

Pages 501-526 have been removed.

V. C. STUDY DESIGN AND EXECUTION

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

- ANOVA: Analysis of Variance
- BTL: Bilateral tubal ligation
- BTO: Bilateral tubal occlusion
- CAB: Clinical Advisory Board
- CCP: Cyclic contraception preparation
- CIN: Cervical intraepithelial neoplasia
- CRO: Contract Research Organization
- DSMB: Data Safety Monitoring Board
- E-CRF: electronic Case Report Form
- EDC: Electronic Data Capture - web based clinical database system
- FSH: Follicle stimulating hormone
- HSG: Hysterosalpingogram
- IEC: Independent Ethics Committee
- IRB: Institutional Review Board
- ITT: Intent to Treat
- LAVH: Laparoscopic assisted vaginal hysterectomy
- LEEP: Loop electrosurgical excision procedure
- LMP: Last menstrual period
- LTF: Lost to follow-up
- NSAID: Non-steroidal anti-inflammatory drug
- OCs: Oral Contraceptives
- OUS: Outside United States
- PMS: Pre-menstrual syndrome
- PP: Per Protocol
- RF: Radio-frequency
- SAE: Serious Adverse Event
- SEO: Safety Endpoint Only
- STD: Sexually transmitted disease
- TAH: Total abdominal hysterectomy
- TVUS: Transvaginal ultrasound
- US: United States
- UTJ: Utero-tubal junction

2. ETHICS

2.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol was reviewed and approved by the investigational sites' IRB's or IEC's. The study protocol revisions and approval dates are presented in Appendix 13.1.1. A list of all IEC's and IRB's consulted in this study is included in Appendix 13.1.3 A.

2.2 Ethical Conduct of the Study

The study was conducted in accordance with the Declaration of Helsinki.

2.3 Patient Information and Consent

All patients signed Informed Consents following inclusion and exclusion assessment and prior to the procedure, and were informed that they could withdraw from the study at any time for any reason and receive alternate conventional therapy.

An example of a Patient Informed Consent is available in Appendix 13.1.3 B.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study is being conducted at fourteen investigational sites in the United States, one site in Australia and one site in Mexico. Prior to initiating the formal protocol, each investigational site was evaluated, trained and deemed qualified by the sponsor. A study investigator manages and is responsible for the conduct of the study at each site. The list of investigative site names and addresses is located in Appendix 13.1.4 A.

Each investigator is a qualified physician in the field of gynecology, is experienced in the use of hysteroscopes, and has agreed to meet the requirements of this protocol as evidenced by submission of the Investigator Agreement form. The list of investigators and co- or sub-investigators and their curricula vitae are located in Appendix 13.1.4 B.

A designated study coordinator at each study site is responsible for collecting and entering all required data into the web-based EDC (electronic data capture) clinical database. A list of the study coordinators can be found in Appendix 13.1.4 C. Curricula vitae of the coordinators are on file with the sponsor and are available for review.

Oversight of the conduct of the clinical trial is managed by the sponsor. Monitoring of all study sites is conducted jointly by the sponsor and the sponsor's consultants. A list of contract research organizations (CRO) and contract monitors utilized for site monitoring is located in Appendix 13.1.4 D.

The sponsor utilizes a Clinical Advisory Board (CAB) to assist in trial management and overall trial guidance. Members of the CAB consist of sponsor medical and clinical advisors as well as selected study investigators. A list of all members who served on the CAB during the course of the trial and their curricula vitae are located in Appendix 13.1.4 E.

Review of clinical trial efficacy and safety data is performed on a regular basis by a Data Safety Monitoring Board (DSMB). The list of DSMB members, as well as their curricula vitae, is included in Appendix 13.1.4 F.

Devices were manufactured by the sponsor in Redwood City, California, U.S. and shipped to the study sites.

Clinical data are reported via a web-based, EDC (electronic data capture) clinical database system (DATATRAK EDC 3.2) provided by DATATRAK International, Mayfield Heights, Ohio, and fully compliant with Code of Federal Regulations, Title 21, Part 11 requirements.

Statistical analysis of the clinical data is performed by QST Consultations Ltd., Allendale, Michigan.

4. INTRODUCTION

It is often desired or necessary for medical reasons to close the fallopian tubes of women for sterilization purposes. The most widely practiced method for sterilization in females is surgical tubal ligation, a procedure in which the fallopian tubes are tied and cut, clamped or electrocoagulated through an incision made in the wall of the abdomen. Tubal sterilization by laparotomy or minilaparotomy for access requires a surgical incision in the abdomen, most often using general anesthesia. When performed endoscopically small incisions are made in the abdomen with blind insertion of a verres needle for abdominal insufflation followed by blind insertion of a trocar. These surgical procedures carry the potential for significant morbidity and even mortality. Patient concern about safety is a common reason for choice of an alternative, less effective contraceptive option, even when sterilization presents an ideal match to individual need.

A new non-surgical technique, the Adiana Transcervical Sterilization System (hereafter referred to as the "Adiana System"), has been developed for performing transcervical sterilization that involves the destruction of the epithelial cell layer within the fallopian tube around a biomaterial implant (Matrix) to create total occlusion of the tube. The Matrix is contained within a Delivery Catheter which has a radiofrequency (RF) electrode array and is delivered through a hysteroscope. With the Delivery Catheter in proper position within the tube, low-level RF energy (< 3 Watts) is delivered in a bipolar manner through the catheter to the electrode array to create a superficial lesion in the fallopian tube. The RF Generator output is automatically regulated to maintain a desired tissue temperature during the lesion formation. Controlling output power with a tissue temperature feedback loop provides the advantages of: 1) controlled cell destruction in a shallow, tubular lesion, 2) limited treatment variability due to differences in patient anatomies, and 3) reduced risk of unintentional damage to other organs. After delivery of RF energy, the Matrix is released from the catheter. The Delivery Catheter is then removed from the patient and the same process is repeated for the other tube. Following the procedure, the Matrix remains implanted within the fallopian tube and surrounding tissue grows into the Matrix, leading to tubal occlusion.

5. STUDY OBJECTIVES

The objectives of this study are 1) to demonstrate that the Adiana System is safe and effective in preventing pregnancy over a 12-month Wearing Period, and 2) to describe the device placement rates, safety of device placement and wearing, and patient satisfaction and comfort with device placement and wearing.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan: Description

This study is a prospective, single-armed, multi-center, international trial of 770 enrolled women desiring permanent sterilization.

Following enrollment, patients complete several screening evaluations to confirm eligibility. These evaluations include collection of demographic and health history data as well as physical and gynecological examinations. Additionally, immediately prior to the treatment procedure, patients undergo a pregnancy test and are evaluated by hysteroscopy. Patients who are found to have abnormalities preventing access to the intramural portion of the fallopian tube are excluded from the study.

Patients who meet all requirements of the study are treated with the investigational device (Intent-to-Treat population). Patients who receive successful bilateral device placement enter a three-month Waiting Period during which time they utilize alternative contraception. During this Waiting Period, patients are assessed at 48 hours, 1 week, 1 month, 2 months, and 3 months post-procedure. The one week assessment includes a transvaginal ultrasound (TVUS), which is performed to confirm the presence of the matrices.

Patients who are not successfully treated and have no devices implanted are followed for safety evaluations for either one week or three months (if they received RF treatment) and are then terminated from the study. Patients who receive unilateral device placements are followed for safety endpoints for the five-year duration of the study.

At the end of the three-month Waiting Period, patients return for an evaluation of tubal occlusion by hysterosalpingography (HSG). Additionally, another TVUS is performed. If the tubes are found to be occluded, patients are allowed to rely on the Adiana System for pregnancy prevention, and enter the Wearing Period of follow-up.

If a fallopian tube is found to be patent at the three-month HSG evaluation, patients are given the option of waiting an additional three months to see if blockage will occur. If patients chose to wait an additional three months, they continue to use alternative contraception and are assessed monthly during the extended Waiting Period. Patients are then re-evaluated for tubal patency by HSG, and undergo a repeat TVUS examination at the six-month Waiting Period evaluation. If the tubes are found to be occluded, patients

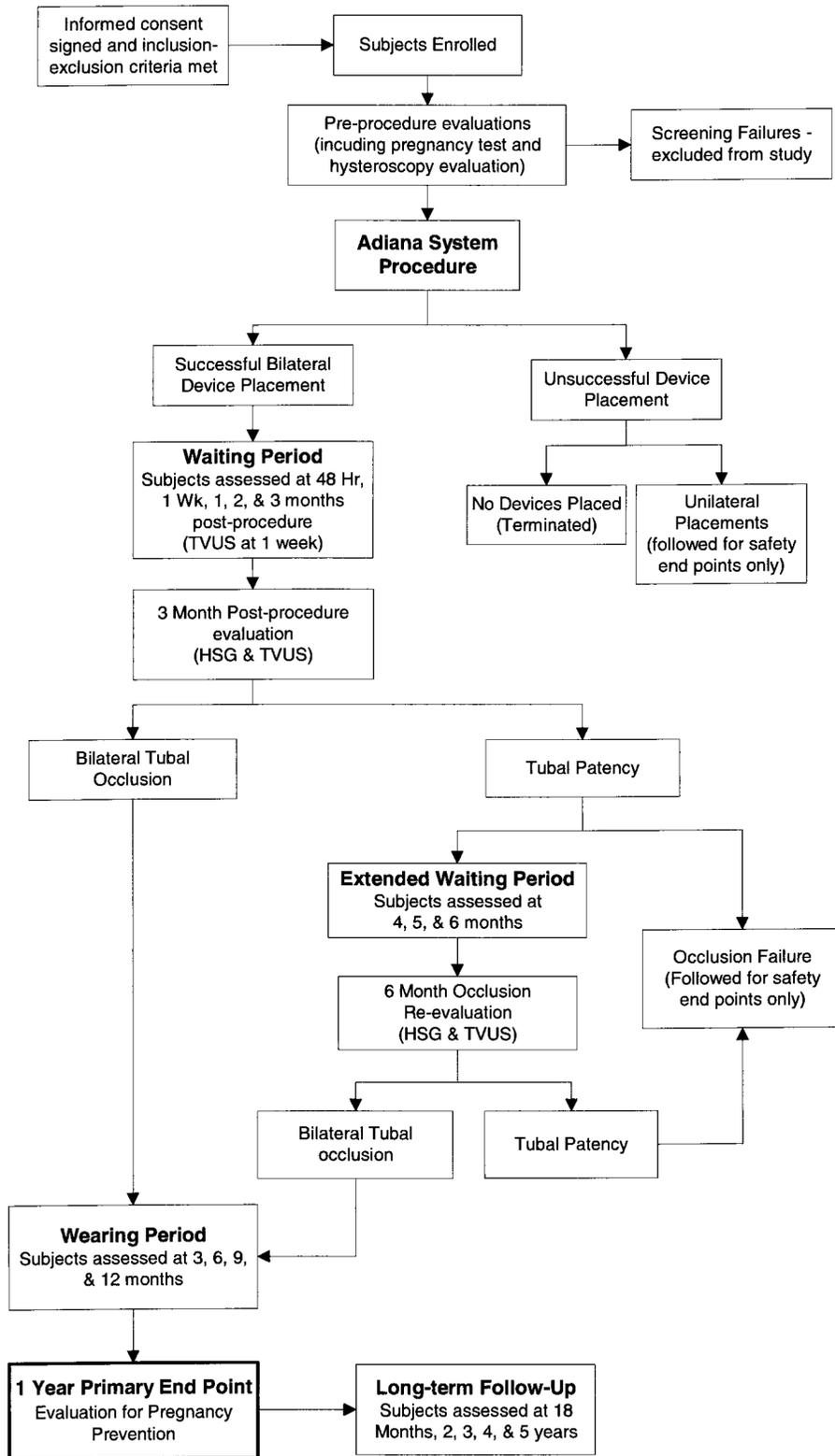
are allowed to rely on the Adiana System for pregnancy prevention, and enter the Wearing Period of follow-up.

Patients who are determined to be bilaterally occluded at either 3-month or 6-month HSG evaluations are allowed to rely on the Adiana System for pregnancy prevention and enter the Wearing Period of follow-up. During the first year of the Wearing Period, patients are assessed at 3, 6, 9, and 12-months. Patients are evaluated for the primary efficacy endpoint of pregnancy prevention after a one-year Wearing Period. Patients are subsequently followed at 18 months and then annually through 5 years of follow-up.

Patients found to be non-occluded at the initial three-month HSG and who do not wish to wait an additional three months, or patients who are found to be non-occluded at the six month HSG re-evaluation, are offered a tubal ligation and are followed for safety endpoints through 5 years of follow-up.

A diagram of the study event sequence is presented in Figure 1.

Figure 1: Study Event Sequence Diagram



6.2 Discussion of Study Design

This multi-center, prospective, single-armed trial was designed to evaluate the safety and effectiveness of the Adiana System in preventing pregnancy over a 12-month Wearing Period. The study design as described in section 6.1 was developed by the sponsor and then reviewed and modified by FDA through an informal pre-IDE meeting process. Additionally, after input from FDA following the IDE submission, the following *sequential analysis plan* with clearly defined stopping rules was defined for the execution of the study:

- The sponsor will enroll patients at a rate not to exceed 50 patients per month.
- When an Initial Enrollment Limit of 150 patients is reached (and a total of at least 100 patients are projected to enter the “Wearing Period”) enrollment will be temporarily suspended.
- Acute measures of procedural success shall be analyzed to ensure that they meet the following criterion:
 - Acute procedural success: Bilateral access rate of 80% or greater (defined as successful placement of a Matrix into both fallopian tubes in any woman treated with the Adiana System)
- Once this group of initially treated patients has achieved 200 patient months of wearing data, enrollment will resume and the study will continue to the planned maximum enrollment, provided the following measures of contraceptive success are achieved:
 - No more than one pregnancy in the first 200 patient months.
 - No more than 5 pregnancies in 1000 patient months.
 - If at any time during the trial the number of pregnancies exceeds a number that would make it statistically impossible for the entire 400 patient cohort to achieve a 95% efficacy claim for a one year Wearing Period, enrollment will be halted. Treated patients will continue to be followed for safety and effectiveness.
- As requested by FDA, any unintended pregnancies occurring in the Waiting Period (contraceptive failures) will be reported to FDA within 10 days after the sponsor is informed.
- The sponsor shall submit a summary to FDA on the results of the data analysis at both the end of the initial enrollment period and at the 200 patient-month point and at the 1000 patient-month point.

6.2.1 Study Patients

This study was initially approved to enroll up to 500 patients at 15 institutions in the US. It was the goal of this study that no fewer than 400 US patients be evaluated for the primary study endpoint. To be evaluated for the primary endpoint, each patient would:

- Have successful bilateral placement of the Adiana System,
- achieve a hysterosalpingogram (HSG) result at the end of the Waiting Period that indicates occluded fallopian tubes,
- terminate alternative contraception at the end of the Waiting Period, and
- be evaluated for pregnancy status for the one year Wearing Follow-up Period

To achieve this goal, and to permit adequate evaluation of the new catheter handle, the study was later expanded to enroll up to 650 patients at up to 15 institutions in the US.

Additionally, the study was approved to enroll up to 100 patients in Australia and up to 100 patients in Mexico.

6.2.2 Clinical Sites

Although this study was approved for enrollment in up to 15 clinical sites in the US, the *sequential analysis plan* for this study utilized a staged “roll-out” to clinical sites. Only six investigational sites (“Tier 1” investigators) were allowed to enroll patients during the Initial Enrollment Period (as described in section 6.2). The early experience with these “Tier 1” investigators then served to influence the training for subsequent investigators once study enrollment resumed.

Ultimately, patients were enrolled at a total of 14 clinical sites in the US, one clinical site in Australia and one clinical site in Mexico. No site was permitted to enroll more than 20% of the total patients enrolled in the study. Investigational sites were encouraged to enroll a minimum of 15 patients.

6.3 Selection of Study Population

The clinical study population screened for enrollment in this study consisted of female patients expressing a desire for permanent sterilization. Since this study results in the end of a patient’s fertility, it was imperative that the participant be fully informed when making a decision to enter this study. Careful attention was paid to the Informed Consent process. Participation in the study was only offered after a patient had decided to permanently terminate her fertility.

Patients were enrolled in this study on an Intent-to-Treat basis. Selection for the trial required that patients have proven fertility; were sexually active; and in a monogamous relationship with a partner who had proven fertility (see section 6.3.1). Patients reporting a health condition that might adversely affect their ability to undergo the procedure (e.g.; history of adenomyosis, pelvic inflammatory disease, etc.) were excluded. Additionally, other multiple exclusion criteria were included to ensure that the study requirements could be met: that patient post-procedural evaluation could be performed without bias and that patients would be able to meet the long-term follow-up requirements of the study (e.g.; history of severe dysmenorrhea, or dysfunctional uterine bleeding, or presence of cancer, etc., see section 6.3.2).

