in clinical practice, surgical treatment is offered to women with more moderate fibroid symptoms and we will enroll these patients in the ULTRA study. We will use ULTRA outcome data to estimate effect sizes and standard deviations to calculate an appropriate sample size for a future randomized trial.

3.0 STUDY OVERVIEW

The ULTRA study is a single-arm trial of 100 premenopausal women with symptomatic uterine fibroids who undergo treatment with the Radiofrequency ablation device. We will evaluate changes in fibroid-related symptoms from pre-treatment values to 3, 6, 12, 18, 24, 30, and 36 months after Radiofrequency ablation. We will also assess operative outcomes including procedure duration, complications, blood loss, post-operative pain, and return to usual activities. We will determine long-term efficacy of Radiofrequency ablation by evaluating the rate of re-treatment for symptomatic fibroids after the Radiofrequency ablation procedure.

Study participants will be recruited at 5 sites within the UC Fibroid Network: UC Davis, UC Irvine, UC Los Angeles, UC San Diego, and UC San Francisco. UC San Francisco will serve as the Coordinating Center for the trial with oversight of all scientific and administrative aspects of the study. All study data will be stored securely in a HIPAA compliant, secure database monitored by the UC San Francisco Coordinating Center. A data safety and monitoring board will oversee participant safety and protection.

4.0 STUDY OBJECTIVES

The ULTRA study will collect essential preliminary data go guide and inform a future multi-centered, randomized trial of Radiofrequency ablation versus myomectomy. The 2 primary study goals are:

1. To create and implement study protocols, measurements and procedures that will serve as a template for future comparative trials of Radiofrequency ablation.

   We will evaluate the efficiency and timeliness of study recruitment. We will create a database and study forms with fibroid specific questionnaires, develop communications and study operations for the coordinating center and each study site, and assess the demand and interest for Radiofrequency ablation among symptomatic women.

2. To collect preliminary data on the changes in fibroid-related symptoms from baseline to 3 years after the Radiofrequency ablation procedure among women with symptomatic fibroids.

   We will assess fibroid-related symptoms prior to Radiofrequency ablation treatment and every 6 months for 3 years after surgery. We will evaluate changes in both bleeding and bulk symptoms using validated questionnaires.

Secondary study objectives are as follows:

1. To determine the rate of re-intervention for recurrent fibroid symptoms following the Radiofrequency ablation procedure.
   Study participants will be queried every 6 months about recurrent fibroid symptoms and interventions including medical management, myomectomy, uterine artery embolization, MR Guided Focused Ultrasound, or hysterectomy.

2. To evaluate short-term operative morbidity among women undergoing the Radiofrequency ablation procedure.

   We will evaluate operative and perioperative morbidity including procedure duration, blood loss, complications, as well as post-operative pain and time to return of usual activities.

3. To evaluate gynecologists' performance during the "learning curve" of introducing the Radiofrequency ablation procedure into practice.

   Gynecologists will be asked to rate the difficulty of the Radiofrequency ablation procedure and their confidence with the procedure among the first 10 study participants.

4. To examine the rate of pregnancy and pregnancy outcomes among women who desire future fertility following the Radiofrequency ablation procedure.

   We will query study participants at baseline regarding the desires for future fertility and every 6 months after the Radiofrequency ablation procedure. We will ask participants to report any pregnancies and the outcome of those pregnancies.

5.0 STUDY SITES

All study sites are within the UC Fibroid Network, a research collaboration among the five Departments of Obstetrics and Gynecology within the University of California hospitals. The UC Fibroid Network serves a diverse patient population and includes gynecologists with expertise in the clinical care of women with fibroids and minimally invasive gynecologic surgery. Three sites have dedicated fibroid centers (UCSD, UCLA, UCSF) and all sites have staff and administrative capabilities to successfully conduct clinical trials (Table 1).

Each study site will have a Site Principal Investigator that will oversee implementation of the study protocol, supervise the site research coordinator, assure timely recruitment of participants, and perform the Radiofrequency ablation procedure on study participants. The Site Co-investigator will collaborate with the Site PI to implement the study protocol and perform Radiofrequency ablation procedures. The Site PI and the Co-investigator will each perform 10 Radiofrequency ablation procedures during the duration of the study.

