A Prospective, Multi Center Pilot Study Evaluating Plaque Photoablation Using the RA-308 Excimer Laser in Subjects with Symptomatic Infrainguinal Lower Extremity Vascular Disease

Protocol: RMS-102

Sponsor:
Ra Medical Systems, Inc.
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Carlsbad, CA 92008

CONFIDENTIALITY STATEMENT

A Prospective, Multi Center Pilot Study Evaluating Plaque Photoablation Using the RA-308 Excimer Laser in Subjects with Symptomatic Infrainguinal Lower Extremity Vascular Disease

Protocol: RMS-102

January 11, 2016

I have read this protocol and agree to conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

_____

Principal Investigator's Signature Date

_____

Name of Principal Investigator (Typed or Printed)

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SYNOPSIS

Study Objective	To evaluate the safety and efficacy of the RA-308 Excimer Laser System and DABRA Catheter for treating subjects with symptomatic infrainguinal lower extremity vascular disease with chronic total occlusions that cannot be crossed with standard guide wires.
Study Device	The RA-308 Excimer Laser System and DABRA 101 Catheter consists of a 308 nanometer wavelength Excimer laser and a fluid filled optical catheter.
Study Design	A multi-center, prospective, non-randomized, open-label study. The study will conducted at a minimum of two sites.
Sample Size	Up to 50 male and female subjects will be enrolled.
Outcome Measures	Procedural success, defined as crossing the target lesion based on angiographic analysis at the time of the procedure. Crossing the target lesion is defined as successfully placing any endovascular device distal to the occlusion. No device related major adverse events.

STUDY POPULATION

Inclusion Criteria

Subjects must satisfy the following criteria before entering the study:

- Signed informed consent obtained.
- Symptomatic infrainguinal lower extremity vascular disease (Rutherford category 3, 4, 5 or 6), stable for at least 2 weeks prior to study inclusion.
- Lesions in the superficial femoral artery (SFA), popliteal, infrapopliteal or tibial arteries
- At least one angiographically identifiable infrageniculate artery
- Patients must be poor surgical candidates, indicated by at least one of the following conditions:
  - Absence of venous autologous grafts (that is, lack of a suitable vein to use for bypass)
  - Poor (diffusely diseased or ≤1mm diameter) or no distal vessels available for graft anastamosis

- High risk of surgical mortality, evidenced by American Society of Anesthesiologists Physical Class 4 or higher
- Have a lesion that is a chronic total occlusion that cannot be crossed with a standard guidewire. NOTE: This can only be determined at the time of the procedure.

Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

- Age below 18 years
- Pregnancy, or plan to become pregnant
- Participation in another cardiovascular or peripheral vascular IDE study
- Myocardial infarction (MI) in prior month
- Stents at treatment site
- Disorders or allergies precluding use of radiographic contrast
- Renal insufficiency severe enough to contraindicate use of radiographic contrast
- Contraindication to treatment with anticoagulants
- Untreated ipsilateral iliac stenosis >70%
- Inability or unwillingness of the patient to comply with intended examinations.
- Unavailability of required procedural or imaging equipment
- Lesion located in a graft
- Hemodynamically significant arrhythmia or left ventricular ejection fraction <20%
- Life expectancy less than 6 months
- Necrosis necessitating major amputation
- Unwillingness of the patient to be anti-coagulated

Time and Events Schedule

Event	**Screening** (Visit 1)	**Procedure** (Visit 2)	**Follow-Up**
		Day 0	≥30 Days
Demographics and Medical History Review	x		
Ankle-Brachial Index (ABI)	x		As needed
Rutherford Classification	x		
Angiography		x	
Crossing Procedure		x	
Device-Related Safety Data		As needed	As needed
Doppler Ultrasound			As needed