Patient enrollment was also monitored (at the request of FDA) to ensure that the age-group stratification of this study was comparable to the age-group stratification of the U.S. Collaborative Review of Sterilization¹ (CREST) study.

6.3.1 Inclusion Criteria

- Women aged 18 to 45.
- Women who are seeking permanent contraception.
- Women who are at risk of becoming pregnant.
- Willing to risk becoming pregnant when relying on the Adiana device for contraception.
- Relatively normal uterine cavity, uterine wall thickness, and uterine size as demonstrated by pelvic sonography.
- Willing to keep a coital/menstrual log.
- Have at least one confirmed pregnancy and one living child.
- Monogamous relationship with a partner who has proven fertility.
- Sexually active (at least 4 acts of intercourse per month).
- Willing to use alternate contraception (either a barrier method or oral contraceptive pills) during the three months following device placement prior to relying on the Adiana device for contraception.
- Willing and able to maintain regular contact with the investigator.
- Women with regular, cyclical menses within 2 months prior to the device placement procedure.
- Able to provide informed consent.

Additionally, the following clarification was added to the inclusion criteria after the start of the trial: Any patient relying on Depo Provera (or other long term continuous hormonal treatment) must have received their last treatment at least 5 months prior to device placement AND must have had two normal, cyclic menses prior to device placement.

6.3.2 Exclusion Criteria

- Women who are unsure of their desire to end their fertility.
- Presence of gross genital infection, including sepsis.
- Presence of chlamydia, gonorrhea, or syphilis.
- Presence of genital cancer (note: CIN1 is acceptable)
- Intra-uterine pathology which would prevent optimal access to the tubal ostium and intramural portion of the fallopian tube, such as large submucous fibroids or uterine adhesions.

¹ Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussel J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol 1996;174:1161-70.

- History of chronic pelvic pain, prior ectopic pregnancy, or fallopian tube surgery, or currently diagnosed severe dysmenorrhea, severe dyspareunia, endometriosis, adenomyosis, or pelvic inflammatory disease.
- Women with unresolved tubal, ovarian or endometrial pathology.
- Uterine neoplasia or precursors to neoplasia.
- Dysfunctional uterine bleeding or intermenstrual bleeding within the prior three months.
- Women who have not had at least two normal periods after the following events: irregular periods treated with oral contraceptives which have since been discontinued, IUD removal, childbirth, or termination of pregnancy.
- Currently taking immunosuppressive medications including steroids.
- Pregnancy.
- Uterine perforation within the last 3 months.
- Contraindications for surgical methods of sterilization.
- Less than three months have passed since the last delivery or abortion.

6.3.3 Removal of Patients from Therapy or Assessment

This clinical study is an Intent-to-Treat study. All patients are expected to continue in the study until terminated per protocol or until the sponsor notifies the investigator in writing that further follow-up is no longer required, except in the event of death or upon the patient's written or verbal request for early withdrawal from the clinical study.

Patients with incomplete treatments (no devices placed) are terminated from the study per protocol as follows:

- No device placement attempted – Patient excluded for hysteroscopic findings:
The patient is followed through the one week visit and then terminated from the study.
- Failed Access, both tubes – no RF treatment and no Matrix implanted:
The patient is followed through the one week visit and then terminated from the study.
- Failed Placement, one or both tubes – RF treatment but no Matrix implanted:
The patient is followed through the three month Waiting Period visit and then terminated from the study.

A patient may only be prematurely terminated from the study if all of the following criteria have been met:

- Failure to comply with the follow-up requirements of the protocol; and
- Prior agreement of the sponsor to remove the patient from the study; and
- A letter from the investigator to the sponsor requesting patient removal from the study.

6.4 Treatments

6.4.1 Treatments Administered

Treatment with the Adiana System consists of device deployment and implantation of a Matrix in each fallopian tube during the treatment procedure for all eligible patients.

The Adiana System provides for female sterilization by occlusion of the fallopian tubes via a hysteroscopic transcervical approach. The Adiana Procedure involves:

- A hysteroscopic, transcervical introduction of a catheter delivery device into the intramural portion of the fallopian tube.
- The application of low power (<3 Watts) RF energy to the intramural portion of the fallopian tube. This power generates heat in the fallopian tube tissue creating a superficial lesion. The RF Generator regulates output power to maintain the desired tissue temperature throughout the lesion formation period.
- The placement of a Matrix in the tubal lumen in the region in which the lesion was formed. The Matrix remains implanted within the fallopian tube and surrounding tissue grows into the Matrix. The circumferential ingrowth around the Matrix's surface results in occlusion of the fallopian tube, which in turn prevents the passage of sperm.
- A "Waiting Period" following the acute implant, during which time the tissue ingrowth occurs and the tube is blocked. During this period, the patient is required to use alternative contraception. For this clinical study, either Oral Contraceptives (OCs) or Cyclic Contraceptive Preparation (CCPs) or barrier method (condom or diaphragm) with spermicide is required.

In order to reduce the possibility of a luteal phase pregnancy occurring (i.e.; treating a patient who may be pregnant), patients not on cyclic contraceptive preparations were scheduled to have the procedure prior to day 12 of their normalized menstrual cycle, and at least three days after the start of menses (in order to enhance the visualization of the tubal ostia). In patients utilizing cyclic contraceptive preparations for at least six months prior to the treatment procedure, the procedure was scheduled prior to the start of menses and at least three days after the start of menses.

In an attempt to reduce the number of potential unilateral device placements, a tubal access protocol was employed at the start of the trial that involved "pre-access" of the first fallopian tube. The detailed tubal access protocol utilized was as follows:

- The first tubal ostia will be visually localized and cannulated with the Adiana Delivery Catheter, but not treated. If this is successful, the second ostium is then cannulated.
- If both are successfully cannulated, the second ostium will then be treated with the Delivery Catheter, including RF and Matrix placement.
- A new Delivery Catheter will be introduced, and the first ostia will then be treated.

An analysis of the first 120 procedures performed utilizing this “pre-access” protocol showed that there was only one patient out of those treated in which a unilateral placement might have occurred. Thus, the pre-access requirement was removed from the protocol in order to eliminate multiple access attempts. It was believed that this would benefit patients by reducing procedure time, and hence the overall risk to patients. This protocol change was submitted to FDA on [REDACTED]

Patients with incomplete treatments (non-bilateral) noted at the time of treatment, or missing matrices noted at the one-week or three-month post-procedural TVUS evaluations, were considered for re-treatment. Initially, the decision on whether to repeat treatment in a given fallopian tube was reached after careful consideration and consultation with the sponsor’s Clinical Advisory Board (CAB). The criteria used by the CAB included patient desire, complexity of initial placement procedure, and possible causes for the missing Matrix (if applicable). A determination that there was a reasonable likelihood of success was necessary prior to any re-treatment attempt.

The protocol was later revised to include further clarification regarding administration of RF treatment and the re-treatment of patients. This protocol change was submitted to FDA on [REDACTED]. The additional information added to the treatment protocol is as follows:

Since the Adiana Procedure requires a 60 second RF treatment followed immediately by Matrix deposition, it may be necessary to re-start RF treatment in the event of an RF Generator error or physician interruption. In the treatment protocol, between 60 and 120 seconds of RF treatment may be provided and constitute a complete RF treatment.

Therefore, restarting the RF Generator to repeat RF energy delivery in a single fallopian tube is permissible only when done acutely and only if the amount of total RF treatment time is less than 120 seconds in any single fallopian tube.

A repeat treatment may be undertaken for a patient in whom the following conditions are met:

The procedure was terminated due to a “correctable” problem (i.e., poor visualization, equipment problems, patient discomfort, etc), AND
No repeat RF treatments in a given tube are permitted (i.e, if a tube has received RF in a prior treatment attempt a repeat treatment is not permitted).

6.4.2 Identity of Investigational Product

The Adiana Transcervical Sterilization System consists of the Adiana Radiofrequency (RF) Generator and an Adiana Delivery Catheter with an implantable Adiana Matrix.

Each patient eligible for treatment with the Adiana System receives a Matrix implant in each fallopian tube, which is deployed using a Delivery Catheter. The RF Generators and the single-use, disposable Delivery Catheters (preloaded with a Matrix at the time of manufacture) are each identified with a manufacturing lot number and a unique serial number.

Two versions of the Delivery Catheter system were utilized in the EASE clinical trial: version 1.0, [REDACTED] and version 1.5, [REDACTED]. These catheters differed in the handle design and proximal shaft configuration. There was no difference in the distal electrode array or the implantable Matrix. Elsewhere in this PMA, this initial design is referenced as the “Original Design” or “Original Handle”. The latter design is referred to as the “Current Design” or “Current Handle”.

During data analysis and programming, internal ‘version’ designations were utilized with the programming of data tables. In order to maintain cohesion with the terminology used within the data tables, the Clinical Report utilizes these same designations. The versions and their corresponding PMA nomenclature are summarized in Table 6-1.

Table 6-1: Delivery Catheter Nomenclature

Description	Functional	Nomenclature in Data Analysis
Original Design	Thumb slider Matrix release	Version 1.0
Current Design	Push Button Matrix release	Version 1.5

Two versions of the RF Generator were utilized in this trial: [REDACTED] (115V) and [REDACTED] (230V). The difference between these two RF Generator versions consisted only of the configuration of the power supply to either 220 volts or 110 volts, which is selectable during manufacture. There are no other differences.

6.4.3 Method of Assigning Patients to Treatment Groups

All patients were enrolled on an Intent-to-Treat basis.

6.4.4 Prior and Concomitant Therapy

Patients are required to use alternative birth control for the three-month Waiting Period following the treatment procedure. Beyond that requirement, no drugs or other concomitant therapy is required as part of the protocol or study design.

6.4.5 Treatment Compliance

All investigational sites were required to complete records regarding investigational device receipt, disposition and return. Investigational site device records were

verified and the device inventory was reconciled by the sponsor. A complete listing of device disposition by patient is presented in Appendix 13.1.6.

6.5 Efficacy and Safety Variables

Following treatment, patients enter a three-month Waiting Period during which time patients utilize alternative contraception. Patients are then followed in the Wearing Follow-up Period. There are periodic evaluations as detailed below in section 6.5.1 (Efficacy and Safety Measurements Assessed) and in Table 6-2 (Schedule of Events). In addition, patients were required to complete a participant diary through the three-month Wearing Visit, detailing menstrual and sexual activity, and any symptoms.

6.5.1 Efficacy and Safety Measurements Assessed

- Waiting Period Follow Up
 - 48 Hour Telephone Evaluation
 - One Week Office Visit
 - TVUS
 - Exam
 - One Month Telephone Evaluation
 - Two Month Telephone Evaluation
 - Three Month Office Visit
 - Exam
 - Hysterosalpingogram
 - TVUS
 - Pregnancy Test
 - Patient to be instructed to terminate alternative contraception if HSG shows tubes are non-patent. End of Waiting Period.
 - Six Month Tubal Occlusion Re-evaluation (performed only if tubal patency noted at three-month HSG evaluation)
 - Hysterosalpingogram
 - TVUS
 - Pregnancy Test
 - Patient to be instructed to terminate alternative contraception if HSG shows tubes are non-patent. End of Waiting Period.
- Wearing Period Follow Up
 - Three Month Office Visit
 - Six Month Office Visit
 - Nine Month Office Visit
 - One Year Office Visit; End of Follow Up for Primary Endpoint
 - Pregnancy Test
 - 18-Month Telephone Evaluation
 - 24-Month Office Visit
 - 36-Month Office Visit
 - 48-Month Office Visit
 - 60-Month Office Visit

- One-year Primary Efficacy Endpoint

Patients were queried at the one year office visit for any report of pregnancy within the Wearing Period, as well as had a urine pregnancy test performed. In cases where patients could not return for an office visit, one year visit data were collected via telephone and patients performed and reported results of a urine pregnancy test. In cases where patients were lost to follow-up or unavailable for assessment at the one-year time point, one-year efficacy data were collected retrospectively at the next successfully completed follow-up visit.

- Telephone Evaluations

Every telephone contact for follow-up employs a standardized telephone query to determine if there is any reason to have the patient return to the office for further evaluation. If any response indicates that the patient might be pregnant, an office pregnancy test is performed. In addition, all telephone follow up evaluations include an assessment of the patient's comfort as well as other potential adverse events. Questions are asked to assess the patient's tolerance to the procedure and the presence or absence of post-procedural discomfort. During the Waiting Period patients were also questioned on their use of alternative contraception to ensure compliance.

- Office Visits

At office visits, patients have their vitals recorded and are evaluated for any complaints of unusual pain or bleeding. Patients are also evaluated for medication usage, both prescription and over-the-counter. Patient satisfaction with the Adiana Procedure is also evaluated. If there is any indication that the patient may be pregnant, by either verbal admission or unusual menstrual events, a pregnancy test is administered.

At the One Week and Three Month Office Visits during the Waiting Period, patients also underwent physical and gynecological examinations, including bimanual pelvic and transvaginal ultrasound examinations.

- Hysterosalpingography

A hysterosalpingogram (HSG) was performed to assess tubal patency at the end of the Waiting Period. Contrast media was applied at a pressure such that distension of the uterine cavity was obtained, approximately 150mm Hg, but was not exceed a pressure of 200mm Hg at any time. A pressure limiting device was recommended to limit distension pressure. Non-iodinated contrast media was utilized for performing post-procedure HSG in patients with allergic hypersensitivity to shellfish, iodine, or iodinated contrast media.

HSG's were performed and evaluated by the investigator, or a trained gynecologist or radiologist at the investigative site. Spot films or videos generated during the HSG

procedures were forwarded to the sponsor for further review. The sponsor notified the investigator if there were any indications of a complication or discrepancy that the investigator may not have noted. This allowed the investigator an opportunity to further review the test results and clarify the findings if necessary.

- Transvaginal Ultrasound (TVUS)

TVUS was used to confirm the presence of the matrices at the One Week Office Visit following the placement procedure and at the end of the Waiting Period. The operator was instructed to measure the transmural wall thickness at the location of the Matrix, the distance from the uterine cavity to the Matrix, and the distance from the serosa to the Matrix. Images showing all three measurements were retained. Videotape of the examination was recorded and forwarded to the sponsor.

The utility of TVUS in detecting Matrix placement or position was unknown at the time of protocol implementation. Data analysis was performed to determine if TVUS at three months post placement has any correlation with three month HSG data.

- Pregnancy Tests

A urine pregnancy test is used for any pregnancy testing during the follow-up portion of the study (after devices are placed).

- Adverse Events

Adverse event data are collected by the research staff at the study site, recorded onto the Source Note forms, and entered into e-CRFs. The data are collected from the patient's medical chart and patient assessment during the procedural and follow up visits.

Adverse events are rated for possible device relatedness in terms of definite, probable, possible, unknown, or no relatedness. Adverse events are also rated by severity as mild, moderate or severe. The investigator at each study site is responsible for rating each adverse event, except for events reported by patients in the participant diaries, which are rated by the patients.

A serious adverse event is defined in accordance with the ICH-GCP Guidelines for Clinical Trials as follows:

Any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

The investigators, as well as the DSMB, are responsible for reviewing all serious adverse events and determining if they are device related or not.

For any device-related serious adverse event or serious unanticipated adverse event, the investigator is to submit to the sponsor a report of the event within 24 hours after the investigator first learns of the event. Serious unanticipated adverse events include stroke, myocardial infarction, or death.



Table 6-2: Schedule of Events

Schedule of Events	Waiting Period			Wearing Period															
	Eligibility	Screening	Placement	Pre-Discharge	48 Hours	One-Week	One Month	Two Month	Three Month	Three Month	Six Month	Nine Month	Follow Up Period	One Year	Follow Up Period	Eighteen Month	Follow Up Period	Annual	
Participant Interview	X																		
Informed Consent Review	X		X																
Inclusion/Exclusion Review	X																		
Medical History		X																	
Medication History		X																	
STD Screening		X																	
PAP Smear		X																	
CBC		X																	
Height		X																	
Weight		X				X								X					X
Blood Pressure		X				X								X					X
Pulse		X				X								X					X
Pelvic Exam		X				X								X					X
Pregnancy Test		X	X											X					X
Patient Questionnaire		X	X	X		X								X					X
Concomitant Medication		X	X	X		X								X					X
Adverse Events		X	X	X		X								X					X
Transvaginal Ultrasound		X				X													X
Hysteroscopy			X																
Hysterosalpingography																			
Patient Diary						X								X					X



6.5.2 Primary Efficacy Endpoint

The primary endpoint of the study will be the pregnancy rate during the one year Wearing Follow Up Period. This endpoint will be evaluated for all patients who undergo successful bilateral treatment, have demonstrated tubal occlusion (by HSG) at the end of the Waiting Period, and are evaluable for the one year primary endpoint.