Table 1. UC Fibroid Network Sites

Site	Site PI	Co-Investigator
UC Davis	Elaine Waetjen, MD	Bahareh Nejad, MD
UC Irvine	Naghmeh Saberi, MD	Marc Vuchinich, MD
UC Los Angeles	Ram Parvataneni, MD	Steve Yu, MD
UC San Diego	Shira Varon, MD	Erin Gross, MD

6.0 STUDY POPULATION

We will recruit women with symptomatic fibroids who meet the following criteria:

INCLUSION CRITERIA

1. Premenopausal (at least 1 menstrual period in last 3 months)
2. Age >21years
3. Fibroids are associated with heavy bleeding, pelvic pressure or discomfort, urinary or bowel symptoms, or dyspareunia
4. Desires surgical management of fibroids
5. Uterus ≤16 weeks in size
6. All fibroids ≤ 10cm in maximum diameter by ultrasound or MRI assessment ***within the last year.***
7. Total number of fibroids ≤6 by ultrasound or MRI assessment ***within the last year. (For this study "Fibroids" will be leiomyomas*** > 2cm)
8. Had a Pap smear within the last 3 years with appropriate follow-up and treatment for cellular abnormalities
9. Endometrial biopsy indicates no hyperplasia or cancer (biopsy only required if age >45 years and has anovulatory heavy bleeding)
10. Able to tolerate laparoscopic surgery
11. Able to give informed consent

EXCLUSION CRITERIA

1. Planned treatment for infertility
2. Pedunculated fibroid with thin stalk (total stalk length is <25% maximum diameter of fibroid)
3. Intracavitary (FIGO Type 0) fibroid
4. Symptomatic fibroids are ***only*** FIGO Type 1 (submucosal with ≥ 50% intracavitary)
5. Planned concomitant surgical procedure in addition to treatment of uterine fibroids
6. Use of Essure or any other metallic, implantable device within pelvis
7. Pregnancy
8. Pelvic infection with the last 3 months
9. History of pelvic malignancy and/or pelvic radiation
10. Known or high suspicion for dense pelvic adhesions
11. Fibroids treated by myomectomy, uterine artery embolism, radio-frequency ablation, MRI Guided focused ultrasound, or cryomyolysis within the last 3 months

Inclusion of Women who Plan Future Pregnancy: The Radiofrequency ablation device has not been studied among women who desire future fertility. Therefore, the FDA states that Radiofrequency ablation is "not recommended for women planning future pregnancy". We will ***include*** women in ULTRA who desire future fertility because we aim to evaluate the impact of Radiofrequency ablation on pregnancy rates and pregnancy outcomes. Women who hope to become pregnant have limited treatment options. They are generally only offered myomectomy because of the 5% chance of ovarian failure following uterine artery embolization and the limited experience with pregnancy following MR Guided Focused Ultrasound. Radiofrequency ablation treatment may be a safe option for women who plan future fertility because the treatment is directed solely to the fibroid, not the surrounding myometrium. Potential study participants will

be informed of the Radiofrequency ablation FDA guidelines for women planning future pregnancy. Study investigators will emphasize the unknown outcomes of Radiofrequency ablation on future fertility and review the following potential risks:

- A decreased ability to become pregnant
- An increased risk of miscarriage
- An increased risk of pregnancy complications such as placenta abruption, that can injure the fetus, or in rare cases, result in fetal death
- An increased risk of uterine rupture during labor, resulting in injury to the patient or fetus, including the rare possibility of fetal death

6.1 Participant Recruitment

Study participants will be recruited through the clinical practices of ULTRA investigators and among the general community of women seeking fibroid treatment. Advertisements for the study will be posted on the fibroid centers' and/or department website and in key clinical areas within our women's health clinics. We will also post advertisements in local newspapers and community boards. Study investigators will identify patients with symptomatic fibroids who meet the inclusion and exclusion criteria and invite them to participate in ULTRA. Study investigators will explain the Radiofrequency ablation procedure as well as the study protocol. Potential study participants will be offered alternatives to Radiofrequency ablation treatment as clinically indicated and available including medical management for heavy bleeding, myomectomy, hysterectomy, uterine artery embolization, and MR Guided Focused Ultrasound.