1.0 INTRODUCTION

1.1 Background

The distribution of Peripheral Artery Disease (PAD), including Chronic Total Occlusions (CTOs), varies with multiple factors, such as age and the presence of cardiovascular risk factors. Aortoiliac disease is associated with young age, females, and current smokers. Femoropopliteal involvement in occlusive PAD is extremely common and, in one series, was present in 80% of symptomatic patients undergoing angiography. The predilection of disease in this segment may be due to its conduit-like nature, with no or few major branches, and torsion or stretching resulting from limb movement. These characteristics may cause relatively more damage of the vaso vasorum and endothelium than other limb segments, leading to accelerated atherosclerosis. Additionally, the flow characteristics following the development of a stenosis may promote long occlusions. Infrapopliteal disease is associated with diabetes mellitus, and diffuse and occlusive disease is common. Despite the complex nature of infrapopliteal disease, endovascular techniques have acceptable limb salvage rates. This approach, therefore, may be increasingly used for CTOs in patients with limited surgical options, due to co-morbidities or lack of bypass conduits or target vessels. Overall, CTOs are more the norm than the exception in PAD. The decision to attempt percutaneous revascularization of CTOs depends on many factors, such as severity of symptoms, and lesion characteristics, including location, calcification and length, and operator experience and institutional availability of the specialized devices.

From 1975-1979 many scientists and institutions worked on the initial development of a family of gas lasers known as the "excimer." Those pioneers were with institutions including Lumonics, Lambda Physik, Avco, and Caltech. The development was initiated in part because of the short wavelength of this type of light source. Monochromatic short wavelength sources were thought to have a variety of commercial and military applications. The name excimer is a contraction of "Excited Dimer," a description of a diatomic molecule in which the component atoms are bound in the excited state, but not in the ground state. The important gas molecules are rare gas halides including argon fluoride, krypton fluoride, and xenon chloride.

The ultraviolet light from an excimer laser is well absorbed by biological matter and organic compounds. Rather than burning or cutting material, the excimer laser adds enough energy to disrupt the molecular bonds of the surface tissue, which effectively disintegrates in a tightly controlled manner through ablation rather than burning. Thus excimer lasers have the useful property that they can remove exceptionally fine layers of surface material with almost no heating or change to the remainder of the material which is left intact. These properties make excimer lasers well suited to precision micromachining organic material, or delicate surgeries such as eye surgery. At lower energy densities, the laser may also be used for dermatological disorder treatment.

Excimer laser light is typically absorbed within the first billionth of a meter (nanometer) of tissue. In the early 1980s, researchers at IBM’s T. J. Watson Research Center observed the effect of the ultraviolet excimer laser on biological materials. They found that the laser made clean precise cuts that would be ideal for delicate surgeries. Subsequent work introduced the excimer laser for use in angioplasty or atherectomy, destroying blockages in arteries using molecular ablation. Xenon chloride excimer lasers, having a wavelength of

308nm, can also treat a variety of dermatological conditions including psoriasis, vitiligo, atopic dermatitis, and leukoderma.

In the late 1980s, 308nm excimer laser atherectomy was developed as an alternative method of percutaneous angioplasty, with the objective of reducing the high rate of restenosis associated with other angioplasty or stenting techniques. Excimer laser atherectomy is a procedure that utilizes an intravascular catheter system to deliver high-energy pulsed laser light to atherosclerotic lesions, or plaque, that are causing stenosis or occlusion of native arteries, or intra-arterial stents, while producing relatively little thermal damage to the vessel wall. The pulses vaporize thin sections of tissue without causing significant damage to surrounding tissue. It is thought that reduction of plaque using laser ablation could be more effective in enlarging the vessel lumen than balloon angioplasty alone. Early data from large observational registry studies published in the early 1990s provided evidence of the safety of the procedure. By 1994, Advanced Interventional Systems (AIS) had commercialized a system and gained FDA approval for the procedure. Later in the decade AIS merged with Spectranetics, Inc., which had developed an excimer for treating peripherals. There are approximately 1,000 Spectranetics lasers placed today, and thousands of excimer laser endovascular procedures are performed each year.

The Ra Medical team, which includes members of the Spectranetics and AIS development teams, began developing the RA-308 Excimer Laser System and DABRA Catheter for crossing lesions in 2006, after the successful launch of the PHAROS EX-308 excimer laser phototherapy system.

1.2 Alternative Treatments and Methods

Patients that have agreed to participate in the study and meet the inclusion criteria and have signed the informed consent form and present on the day of treatment for the endovascular diagnostic procedure will be considered for the study. It is at this point when it will be determined that the patient meets all of the inclusion criteria. If the patient's lesion can be crossed with a guide wire or if the physician feels that other options are more appropriate for the patient, the patient will be treated with the laser catheter and not be included in the study.