This study is powered to have an 80% chance of stating the true failure rate is less than 5%, with a 95% confidence. This would yield a minimum effectiveness rate of 95% (1-failure rate).

6.5.3 Secondary Endpoints

Device Placement Rate

The device placement rate will be reported on both a per tube and per patient basis. Any patient meeting the selection criteria and will be included in this analysis. Failure to treat a tube will be analyzed with respect to reason for failure: device related, patient related, or procedure related.

Patient satisfaction and comfort with the placement procedure

Absence of patient discomfort with the acute device placement determined by verbal questionnaire up to 48 hours post placement.

Patient satisfaction and comfort with device wearing

Absence of patient discomfort during device wearing, based on verbal questionnaire during periodic follow up contacts.

Safety of the device placement procedure

Absence of adverse events which affect the safety of the patient, as evaluated during placement and up to 48 hours post placement.

Safety of device wearing

Absence of adverse events which affect the safety of the patient during device wearing.

6.5.4 Safety Endpoints

Adverse Events

All adverse events reported for the Intent-to-Treat population during the study will be listed, documenting course, severity, possible relationship to device, and outcome.

6.5.5 Appropriateness of Measurements

One-year pregnancy rates are the standard reported in published literature for contraceptive devices as well as FDA guidance documents (i.e.; Guidance for Industry – Uniform Contraceptive Labeling 1998); thus, it was determined that a one-

year pregnancy rate was the most appropriate measure for the primary efficacy endpoint of this study.

6.6 Data Quality Assurance

The sponsor has designed quality assurance procedures to ensure that complete, accurate, and timely data are collected; that the study protocol requirements are followed; and that all complications and adverse events are reported in a timely manner.

Standardized Source Note Forms are used for the collection and recording of data at all investigative centers. Investigators and study coordinators are responsible for the completion of these forms at each study visit. To facilitate patient reporting of menstrual, sexual activity, and any symptoms experienced, patients were required to complete a participant diary. Diaries were completed on a monthly basis from the treatment procedure through the three-month Wearing Visit. Information provided from the diaries was reconciled onto the Source Note Forms at follow-up visits.

Investigators and study coordinators are responsible for timely entry of data into electronic Case Report Forms (e-CRF's) in a web-based, electronic data collection (EDC) clinical database. Review of all data entered in the e-CRF's is performed during regularly scheduled on-site monitoring visits performed by the sponsor and the sponsor's consultants. Data in the e-CRF's are compared to individual patient records and other supporting documents to identify inconsistent or missing data and adverse events. Data problems are addressed by queries entered in the EDC clinical database, by phone or written communication with the investigative centers, and/or during site visits. All hard copy forms and data files are secured to ensure confidentiality.

Investigators maintain all source documents required including: diagnostic test reports, laboratory results, completed Source Note Forms, supporting medical records and Informed Consent forms. The source documents are referenced during regular monitoring visits to verify the information documented in the e-CRF's in the EDC clinical database.

Pre-operative diagnostic tests are evaluated by the investigator and other appropriate professionals at each investigative center to determine the patient's suitability for the clinical study.

Follow-up diagnostic tests (HSG and TVUS examinations) are performed and evaluated by the investigator or a trained gynecologist or radiologist at the investigative site. Spot films or videos generated during the HSG and TVUS procedures are forwarded to the sponsor. The sponsor notifies the investigator if there are any indications of a complication or discrepancy that the investigator may not have noted. This allows the investigator an opportunity to further review the test results and clarify the findings if necessary.

6.7 Core Lab HSG Review

In addition to HSG review by the site investigators, a retrospective review of all HSGs performed during the trial was performed by two independent reviewers. The primary goal of these reviews was to provide independent assessment of tubal occlusion status from that reported by the investigative sites. The independent reviewers were blinded to clinical site evaluation of occlusion outcome. Patency was defined as visualization of contrast flow into the fallopian tube past the implanted Matrix. In addition, the reviewers evaluating HSGs reported on a number of other variables related to HSG technique or occlusion outcome (e.g.; cornual filling, proximal tube filling, evidence of cervical leakage, etc.).

HSG's that were determined to require further review, by either one or both of the reviewers, underwent an adjudication process. The adjudication process consisted of the Sponsor, a Clinical Advisor, and reviewer(s) reviewing the HSG's in question. The outcome of adjudication was either determining the need for a repeat HSG, or drawing conclusion on the submitted HSG record reviewed. Additional input was provided by the investigators, as necessary.

Results of the Core Lab HSG review will be summarized and presented.

6.8 Statistical Methods and Determination of Sample Size

6.8.1 Statistical and Analytical Plans

All statistical processing will be performed using SAS[®] software unless otherwise stated. Continuous endpoints will be summarized with sample size, mean, median, standard deviation, and range. Categorical endpoints will be summarized with sample size, frequency counts, and percentages.

6.8.1.1 Data Presentation

Data from the EASE clinical trial as of March 1, 2007, are being presented in three groups: the first group contains a data summary of the US clinical trial experience (hereafter referred to as "US"); the second group contains a data summary of the Australia and Mexico clinical trial experience (hereafter referred to as "OUS"); and the third group contains a data summary of both groups combined (hereafter referred to as "Total").

6.8.1.2 Populations

An Intent-to-Treat (ITT), a Per-Protocol Analysis (PP), and a Safety-End-Point-Only Analysis (SEO) will be performed. The ITT and SEO populations will be used for the safety analyses. Efficacy analyses will be performed on the PP population.

The ITT population will include all patients who are enrolled in the study and have device placement attempted. Based on final treatment outcome and

evaluability for the one year primary efficacy endpoint, the Intent-to-Treat population is further divided into two sub-populations: a Per Protocol population and a Safety Endpoint Only population.

The PP population is a subset of the ITT population and will include patients who meet the following criteria:

- Have undergone successful bilateral treatment
- Have demonstrated tubal occlusion (by HSG) at the end of the Waiting Period
- Evaluable for the 1 year primary endpoint

The SEO population is a subset of the ITT population and will include patients who meet the following criteria:

- Had device deployment attempted, but did not receive successful bilateral treatment:
 - No RF treatment, no matrices placed
 - Received RF treatment, but no Matrix implanted in one or both tubes
- Or, did not have demonstrated tubal occlusion at the end of the Waiting Period
- Or, were not evaluable for the 1 year primary endpoint (e.g., no longer relying)

6.8.2 Statistical Analyses

6.8.2.1 Demographic and Baseline Characteristics

Demographic (age, race, gender, and ethnicity) and baseline characteristics will be summarized. Descriptive statistics will be provided. Quantitative measures will be summarized with means, medians and ranges, while qualitative measures will be summarized with frequency counts and percentages.

6.8.2.2 Primary Efficacy Analyses

The primary endpoint of the study will be the pregnancy rate during the 12-month Wearing Period, and will be summarized with descriptive statistics including sample size, frequency counts, percentages, and 95% one-sided confidence intervals based on SAS[®] (version 8.2 or later) PROC LIFETEST, which will utilize life-table methods. Additionally the pregnancy rate will be determined for the 24- and 36-month time points utilizing the same life-table methods.

Comparisons of the 12-month rates to other pregnancy prevention methods (historical controls) will be provided, including comparisons to the results

published in the CREST Study (Peterson, et al; Collaborative Review of Sterilization, 1996) as well as results from other sterilization device and procedure studies described in the literature since publication of the CREST study.

Due to the differences in study size between CREST and the EASE trial (and between the EASE trial and the individual method sub-populations in CREST) comparisons will be made based on an analysis of the *differences in the point estimates* and the confidence interval of those differences. (Appendix 13.1.7 includes background information on this methodology.)

In addition, an analysis will be provided that addresses the difference in the age of the populations in CREST as compared to the EASE population.

6.8.2.3 Analysis of Long-term Efficacy

Comparisons of the 24- and 36-month rates to other pregnancy prevention methods (historical controls) will be provided, including comparisons to the results published in the CREST Study (Peterson, et al; Collaborative Review of Sterilization, 1996) as well as results from other sterilization device and procedure studies described in the literature since publication of the CREST study. These comparisons will be made based on an analysis of the *differences in the point estimates* and the confidence interval of those differences.

6.8.2.4 Secondary Analyses

Secondary efficacy endpoints will be summarized with descriptive statistics. Quantitative measures will be summarized with means, medians and ranges, while qualitative measures will be summarized with frequency counts and percentages.

6.8.2.5 Pooling Analyses

The clinical study is being conducted under a common protocol for each study site with the intention of pooling the data for analysis.

An analysis of variance (ANOVA) or Cochran-Mantel-Haenszel test with a factor of stratification as described below will be conducted to provide a comparison of demographic characteristics and pre-operative factors by study center to evaluate the pooling of data across clinical sites, as appropriate to the variable being analyzed. Continuous data will be analyzed by ANOVA and categorical data by Cochran-Mantel-Haenszel. Three stratification analyses will be performed for each variable. The first will involve a stratification of US versus OUS clinical sites. The second will involve stratification for US clinical sites only while the third will involve stratification for the OUS clinical sites only. Statistically significant non-homogeneity will be investigated. This will include a sensitivity analysis to determine the effect of the extreme responding

analysis center or centers and a discussion of the impact of the findings.

The consistency of the final HSG results and the one year pregnancy prevention rate will be analyzed using a logistic regression model with a factor of stratification (see above) to validate that the primary efficacy data may be pooled to facilitate common statistical and clinical conclusions. Statistically significant non-homogeneity will be investigated. This will include a sensitivity analysis to determine the effect of the extreme responding analysis center or centers. Sufficient details with accompanying narrative will be presented to permit assessment and review of the treatment effect in the event of a significant statistic. Conversely, if the outcome of the tests have p-values greater than 0.10, the data will be pooled to permit assessment of the common treatment effect based on all clinical sites.

During the course of the study, there were two versions of the Adiana Delivery Catheter. (The differences involved changes to the handle and proximal catheter shaft as well as the release mechanism; there were no changes to the RF energy delivery mechanism or to the implant.) Comparison of three-month HSG results and the one year pregnancy prevention rate between these two versions will be investigated with a logistic regression model with a factor of version. Sufficient details with accompanying narrative will be presented to permit assessment and review of the treatment effect in the event of a significant statistic. On the other hand, if the outcome of the tests have p-values greater than 0.10, the data will be pooled to permit assessment of the common treatment effect based on all versions of the device.

6.8.2.6 Safety Analyses

All patients for whom device placement was attempted will be included in the safety analyses.

Adverse Events

All adverse events reported during the study will be listed for the ITT population, documenting course, severity, possible relationship to device, and outcome. Verbatim terms will be classified to preferred terms (and in some select cases lower level terms) and related system organ class using the MedDRA dictionary. The preferred terms and system organ classes will then be tabulated. All reported adverse events will be summarized by the number of patients reporting adverse events, system organ class, preferred term, severity, and relationship to device.

6.8.3 Determination of Sample Size

This study is powered to have an 80% chance of stating the true failure rate is less than 5%, with a 95% confidence. This would yield a minimum effectiveness rate of 95% (1-failure rate).

This study was initially approved to enroll up to 500 patients at 15 institutions in the US. It was the goal of this study that no fewer than 400 US patients be evaluated for the primary study endpoint. This was defined as:

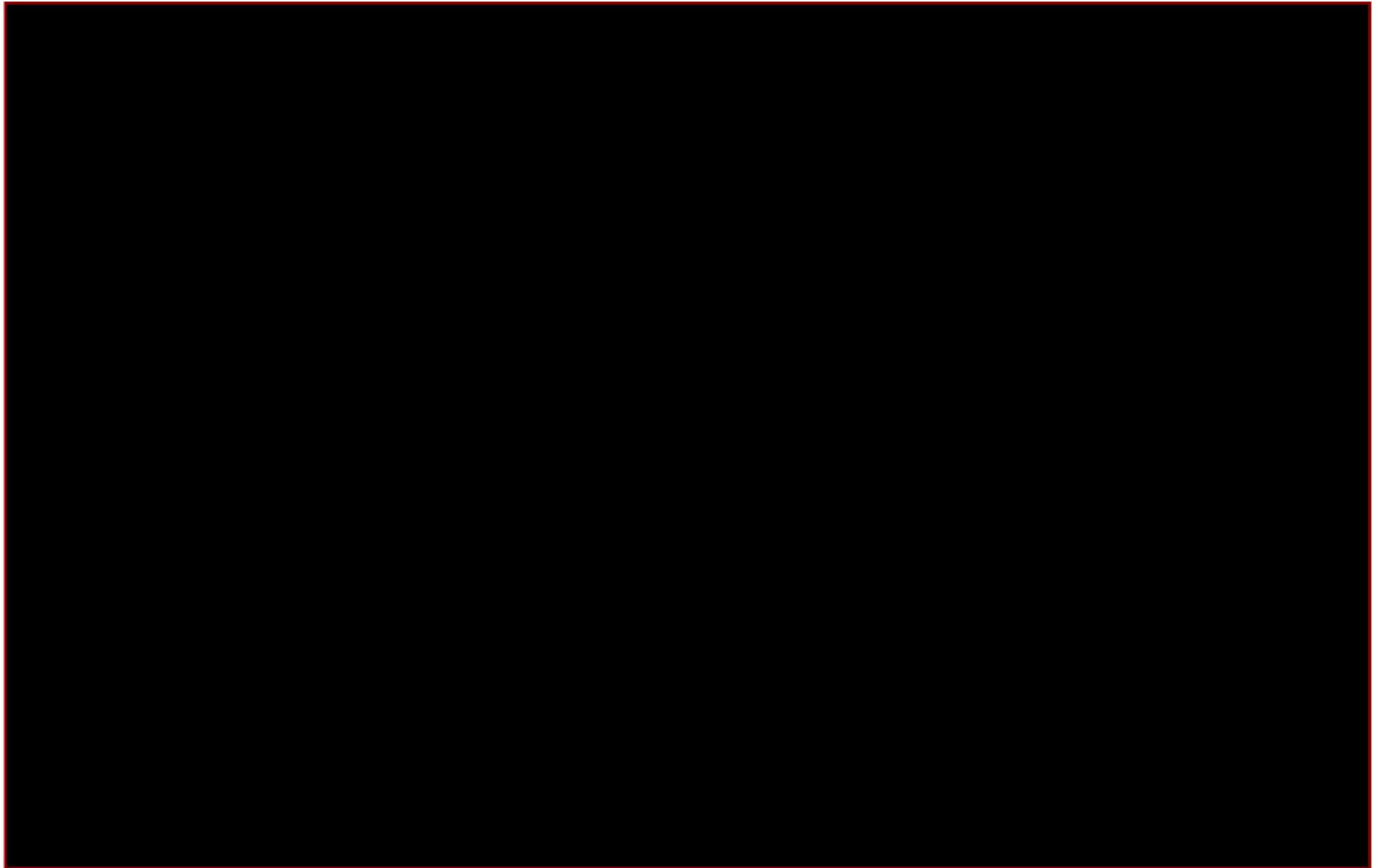
- Having successful bilateral placement of the Adiana System
- Achieving a hysterosalpingogram (HSG) result at the end of the Waiting Period that indicates occluded fallopian tubes
- Terminating alternative contraception at the end of the Waiting Period
- Reporting on pregnancy status for the one year Wearing Follow-up Period

To achieve this goal, and to permit adequate evaluation of the new catheter handle, the study was approved to enroll up to 650 patients at up to 15 institutions in the US.

Additionally, the study was expanded to enroll up to 100 patients in Australia and up to 100 patients in Mexico.

6.9 Changes in the Conduct of the Study or Planned Analyses

Changes to the study protocol as of March 1, 2007 are presented in Table 6-3 below.



V. D. RESULTS

V. D. 1. DEMOGRAPHICS

7. STUDY PATIENTS

7.1 Disposition of Patients

A total of 770 patients were enrolled in the EASE trial between November 13, 2002 and April 28, 2005 at 16 investigative sites. Six hundred and twenty-seven (627) of these patients were enrolled at 14 sites in the US, and 143 patients were enrolled at two international sites.

Patients who were enrolled in the study and had device deployment attempted comprise the Intent-to-Treat population. Based on final treatment outcome and evaluability for the one year primary efficacy endpoint, the Intent-to-Treat population is further divided into two sub-populations: a Per Protocol population and a Safety Endpoint Only population (as previously described in Section 6.8.1.2). Table 7-1 below summarizes subject enrollment and evaluability for each of these populations. Table 7-2 presents this information by investigative site, showing the percentage of enrolled patients at each site who are ultimately evaluated for primary efficacy outcome. Additionally, a listing of patients included in each of these populations can be found in Appendix 13.2.1.