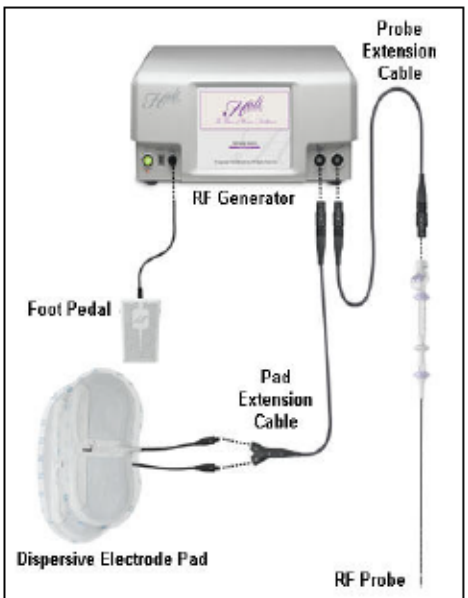
6.2 Informed Consent

The study aims and procedures will be explained initially by the study investigators during a fibroid consultation visit. A trained research coordinator will then confirm that the patient meets the inclusion and exclusion criteria and review in detail the study consent form and protocol with emphasis on the length of follow-up and required follow-up procedures. The study investigator will answer any additional questions about Radiofrequency ablation or study procedures. The study investigator will discuss with the participant the risk that the Radiofrequency ablation procedure cannot be performed at the time of surgery (e.g. due to dense pelvic adhesions) and inquire what alternative treatment options the participant would desire (e.g. an open abdominal myomectomy). The participant will then sign the study consent form. In addition, the participant will sign a standard surgical consent form unique to each study site that details the Radiofrequency ablation procedure, risks, benefits, and alternative therapies.

7.0 THE RADIOFREQUENCY ABLATION DEVICE

All study participants will undergo a standard Radiofrequency ablation procedure using the Halt System™. The Radiofrequency ablation Device is comprised of two primary components (Figure 1):

1. <u>The Electrosurgical Radiofrequency Generator (Halt 2000):</u> The generator is a nondisposable component that delivers radiofrequency energy through a Probe Extension Cable (TU1200) to a probe placed within the fibroid. The generator includes 3 accompanying components: 1) a pneumatic foot pedal to turn the generator on and off, 2) a medical grade power cord to



deliver AC power to the generator, and 3) a dispersive electrode pad set (TSP115) that provide the energy return path delivered through the probe.

2. The Electrosurgical Radiofrequency Probe (Tulip or TU1000): The probe is a hand piece with a trocar-pointed shaft. At the end of the shaft are 7 needle electrodes that are deployed within the fibroid. The probe connects to the Halt 2000 with the Radiofrequency Probe Extension Cable (TU1200).

The Halt 2000 can deliver up to 200W of power. An automated ablation algorithm sets the duration of ablation based on the volume of tissue to be treated calculated from the length of the deployed probes within the fibroid.

7.1 Preoperative Preparation

All study participants will undergo a preoperative complete blood count, type and screen, and pregnancy test (serum or urine HCG within 48 hours of surgery). In addition, all study participants will be evaluated preoperatively by a member of the anesthesia care team (MD or CNA) to determine individual risks of general anesthesia. Additional preoperative preparation will be left to the discretion of the treating gynecologist in accordance with the participants' medical history and the clinical practice and protocols of each study site.

7.2 The Radiofrequency ablation Procedure

The Radiofrequency ablation procedure will vary somewhat among study participants based on the size, number, and location of fibroids as well as the surgical protocols and practices at each study site. Gynecologists may select which laparoscopic port system is used and which laparoscopic entry procedure they prefer for the Radiofrequency ablation procedure. Any standard laparoscopic 10-12mm ultrasound probe may be used. However, all Radiofrequency ablation procedures will proceed with several uniform steps as follows:

1. Sequential compression devices are placed on the bilateral lower extremities.
2. Antibiotics ***are not*** given as surgical prophylaxis per ACOG guidelines for laparoscopy.
3. General anesthesia is induced.
4. A Foley catheter is placed in the bladder.
5. A pelvic exam is performed with note of the uterine size.
6. An IUD is removed if present.
7. A HUMI plastic uterine manipulator is placed in the uterus with the patient in dorsal lithotomy position (optional).
8. Grounding pads are placed on the bilateral thighs 1cm above the patella with good skin contact.
9. A 5mm umbilical port site is placed for a 5mm laparoscope.
10. A 10-12mm midline port site is placed for the ultrasound.
11. The ultrasound is used to locate and measure all uterine fibroids and fibroid measurements are recorded.
12. The Radiofrequency Probe is placed into the abdomen percutaneously under direct visualization.
13. The Radiofrequency Probe is used to perform the fibroid ablation following the Instructions for Use of the Radiofrequency ablation system. The ablation algorithm will guide the length of the ablation procedure. Care will be taken to avoid the pelvic sidewall, bladder, and bowel.