There are several commercially available CTO crossing methods and atherectomy systems on the market today. These include standard guide wire manipulation. Standard guide wire recanalization should initially be attempted, even for long, occlusive lesions. Although the inability to remain intraluminal or re-enter the true lumen distally are the main reasons for failure of this technique, there is still a relatively high chance of success. For aortoiliac lesions, an ipsilateral retrograde femoral approach is usually the simplest, but an alternative approach from contra lateral femoral or brachial access may be needed. For superficial femoral artery (SFA) lesions, a contra lateral femoral approach with a crossover sheath is usually needed, but for more distal lesions, such as infrapopliteal, an ante grade femoral approach may be preferable, so that device torquability and push ability is optimized.

1.3 Rationale for the RA-308 Excimer Laser System

The RA-308 Excimer Laser system may cross calcified lesions without subluminal penetration, common when using the standard guide wire approach. Additionally, the energy delivered within the patient with the excimer laser is much lower than when using mechanical surgical methods. This may result in less vascular trauma and may improve the clinical outcome for the patient.

1.4 Previous Clinical Experience

The RA-308 Excimer Laser System and DABRA Catheter have been used on three patients to date. Their peripheral vascular blockages were ablated (crossed) and the patients were then treated with balloon angioplasty. There were no adverse events and the procedural outcomes were excellent.

1.5 Risk Analysis

We believe that the procedure does not pose a significant risk to the patient. The patients are likely candidates for amputation. In addition, the procedure does not pose additional risk to the patient because of the following:

- The endovascular procedure will occur anyway, regardless of whether or not the laser is used. This endovascular procedure is used to help diagnose the precise nature of the disease, the location of any stenosis, and treatment will be initiated with common endovascular tools, such as guidewires and balloons. The DABRA laser catheter will be attempted only after these tools fail or if the physician determines that there is no other option.
- The catheter does not present a potential for serious risk to the health, safety, or welfare of the subject, because they already have a high probability of amputation. In addition, the potential adverse events related to the DABRA catheter have low risk to these patients. Perforation is easily mitigated and repaired with a tamponade technique, and embolism or debris from any of these procedures is likely to be filtered downstream by the narrowing of the vasculature.
- The catheter is not implanted, and is not of substantial importance in treating the disease. It only crosses the lesion to allow therapeutic treatment. It is a small part of a much more complicated procedure. The energy delivered by the DABRA catheter is orders of magnitude less than other technologies, including mechanical, barometric, radiofrequency, and ultrasonic or sonic.
- All endovascular interventionalists have the skill and training to use this device safely. Excimer lasers have been used for over 20 years, and their operation is no more difficult than using a stand alone guide wire. The only difference is depressing the footswitch.

2.0 STUDY OVERVIEW

2.1 Study Design

The study is a multi center, prospective, non-randomized, open-label study conducted at two investigational centers in the US, one in southern Mississippi and one in southern California, with at least two operators at each site. 50 subjects can be enrolled. Follow-up

occurs at the end of the procedure in the form of an angiogram to determine if the lesion was crossed. Additional follow-up may not necessary because of the binary nature of the crossing, and also because any future follow-up would be assessing the effectiveness of adjunct therapy, e.g. balloon angioplasty. Long term results are entirely dependent on this subsequent treatment. Because the DABRA crosser only allows adjunct devices to be used, 30-day follow-up measuring the performance of the adjunct therapy might affect the physician's choice of therapy, and compromise the patient's treatment. Therefore, 30-day follow-up, which evaluates the effectiveness of the adjunct therapy, might raise ethical concerns.

However, the follow-up can be done by ABI, Doppler ultrasound, auscultation, or by discussion of the level of claudication and motion pain with the patient.

2.2 Study Objectives

To evaluate the safety and efficacy of the RA-308 Excimer Laser System and DABRA Catheter for treating subjects with symptomatic infrainguinal lower extremity vascular disease with chronic total occlusions that cannot be crossed with standard guide wires, or lesions where an attempt to cross would, in the opinion of the interventionalist, result in either a subintimal path or a perforation.

2.2.1 Outcome Measures

Procedural success, defined as crossing the target lesion based on angiographic analysis. Crossing the target lesion is defined as successfully placing any endovascular device distal to the occlusion.

No device related major adverse events

3.0 STUDY POPULATION

3.1 General Considerations

Subjects will undergo baseline evaluation to determine eligibility for the study. Subjects who do not meet the entry criteria are considered screening failures. Case report forms do not need to be completed for screening failures; however, a record for each patient screened and the reason for screening failure must be indicated in the screening log.