Table 7-1: Summary of Patient Enrollment and Evaluability

	US	OUS	Total
Number of Subjects Enrolled	627	143	770
Number of Subjects Included in the Intent-to-Treat Analyses	528	117	645
Number of Subjects Included in the Per-Protocol Analyses	447	106	553
Number of Subjects Included in the Safety-End-Point-Only Analyses	60	11	71

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Table 7-2: Summary of Patient Enrollment and Evaluability by Investigative Site

Site	Investigator	EASE		
		Enrolled	ITT ^a	PP ^a
1		100	84 (84.0 %)	71 (71.0 %)
2		99	84 (84.8 %)	74 (74.7 %)
3		5	4 (80.0 %)	4 (80.0 %)
4		16	11 (68.8 %)	10 (62.5 %)
5		12	9 (75.0 %)	7 (58.3 %)
6		25	21 (84.0 %)	18 (72.0 %)
7		70	60 (85.7 %)	41 (58.6 %)
8		14	9 (64.3 %)	9 (64.3 %)
9		64	59 (92.2 %)	48 (75.0 %)
10		25	24 (96.0 %)	22 (88.0 %)
11		30	20 (66.7 %)	17 (56.7 %)
13		59	52 (88.1 %)	44 (74.6 %)
14		83	69 (83.1 %)	66 (79.5 %)
15		72	58 (80.6 %)	55 (76.4 %)
16		36	33 (91.7 %)	27 (75.0 %)
17		60	48 (80.0 %)	40 (66.7 %)

^a Percentages are percent of enrolled subjects at each site.

Note: There was no site #12 in the EASE trial.

SOURCE: BARMSTRONG\adiana\ease3\i_enrlinv (May 31, 2007 14:08)

Of the 770 total patients enrolled in the study, 178 have discontinued from the study as of March 1, 2007. One hundred and twenty-five (125) of these 178 patients were discontinued from the study prior to treatment due to either screening failure, voluntary withdrawal from the study, or exclusion during hysteroscopy for pathology that prevented access to the fallopian tubes (specific reasons for screening failures and exclusion on hysteroscopy are detailed in Appendix 13.2.2).

Twenty (20) patients were discontinued from the study per protocol after undergoing failed placement attempts in which no implants were placed. In 16 of these patients, no RF was delivered nor devices implanted. These 16 patients were terminated per protocol after one week of follow-up. In four (4) subjects, RF was delivered, but no devices were implanted. These four subjects were terminated per protocol after three months of follow-up.

The remaining 33 patients discontinued from the study following treatment. Of these 33 patients, 18 were patients relying on the Adiana System for pregnancy prevention, and 15 were patients being followed for safety endpoints only. Additionally, of the 33 patients who have discontinued from the study following treatment, 28 discontinued during the first year of follow-up.



Of the 28 patients discontinued in the first year of follow-up, 14 were patients relying on the Adiana System for pregnancy prevention and 14 were patients being followed for safety endpoints only. The 14 relying patients were discontinued from the study and thus not evaluated for the primary efficacy endpoint for the following reasons: voluntary withdrawal from the study (n=2); termination by the investigator for protocol non-compliance (n=1); and lost to follow-up (n=11).

Table 7-3 below summarizes the reasons for study discontinuation by population, as well as by year of follow-up. A detailed listing of all enrolled patients discontinued from the study is located in Appendix 13.2.2. A listing of patients discontinued from reliance on the Adiana System and excluded from the efficacy analysis is located in Appendix 13.2.4, as well as documentation detailing reasons for reliance discontinuation.

Table 7-3: Summary of Patient Current Study Status/Discontinuation

	US	OUS	Total
Number of Subjects Enrolled	627	143	770
Number of Subjects Currently on Study	478	114	592
Reason for Premature Study Discontinuation			
Screening failure	35	5	40
Voluntary withdrawal from study prior to treatment	54	21	75
Excluded for pathology/procedural criteria	10	0	10
Procedural failure – no implants placed	18	2	20
During Year 1			
Lost to follow-up	19	0	19
Voluntary withdrawal from the study	8	0	8
Violation or non-compliance	1	0	1
Death	0	0	0
Other	0	0	0
During Year 2			
Lost to follow-up	1	0	1
Voluntary withdrawal from the study	3	1	4
Violation or non-compliance	0	0	0
Death	0	0	0
Other	0	0	0
During Year 3			
Lost to follow-up	0	0	0
Voluntary withdrawal from the study	0	0	0
Violation or non-compliance	0	0	0
Death	0	0	0
Other	0	0	0

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The disposition of study patients in the US, OUS, and Total populations through the one-year follow-up time point are detailed in Figures 2, 3, and 4 respectively.



Figure 2: Patient Disposition Flowchart through Primary Endpoint (US)

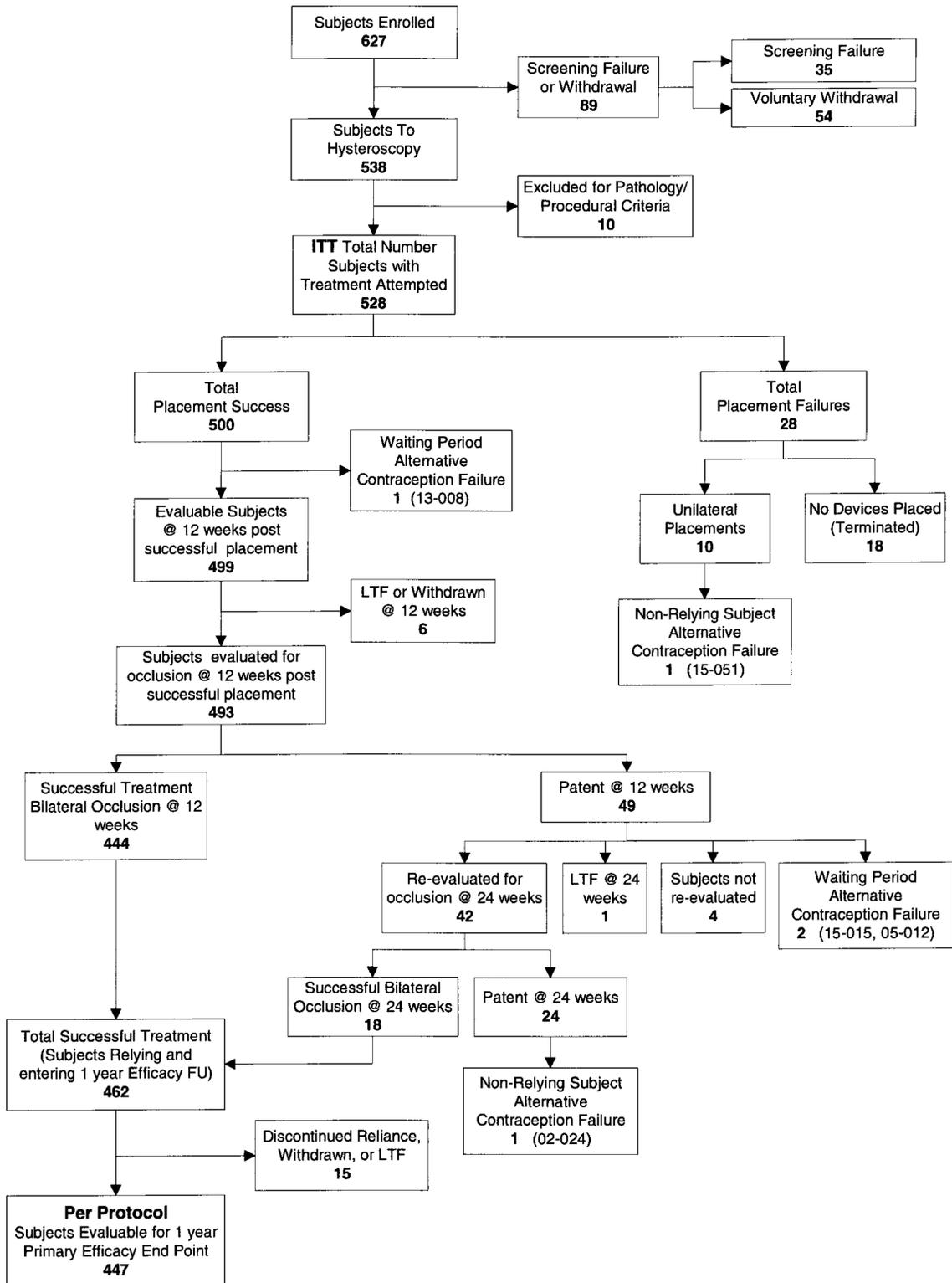


Figure 3: Patient Disposition Flowchart through Primary Endpoint (OUS)

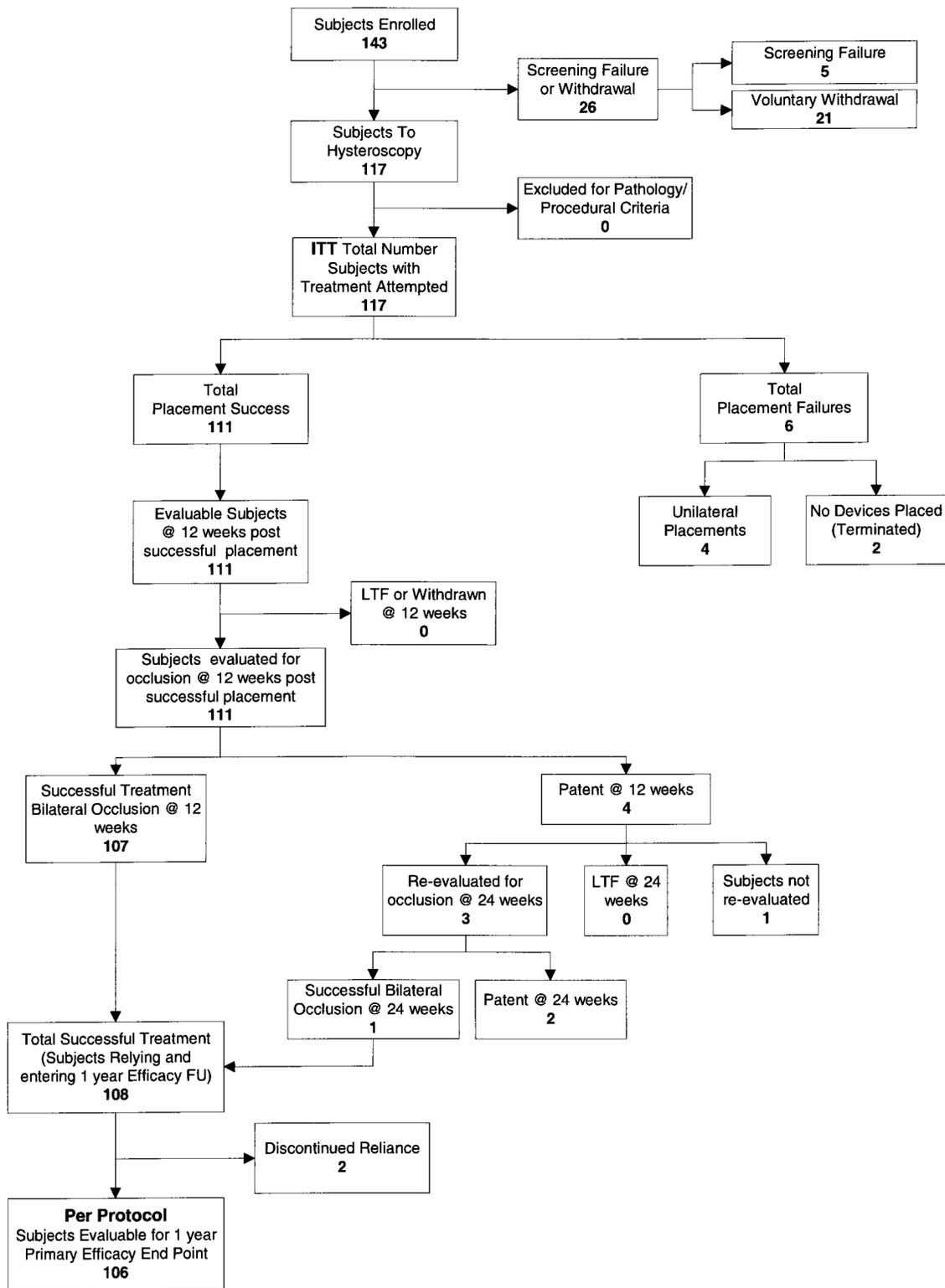
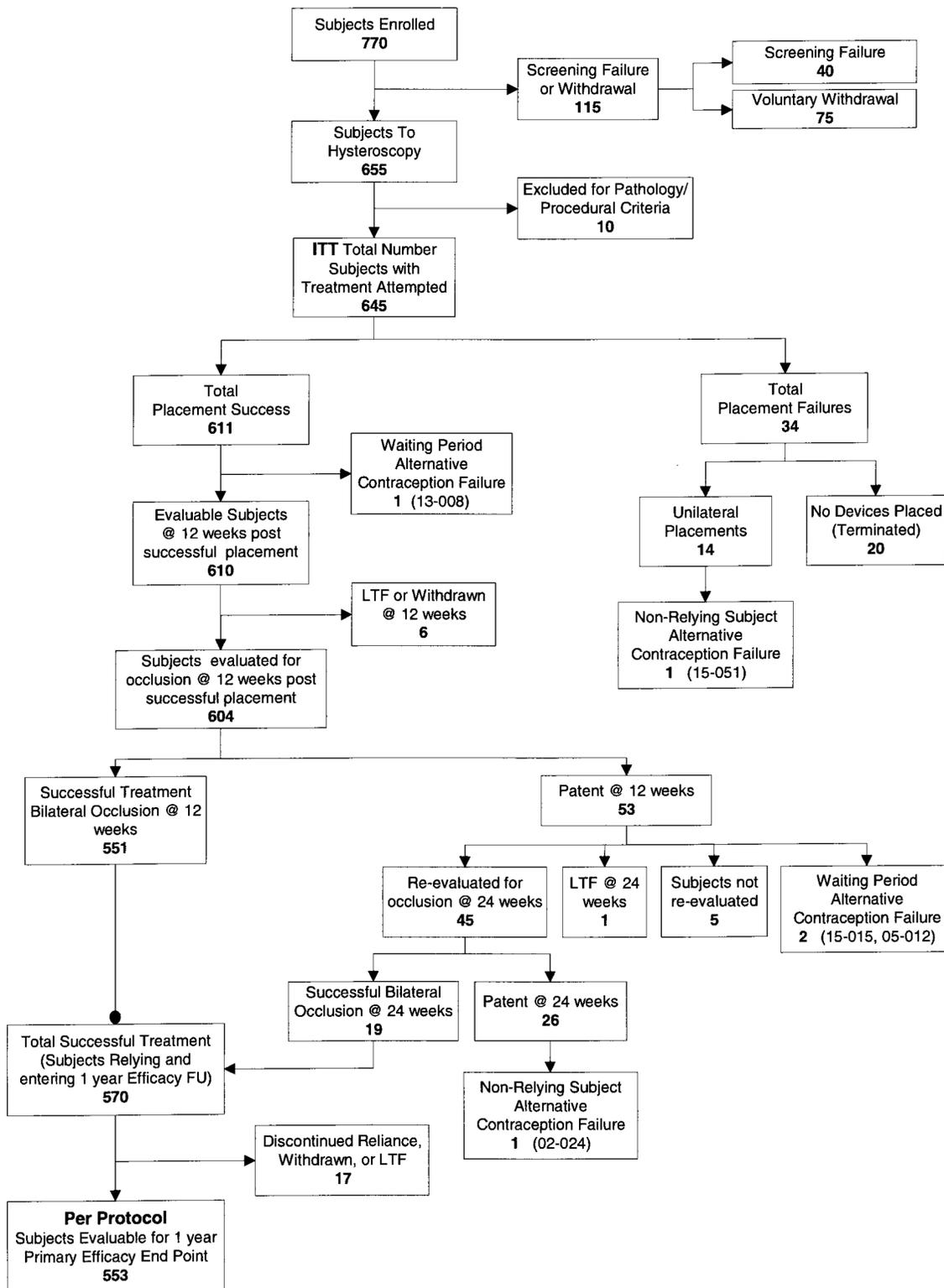


Figure 4: Patient Disposition Flowchart through Primary Endpoint (Total)



7.2 Protocol Deviations

As of March 1, 2007, a total of 91 protocol deviations have been documented in 83 patients. Based on a review of all protocol deviations, there are no issues that would have a material impact on the study. The protocol deviations are presented by category and study population in Table 7-4 and are summarized below. Additionally, a listing of all protocol deviations by investigative site is located in Appendix 13.2.3.