14. All fibroids visualized with intraoperative ultrasound are treated with the Radiofrequency Probe.
15. Submucosal fibroids are treated after removing the HUMI uterine manipulator. The HUMI uterine manipulator can be used to help position the Radiofrequency Probe in the fibroid, but then the manipulator is removed before heat is delivered to the fibroid.
16. The Radiofrequency Probe and laparoscopic ports are removed.
17. The 10-12 mm port site fascia may be closed at the discretion of the surgeon.
18. The skin is closed with surgical glue or sutures at the discretion of the surgeon.
19. The patient is discharged from the recovery room after meeting recovery room discharge criteria.
20. Discharge medications include nonsteroidal anti-inflammatories and narcotic analgesia at the discretion of the gynecologist.

7.3 Unanticipated Surgical Findings

At the time of surgery, unanticipated surgical findings may create an obstacle to performing the Radiofrequency ablation procedure (e.g. dense pelvic adhesions). In this case, the surgeon may elect to perform another fibroid treatment such as abdominal myomectomy or hysterectomy guided by the preoperative discussion with the participant regarding her desire under these circumstances. In addition, if an adnexal mass is visualized intraoperatively and the surgeon feels it should be removed, she/he may complete this surgery. Finally, if a subserosal or pedunculated fibroid is visualized that was felt to have a broad base but appears to have a narrow stalk, it may be removed via laparoscopic myomectomy.

7.4 Procedure Training and Support

Study investigators will be trained to perform the Radiofrequency ablation procedure during a one day in-service conducted by Halt Medical. The training includes didactic sessions and hands-on simulation of laparoscopic ultrasound and use of the Radiofrequency Probe. A trained Radiofrequency ablation physician employed by Halt Medical will be present in the operating room to provide technical support during the first 5 cases each investigator performs. This Radiofrequency ablation trainer can be present for additional cases at the request of the investigator as needed for additional support.

7.5 Use of Radiofrequency ablation Outside of The ULTRA Study

The procurement of Radiofrequency ablation to the UC Operating Rooms is through the UC policies and procedures for IRB approved clinical trials, not through the pathway for device use in general clinical practice. Therefore, there will be no use of Radiofrequency ablation at study sites outside of participants enrolled in ULTRA/ULTRA Registry. Study investigators will not use Radiofrequency ablation for patients undergoing procedures who are not enrolled in ULTRA/ULTRA Registry. Among study participants, investigators will only use Radiofrequency ablation according to the ULTRA protocol.

8.0 MEASURED VARIABLES

8.1. Outcome Variables

Outcomes will be measured at baseline prior to the Radiofrequency ablation procedure and at multiple time points for 3 years after the Radiofrequency ablation procedure. Questionnaires will be administered to evaluate patient-reported fibroid symptoms, operative outcomes, adverse events, the rate of re-intervention for fibroid symptoms, and surgeon self-assessment of skill and satisfaction. In the following section, outcome measurements are described in detail.

8.1.A Questionnaires to Assess Symptoms

These are validated questionnaires to assess the change in symptoms over time following the Radiofrequency ablation procedure.

1. Uterine Fibroid Symptom-Quality of Life (UFS-QOL)**:** The UFS-QOLis a standardized questionnaire to evaluate fibroid-specific symptoms including heavy bleeding and urinary and bowel symptoms as well as the impact of fibroid symptoms on quality of life.[4,5] The UFS-QOL has been used widely in studies of uterine preserving fibroid treatments including trials of Uterine Artery Embolization and MR Guided Focused Ultrasound.