The investigator and/or designated study personnel are responsible for screening all potential candidates and selecting those who are appropriate study candidates as defined by the following inclusion and exclusion criteria.

Signed informed consent will be obtained from the patient before any specific study procedures are undertaken. The patient will sign one original informed consent and a copy will be provided to them. The study requirements should be discussed with the patient with ample time provided for the consent review. All required parties (e.g., patient, witness, investigator or designee) should sign and date on the same consent as the patient.

3.2 Inclusion Criteria

Subjects must satisfy the following criteria before entering the study:

- Signed informed consent obtained.
- Symptomatic infrainguinal lower extremity occlusive vascular disease (Rutherford category 3, 4, 5 or 6), stable for at least 2 weeks prior to study inclusion.
- Lesions in the superficial femoral artery (SFA), popliteal, or infrapopliteal arteries
- At least one angiographically identifiable infrageniculate artery
- Patients must be poor surgical candidates, indicated by at least one of the following conditions:
  - Absence of venous autologous grafts (that is, lack of a suitable vein to use for bypass)
  - Poor (diffusely diseased or ≤1mm diameter) or no distal vessels available for graft anastamosis
  - High risk of surgical mortality, evidenced by American Society of Anesthesiologists Physical Class 4 or higher
- Have a lesion that is a chronic total occlusion that cannot be crossed with a standard guidewire. NOTE: This can only be determined at the time of the procedure.

3.3 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

- Age below 18 years
- Pregnancy, or plan to become pregnant
- Participation in another cardiovascular or peripheral vascular study
- Myocardial infarction (MI) in prior month
- Stents at treatment site
- Disorders or allergies precluding use of radiographic contrast
- Renal insufficiency severe enough to contraindicate use of radiographic contrast
- Contraindication to treatment with anticoagulants
- Untreated ipsilateral iliac stenosis >70%
- Inability or unwillingness of the patient to comply with intended examinations.
- Unavailability of required procedural or imaging equipment
- Lesion located in a graft
- Hemodynamically significant arrhythmia or left ventricular ejection fraction <20%
- Life expectancy less than 6 months
- Necrosis necessitating major amputation
- Unwillingness of the patient to be anti-coagulated

4.0 STUDY DEVICE DESCRIPTION

4.1 The RA-308 Excimer Laser System

The RA-308 Excimer Laser System is a self-contained unit that connects to a sterile energy delivery catheter for use in vascular procedure under fluoroscopic guidance. The laser

energy is commanded by a footswitch that connects to a control system to generate and monitor the laser energy pulses.
The laser energy is ultraviolet at 308nm and is delivered to the surgical site by the single-use catheter that is used in conjunction with other catheter and vascular technology to complete the surgical system.
The energy and density of the laser beam is sufficient to ablate tissue within 50µm of the tip. There is no significant off-axis radiation.
The catheter is inserted into a patient's peripheral vasculature through a previously inserted guiding support catheter, allowing the physician to deliver laser energy targeted to a blockage (lesion) in the blood vessel. Laser energy impinged on the blockage ablates, or debulks, the lesion material thus producing a channel through the blockage.

4.2 Excimer Laser for Use in Plaque Photoablation

Refer to the device Instructions for Use for a thorough description of the procedure.

Procedure Description
The excimer laser crossing procedure is performed in the Catheter Laboratory using standard endovascular techniques. Following introduction to the vascular system and diagnosis using fluoroscopy, including determining that a standard guidewire cannot cross the lesion, the following general guidelines are followed:
1. Insert a commercial guide wire to the blockage.
2. Pass an appropriate guiding catheter (support catheter) over the wire to the lesion. (Steps 1 & 2 can be reversed depending on physician choice.)
3. Remove the guide wire if one fails to cross the CTO or if, at the physician's discretion, angiographic factors determine that a guide wire should not be used because of the presence of a rounded or eccentric stump might bias the guide to a subintimal route, or other complicating factor.
4. Save the initial guide wire and insert the laser catheter and perform a stepwise crossing of the lesion.
5. Cross the CTO with the laser catheter following the step-by-step procedure in the instructions for use.
6. Exchange the laser catheter with the previous wire or another wire.
7. Remove the guide catheter leaving the guide wire in place and, at the physician's discretion, insert other endovascular devices to enhance blood flow.