7.2.1 Informed Consent Deviations

There were 25 protocol deviations associated with the informed consent process. In the majority of these cases (n=17), the deviation was the result of a component of the screening evaluation being performed prior to the patient signing an informed consent form. In four other cases, the consent form was signed by the patient, but not countersigned by the investigative site until a later date. In three additional cases, the patient signed a version of the IRB approved consent form that was missing the IRB approval stamp. In one case, the investigative site's copy of a patient's signed Informed Consent form has been misplaced (this patient voluntarily withdrew consent during the screening process and never underwent treatment with the Aadiana System).

In all of the above cases, the described oversight was recognized and the patient signed an IRB or IEC approved informed consent prior to being treated with the Aadiana System.

7.2.2 Inclusion/Exclusion Criteria Deviations

There were four cases in which patients were enrolled and treated in the study but did not meet the final inclusion/exclusion criteria utilized for the trial. Early in the trial, two patients were enrolled and treated despite having amenorrhea due to breastfeeding or the use of Depo Provera. The exclusion criteria in the protocol were subsequently revised to include the requirement that patients must have at least two normal menstrual cycles after the following events: irregular periods treated with oral contraceptives (or other monthly cyclic, hormonal birth control) which have since been discontinued, IUD removal, childbirth, or termination of pregnancy.

In another case, during the screening process the patient reported a single episode of intermenstrual bleeding approximately two weeks prior to her last spontaneous menses. This was the first time she had ever experienced intermenstrual/ovulatory bleeding. The investigator felt that this single episode of intermenstrual bleeding was not clinically significant. The sponsor was consulted and agreed with the investigator's assessment and approved this deviation.

In the last case, the patient was enrolled and treated by a sub-investigator despite the fact that the patient had a known history of intra-abdominal adhesions, and should have been excluded due to contraindication for surgical methods of sterilization. This

deviation from the study exclusion requirements was noted by the sponsor after patient treatment had occurred, and after patient enrollment and treatment had been concluded in the study. There were no other instances of inclusion/exclusion criteria deviations at this investigative site. This patient was successfully treated and is relying on the Adiana System for pregnancy prevention.

7.2.3 Screening Deviations

There were 11 screening deviations documented during this study. The majority of these were cases in which the investigative site neglected to perform a screening test (STD test or FSH level) prior to treatment. These tests were subsequently performed when the oversight was discovered (except STD tests in two patients). There were no results from these tests that would have prevented patient treatment from occurring.

Additionally, in one case, a patient's baseline Pap Test was performed outside of the screening window allowed for that test (more than three months prior to the treatment procedure).

7.2.4 Treatment Deviations

There were a total of 41 protocol deviations associated with patient treatments. Eighteen (18) of these were related to treatments that were performed outside the "day 3 to 12" treatment window. To limit the possibility of a luteal phase pregnancy (i.e.; treating a patient who may be pregnant) the study protocol directed that Adiana treatments be performed between days 3 and 12 of a patient's menstrual cycle. For various reasons – usually scheduling, a specific patient request, misinterpreting hormonal birth control usage, or misreporting/misinterpreting menstrual dates – there were 18 occasions when a patient was treated outside the prescribed treatment window. None of these cases resulted in a procedure-related adverse event.

Two patients received a repeat Matrix placement in a single fallopian tube. This was done because the investigators were not confident that the first Matrix had been successfully placed in the tube. After sponsor review of these cases, investigators were advised that they must follow re-treatment procedures as outlined in the protocol. There were no complications and the patients are currently relying on the Adiana device for pregnancy prevention.

To reduce the chances for fluid overload, and at the request of FDA, the study protocol limited the total procedure time to 30 minutes. In 21 treatments (at 10 sites), physicians exceeded this limit in an effort to complete the procedure. Investigators have stated that in the presence of careful fluid monitoring and a reasonable expectation that the procedure will be successfully completed, it is a lower clinical risk to extend the case than to terminate the treatment and subject the patient to a subsequent laparoscopic tubal ligation. Of the 21 treatments that exceeded the 30 minute time limit, 10 resulted in successful bilateral device placement. The mean treatment time for all 21 treatments was 37.33 minutes, with a range of 31 to 51

minutes. None of these patients experienced any complications related to the extended procedure time.

7.2.5 Follow-up Deviations

There have been ten protocol deviations associated with patient follow-up visit schedules following the treatment procedure. In seven instances, a patient's follow-up schedule was accidentally altered, resulting in two or more follow-up visits being performed off-schedule. These alterations occurred due to sponsor error in calculating visit target dates. These errors have since been corrected and these patients are now following the standard follow-up schedule.

Three other follow-up visit deviations occurred for various miscellaneous reasons:

- Clinical site collected data for patient's 48 Hr and 1 Wk visits on the same day, due to patient living significant distance from clinic.
- Patient's misunderstanding regarding instructions to begin relying on the device resulted in patient not relying until three-month Wearing visit.
- Patient non-compliance for return visit to determine tubal occlusion status resulted in patient not having 3M, 6M, and 9M Wearing visits performed. Patient is not bilaterally occluded and is being followed for safety endpoints only. Patient is now on post-procedure follow-up schedule in accordance with other patients being followed for safety endpoints only.

Table 7-4: Summary of Protocol Deviations

	US	OUS	Total
Number of Subjects Enrolled	627	143	770
Number of Subjects with Protocol Deviations	64	19	83
Protocol Deviations ¹	71	20	91
Informed Consent	18	7	25
Inclusion/Exclusion Criteria	4	0	4
Screening	9	2	11
Treatment Procedure	32	9	41
Follow-up	8	2	10

¹ Subjects may have had more than one deviation.

SOURCE: BARMSTRONG\adiana\ease3\i_prot (Jun 5, 2007 08:47)



8. EFFICACY EVALUATION

8.1 Data Sets Analyzed

Of the 770 patients enrolled in the EASE trial, 645 had treatment attempted (ITT population). Of these 645 patients, 553 were successfully treated and evaluated for the one-year primary endpoint (Per Protocol population).

Demographic and baseline characteristics are presented for the ITT and PP populations, as well as the enrolled patient population for the purpose of completeness (Section 8.2). In addition to the results presented for the enrolled, ITT, and PP populations in this section, all results are further categorized into US, OUS, and Total data groupings for each of these populations, which are detailed in tables 11.1.1.1.1 through 11.1.4.3.2.

Acute procedural results are presented for the 645 patients in the ITT population (Section 8.3). Acute procedural success analyses are categorized into US, OUS, and Total data groupings, as well as subsets of the two Delivery Catheter versions. Other procedural results in this section (e.g. procedure duration and anesthesia type) are presented for both the ITT and PP populations. For both populations, results are further categorized into US, OUS, and Total data groupings, as well as subsets of the two Delivery Catheter versions. In addition to the tables presented in this section, further detailed acute procedural results can be found in Tables 11.2.1.1 through 11.2.5.2.2.

Tubal occlusion and final treatment success results are presented for the 645 patients in the ITT population (Sections 8.4 through 8.8). Results are further categorized into US, OUS, and Total data groupings, as well as subsets of the two Delivery Catheter versions. In addition to the tables presented in these sections, further detailed results can be found in Tables 11.2.13.1.1 through 11.2.13.2.

Primary efficacy analyses are presented for the 553 patients in the PP population (Section 8.9), as well as the long-term efficacy analyses (Section 8.11) and analysis of secondary endpoints (Section 8.12). All results are further categorized into US, OUS, and Total data groupings.

8.2 Demographic and Other Baseline Characteristics

Subjects enrolled in the EASE trial were women between the ages of 18 and 45 years. Patient enrollment was monitored in an effort to achieve a similar age-group stratification to that of the CREST study. The median age and the age groups for the enrolled, ITT, and PP populations as well as the results from the CREST study are shown in Table 8-1 below.

Table 8-1: Age Demographics

	Enrolled	ITT	PP	CREST
Number of Subjects	770	645	553	10,685
Median age (years)	31	31	32	30
Age groups (%)				
18-27 yr	25.8%	24.2%	23.9%	32.6%
28-33 yr	47.3%	47.8%	47.6%	35.4%
34-45 yr	26.9%	28.1%	28.6%	32.0%

Most of the women enrolled in this study were Caucasian (73.8%) and had been pregnant at least twice (91.4%). All patients have been pregnant at least once. Table 8-2 details the basic demographic information for the enrolled, ITT and PP populations.

Table 8-2: Baseline Demographics

	Enrolled	ITT	PP
Number of Subjects	770	645	553
Race			
Caucasian	568 (73.8%)	488 (75.7%)	421 (76.1%)
African-American	64 (8.3%)	47 (7.3%)	42 (7.6%)
Asian	5 (0.6%)	2 (0.3%)	2 (0.4%)
Hispanic	120 (15.6%)	98 (15.2%)	81 (14.6%)
Other ¹	13 (1.7%)	10 (1.6%)	7 (1.3%)
Gravidity			
< 2	66 (8.6%)	57 (8.8%)	50 (9.0%)
2	240 (31.3%)	207 (32.1%)	170 (30.7%)
> 2	461 (60.1%)	381 (59.1%)	333 (60.2%)
Parity			
< 2	140 (18.2%)	117 (18.1%)	99 (17.9%)
2	374 (48.7%)	316 (49.0%)	262 (47.4%)
> 2	254 (33.1%)	212 (32.9%)	192 (34.7%)
Weight, mean (lbs)	162.5	161.8	161.0
Height, mean (in)	64.7	64.7	64.6

¹ Other races included Caucasian/Hispanic, Brazilian, Hispanic/African American, Pacific Islander, East Indian, Iranian, Native American, American Indian, Indian, and Polynesian.



The average menstrual cycle length for women enrolled in this study was 28.2 days, and the mean duration of menses was 4.6 days. Slightly less than half of the enrolled women (47.1%) were using some form of hormonal contraception (oral contraceptives, Nuvaring, patch, etc.). This incidence of hormonal contraceptive use is of note because it is anticipated that these patients may have a higher incidence of dysmenorrhea and menstrual cycle changes noted after cessation of hormonal contraception.

The menstrual, contraceptive, and gynecological history for the enrolled, ITT and PP populations is presented in Tables 8-3 and 8-4.

Table 8-3: Menstrual and Contraceptive Use History

	<u>Enrolled</u>	<u>ITT</u>	<u>PP</u>
Number of Subjects	770	645	553
Duration of menses, mean (days)	4.6	4.6	4.5
Periodicity of menses, mean (days)	28.2	28.1	28.1
Contraception prior to study entry			
Hormonal	361 (47.1%)	311 (48.2%)	263 (47.6%)
Non-Hormonal	352 (46.0%)	289 (44.8%)	249 (45.0%)
None	53 (6.9%)	45 (7.0%)	41 (7.4%)



Table 8-4: Gynecological History

	Enrolled	ITT	PP
Number of Subjects	770	645	553
Endometriosis	14 (1.8%)	11 (1.7%)	10 (1.8%)
Uterine Fibroids	15 (1.9%)	9 (1.4%)	9 (1.6%)
Uterovaginal prolapse	5 (0.6%)	5 (0.8%)	4 (0.7%)
Adnexal Mass	29 (3.8%)	25 (3.9%)	21 (3.8%)
Pelvic Pain not Associated with Menses	18 (2.3%)	14 (2.2%)	11 (2.0%)
Sexually transmitted Disease			
Chlamydia	38 (4.9%)	28 (4.3%)	22 (4.0%)
Gonorrhea	5 (0.6%)	5 (0.8%)	3 (0.5%)
Other	67 (8.7%)	58 (9.0%)	51 (9.2%)
Previous Gynecological Surgeries/Procedures			
Therapeutic Abortion	204 (26.5%)	172 (26.7%)	152 (27.5%)
Spontaneous Abortion	207 (26.9%)	170 (26.4%)	144 (26.0%)
Cesarean Delivery	177 (23.0%)	143 (22.2%)	120 (21.7%)
Endometrial Ablation	2 (0.3%)	1 (0.2%)	1 (0.2%)
Hysteroscopy	6 (0.8%)	5 (0.8%)	3 (0.5%)
D&C	158 (20.5%)	135 (20.9%)	119 (21.5%)
Other	167 (21.7%)	141 (21.9%)	123 (22.2%)



V. D. 2. ACUTE PROCEDURAL RESULTS

8.3 Acute Procedural Results

8.3.1 Acute Procedural Success

Acute procedural success is defined as successful bilateral tubal access followed by successful bilateral RF treatment and Matrix placement.

Acute Procedural Success (Results by Procedure)

The 645 patients in whom treatment was attempted had a total of 653 procedures performed (eight patients underwent a second re-treatment procedure, see Section 8.3.2). One treatment procedure was aborted prior to tubal access or device deployment being attempted due to hysteroscopic procedural complications (the physician could not maintain adequate uterine distension to perform the procedure due to a patulous cervix); thus, 652 procedures are included in the acute procedural success analyses.

Of the 652 procedures in which device usage was attempted, 616 achieved acute procedural success (94.5%). Table 8-5 summarizes acute procedural success rates for all procedures performed for the US, OUS, and Total populations (see also Table 11.2.1.1).

Table 8-5: Summary of Acute Procedural Results

	US	OUS	Total
Total Number of Subjects	528	117	645
Number of Subjects with Single Treatment	520	117	637
Number of Subjects with Repeat Treatment	8	0	8
Acute Procedural Success (by Procedure) ¹			
Total Number of Successful Bilateral Placements	505 (94.4%)	111 (94.9%)	616 (94.5%)
Successful on 1 st Treatment Attempt ²	498 (94.5%)	111 (94.9%)	609 (94.6%)
Successful on 2 nd Treatment Attempt ²	7 (87.5%)	0 (0.0%)	7 (87.5%)
Unilateral Placement – Right Tube	3 (0.6%)	0 (0.0%)	3 (0.5%)
Unilateral Placement – Left Tube	8 (1.5%)	4 (3.4%)	12 (1.8%)
No Devices Placed	19 (3.6%)	2 (1.7%)	21 (3.2%)
Total Placement Success (by Subject) ³			
Total Number of Successful Bilateral Placements	500 (94.7%)	111 (94.9%)	611 (94.7%)
Unilateral Placement – Right Tube	3 (0.6%)	0 (0.0%)	3 (0.5%)
Unilateral Placement – Left Tube	7 (1.3%)	4 (3.4%)	11 (1.7%)
No Devices Placed	18 (3.4%)	2 (1.7%)	20 (3.1%)

¹ Denominator is total number of procedures (652). Subject [REDACTED] did not have device placement attempted.

² Denominator for 1st Treatment Attempt is the number of initial treatments (645), whereas, the denominator for 2nd Treatment Attempt is the number of second treatments (8).

³ Denominator is total number of subjects (645).

The *pre-access* treatment protocol (performed early in the study as previously described in Section 6.4) was utilized in 120 of 652 treatment procedures (18.4%). The majority of the procedures performed (n=532, 81.6%) did not utilize the *pre-access* treatment protocol. Acute procedural success rates were slightly better for the procedures performed with the *pre-access* treatment protocol (95.8% with versus 94.2% without); however, this difference was not statistically significantly different (p = 0.66, Fisher's Exact Test). Results of this analysis for the US, OUS, and Total patient populations are presented in Table 11.2.1.4.

Acute procedural results were also analyzed for the two Delivery Catheter versions utilized in this trial. Acute procedural success rates for the total population were slightly better for the version 1.5 catheter (95.5% version 1.5 vs. 93.6% version 1.0), but not significantly different (p = 0.31, Fisher's Exact Test). This analysis also included evaluation of the acute procedural results by Delivery Catheter version for the procedures that utilized the *pre-access* treatment protocol and those that did not. Since the *pre-access* treatment protocol was discontinued before use of the version 1.5 Delivery Catheter was initiated, a comparison between versions for procedures performed with the *pre-access* treatment protocol was not possible. Results of the comparison between versions for procedures without the *pre-access* treatment protocol showed that the acute procedural success rates for the version 1.5 catheter (95.5%) were slightly better than the version 1.0 catheter (92.3%), but again, not significantly different (p = 0.14, Fisher's Exact Test). Detailed results of these analyses are presented in Table 11.2.1.5.

A further analysis of tubal access rates was performed to determine if outcome results varied depending on which side was treated first. Results of this analysis are presented in tables 11.2.2.1.1 and 11.2.2.1.2. There was not a significant difference in tubal access success rates depending on which side was treated first (left side success was 93.9% versus right side success of 93.5% for all procedures performed in the study).