2. SF-36: The SF-36 is a widely used, validated questionnaire to assess overall quality of health.[6] There are 2 primary domains: Mental Health and Physical Health. The SF-36 has been used in multiple studies of women's health for a wide range of conditions including heavy uterine bleeding and symptomatic fibroids.

3. Menstrual Impact Questionnaire (MIQ): The MIQ is a validated questionnaire to evaluate the impact of heavy menstrual bleeding on quality-of -life.[7] The MIQ has been used in trials of heavy bleeding that includes women with uterine fibroids.

4. Overall Treatment Effect**:** The Overall Treatment Effect used for this study is modified from a validated questionnaire to determine changes in symptoms following a medical intervention.[8] The OTE consists of three questions that query women about whether symptoms have improved or not since treatment. Theses questionnaires have been compared with measures from the UFS-QOL among gynecologic patients.[9] Three additional questions are generally linked to the OTE to asses overall patient satisfaction with treatment. This 6 question adapted OTE has been used in prior studies of women undergoing the Radiofrequency ablation procedure.

5. Sexual Health Outcomes in Women Questionnaire (SHOW-Q): This is a sexual functioning measure used to assess the impact of pelvic problems on various domains of sexual functioning for women's health studies.

8.1.B Perioperative Outcomes

Perioperative outcomes will be assessed during surgery, immediately after surgery in the recovery room, and postoperatively for 6 weeks. We will collect standard perioperative variables for a surgical procedure to evaluate safety and efficacy including the duration of surgery, recovery time, and adverse events. Table 1 outlines key perioperative outcomes. Adverse events are described in section 9.0.

Table 1. Perioperative Outcomes	
Intraoperative Outcomes	• Procedure time *skin to skin time *total OR time • Fibroids detected by intraoperative ultrasound, not visualized on preoperative imaging *Total number *Location of each fibroid *3 dimensions in cm of each fibroid • Estimated blood loss • Unanticipated operative findings • Adverse events • Mechanical malfunction with equipment
Immediate Postoperative Outcomes (Recovery Room)	• Unplanned/unanticipated intraoperative procedures • Time in recovery room • Hospital admission • Gynecologist rating of procedure difficulty • Participant rating of pain on Visual Analogue Scale • Adverse events
Delayed Postoperative Outcomes (Within 6 weeks of Radiofrequency ablation)	• Days to return to normal activities • Days to return to work if applicable • Clinic or hospital visits related to surgery of fibroid symptoms • Adverse events • Pregnancies and pregnancy outcomes

8.1.C Long Term Operative Outcomes

Long term outcomes related to surgery will include measures related to treatment failure, long-term morbidity, and pregnancy as follows:

1. Treatment Failure: We will ask participants to report any additional fibroid treatment including medical management for fibroid-related symptoms, myomectomy, hysterectomy, uterine artery embolization, MR Guided Focused Ultrasound, endometrial ablation, dilation and curettage, or any new and emerging fibroid treatments.
2. Adverse Events
3. Pregnancy and pregnancy outcomes: Participants will report all known pregnancies following Radiofrequency ablation. For each pregnancy, we will query participants about whether the pregnancy resulted in a miscarriage, abortion, or continued pregnancy. For continued pregnancies, we will ask participants to report obstetric outcomes including gestational age at birth, mode of delivery (vaginal or cesarean), and complications (e.g. placenta previa, placental abruption, preeclampsia).

8.1.D Schedule of Outcome Assessment

Outcomes will be assessed at varying timepoints from before the Radiofrequency ablation procedure to 3 years following the procedure (Table 2). In-person study visits will occur prior to surgery at the Screening Visit (SV), on the day of surgery called the Baseline Visit (BV), and 6

weeks following surgery. All other follow-up data will be collected through mailed or on-line questionnaires, or phone interviews.

Table 2. Schedule of Outcome Assessment and Participant Renumeration													
	SV	BV	2 day	1 wk	3 wk	6 wk	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
In person visit	X	X				X							
Questionnaires to Assess Symptoms	X			X		X	X	X	X	X	X	X	X
Perioperative Outcomes		X	X	X	X	X							
Long Term Operative Outcomes							X	X	X	X	X	X	X

8.2 ADDITIONAL MEASUREMENTS

We will collect additional subjective and objective measurements that will be used to: 1) describe the study population and 2) serve as confounding factors in multivariable analysis of the change in fibroid-related symptoms over time.