5.0 STUDY EVALUATIONS

5.1 Overview

The visit schedule and procedures required by this protocol are summarized below:

Event	Screening (Visit 1)	Procedure (Visit 2)	Follow-Up
		Day 0	≥30 Days
Demographics and Medical History Review	x		
Ankle-Brachial Index (ABI)	x		As needed
Rutherford Classification	x		
Angiography		x	
Crossing Procedure		x	
Device-Related Safety Data		As needed	As needed
Doppler Ultrasound			As needed

5.2 Screening

Prior to any study-specific tests or procedure, the benefits and risks of the study must be explained and written informed consent must be obtained from the subject.

The following tests and activities must be performed to verify eligibility:

- Documentation of subject demographic information
- Documentation of relevant medical history
- Rutherford classification
- Review of all inclusion/exclusion criteria to confirm subject eligibility

5.3 Procedure

The following information will be collected for study subjects:

- Pre-laser treatment stenotic assessment using angiography
- Laser treatment procedure time
- Post-laser treatment stenotic assessment using angiography
- Adjunctive procedures, if any, as recommended by the physician
- The duration of lasing
- Device related safety data

5.4 Follow-Up (≥30 days)

The following information may be collected:

- Ankle-brachial index
- Rutherford classification
- Device-related safety data
- Auscultation
- Doppler ultrasound
- Any other relevant information provided by the patient

6.0 STATISTICAL METHODS

6.1 Primary Objective

The primary objective of this study is to demonstrate that the Ra device meets its performance goal of a success rate in crossing vascular lesions of at least 65%. A study of the predicate device observed 37 successes in a trial of 47 patients, or a 79% success rate with a 95% confidence interval of 65-88% (Wilson score interval). The performance goal for the Ra device is thus set to be a success rate of at least 65% and the primary objective is to show that the Ra device exceeds this performance goal in a single-arm multi-site pivotal trial. Crossing success rate will be a binary endpoint, where successful crossing of a lesion is defined as crossing the target lesion based on angiographic analysis.

6.2 Statistical Methodology

Primary Objective Test

The primary objective will be tested with a one-sided exact binomial test using a significance level of 0.025.

6.3 Hypothesis

The following null hypothesis will be tested with an overall significance level of 0.025

$$H_0: p \leq 65\%$$

where p is the Ra device crossing success rate. The alternative hypothesis is:

$$H_a: p > 65\%$$

6.4 Study Design

This study will be a non-randomized, single arm, prospective, multi-site clinical trial. The primary effectiveness endpoint will be evaluated using a one-sided test comparing the Ra device crossing success rate to the performance goal of 65%. The lower 95% confidence interval for the success rate of the predicate device was 65%.

6.5 Sample Size Rationale

The required number of subjects to achieve 80% probability to demonstrate the Ra device meets the performance goal when the true success rate is 97% was calculated in the Power Analysis of One Proportion Procedure of NCSS Power Analysis Statistical Software (PASS), Version 14. A 97% success rate was observed in a trial of 78 patients using a similar device (Visona 1998). A sample size of 14 patients yields a 94% probability of meeting the PG of 65% crossing success when the true Ra device rate is 97%; the study will conclude that the PG has been met if 13 or more of the 14 patients are successes. A sample size of 50 patients yields a 99.99% probability of meeting the PG; the study will conclude that the PG has been met if 40 or more of the 50 patients are successes.

6.6 Data Analysis

The categorical data will be summarized descriptively with frequencies along with the associated percentages. The continuous variables will be summarized by number of subjects, mean, median, standard deviation, minimum and maximum.

6.6.1 Adverse Events

The number of subjects with at least one adverse event will be tabulated.
The number of subjects and the number of adverse events will be tabulated by severity and causality and relationship to the treatment procedure.

7.0 RISK ANALYSIS

7.1 Summary of Potential Benefits

The potential benefit of the RA-308 Excimer Laser System and DABRA Catheter is that occlusions in the vasculature may be crossed. Through an endovascular approach, the device may assist in improving blood flow to limbs and/or enable treatment with other devices and technologies.

7.2 Summary of Potential Risks

Use of the RA-308 Excimer Laser System and DABRA Catheter may contribute to the following complications:

Procedural Complications
Spasm
Major dissection
Thrombus
Distal embolization
Perforation
Other

Serious Adverse Events
Death
Re-intervention
ALl
Major amputation
Bypass surgery
Hematoma with surgery

In-Hospital Complications
Re-occlusion
Renal failure
Pseudoaneurysm
Bleeding

Other Potential Adverse Events
Nerve injury
AV fistula formation
Endarterectomy
Infection

No long-term adverse effects of peripheral Excimer laser treatment are known at this time.