Total Placement Success (Results by Patient)

Treatment was attempted in 645 patients, of which 604 patients had placement success on the initial treatment attempt (93.6%). Eight patients underwent a second treatment procedure (see Section 8.3.2). Seven of these eight patients were successfully treated. Thus, overall a total of 611 of the 645 patients in whom treatment was attempted achieved bilateral placement success (94.7%). These results are presented for the US, OUS, and Total populations in table 8-5 above (also presented in Table 11.2.1.1).

Placement success rates by patient were analyzed for each investigative site and are presented in Table 11.2.1.2. Success rates varied from 85.7% to 100.0%. It is important to note that the five investigators who had 100% device placement success

rates were at the clinical sites that treated the fewest patients. Additionally, an analysis of device placement success stratified by the number of patients at the clinical sites (those with 30 or less subjects and those with more than 30 subjects) was performed (a summary of this analysis can be found in Table 11.2.1.3). Results showed that the seven sites treating less than 30 patients had the same rate of placement success (94.9%) as the nine sites treating greater than 30 patients (94.7%). These results all suggest that successful cannulation of the fallopian tubes and device placement is not correlated to a physician learning curve.

8.3.2 Retreated Patients

A total of eight patients underwent a second treatment procedure (Note that these re-treatments occurred prior to discussions with FDA on suitable re-treatment procedures, and prior to implementation of explicit protocol guidance on re-treatment).

Three of the eight patients failed to achieve successful bilateral device placement at the time of the initial procedure either due to an inability to access a fallopian tube with the Delivery Catheter (n=1, patient ID: [REDACTED]), or due to technical device failures that prevented successful treatment (n=2, patient ID: [REDACTED]). All three of these patients were successfully re-treated during the second procedure. Subsequent HSG evaluation showed two of the three patients to be bilaterally occluded and able to rely on the Adiana System for pregnancy prevention (patient ID: [REDACTED]). The third patient, who had evidence of tubal patency, is not relying on the Adiana System and is being followed for safety endpoints only (patient ID: [REDACTED]).

Five of the eight re-treated patients were initially evaluated with a successful bilateral placement on the day of the procedure. Following either the post-procedure TVUS evaluation, or the three-month HSG/TVUS evaluations, one Matrix was reported as 'missing' in these patients. (The possible causes for missing matrices are discussed in section 8.5.3). Four of these five patients were successfully re-treated during a repeat procedure (Patient ID: [REDACTED]). Re-treatment was not accomplished in the fifth patient due to an inability to access the tube with the Delivery Catheter (Patient ID: [REDACTED]). All four of the successfully retreated patients were bilaterally occluded on subsequent HSG evaluation and began relying on the Adiana System for pregnancy prevention; however, it was later discovered that one of these patients was mistakenly retreated in the wrong tube due to an inverted HSG image and actually had tubal patency (Patient ID: [REDACTED]). This patient became pregnant before this physician error was discovered (refer to Section 9.4.1 and Appendix 13.3.4 for further details).

To summarize, seven of the eight patients who underwent a second procedure were successfully treated. Five of the successfully re-treated patients have been evaluated as having bilateral tubal occlusion on HSG evaluation and are currently relying on the

Adiana System for pregnancy prevention. The remaining three patients are being followed for safety endpoints only. Detailed case reports for each of these patients can be found in Appendix 13.3.1.

8.3.3 Acute Procedural Failures

Of the 645 patients in whom treatment was attempted, 34 patients (5.3%) were not successfully treated. As described in Table 8-5, 14 of these patients received unilateral device placement. The remaining 20 patients did not have any devices placed. Sixteen (16) of these 20 patients did not receive RF treatment or Matrix placement. In the remaining 4 cases, the patients received RF treatment, but no matrices were placed. Detailed case reports for these 34 patients can be found in Appendix 13.3.2.

In one of the above patients, the treatment procedure was aborted prior to tubal access or device deployment being attempted (Patient ID: [REDACTED]). The physician could not maintain adequate uterine distension to perform the procedure due to a patulous cervix. Because this case was aborted for procedural reasons and neither tubal access nor device deployment was attempted, this case is not included in the following analyses.

Of the eight patients who underwent second treatment procedures, three experienced acute placement failures during their first treatment procedure and are included in the following analyses. (The other five patients had acute device placement success but were found to be missing a Matrix at later evaluation, see Section 8.5.3). Detailed case reports for these eight patients can be found in Appendix 13.3.1.

Thus, there were a total of 36 acute procedural failures in patients who had device deployment attempted. Reasons for these failures are summarized in Table 8-6 below.

Table 8-6: Acute Procedural Failures

	US	OUS	Total
Number of Procedures	535	117	652
Total Procedural Failures	30 (5.6%)	6 (5.1%)	36 (5.5%)
Anatomical Cause	23 (4.3%)	6 (5.1%)	29 (4.4%)
Procedural Complication	1 (0.2%)	0 (0.0%)	1 (0.2%)
Technical Device Failure	6 (1.1%)	0 (0.0%)	6 (0.9%)



In the majority of cases (n=29), device placement was unsuccessful due to anatomical causes. The types of anatomical complications experienced included: suspected tubal blockages (n=20); extremely lateral tube location (n=3); uterine adhesions (n=1); poor visualization of ostia (n=1); and other varied tubal abnormalities (n=4).

In one case, the procedure was aborted after attempted tubal access due to a broken hysteroscope. This patient underwent a second treatment attempt at a later date and was successfully treated.

In only six cases, or less than 1% of all procedures performed (6/652, 0.9%), technical device issues prevented successful completion of the procedure. One failure was due to an RF Generator issue, and the remaining five were due to Delivery Catheter malfunctions.

In the one case involving an RF Generator, treatment was unsuccessful because multiple RF Generator fault codes disrupted two sequential attempts to deliver RF treatment. The procedure was terminated as further RF delivery would have exceeded the 120 second time limit. The RF Generator was returned to the sponsor, and investigation of the returned product determined that the fault codes occurred due to insufficient connection of the cable to the RF Generator (user error, the cable was not fully inserted). A letter was sent to the investigator reiterating steps to take to ensure proper connection. This event was an isolated occurrence in the trial.

The remaining five procedural failure cases were all related to non-deployment of the Matrix from the Delivery Catheter. Multiple catheters failed in each of these cases due to two different failure modes: 1) push rod failure, and 2) crimp failure. These failure modes are discussed in further detail in section 8.3.4.

8.3.4 Device Deployment Overview

A total of 1460 Delivery Catheters were opened at clinical sites for use in the clinical trial. Forty-six (46) of these Delivery Catheters were opened but did not come into contact with the patient or have device deployment attempted. The 46 opened and not used devices are summarized in Table 8-7 below for completeness.

Catheters that were opened before the patients' ineligibility to participate in the study was determined (via hysteroscopy) are categorized as *Patient Exclusion*. Extra catheters that were opened during the procedure and not used are categorized as *Not Needed*. Catheters that were opened for intended use during a procedure that was ultimately aborted are categorized as *Treatment Aborted*. *Sterility Compromised* catheters were opened and intended for use; however the device was contaminated during the procedure (e.g., fell on the floor or breach of sterile field) prior to use. Devices that *Failed Inspection* prior to use were also not used. Every attempt was made by the sponsor to retrieve the devices that did not meet this pre-procedure inspection. Eight of the eleven failed inspection catheters were returned for investigation and processed through the sponsor's returned goods and complaint system.

Table 8-7: Opened and Unused Devices

	<u>Number of Devices</u>	<u>Number Disposed</u>	<u>Number Returned for Investigation</u>
Total Opened and Not Used Devices	46	38	8
Reason Opened and Not Used			
Patient Exclusion	8	8	0
Not Needed	4	4	0
Treatment Aborted	6	6	0
Sterility Compromised	17	17	0
Failed Inspection	11	3	8

The remaining 1414 Delivery Catheters were utilized for a tubal access attempt in a patient treatment procedure. Of these, 1243 (87.9%) of the Delivery Catheter deployment attempts were successful, with successful tubal access followed by successful RF treatment and then Matrix placement. The majority of unsuccessful Delivery Catheter usages were a result of an inability to achieve tubal access due to anatomical or procedural causes. Only 53 of the total 1414 catheters usages (3.7%) were unsuccessful due to technical device faults. The majority of technical device faults were followed by successful treatment with another device. Only six patients experienced procedural failures due to technical device faults (these are described further below). Table 8-8 below summarizes the total Delivery Catheter device usage



in the clinical trial. Additionally, Tables 11.2.3.1.1 and 11.2.3.1.2 present these results for the US, OUS, and Total populations.

Table 8-8: Summary of Delivery Catheter Device Usage¹

Total Number of Catheters Used	1414
Total Number of Successful Usages	1243
Number of Catheters Used per Tube ²	
N	1280
Mean	1.1
STD	0.35
Min.-Max.	1.0-4.0
Total Number of Unsuccessful Catheter Usages ³	171 (12.1%)
Anatomical Irregularities	54 (3.8%)
Procedural Complications	60 (4.2%)
Unknown	4 (0.3%)
Technical Device Faults	53 (3.7%)
Mechanical	30 (2.1%)
Electrical	23 (1.6%)

¹ Numbers in table reflect the required use of multiple catheters for treatment of multiple fallopian tubes.

² The N is the number of tubes treated, with the mean representing the average number of catheters per tube.

³ More than one type of failure could have been experienced per side.

An analysis of device usage by Delivery Catheter version was also performed (details of this analysis can be found in Table 11.2.3.2). When considering the results of this analysis, it should be noted that Delivery Catheter version 1.0 was used at the start of the trial (n=761), and version 1.5 was used in the latter half of the trial (n=653).

Results of the comparison of the device versions showed that 91.9% of version 1.5 usages were successful compared to 84.5% with version 1.0. Additionally, of the technical device faults, 1.7% occurred with version 1.5 and 5.5% with version 1.0. The improved catheter usage rates seen with the 1.5 version are not unexpected for two reasons: 1) device usage improved as physicians became more accustomed to using the device (e.g., fewer devices damaged during use); and 2) technical device faults decreased through the course of the study as manufacturing issues were corrected via corrective actions implemented within the Cytec CAPA system (these are discussed further below).

The 171 total unsuccessful catheter usages were reviewed to see if the side that was treated was a factor in these cases. The proportions of failures for each side were not statistically different, p=0.14: 75/698 unsuccessful catheter usages occurred during a treatment attempt in the left tube and 96/716 during treatment in the right.

It is important to note that the majority of the 171 unsuccessful Delivery Catheter usages, were a result of an inability to achieve tubal access due to anatomical (n=54) or procedural (n=60) causes. Of the 54 Delivery Catheter usages that were unsuccessful for patient anatomical reasons, the majority (n=37) resulted in ultimate failed tubal access due to suspected tubal blockage or stenosis (more than one catheter may have been used prior to aborting the procedure). Other types of anatomical complications that prevented tubal access included: extremely lateral tube location (n=4); uterine adhesions (n=1); poor visualization of ostia (n=3); and other varied tubal or non-specific anatomic abnormalities (n=9).

Of the 60 unsuccessful usages resulting from procedural complications, the majority of cases (n=47) were because the catheter was damaged (tip bent or catheter kinked) during attempted tubal access. Other procedural complications that resulted in a lack of tubal access for that device included: physician preference for a new catheter (n=9); and hysteroscope damaged during access attempt (n=1). The remaining three procedural Delivery Catheter usage failures were due to physician error in use of the device (n=2) and immediate Matrix migration out of the tube following placement (n=1).

Technical device faults that occurred in the trial were minimal, and the majority of cases were followed by a successful treatment attempt with another device. Only 53 of the total 1414 catheters usages (3.7%) failed due to technical device faults. In only six treatment procedures, or less than 1% of all procedures performed (6/652, 0.9%), technical device issues prevented successful completion of the procedure. One failure was due to an RF Generator issue, and the remaining five were due to Delivery Catheter malfunctions.

Every attempt was made to have product that experienced technical difficulties returned to the sponsor for further investigation, and this was done in the majority of these cases. From the results of these investigations, the technical device faults observed were categorized into two types: electrical (n=23) and mechanical (n=30).

As described elsewhere (see RF Generator Instruction Manual, Software Requirement Specifications) the Adiana RF Generator, Cable and Catheter function together as a system to ensure proper catheter placement, RF treatment and Matrix release. Multiple sensors and connections are monitored during use. Fault codes are often generated that signify either issues with the use of the device, the condition of the device, or the underlying patient anatomy. It is sometimes difficult to unequivocally attribute an electrical issue to one specific cause. Of the 23 electrical faults experienced in the trial, there were 13 cases in which a fault code indicated that a Catheter should be replaced, and it was replaced. There were 7 cases in which a Cable was determined by the clinical staff to be the cause of a fault. Another Cable and Catheter were then used to complete the procedure. In one case, the failed usage

was the result of an internal RF Generator error (This was a “OL” fault, which was later addressed during a software version update approved under [REDACTED])

In the remaining two unsuccessful catheter usages due to an electrical fault, an insufficient connection of the Cable to the RF Generator (user error) triggered electrical fault codes for two catheters, which resulted in the patient not being successfully treated (Patient ID: [REDACTED]). A letter was sent to the investigator reiterating steps to take to ensure proper connection of the Cable to the RF Generator. This event was an isolated occurrence in the trial. This was the only procedure in the trial in which a patient was unsuccessfully treated due to an electrical fault issue.

There were 30 technical device faults reported in the trial that were attributed to mechanical product failures within the Delivery Catheter. Three different mechanical failure modes were observed: a “push-rod failure”; a “crimp failure”; and a “set screw failure”.

There were a total of 21 “push rod” failures that occurred in 18 patients. These failures occur when the electrode sheath, as it is retracted over the Matrix, does not properly track backwards. The sheath is pulled over the push rod and the tip of the push rod either catches on the electrode, or the sheath tears and exposes the tip of the push rod as the sheath continues to move back. This occurred 13 times with the 1.0 Delivery Catheter version and 8 times with the 1.5 version. In 15 of the cases, the procedure was successfully completed with another device. In the remaining three cases, the failure occurred in two catheters, resulting in a failure to treat the patient (Patient ID: [REDACTED]). Subsequent corrective action and extensive investigations in the eight failures of the 1.5 catheter version indicated that reducing the distal electrode band spacing by 0.005 inch will dramatically reduce this failure mode. This change has been implemented and was described and included in Module 1.

There were eight cases where a Matrix failed to release during use due to a manufacturing error (the ‘crimp’ failure) with the 1.0 Delivery Catheter version. In two patients, this failure occurred in multiple catheters, resulting in a failure to treat the patient (Patient ID: [REDACTED]). The version 1.5 handle has no ‘crimp’ and therefore had no such failure mode.

There was one case using the 1.5 version of the Delivery Catheter in which the Matrix failed to release due to a “set screw” manufacturing error. This case was successfully completed with another catheter. In this case, as well as the other mechanical failure cases discussed above, corrective action within the Cytc CAPA system was implemented to address these errors.

8.3.5 Procedure Duration

The total procedure time is measured as the time from the hysteroscope insertion to the removal of the hysteroscope. Total procedure duration results for the 652 completed procedures in the ITT population and the 559 procedures in the PP population are shown in Table 8-9. The average procedure time was approximately eleven minutes, with the shortest treatment time being four minutes and thirty-six seconds. Procedures in which the *pre-access* treatment procedure was performed took an average of approximately four minutes longer than procedures in which *pre-access* was not performed. Detailed procedure duration results for both the ITT and PP populations are presented for the US, OUS, and Total data groupings in Tables 11.2.4.1.1.1 through 11.2.4.2.2.

Table 8-9: Procedure Duration

	<u>ITT</u>	<u>PP</u>
Total Number of Procedures	652	559
Procedure Duration (min:sec)		
N	650	559
Mean	11:54	11:02
STD	7:08	5:44
Min.-Max.	4:36-50:35	4:26-48:22
Procedure Duration with Pre-access (min:sec)		
N	119	110
Mean	15:56	14:56
STD	6:38	5:34
Min.-Max.	6:21-41:32	6:21-33:30
Procedure Duration without Pre-access (min:sec)		
N	531	449
Mean	11:00	10:04
STD	6:56	5:22
Min.-Max.	4:36-50:35	4:36-48:22

Procedure duration was also analyzed for the two Delivery Catheter versions that were used in this study. Results for the ITT and PP populations are presented in tables 11.2.4.1.2 and 11.2.4.2.2, respectively. In both populations, the procedure time is significantly shorter for the version 1.5 Delivery Catheter. Some of this difference between the catheter versions can be attributed to the fact that *pre-access* was not performed with the version 1.5 catheter, which was used in the latter half of treatments performed in the study. However, when comparing the procedure times for only the cases in which *pre-access* was not performed, there is still a significant difference ($p < .001$, ANOVA) between the versions. The changes made to the version 1.5 Delivery Catheter are not believed to be the major contributor to this difference; rather, experience gained by the physicians in the deployment of the



device and execution of the treatment procedure in general are thought to account for the decreased procedure times seen later in the study with the version 1.5 Delivery Catheter. In other words, while prior analysis has shown that an absolute procedural success is not associated with a 'learning curve', the speed at which the operator can complete a procedure may improve with experience.