8.2.A Preoperative Assessment, Study Participants

At baseline, we will query women about their general and reproductive health and obtain baseline data on fibroid size, number, and location as outlined in Table 3.

Table 3. Preoperative Assessment, Study Participants	
Participant-Reported Baseline Measures	• Demographic characteristics (age, race/ethnicity, education) • Medical and surgical history • Reproductive history (including pregnancy and pregnancy outcomes) • Medication use • Complementary and alternative therapy use • Desire for future fertility
Objective Baseline Measures	• Weight • Height • Uterine size by bimanual exam • Vital signs • Fibroid characteristics on ultrasound or MRI *Total number *Location of each fibroid *3 dimensions in cm of each fibroid • Hematocrit/Hemoglobin (if available)

8.2.B Preoperative Assessment, Study Gynecologists

At baseline, participating gynecologists will be queried regarding their practice setting, training, and laparoscopic skill and experience as outlined in Table 4.

Table 4. Preoperative Assessment, Study Gynecologists	
General Characteristics and Training	• Demographic characteristics (age, race/ethnicity, gender) • Work history • Year completed residency • Fellowship/Advanced Training in Laparoscopy • Surgical volume • Practice setting (e.g. fibroid specialty clinic)
Surgical Skill and Competence	• Self-rated comfort level with various laparoscopic procedures • Prior use of intra-operative ultrasound and/or radiofrequency ablation

9.0 ADVERSE EVENTS

We will assess adverse outcomes in the perioperative period (the day of surgery until 6 weeks following surgery) as well as each study visit for 3 years after the procedure. We will ask the treating gynecologist about adverse events within 6 weeks of surgery. After 6 weeks when the participants may not have regular contact with the gynecologist, we will query study participants directly about adverse events.

We will list the known potential adverse events following Radiofrequency ablation treatment and ask for a yes/no response to determine whether it occurred. In addition, we will evaluate potential unknown adverse events by ask the treating gynecologists the following question "Have there been any adverse outcomes associated with the Radiofrequency ablation treatment that are not listed in this form?" Study participants will be asked "Have there been any negative changes in your health since your last study visit?"

Each reported adverse event will have a case report form that documents further details related to the adverse event including when it occurred, how it was diagnosed and treated, and the final clinical outcome.

Potential adverse events related to undergoing Radiofrequency ablation to be reported by the treating gynecologist within 6 weeks of surgery are:

1. Intraoperative injury to genitourinary or gastrointestinal tract, or other abdominal or pelvic organs
2. Blood transfusion
3. Unplanned visit to the Emergency Room or admission to the hospital
4. Pulmonary embolus or deep vein thrombosis
5. Major nerve injury with sensory or motor deficits
6. Infection at the site of the skin incision
7. Infection of the uterus or fibroid
8. Urinary tract infection
9. Hematoma at the site of trochar placement
10. Hernia at the site of trochar placement

11. Skin burn at the site of dispersive pad on bilateral thighs
12. New onset pelvic pain that persists >6 weeks after Radiofrequency ablation procedure

Potential adverse events related to undergoing Radiofrequency ablation to be reported by study participants from 6 weeks to 3 months after surgery are:

1. Hernia at the site of trochar placement
2. New onset pelvic pain

9.1 Adverse Event Grading Scale

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC), version 4. Using this system, adverse events are classified as follows:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to Adverse Event

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9.2 Reporting of Adverse Events

Grade 4 or 5 adverse events will be reported to the respective institution's Institutional Review Board (IRB) and the UCSF Coordinating Center within 24 hours. The UCSF Coordinating Center will notify the study sponsor, the UCSF IRB, and the Data and Safety Monitoring Board (DSMB) Chair within 24 hours of the adverse event. The DSMB will receive a report of all adverse events every 4 months, categorized with the appropriate severity grading. The DSMB report will include details of the adverse event as reported in the Adverse Event Case Report Form.

10.0 DATA AND SAFETY AND MONITORING PLAN

The Data and Safety and Monitoring Board will be an independent committee with members who are not employed by the University of California. The committee will consist of two academic obstetrician/gynecologist with expertise in clinical studies of gynecologic interventions and the conduct of clinical trials, and a biostatistician with expertise in clinical trials and interim monitoring.