8.0 ADVERSE DEVICE EVENTS

8.1 Definition

An adverse event is any untoward medical occurrence in a clinical investigation subject administered the medical device and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the device, whether or not the event is considered causally related to the use of the device.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

For adverse events to be considered sporadic or intermittent, the events must be similar in nature and severity.

Elective procedures/surgeries that occur during the study will not be considered adverse events.

8.2 Serious Adverse Events

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)
Adverse event that:
a) led to a death,
b) led to a serious deterioration in health that either:
1) resulted in a life-threatening illness or injury, or
2) resulted in a permanent impairment of a body structure or a body function, or
3) required in-patient hospitalization or prolongation of existing hospitalization, or
4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report
*SADE and SAE definitions adopted from MEDDEV 2.7/3, December 2010, CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC.

9.0 ETHICS

9.1 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

9.2 Institutional Review Board (IRB)

The investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the Internal Review Board of the facility and a copy of this approval has been received by the sponsor.

During the conduct of the study, investigators must submit progress reports to the IRB as required and request re-review and approval of the study at least once a year. After the study is concluded, the investigator should notify the IRB of this status and prepare a final report for IRB review.

9.3 Non-Compliance

Departures from the protocol and applicable regulatory requirements should be documented on the non-compliance log. Subject non-compliance, which is not the control of the Investigator and is a subject right, does not need to be reported on the log. Non-compliance issues include, but are not limited to, informed consent not obtained, inclusion or exclusion criteria not met, missed visits due to site oversight, protocol visits conducted outside the defined time period, required testing not completed.

In an emergency, the investigator shall notify the sponsor and the IRB (as required by the facility regulations) of any deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency has occurred.

10.0 DEVICE ACCOUNTABILITY

It is the responsibility of the investigator to ensure that all study devices received at the site will be accounted for throughout the clinical investigation. The monitor will check device accountability during monitoring visits. Unless otherwise instructed by the sponsor, the investigator agrees to return all study devices to the sponsor.

11.0 MONITORING RESPONSIBILITIES

Ra Medical Systems, Inc. will serve as the sponsor of this clinical investigation. It is the responsibility of Ra Medical as the sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met.

The procedural success determination is crossing the lesion that could not be crossed with a standard guide wire, and therefore not subject to bias. The procedural success is determined using fluoroscopic angiography and is not subject to bias, interpretation, or quantification,

because the lesion is either crossed or not crossed. Because of these facts, third party involvement in determining procedural success would have no added value and provide no additional verification. The placebo effect also need not be considered. It is not possible for the patient to affect the blockage during the procedure.

All information and data sent to Ra Medical concerning subjects and their participation in this investigation will be considered confidential. Only authorized Ra Medical personnel, Ra Medical representatives, and regulatory agencies will have access to these confidential files. All data used in the analyses and reporting of this investigation will be coded without identifiable reference to the subject.

11.1 Source Documentation

Source documents are original records, or certified copies of original records, that contain clinical findings, observations or other activities in a clinical trial (e.g., hospital records, clinical and office charts, laboratory notes, subject diaries, or evaluation checklists) necessary for the reconstruction and evaluation of the clinical trial.

Source document worksheets may be used to supplement other medical records, but should not be reviewed as the only source. Worksheets must be treated as medical records, that is, signed and dated by the person performing the evaluation.

Photocopies of source documents are acceptable for review only if the original document can be provided upon request.

The monitor will check the case report form (CRF) data points against the source document data points during a monitoring visit.

11.2 Monitors

Field and monitoring personnel contact information is as follows:

Ra Medical Systems, Inc.
1930 Kellogg Avenue
Carlsbad, CA 92008
Tel: +1-877-635-1800
Fax: +1-760-804-1657

11.3 Monitoring Visits

Prior to beginning the study, Ra Medical personnel will contact the investigator to discuss the investigational plan and to review the data requirements in detail.

The monitor will visit the investigator during the study to monitor progress, verify that all study requirements are completed and answer any questions that may arise. During these visits, the monitor may review the subject records to verify that all records and files are current and to assure compliance with all requirements of this investigational plan.