8.3.6 Summary of Procedural Medications

8.3.6.1 Procedural Sedatives and Analgesics Summary

The study protocol did not define specific sedative agents or analgesics to be utilized for the treatment procedure. Treating physicians were allowed to use medications and dosages as they deemed appropriate for the procedure based on their experience in performing hysteroscopic procedures and as necessary for individual patient requirements. Thus, several different procedural medication combinations were used in this trial. Table 8-10 summarizes the sedative and analgesic combinations used in the US, OUS, and Total patient populations (also refer to Tables 11.2.5.1.1.1 and 11.2.5.1.1.1).

Table 8-10: Summary of Procedural Sedative and Analgesic Medications

	US	OUS	Total
Number of Subjects	528	117	645
Anesthetics/Analgesics/Sedatives	228 (43.2%)	114 (97.4%)	342 (53.0%)
Topical/Local Anesthetic	3 (0.6%)	1 (0.9%)	4 (0.6%)
NSAIDs/Oral Analgesia	1 (0.2%)	0 (0.0%)	1 (0.2%)
NSAIDs/Oral Analgesia + Topical/Local Anesthetic	149 (28.2%)	60 (51.3%)	209 (32.4%)
Minimal Sedation ¹	0 (0.0%)	0 (0.0%)	0 (0.0%)
Minimal Sedation ¹ + Topical/Local Anesthetic	2 (0.4%)	0 (0.0%)	2 (0.3%)
Minimal Sedation ¹ + NSAIDs/Oral Analgesia	2 (0.4%)	4 (3.4%)	6 (0.9%)
Minimal Sedation ¹ + NSAIDs/Oral Analgesia + Topical/Local Anesthetic	71 (13.4%)	49 (41.9%)	120 (18.6%)
Moderate Conscious Sedation ²	300 (56.8%)	3 (2.6%)	303 (47.0%)

¹ Non-narcotic medications for anxiolysis.

² IV narcotic medications.

It is important to note that no patients required intubation or the use of general anesthesia. The majority of patients in the trial (n=342, 53.0%) required only minimal sedation or analgesia. Of these patients, most received a combination of a topical or local anesthetic (paracervical block) with a non-steroidal anti-inflammatory drug and/or an anxiolytic agent (n=331, 51.3%).

Moderate conscious sedation, which included the administration of an

intravenous narcotic medication such as Fentanyl or Propofol, was used in 303 patients (47.0%). The use of narcotic sedation in this study varied greatly amongst clinical sites. Table 8-11 shows an analysis of topical or local anesthetic and analgesic/sedative use only versus moderate conscious sedation use at each of the clinical sites. Eight sites used very little or no moderate conscious sedation in their patients, while at least five other sites used it more than 85-100% of the time.

Table 8-11: Procedural Sedative and Analgesic Medications by Site

Investigative Site	Number of Subjects (n)	Anesthetics/Analgesics/Sedatives n (%)	Moderate Conscious Sedation n (%)
[REDACTED]	4	0 (0.0%)	4 (100%)
[REDACTED]	24	0 (0.0%)	24 (100%)
[REDACTED]	20	0 (0.0%)	20 (100%)
[REDACTED]	58	1 (1.7%)	57 (98.3%)
[REDACTED]	84	13 (15.5%)	71 (84.5%)
[REDACTED]	60	20 (33.3%)	40 (66.7%)
[REDACTED]	52	19 (36.5%)	33 (63.5%)
[REDACTED]	59	25 (42.4%)	34 (57.6%)
[REDACTED]	84	68 (81.0%)	16 (19.0%)
[REDACTED]	11	10 (90.9%)	1 (9.1%)
[REDACTED]	48	45 (93.8%)	3 (6.2%)
[REDACTED]	9	9 (100%)	0 (0.0%)
[REDACTED]	9	9 (100%)	0 (0.0%)
[REDACTED]	21	21 (100%)	0 (0.0%)
[REDACTED]	69	69 (100%)	0 (0.0%)
[REDACTED]	33	33 (100%)	0 (0.0%)

The site where the procedure was done and the presence of an anesthesiologist appeared to significantly affect the choice of procedural anesthesia. It was casually observed that sites at which an independent anesthesiologist administered pain management medication tended to medicate all patients as a routine practice. Sites at which the primary operator managed patient treatment and provided clear verbal feedback to patients during the procedure tended to use less significant levels of analgesic medications.

Additionally, the difference seen in the degree of sedation used between the US and OUS clinical sites is also believed to be attributable to the same differences in administration of pain management as noted above. At the OUS sites, the primary operators managed administration of pain medication. Only 2.6% of the OUS patients required the use of IV narcotics. The majority of OUS patients (95.6%) received a combination of a topical or local anesthetic (paracervical block) with a non-steroidal anti-inflammatory drug and/or an anxiolytic agent. In contrast, 56.8% of the US patients received some type of



IV narcotic medication during the procedure.

The procedural sedative and analgesic medications were analyzed for the PP population in addition to the ITT results shown above (see Tables 11.2.5.2.1.1 and 11.2.5.2.1.2), as well as by Delivery Catheter device version for both the ITT and PP populations (see Tables 11.2.5.1.2 and 11.2.5.2.2). There were no significant differences noted in the medications used between the ITT and PP populations or the device versions.

8.3.6.2 Other Procedural Medications

The use of antibiotics for hysteroscopy prophylaxis was left to the discretion of the treating physician and was not required per the study protocol. In the ITT population, antibiotics were given for hysteroscopy prophylaxis in only 24 (3.7%) of the patients. Other procedural medications utilized as needed by physicians included antiemetics (38.4% of patients) and anticholinergics (8.4% of patients). These results are presented for the ITT and PP populations in Tables 11.2.5.1.1.1 through 11.2.5.2.2.

8.4 One-Week TVUS Results

Of the 645 patients in whom treatment was attempted, 611 received bilateral device placement. These 611 patients were evaluated by TVUS within one week of the treatment procedure and results are shown for the US, OUS, and Total populations in Table 8-12 below.

Table 8-12: Summary of Post-Placement TVUS

	US	OUS	Total
Number of Subjects	528	117	645
Acute Treatment Success (Bilateral Devices Placed)	500	111	611
TVUS Result			
Bilateral Devices Visualized	494 (98.8%)	110 (99.1%)	604 (98.9%)
Unilateral Device Visualized – Right Tube	1 (0.2%)	0 (0.0%)	1 (0.2%)
Unilateral Device Visualized – Left Tube	4 (0.8%)	1 (0.9%)	5 (0.8%)
No Devices Visualized	1 (0.2%)	0 (0.0%)	1 (0.2%)
Not Performed	0 (0.0%)	0 (0.0%)	0 (0.0%)

Of the 611 TVUS procedures performed, operators were able to identify bilateral matrices in place in 604 (98.9%) of the cases. In the remaining seven cases, only one Matrix could be visualized in six of the cases, and no matrices were visualized in one case.



In four of the seven TVUS procedures in which matrices were not identified, visualization of one or both of the matrices was prevented due to difficulties performing the TVUS procedure on the patient (e.g., position of the uterus, gastric movement). These four patients (Patient ID: [REDACTED]) were subsequently evaluated at the three-month follow-up visit, at which time TVUS examination identified both matrices and HSG evaluation confirmed bilateral occlusion in all four patients. These patients are currently relying on the Adiana System for pregnancy prevention and their follow-up is ongoing in the study.

In the remaining three of the seven patients in whom bilateral matrices were not visualized at one week, subsequent three-month TVUS evaluation again only identified a unilateral Matrix, and HSG evaluation showed tubal patency on the same side as the missing Matrix (Patient ID: [REDACTED]). These patients elected to undergo tubal ligation procedures and are still enrolled in the study and being followed for safety endpoints only.

Two additional patients were noted to have a missing Matrix on a one-week TVUS examination (Patient ID: [REDACTED]). These were patients who underwent a re-treatment procedure without waiting for the three-month evaluation. Following the second treatment procedure, bilateral matrices were visualized at the second one-week post-procedure TVUS evaluation. These results are represented in Table 8-12 above. However, it should be noted that these patients had only a unilateral Matrix identified on the TVUS examination following the first treatment procedure.

In one case (Patient ID: [REDACTED]) the treating physician suspected that a Matrix was not placed at the time of procedure, which was confirmed at the one-week post-procedure TVUS. Based on the strong recommendation of the investigator, this patient was re-treated without waiting for the three-month evaluation. A detailed case report for this patient can be found in Appendix 13.3.1.

In the second case (Patient ID: [REDACTED]), further review of the treatment procedure video (after the post-procedure TVUS identified only a unilateral Matrix) revealed that the Matrix was actually withdrawn from the tube during the release of the Matrix due to the operator pulling back on the catheter during release. This patient was re-treated based on this conclusive evidence of acute unilateral device placement. A detailed case report for this patient can be found in Appendix 13.3.1.

Thus, the post-procedure TVUS examination failed to visualize one or both matrices in a total of nine patients who were believed to have had successful acute bilateral treatment. Five of these patients were correctly identified as having only a unilateral Matrix in place on the post-procedure TVUS examination. These patients are included in the analysis of potential causes for missing matrices in Section 8.5.3. The remaining four patients identified as missing matrices on the post-procedure TVUS examination were false negative findings, and all four of these patients were ultimately a final treatment success.

V. D. 3. TUBAL OCCLUSION EVALUATIONS

8.5 Three-month Tubal Occlusion Evaluations

Of the 645 patients in whom treatment was attempted, 611 received successful bilateral device placement. Of these 611 patients, 604 were evaluated by HSG and TVUS three months following the treatment procedure. Seven patients were not evaluated by HSG or TVUS for the following reasons: alternative contraception failure during the Waiting Period (n=1, refer to Section 9.4.1 and Appendix 13.3.4 for further details); lost to follow-up (n=5); or withdrawal from the study (n=1). A summary of the tubal occlusion evaluations for the ITT population is presented in Table 8-13 below (US, OUS and Total population occlusion results are summarized in Tables 11.2.13.1.1 and 11.2.13.1.2).

Table 8-13: Summary of Occlusion Evaluations

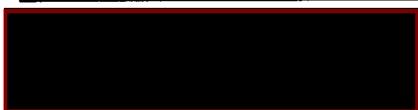
Number of Subjects	Total 645		
	3 Months	6 Months	Final Status
Not Evaluated	41	8	41
Evaluated	604	45	604
HSG Result¹			
Bilateral Occlusion	551 (91.2%)	19 (42.2%)	570 (94.4%)
Unilateral Occlusion–Right Tube	21 (3.5%)	8 (17.8%)	11 (1.8%)
Unilateral Occlusion–Left Tube	24 (4.0%)	15 (33.3%)	20 (3.3%)
Both Tubes Patent	5 (0.8%)	1 (2.2%)	1 (0.2%)
Equivocal	3 (0.5%)	2 (4.4%)	2 (0.3%)
TVUS Result¹			
Bilateral Devices Visualized	598 (99.0%)	27 (60.0%)	598 (99.0%)
Unilateral Device Visualized–Right Tube	1 (0.2%)	0 (0.0%)	1 (0.2%)
Unilateral Device Visualized–Left Tube	3 (0.5%)	0 (0.0%)	3 (0.5%)
No Devices Visualized	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Evaluated	2 (0.3%)	18 (40.0%)	2 (0.3%)
Final Treatment Success²			
Rely on Adiana Devices as Only Form of Birth Control	551 (85.4%)	19 (2.9%)	570 (88.4%)

¹ Denominator is the number of Evaluated subjects at each time point

² Denominator is total number of subjects (645).

8.5.1 Three-month HSG Results

Of the 604 patients evaluated by HSG at three months post-procedure, 551 (91.2%) were evaluated as having bilateral tubal occlusion and were able to begin reliance on the Adiana System for pregnancy prevention. Fifty-three patients (8.8%) had demonstrated tubal patency and were eligible for HSG re-evaluation after an extended Waiting Period (see Section 8.6).



8.5.2 Three-Month TVUS Results

Of the 604 patients evaluated by HSG at three months post-procedure, 602 were also evaluated by TVUS. Operators were able to identify bilateral matrices in place in 598 (99.0%) of the 602 TVUS examinations. In the remaining four cases, only a unilateral Matrix was identified (see Table 8-13).

Three of the four patients in whom only a unilateral Matrix was visualized, were patients who also only had unilateral matrices identified on the one-week TVUS examination (Patient ID: [REDACTED]). The three-month HSG evaluations in these patients confirmed tubal patency on the same side as the missing Matrix. These patients elected to undergo tubal ligation procedures and are still enrolled in the study and being followed for safety endpoints only.

The fourth patient in whom only a unilateral Matrix was visualized, had bilateral matrices identified in place on the one-week TVUS examination (Patient ID: [REDACTED]). Additionally, the three-month HSG results indicated bilateral tubal occlusion. A later repeat TVUS examination performed by the investigator was ultimately successful in identifying both matrices; therefore, the findings of the three-month TVUS evaluation were a false negative.

Two additional patients were noted to have a missing Matrix on a three-month TVUS examination (Patient ID: [REDACTED]), which was confirmed by observed tubal patency on the same side on HSG examination. Both of these patients had bilateral matrices identified on their first post-procedure TVUS examinations. Following identification of unilateral matrices, these patients underwent a second treatment procedure. One patient was not successfully re-treated (Patient ID: [REDACTED]). The other patient was successfully re-treated, and had successful bilateral Matrix visualization at the second three-month TVUS evaluation. This patient was also bilaterally occluded on the second three-month HSG, and is currently relying on the Adiana System for pregnancy prevention (Patient ID: [REDACTED]). These results are reflected in Table 8-13 above.

Thus, in considering the results of all TVUS examinations performed at three months post-procedure, there were a total of six patients with only unilateral matrices identified. Three of these were patients who were already suspected to be missing a Matrix from results of the post-procedure TVUS examination. The remaining three had bilateral matrices identified on their one-week post-procedure TVUS, and were newly identified as missing a Matrix at the three-month TVUS: In two of these patients, a missing Matrix was confirmed by observed tubal patency on the same side on HSG examination. The last patient had bilateral tubal occlusion on the three month HSG examination and bilateral matrices were later identified on a subsequent TVUS; thus, this result was a false negative finding.

8.5.3 Summary of Missing Matrices

Nine patients were identified as missing matrices on the one-week post-procedure TVUS, and three patients were newly identified as missing matrices on the three-month TVUS examinations. Later TVUS evaluations subsequently identified that five of these twelve patients actually had bilateral matrices in place and HSG evaluations confirmed bilateral tubal occlusion. Thus, these five patients were false negative TVUS findings.

These combined TVUS results show that TVUS has value as a diagnostic examination in the evaluation of patients presenting with a three-month HSG showing tubal patency. In these cases, TVUS can be used to determine if matrices are in place, and whether a patient should consider waiting an additional three months for tubal occlusion re-evaluation.

The remaining seven patients were correctly identified as missing a unilateral Matrix. Table 8-14 below summarizes the findings for these patients.

Table 8-14: Summary of Patients with Missing Matrices

<u>Patient ID</u>	<u>Likely Cause</u>	<u>Failure Side</u>	<u>Catheter Version</u>	<u>Shelf -age (Months)</u>
<u>One-Week Evaluation</u>				
[REDACTED]	acute treatment failure	right	1.0	5.3
[REDACTED]	acute treatment failure	right	1.0	6.2
[REDACTED]	unknown	right	1.5	4.2
[REDACTED]	unknown	right	1.5	3.6
[REDACTED]	unknown	right	1.5	2.4
<u>Three-Month Evaluation</u>				
[REDACTED]	matrix migration	right	1.0	6.5
[REDACTED]	matrix migration	left	1.0	7.8

In two of the seven patients identified above, the cause of the missing Matrix is attributable to unsuccessful Matrix placement at the time of the procedure. In these two cases, the unilateral placement was not recognized or confirmed until the one-week post-procedure TVUS.

In one case (Patient ID: [REDACTED]), further review of the treatment procedure video (after the post-procedure TVUS identified only a unilateral Matrix) revealed that the Matrix was actually withdrawn from the tube during the release of the Matrix due to the operator pulling back on the catheter during release. Thus, in this case there is conclusive evidence of acute unilateral device placement.