The DSMB will be charged with overseeing participant safety and monitoring the scientific validity of the trial. Prior to initiating the study, the DSMB will review and approve the study protocol. The DSMB will meet in-person or by conference call every 4 months for the first year of the study or until all study participants are recruited. The DSMB will then meet annually during the remaining 3 years of the study. All DSMB meetings will consist of a closed session

with the 3 members of the DSMB and an open session that includes the Principal Investigator, Study Statistician, Study Project Director and clinical site Principal Investigators.

The DSMB will review the following outcomes during each meeting:

1. Recruitment and retention data including compliance with enrollment criteria, screening to enrollment ratio, dropout rate and reason for dropouts
2. Demographic data of study participants
3. Intraoperative and Immediate Postoperative Outcomes listed in Section 8.1.B.
4. Adverse Events as described in Section 9.0

The DSMB will make recommendations for protocol changes or amendments to the Principal Investigator and Steering Committee. The Principal Investigator will provide a written response to the DSMB within 2 weeks of the DSMB report. Full details of the DSMB are described in the ULTRA DSMB Charter.

11.0 Participant Remuneration

Study participants will be provided with small values of debit or gift cards for their time and commitment to the study as follows: $20 at the Baseline Week 6, Month 3, Month 6, Month 12, Month 18, Month 24, Month 30, and Month 36 visits. Participants will also be paid for the cost of parking and transportation for study related activities.

12.0 STATISTICAL CONSIDERATIONS

The primary analyses will evaluate changes from baseline to 1, 3, 6, 12, 18, 24, 30, and 36 months after Radiofrequency ablation treatment in all patient-reported outcomes including scores for the UFS-QOL and other standardized symptom and quality of life questionnaires. We will use ANOVA to evaluate the overall differences among these multiple time points in change scores, adjusting for potential confounding factors and baseline values to increase power. We will test the normality assumption and use nonparametric alternative models if the normality assumption is violated. We will use paired t-tests to directly compare mean scores from baseline to all follow-up time points.

Additional Planned Analyses**:** Descriptive analysis of the following outcomes will be reported with proportions and standard deviations for categorical outcomes and means with standard deviations for continuous outcomes.

1. Operative Outcomes: We will report intraoperative and immediate and long-term postoperative outcomes as described in Section 8.1.B.

2. Treatment Failure: Treatment failure is defined as any additional treatment for fibroids after the Radiofrequency ablation procedure including medical management for fibroid-related symptoms, myomectomy, hysterectomy, uterine artery embolization, MR Guided Focused Ultrasound, endometrial ablation, dilation and curettage, or any new and emerging fibroid treatments.

3. Resource Utilization: Medical resource utilization is measured by the number of hospitalizations, unplanned physician or clinic visits, and missed days of work or usual activities due to Radiofrequency ablation treatment.

4. Pregnancy Outcomes**:** We will report the proportion of women who become pregnant following Radiofrequency ablation treatment among all study participants and among the subgroup of women who report that they are actively trying to become pregnant prior to undergoing Radiofrequency ablation. For women who do become pregnant during the study, we will report the proportion who undergo miscarriage, abortion, or live births. We will also report obstetrical and perinatal complications.

Sample Size Calculation: The sample size of 100 was selected to allow each site investigator to perform an adequate number of cases to become competent and comfortable with the Radiofrequency ablation Procedure in anticipation of conducting future comparative trials. Each investigator (n=10) will perform 10 procedures, the first 5 cases with Halt support staff in the operating room and the remaining 5 cases independently. After 10 cases, the investigator will have the appropriate expertise to conduct a comparative trial of Radiofrequency ablation without requiring a "run-in" period of training cases.

The sample size of 100 will also provide sufficient power to evaluate the efficacy of Radiofrequency ablation as measured by changes in the UFS-QOL score from baseline to 3, 6, 12,24, and 36 months following the procedure. Prior studies of women who undergo Radiofrequency ablation have shown the standard deviation of the UFS-QOL to be 21.7. Assuming 5% type 1 error and 90% power, we will be able to detect a minimal change of 7.2 in the UFS-QOL. This is a clinically significant change because meaningful improvements in quality of life are generally felt to occur with a minimum 10 point change in the UFS-QOL from baseline.

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