APPENDIX A

Informed Consent

Protocol Clinical Protocol 05-203-84-10000102

RMS-102

A prospective, multi center pilot study evaluating plaque photoablation using the RA-308 Excimer Laser in subjects with symptomatic infrainguinal lower extremity vascular disease

Patient Informed Consent Form

1. Participant's Name _____

2. Purpose of Project

You have been invited to participate in a research study sponsored by Ra Medical Systems and Dr. _____. The purpose of this study is to evaluate a device for patients with lower leg vascular disease. The device being evaluated in this study is called Ra Medical Systems **RA-308 Excimer Laser System and DABRA Catheter.** This device will be used to remove plaque build-up in your lower leg blood vessels.

You are being asked to volunteer for this study since you are planning to have treatment for vascular disease. Since plaque removal is a standard approach for lower leg vascular disease and excimer lasers have been commonly used for this procedure, this device is being evaluated in patients such as you to evaluate how well it performs. Alternative procedures are amputation, bypass surgery, ultrasonic crosser, mechanical crosser, drilling crosser, or rotoblator crosser.

3. Description of Research

The research study to evaluate the RA-308 Excimer Laser and DABRA Catheter is designed to evaluate the performance of this device in 50 patients such as you who are scheduled for lower leg vascular treatment. In this study, patients who participate will undergo the plaque (material causing the blockage) removal from the blood vessels as regularly performed by the surgeon. However, the removal will use the excimer laser. After taking an x-ray of the affected vessels the surgeon will insert a catheter or small tube into the groin and then into the leg vessels. The surgeon will advance the tubing into the affected area that has the blockage and using the laser he will attempt to clear the blockage. The surgeon will then remove the tubing and take another x-ray. Your participation is complete at the end of the procedure.

4. Risks

The potential risks associated with participating in this study are those risks which are part of vascular surgery treatment and of every surgical procedure. These risks can include infection, bleeding, pain, tearing of the vessels, creating a blood clot and other post-surgical complications. You may have bruising in your upper leg where the catheter is inserted into your femoral artery, and this may be painful. There is also a slight chance of infection where the catheter is inserted. You may experience an allergic reaction to the dye, although this is uncommon and is usually very mild.

Additionally, the fluoroscopy results in a limited level of radiation exposure similar to that of a series of X-rays. Your physician will describe these complications to you during your discussion of your planned vascular surgery.

5. Benefits

The potential benefit that may be derived from my participation in this study is that your vascular blockage will be cleared and blood flow to your legs may be improved.

6. Confidentiality & Voluntary Participation

You are in my rights to request any clarification and obtain any information regarding this research at any time during the course of this study. Furthermore, you are free to withdraw from the study at any time that you so desire and if you make that decision it will not affect any future treatment that you may require at the facility.

Your medical records and study records may be reviewed by the sponsor of the study, Ra Medical Systems, or by regulatory and other governmental agencies. However, the information obtained in this study will be held confidential and that at no time will your privacy be violated.

7. Compensation

The facility will be available to provide you with medical or surgical treatment at no cost, in the event of damages directly resulting from any of the procedures of the research project. In the event of permanent damage, you are entitled to be compensated in accordance with damages suffered.

8. Contact Person

If at any time during the study you have questions regarding the research or your participation, you can call your physician, Dr. _____, Principal Investigator, at _____ (phone number). You can also contact _____, who represents study participants to the Institutional Review Board, a committee whose purpose is to safeguard your rights and welfare during the study.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT:

I have been given an opportunity to ask any questions regarding this research, and my participation, and my physician has answered all my questions. By signing this consent form, I understand that I have not waived any of my legal rights. I will receive a copy of this consent form, which will show all signatures and dates.

I hereby willingly give my consent to participate in the above-described medical research.

PATIENT SIGNATURE	PERSON EXPLAINING THE STUDY
PATIENT NAME (PRINT)	PRINT NAME
ADDRESS:	ADDRESS:
DATE	DATE

I have discussed this research with the patient (and/or his or her legally authorized representative) using language which is understandable and appropriate. I believe that I have fully informed this patient of the nature of this study, and its benefits and risks, and I believe the patient understood this explanation.

WITNESS	RESEARCHER
NAME:	NAME:
DATE	DATE

APPENDIX B

Case Report Forms

APPENDIX C

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need

special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The

specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.