In the second case (Patient ID: [REDACTED]), the treating physician strongly suspected that a Matrix was not placed at time of procedure. As per protocol, the physician did not immediately attempt to place another Matrix; but rather, waited for the results of the post-procedure TVUS which confirmed the unsuccessful placement. This evidence strongly supports the conclusion that only one Matrix was placed during the initial placement procedure.

Thus, only 5 patients of the 611 with successful bilateral treatment (0.8%) experienced an unexplained loss of a Matrix. This rate compares very favorably to the 3.6% device expulsion/unsatisfactory location rate observed in the pivotal clinical trial for the Essure™ Permanent Birth Control System.²

The cause of the missing Matrix in these five patients is not known. It is possible in the three cases that were identified at one week post-procedure, that the missing Matrix was actually not successfully placed. It cannot be determined definitively if this was the case, or if Matrix migration occurred in these three cases. However, in the two patients where a missing Matrix was identified at three months (after being identified in place post-procedure), the most likely cause is Matrix migration from the tube.

These five cases were further explored for trends or possible causes for loss of Matrix; however, due to the small number of cases, no obvious trends or causes could be discerned. No significant differences were seen in terms of the side on which the failure occurred (4 right versus 1 left) or which version of Delivery Catheter was used (3 version 1.5, versus 2 version 1.0). The mean age of these five patients was 33 years, with a range of 27-37 years. Additionally, the shelf age of the product used in these five cases was also considered. The mean shelf age was 5.2 months, with a range of 2-8 months. In three cases, the shelf age of the missing matrices was between 0-4 months, and in two cases it was between 5-8 months. No product used in these cases was greater than eight months old, indicating that increasing shelf age of the product was not a cause of Matrix migration. Thus, it is not possible to hypothesize a common cause for the missing matrices in these five cases.

8.6 Six-Month Tubal Occlusion Re-evaluations

Per protocol, the women who had bilateral Matrix placement but did not demonstrate bilateral occlusion during their first HSG three months following the procedure, had the option of waiting an additional three months to undergo a repeat HSG. Of the 53 women who had tubal patency at three months post-procedure, 45 patients received a second HSG evaluation. Eight patients were not evaluated by a repeat HSG for the following reasons: alternative contraception failure during the extended Waiting Period (n=2, refer to Section 9.4.1 and Appendix 13.3.4 for further details); lost to follow-up (n=1);

² Summary of Safety and Effectiveness Data, Page 6, Table 2. See: <http://www.fda.gov/cdrh/pdf2/p020014b.pdf>

declined to extend Waiting Period and elected to have a surgical tubal sterilization (n=1); or were missing Matrix during three-month TVUS evaluation and subsequently elected bilateral tubal sterilization (n=4).

Of the 45 patients evaluated by repeat HSG, 19 (42.2%) demonstrated bilateral occlusion and began reliance on the Adiana System for pregnancy prevention. The remaining 26 patients were found to have persistent tubal patency. These patients were offered a bilateral tubal sterilization and either withdrew from the study or are being followed for safety evaluation only. Final HSG results are presented in Table 8-13 above.

An analysis of final HSG results by investigative site was performed and is presented in Table 11.2.13.1.3. Bilateral tubal occlusion rates for the sites ranged from 77.8% to 100%. Several of the sites that treated the fewest number of patients had 100% bilateral occlusion rates. Additionally, an analysis of occlusion rates stratified by the number of patients at the clinical sites (those with 30 or less subjects and those with more than 30 subjects) was performed (a detailed summary of this analysis can be found in Table 11.2.13.1.4). Results showed that the seven sites treating less than 30 patients had a final bilateral occlusion outcome rate (93.5%) similar to the nine sites treating greater than 30 patients (94.5%). These above results indicate that, as seen with the acute procedural success results, successful bilateral occlusion results do not appear to be correlated to the degree of physician experience in performing the Adiana Procedure.

8.6.1 Summary of Tubal Patency

Of the 604 patients evaluated by HSG at three months post-procedure, 53 patients had demonstrated tubal patency. Eight of these patients did not undergo a repeat HSG. The remaining 45 patients did undergo a repeat HSG evaluation after waiting an additional three months, and 26 of those patients were found to have persistent tubal patency or equivocal results. Of these, three patients were identified as missing matrices, and therefore, are not included in this summary as this is an analysis of patients who were confirmed to have bilateral matrices in place, and yet had occlusion failure (Note: these patients were included in the summary of patients missing matrices, see Section 8.5.3). Thus, there were a total of 31 (5.1%) patients who had bilateral matrices confirmed in place, but could not rely on the Adiana System due to failed or equivocal tubal occlusion identified on HSG.

These 31 patients had a total of 32 tubes that were identified as being patent. Two tubes had equivocal findings on HSG that prevented definitive determination of tubal occlusion. These two cases are conservatively included in the analysis of occlusion failures. Table 11.2.13.1.6 summarizes the findings of the 34 occlusion failures in these 31 patients.

The 34 incidences of failed tubal occlusion were further evaluated for trends or possible causes. No significant difference was seen between the versions of Delivery Catheter used (16 version 1.5, versus 18 version 1.0). The 34 incidences of failed



occlusion were evaluated to determine if the side on which the occlusion failure occurred was a factor in these cases. The proportions of occlusion failures for each side were not statistically different, $p=0.22$: 21/604 patent right tube and 13/604 patent left tube.

The age demographics of these 31 patients were also reviewed. The mean age of these patients was 32 years, with a range of 23-42 years. When stratified by age group, 5 patients were in the 18-27 year age group (16.1%); 17 were in the 28-33 age group (54.8%); and 9 were in the 34-45 age group (29.0%). When considering this age distribution of the patients with tubal occlusion failures in conjunction with the age distribution of patients in the ITT population, these results do not indicate any tendency for tubal occlusion failure in a particular age group.

Finally, the shelf age of the product used in these 34 cases was analyzed. The mean shelf age was 4.9 months, with a range of 2-12 months. In 22 cases, the shelf age of the missing matrices was between 0-4 months (64.7%); in 8 cases it was between 5-8 months (23.5%); and in 4 cases it was between 9-12 months (11.8%). Since relatively few occlusion failures occurred in cases where product was more than eight months old, extended shelf age is not believed to be a factor in the cause of these failures.

In considering the results from these analyses, there does not appear to be any clear trends that would indicate a patient age demographic, procedural, or device-related cause for the tubal occlusion failures observed in this study.

V. D. 4. FINAL TREATMENT SUCCESS – RELIANCE

8.7 Final Treatment Success (Relying Population)

Final Treatment Success is defined as successful bilateral occlusion as evaluated by HSG.

Of the 604 patients who had successful bilateral device placement and were evaluated for occlusion by HSG, a total of 570 patients had demonstrated bilateral occlusion (551 bilaterally occluded at three-month HSG and 19 bilaterally occluded at repeat six-month HSG).

Thus, overall, of the 645 patients in whom treatment was attempted, a total of 570 achieved final treatment success (88.4%) and were able to begin reliance on the Adiana System for pregnancy prevention. Final treatment success results are summarized for the US, OUS, and Total populations in Table 11.2.13.2.

Final treatment success rates were analyzed for each investigative site and are presented in Table 11.2.13.1.3. Success rates varied from 77.8% to 100%. Rates at the high and low end of this range occurred at sites with small numbers of treated patients, and represent either no failures, or one or two failures. When these chance events occurred in a small cohort of patients, they created the extreme results seen in the success rates. Once again, there was no indication from the data that final treatment success was correlated to the level of physician experience in performing the treatment procedure.

8.7.1 Core Lab Review Results

In addition to HSG review by the investigative site, a retrospective review of all HSGs performed on the study was performed by two independent Core Lab reviewers. This review was undertaken after review of a pregnancy event in a relying patient found that the HSG films had been misinterpreted. The primary goal of these analyses was to provide independent assessment of tubal occlusion status from that reported by the investigative sites. The reviewers were blinded to clinical site evaluation of occlusion outcome. Patency was defined as visualization of contrast flow into the fallopian tube past the implanted Matrix. In addition, the reviewers evaluating HSGs reported on a number of other variables related to HSG technique or occlusion outcome (e.g.; cornual filling, proximal tube filling, evidence of cervical leakage, etc.).

HSG's that were determined to require further review, by either one or both of the reviewers, underwent an adjudication process. The adjudication process consisted of the sponsor, a clinical advisor, and reviewer(s) reviewing the HSG's in question. The outcome of adjudication was either determining the need for a repeat HSG, or drawing conclusion on the submitted HSG record reviewed. Additional input was provided to the adjudication group by the investigators, as necessary.

The Core Lab reviewers each reviewed a total of 734 HSG's from 605 subjects thought to have bilateral device placement at the time of the procedure. Of the 734 HSG's reviewed, 536 were concluded by both reviewers to concur with the investigator findings of tubal occlusion or patency, or a later identified tubal patency as a result of a pregnancy outcome. There were 198 instances of some level of discrepancy between the site investigator and the two independent reviewers. Of these 198 HSG's that underwent additional review and adjudication only 48 resulted in an attempt for repeat HSG, with the remaining adjudicated. Therefore, of the original HSGs 686/734 (93.5%) were adequate to evaluate tubal patency.

Results of the repeat HSGs revealed only four instances (0.7%) in which the Core Lab reviewers reported a finding of tubal patency in a subject that was not reported by the investigative site. According to this Core Lab review, 601 of the 605 (99.3%) patients who had HSG's performed during the EASE trial had final tubal occlusion findings reported by an investigator that were confirmed by the Core Lab review.

These analyses demonstrate that the Adiana device is capable of providing occlusion of fallopian tubes, and that the occlusion of the tube by the device can be readily assessed by an adequately performed and evaluated HSG at three months after the procedure.

A copy of the Core Lab report can be found in Appendix 13.4.

V. D. 5. EFFICACY RESULTS

8.8 Analysis of Primary Efficacy

The primary efficacy endpoint for this study is the pregnancy prevention rate after one year of reliance on the Adiana System for pregnancy prevention. This endpoint is evaluated for the Per Protocol population (all patients who underwent successful bilateral treatment, had demonstrated tubal occlusion [by HSG] at the end of the Waiting Period, and were evaluated for the one year primary endpoint).

During the one-year follow-up period, there were six (6) pregnancies in the 553 Per Protocol patients. Three of these six events were attributable to physician error (specifically, HSG interpretation error). The remaining three events were due to method failure (no causal feature was identified). A summary of these pregnancy events follow in Section 9.4.1 (also see Appendix 13.3.4 for further details).

Primary efficacy success in this study was defined as a one-year pregnancy prevention rate greater than 95% at a 95% level of confidence. The one-year pregnancy prevention rate in the EASE trial derived with life-table methods is 98.9%, with a single-sided, lower confidence bound of 98.2%. Thus, the lower one-sided 95% confidence bound of the observed pregnancy rate exceeds the minimum effectiveness rate of 95% defined for this study.

The primary efficacy results considering all pregnancies, as well as only the method failures, are summarized for the US, OUS, and Total populations in Tables 8-15 and 8-16 below.

Table 8-15: Summary of One-Year Primary Efficacy Endpoint – All Pregnancies

	US	OUS	Total
Number of Subjects	447	106	553
Pregnancy During 12 Months Wearing Device			
Yes	4 (0.9%)	2 (1.9%)	6 (1.1%)
No	443 (99.1%)	104 (98.1%)	547 (98.9%)
95% CI ¹ for % No	(98.4 , 100)	(95.9, 100)	(98.2 , 100)

¹ One-sided confidence interval derived with life-table methods. A total of 570 subjects that relied on the device were included in the analysis.



Table 8-16: Summary of One-Year Primary Efficacy Endpoint – Method Failure Pregnancies

	US	OUS	Total
Number of Subjects	447	106	553
Pregnancy During 12 Months Wearing Device			
Yes	3 (0.7%)	0 (0.0%)	3 (0.5%)
No	444 (99.3%)	106 (100%)	550 (99.5%)
95% CI ¹ for % No	(98.7 , 100)	(100 , 100)	(99.0 , 100)

¹ One-sided confidence interval derived with life-table methods. A total of 570 subjects that relied on the device were included in the analysis.

In order to more fully evaluate the efficacy of the Adiana System, a comparison was made between the Adiana System’s one-year pregnancy prevention rates and the corresponding rates of other methods as presented in the CREST study. As a preliminary evaluation, the two-sided 95% confidence limits of the observed rate for each method were compared to each of the other methods; this analysis allowed for the relative performance of the various methods to be determined. The one-year failure rates and the two-sided 95% confidence interval efficacy ranges from the CREST study and the Adiana System, ordered by decreasing efficacy ranges, are summarized in Table 8-17. (Two-sided confidence intervals were used for all comparisons to the CREST methods to match the analysis used therein.)

Table 8-17: CREST Methods: One-Year Failures

	Failure per 1000 patients		95% CI ¹
	Point Estimate	95% CI	Efficacy Range
Post Partum Partial Salpingectomy	0.6	0.0 to 1.9	99.81 – 100
Unipolar Coagulation	0.7	0.0 to 2.1	99.79 – 100
Bipolar Coagulation	2.3	0.3 to 4.3	99.57 – 99.97
Silicon Rubber Band Application	5.9	3.3 to 8.5	99.15 – 99.67
Interval Partial Salpingectomy	7.3	0.0 to 15.5	98.45 – 100
Adiana (US)	8.9	0.2 to 17.5	98.25 – 99.98
Adiana (Total)	10.8	2.2 to 19.4	98.06 – 99.78
Spring Clip Application	18.2	11.5 to 24.9	97.51 – 98.85
Adiana (OUS)	18.9	0.0 to 44.8	95.52 - 100
All Methods	5.5	4.0 to 7.0	99.30 – 99.60
Comparable Methods ²	7.5	5.7 to 9.2	99.08 – 99.43

¹ Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

² Two-sided confidence interval derived with life table methods.



Pursuant to FDA request, the following three tables have been added to this report.

The first two tables include revised Life Table analyses for Year One Efficacy utilizing a two-sided confidence interval. Tables 8-15 and 8-16 have been repeated with two sided intervals in tables 8-15A and 8-16A, respectively.

Table 8-17A has been revised to include the number of subjects in each method.

Table 8-15A: Summary of Primary Endpoint: Pregnancy Rate for 12 Months Wearing Devices

	US	OUS	Total
Number of Subjects	447	106	553
Pregnancy During 12 Months Wearing Device			
Yes	4 (0.9%)	2 (1.9%)	6 (1.1%)
No	443 (99.1%)	104 (98.1%)	547 (98.9%)
95% CI ¹ for % Yes	(0.02 , 1.75)	(0.00 , 4.48)	(0.22 , 1.93)

¹ Two-sided confidence interval derived with life-table methods. A total of 570 subjects that relied on the device were included in the analysis. Success rates were significantly better than 95% at the one-sided alpha 0.05 level, see Table 8-15 of the Clinical Trial Report.

Table 8-16A: Summary of Primary Endpoint: Method Failure Pregnancy Rate for 12 Months Wearing Devices

	US	OUS	Total
Number of Subjects	446	104	550
Pregnancy During 12 Months Wearing Device			
Yes	3 (0.7%)	0 (0.0%)	3 (0.5%)
No	443 (99.3%)	104 (100.0%)	547 (99.5%)
95% CI ¹ for % Yes	(0.00 , 1.41)	(0.00 , 0.00)	(0.00 , 1.15)

¹ Two-sided confidence interval derived with life-table methods. A total of 570 subjects that relied on the device were included in the analysis. Success rates were significantly better than 95% at the one-sided alpha 0.05 level, see Table 8-16 of the Clinical Trial Report.

Table 8-17A: CREST Methods: One-Year Failures

	N ¹	Failure per 1000 pts Point Estimate	95% CI	95% CI ² Efficacy Range
Post Partum Partial Salpingectomy	1637	0.6	0.0 to 1.9	99.81 – 100
Unipolar Coagulation	1432	0.7	0.0 to 2.1	99.79 – 100
Bipolar Coagulation	2267	2.3	0.3 to 4.3	99.57 – 99.97
Silicon Rubber Band Application	3329	5.9	3.3 to 8.5	99.15 – 99.67
Interval Partial Salpingectomy	425	7.3	0.0 to 15.5	98.45 – 100
Aiana	570	10.8	2.2 to 19.4	98.06 – 99.78
Spring Clip Application	1595	18.2	11.5 to 24.9	97.51 – 98.85
All Methods	10685	5.5	4.0 to 7.0	99.30 – 99.60
Comparable Methods ³	7616	7.5	5.7 to 9.2	99.08 – 99.43

¹ Number of women sterilized.

² Two-sided confidence interval derived with life table methods.

³ Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically.