TITLE PAGE

Protocol Number: C-16-EN14

Protocol Title: A Single-Center Pilot Study of a Novel Multi-Wavelength Laser for Tattoo Removal

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[redacted]

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Version, Date: Version 1.0 Dated August 08, 2016

Statement of Compliance

The study will be conducted in accordance with the design and specific provisions of this IRB/EC-approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

NOTE: The confidential information in the following document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and applicable Independent Review Board/Ethics Committee. By accepting this document, you agree that the information contained herein will not be disclosed to others, without written authorization from Cutera, Inc. except to the extent necessary to obtain informed consent from those persons to whom the device will be administered.

Protocol Signature Page – Principal Investigator

PROTOCOL C-16-EN14

Study Title: ***A Single-Center Pilot Study of a Novel Multi-Wavelength Laser for Tattoo Removal***

Protocol Version 1.0, Dated August 08, 2016

I have received and read the protocol dated **August 08, 2016** and agree to adhere to the requirements. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or informed consent form must first be approved by Cutera, Inc. and the Independent Review Board (IRB)/Ethics Committee (EC), except those changes necessary to eliminate apparent immediate hazards to subjects. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding their role in the study. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements, and with the reviewing IRB/EC requirements. I agree to commence this study only after documented IRB/EC approval is obtained.

Principal Investigator

_____	_____
Signature	Date

_____
Printed Name

Table of Contents

Protocol Summary

Title	A Single-Center Pilot Study of a Novel Multi-Wavelength Laser for Tattoo Removal
Objective	To evaluate the safety and efficacy of an investigational version of the Cutera enlighten™ laser that offers multiple wavelengths for tattoo removal.
Study Design	A single-center prospective, open-label, uncontrolled pilot study.
Enrollment	A maximum of 10 subjects
Primary Endpoint	• Degree of tattoo clearing at 6 weeks post-final treatment as assessed by the Investigator (Physician's Global Assessment of Improvement).
[redacted]	[redacted]
Subject Population	Female or male subjects, age 18 to 65 years, Fitzpatrick skin types I-VI
Planned Schedule	First subject enrolled: September 2016 Last subject last visit: December 2018

1 PURPOSE

The purpose of this investigation is to evaluate the safety and efficacy of an investigational version of the Cutera enlighten™ laser for tattoo removal. Currently, the enlighten laser offers two wavelengths: 532nm[redacted] and 1064nm Nd:YAG. The version of the laser under investigation allows the user to treat at a wavelength of 670nm.

2 BACKGROUND INFORMATION

2.1 Tattoo Removal

Millions of people thought to have tattoos in the western world. Recently, the numbers have been increasing due to high demand for tattoos especially among teens and younger adults. As a result of this high demand, tattoo removal has become a common cosmetic procedure [1].

Tattoos are exogenous (foreign) pigment particles implanted into the dermis. They vary in size, composition and dermal depth. There are five types of tattoos: professional, amateur, cosmetic, traumatic, and medical [2-5]. Tattoos are created using a variety of pigments and/or combinations comprised of inorganic and/or organic compounds, such as chromium, mercury, iron, copper, carbon and polycyclic compounds[6].

The non-selective tattoo removal mainly consists of the mechanical, such as salabrasion, and excision; chemical, such as trichloroacetic acid; and thermal methods such as electrocautery, cryotherapy, and continuous wave laser therapy[4]. These invasive methods vary in effectiveness and always result in scarring and dyspigmentation.

Recent technology involves the use of pulsed lasers, namely q-switched or quality-switched (QS) lasers which produce nanosecond laser pulses by suddenly releasing all of the excited-state energy from the laser medium. This concept is based on the principle of selective photothermolysis which imply (1) the use of the wavelength matching the absorption spectra of the tattoo pigment and (2) the delivery of the heat to target pigment particle within pulse duration shorter than its thermal relaxation time. This allows selective destruction of target chromophore in the skin without damage to the surrounding tissue.

Currently, there are four different types of nanosecond QS lasers widely used for tattoo removal: 532 nm (Nd:YAG), 1064 nm (Nd:YAG), 755 nm (Alexandrite) and 694 nm (Ruby) wavelengths. 1064 nm (Nd:YAG) and 755 nm (Alexandrite) wavelengths are used for black and blue tattoos, 694 nm (Ruby) wavelength for blue, black and green tattoos; 532 nm (Nd:YAG) wavelength for red tattoos. Besides tattoo color, tattoo type, tattoo age, tattoo location, patient age, and patient skin type are also part of considerations for the selection of optimal laser(s) and parameters in each patient. Depending on the composition of colors used in tattoos, more than one laser may be used.

To date, nanosecond QS lasers have been successfully used and found to be safe and effective for tattoo removal [7-18]. Transient or permanent hypopigmentation may be observed with shorter wavelengths, such as 532 nm (Nd:YAG) 755 nm (Alexandrite) and 694 nm (Ruby) as they compete with the melanin in the epidermis. Thus, shorter wavelengths are not recommended for treatments in darker skin types. Longer wavelength 1064 nm (Nd:YAG), on the other hand, is considered to be safe in darker skin types

because of decreased melanin absorption. Still, lower fluences are recommended for treatment of darker skin patients with Nd:YAG lasers. Scarring is rarely observed following treatments with QS lasers as water is no longer the target chromophore.

There are some challenges associated with tattoo removal. If mixtures of pigments and/or multicolors are used, a complete clearing of the tattoo may not be achieved with lasers[19]. Different colors are usually mixed to achieve various levels of brightness and lightness. Another contributing factor to unsuccessful outcome is that most tattoo pigments are not regulated and may include various elements and chemical compounds. When the exact compound of the tattoo pigment is not known, paradoxical darkening of the pigment may happen following tattoo removal, which may be difficult to remove [20-23]. Additionally, white, orange, yellow and brown tattoo inks are particularly difficult to treat[24].

Although the mechanism of action is not clearly understood, the effects of the lasers on the pigment are thought to be: 1) photothermal/photochemical and 2) photoacoustic/photomechanical[25, 26]. Conversion of absorbed energy into heat (photothermal effect) breaks the chemical bonds inside the pigment and causes pigment modification. At the same time, the ultrashort heating of the particle shell may cause heating of the surrounding tissue via rapid thermal expansion resulting in shock waves. These shock waves may help destroy the surrounding cellular structures and tattooed compounds mechanically (photoacoustic/photomechanical). The resultant fragmented particles are then removed by three mechanisms: 1) transepidermal elimination, 2) removal via lymphatics, and 3) rephagocytosis by other cells (inflammatory or resident cells) in the dermis.

Histological examinations show that the tattoo pigments are exclusively found intracytoplasmatically in lysosomes which is a result of active phagocytosis in dermal cells, such as macrophages and fibroblasts[27, 28]. In electron microscopy of black tattoos immediately after treatment with 1064 nm Nd:YAG, vacuoles were observed in the dermis [29]. Vacuoles were lined by remnants of pigment-containing cells, flattened cell nuclei and disrupted lysosomes. Cells without pigment located close to the vacuoles were not affected. One week after treatment, a moderate chronic inflammatory infiltrate was observed in the dermis and all tattoo particles were phagocytosed and intracellular within fibroblasts and macrophages. At one month post-treatment, all residual pigment particles were within lysosomes with mild residual inflammatory infiltrate around dermal vessels.

Although nanosecond QS lasers are safe and effective in the treatment of tattoos, treatment sessions are often painful and as many as 6 to 10 treatments are necessary to achieve acceptable clearance. It could be argued that this is a result of most tattoo particles ranging in size from 40 to 300 nm in vivo and their thermal relaxation times being mostly in the picosecond range[30]. For example, the most common pigment particle, carbon black in india ink, which is shown to be about 40 nm in diameter, will approximately have a thermal relaxation time of 1 nanosecond[31]. In that case, a thermally confined disruption of the particle can only be achieved via picosecond pulses. This suggests that energy delivery in the picosecond range be more effective and require lower fluences than the nanosecond range. Moreover, the resultant ultra-short pulses with higher peak temperatures should decrease adverse effects, such as dyspigmentation as the heat transfer to the surrounding tissue is significantly minimized.

Up to date, various studies of picosecond QS lasers, both in vitro and in vivo, have been conducted to test the hypotheses on the potential benefits of picosecond QS lasers[30-34]. In a split-tattoo study, Ross et all reported better clearing in 75% (12/16) of tattoos with on picosecond side than the clearing

on the nanosecond side following 4 treatments with QS Nd:YAG[31]. Electron microscopic findings were similar for both picosecond and nanosecond exposures and no adverse events were noted. In an animal study comparing a picosecond titanium:sapphire (795 nm, 500 picoseconds) laser with QS alexandrite (755 nm, 50 nanoseconds), greater clearing was observed on the areas treated with picosecond laser and there were no adverse events[32]. Izikson et al compared picosecond (758 nm, 500 picoseconds) and nanosecond QS alexandrite (755 nm, 30-50 nanoseconds) lasers in an animal model and reported that picosecond achieved greater tattoo clearance after single treatment[30]. Additionally, two other clinical studies using the picosecond QS alexandrite (755 nm with 500 – 900 and 750 – 900 picoseconds) laser indicated that greater clearance was achieved with lesser number of treatments[33, 34].

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3 STUDY OBJECTIVES

The objective of this study is to evaluate safety and efficacy of treatment with investigational wavelengths of the Cutera enlighten laser for tattoo removal.

4 STUDY DESIGN

This is a single-center prospective, open-label, uncontrolled pilot study in up to 10 male or female subjects, age 18 to 65 years, who desire laser removal of a tattoo containing single or multi-color ink. Subjects will receive [redacted] laser treatments, [redacted], and will be followed at 6 weeks [redacted]). At the Investigator's discretion, an optional follow-up visit may be conducted at 12 weeks [redacted]) post-final treatment.

[redacted]

[redacted]

4.1 Study Endpoints

4.1.1 Efficacy endpoints

4.1.1.1 Primary Efficacy Endpoint

- Degree of tattoo clearing at 6 weeks post-final treatment as assessed by the Investigator (Physician's Global Assessment of Improvement).

[redacted]

[redacted]

4.1.3 Safety Endpoint

- Incidence and severity of adverse device effects during the study period, including subject pain level during laser treatment.

4.2 Study Duration

Subjects enrolled in this trial will be asked to participate for up to 15 months, [redacted]. [redacted] 1 screening visit, [redacted] laser treatment visits [redacted], and 1 required follow-up visit at 6 weeks [redacted]) post-final treatment. At the Investigator's discretion, an optional follow-up visit may be conducted at 12 weeks [redacted] post-final treatment.

The screening and first laser treatment may be combined into one visit provided that the informed consent process has been completed (see Section 12.2) and the subject has signed the IRB/EC-approved Informed Consent Form **prior to** the commencement of any study-related procedures and device treatments.

4.3 Blinding and Randomization of Photographs

4.3.1 Blinding

A panel of independent reviewers may assess subject photographs taken at baseline, 6 weeks and 12 weeks post-final treatment. The reviewers will be blinded to the type of treatment device, the parameters used, the subject data, the temporal order of photographs (before and after), and follow-up time point.

4.3.2 Randomization of Photographs

The presentation order of subject photographs will be randomized. First, a unique identification number will be assigned to each pair of subject photographs (1 baseline and 1 post-treatment), then the order of photograph presentation will be assigned by randomizing the identification numbers. In addition, the location of the baseline photograph on the assessment page will be randomized such that each photograph pair will be arranged with the baseline photograph located either on the right side or left side of the page. Minitab statistical package, version 16.2.2.0 (Minitab Inc., State College, Pennsylvania) will be used to do randomizations. The photograph pairs from each subject will be then organized according to randomization and will be presented to the blinded reviewers for assessment.

4.4 Study Effectiveness Assessments

4.4.1 Investigator Assessments

4.4.1.1 Investigator's Global Assessment of Improvement

At 6 weeks, [redacted], the Investigator will be asked to rate the degree of tattoo clearing observed in the subject's treated area using the Physician's Global Assessment of Improvement Scale:

4 = Very Significant or Complete Clearing ([redacted]
3 = Significant Clearing [redacted]
2 = Moderate Clearing [redacted]
1 = Mild Clearing ([redacted]
0 = No Clearing [redacted]

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4.5 Study Safety Assessments

4.5.1 Incidence and Severity of Adverse Events:

Following the first laser treatment, adverse device effects (ADEs) will be assessed post-treatment and at each subsequent subject visit using the following scale:

1= mild: requires minimal or no treatment and does not interfere with the Subject's daily activities.
2= moderate: may cause some interference with functioning.
3= severe: interrupts Subject's usual daily activity and may require treatment.

4.5.2 Treatment-related Discomfort

Subjects will be asked to rate the average amount of discomfort experienced during laser treatment using the Pain Rating Scale found in Appendix 2.

4.6 Photographs

Standardized digital photographs will be taken of each subject's treatment area at baseline, prior to all laser treatments, immediately following laser treatments and at each follow-up visit. Any jewelry will be removed from the area being photographed. Photographs will be taken in the same windowless room equipped with adequate lighting. The room lighting, camera positioning and subject positioning should be consistent for all study visit photographs. Digital camera settings (including any flash settings) should remain the same for all photographs and the highest resolution settings should be utilized.

4.7 Study Discontinuation

The sponsor (Cutera, Inc.) has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following: incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects; subject enrollment is unsatisfactory; number of protocol deviations is unacceptable; data recording is inaccurate or incomplete; or questionable study site compliance with ICH-E6, Good Clinical Practice.

4.8 Investigator Selection

The Investigator will be invited to participate in the study based on his or her medical specialty, experience conducting clinical research studies and experience in the use of light-based devices for aesthetic indications. Access to potential study subjects and the Investigator's sincere interest in this study along with expressed willingness to cooperate with the study process and requirements was also considered.

5 STUDY POPULATION

5.1 Study Subject Recruitment and Selection

Up to 10 male or female subjects, ages 18 to 65, with Fitzpatrick Skin Type I-VI who desire laser treatment for tattoo removal will be studied. Subjects will be recruited to participate from the local population. Subjects may also be recruited from the Investigator's existing patient database or from patients who present themselves to the study site requesting treatment. Only subjects who meet study eligibility criteria and who provide written informed consent will be enrolled into the study.

Each subject will be evaluated by the Investigator to assess his/her suitability for entry into the study according to the following inclusion and exclusion criteria.

5.1.1 Inclusion Criteria

To be included in the study, subjects must meet all of the following Inclusion Criteria:

1.	Female or Male, 18 to 65 years of age (inclusive).
2.	Fitzpatrick Skin Type I – VI (Appendix 3).
3.	Target tattoo contains single or multi-color ink.
4.	Subject must be able to read, understand and sign the Informed Consent Form.
5.	Must be willing and able to adhere to the treatment and follow-up schedule and post-treatment care instructions.
6.	Wiling to cover tattoos with a bandage or clothing; and/or have very limited sun exposure and use an approved sunscreen of SPF 50 or higher on the treated area starting 2 to 4 weeks before the treatment and/or every day for the duration of the study,

	including the follow-up period.
7.	Willing to have digital photographs taken of the treatment area and agree to use of photographs for presentation, educational or marketing purposes.
8.	Agree to not undergo any other procedure(s) for tattoo removal during the study (as applicable).
9.	Post-menopausal or surgically sterilized, or using a medically acceptable form of birth control at least 3 months prior to enrollment and during the entire course of the study, and no plans to become pregnant for the duration of the study.

5.1.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following Exclusion Criteria:

1.	Participation in a clinical trial of a drug or another device in the target area during the study.
2.	Target tattoo contains only black ink.
3.	History of allergic reaction to pigments following tattooing.
4.	History of allergy to local anesthetics.
5.	History of allergy to topical antibiotics.
6.	History of malignant tumors in the target area.
7.	Skin abnormalities in the target area, e.g., cuts, scrapes, wounds, scars, large moles.
8.	Pregnant and/or breastfeeding.
9.	Having an infection, dermatitis or a rash in the treatment area.
10.	Significant concurrent illness, such as diabetes mellitus or cardiovascular disease, e.g., uncontrolled hypertension.
11.	Suffering from coagulation disorders or taking prescription anticoagulation medications.
12.	History of keloid scarring, hypertrophic scarring or of abnormal wound healing.
13.	History of immunosuppression/immune deficiency disorders or currently using immunosuppressive medications.
14.	History of vitiligo, eczema, or psoriasis.
15.	History of connective tissue disease, such as systemic lupus erythematosus or scleroderma.
16.	History of seizure disorders due to light.
17.	Any use of medication that is known to increase sensitivity to light according to Investigator's discretion.
18.	History of disease stimulated by heat, such as recurrent herpes simplex and/or herpes zoster (shingles) in the treatment area, unless treatment is conducted following a prophylactic regimen
19.	History of radiation to the treatment area or undergoing systemic chemotherapy for the treatment of cancer.
20.	History of pigmentary disorders, particularly tendency for hyper- or hypo-pigmentation.
21.	Systemic use of corticosteroid or isotretinoin within 6 months of study participation.
22.	Anytime in life, having have used gold therapy (gold salts) for disorders such as rheumatologic disease or lupus.
23.	Excessively tanned in areas to be treated or unable/unlikely to refrain from tanning during the study.

24.	Current smoker or history of smoking within 6 months of study participation.
25.	As per the Investigator's discretion, any physical or mental condition which might make it unsafe for the subject to participate in this study.

5.2 Subject Numbering

If a subject meets the study eligibility criteria and is willing to participate, the subject will be assigned a study subject identification number. This number is comprised of a sequential subject number and the subject initials (first and last names).

5.3 Subject Discontinuation Criteria

If possible, every subject should remain in the study until completion of the required follow-up period. However, participation in this study is completely voluntary and a subject can choose to withdraw from the study at any time. Decision to withdraw will not affect or prejudice the subject's continued medical care in any way. In those instances, the investigator will attempt to obtain a final clinical assessment and an adverse device effect evaluation for the subject prior to this withdrawal. A subject will be considered lost to follow-up only after three unsuccessful, documented attempts to contact the subject have been made.

In addition, a subject can be discontinued for any of the following reasons: the Principal Investigator decides that continuing in the study would not be in the subject's best interest, a subject is noncompliant with the protocol, a subject has a serious reaction to the treatment, a subject develops any of the exclusion criteria during the study period or the study is stopped by the study sponsor.

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7 ADVERSE DEVICE EFFECTS

[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted].

[redacted]

7.2 Recording ADEs and SADEs

All ADEs/SADEs will be: (1) evaluated and must be recorded in the subject's medical chart and in the study case report forms (CRFs); (2) monitored and tracked from the time of the first treatment with the Cutera enlighten laser system.

At each contact with the subject, the investigator must seek information on ADEs/SADEs by specific questioning and, as appropriate, by examination. ADEs/SADEs may be observed by the investigator and/or clinical research staff, elicited from the subject and/or family member or volunteered by the subject. All observed and volunteered adverse signs and symptoms, anticipated or unanticipated, regardless of severity or frequency, will be recorded in the case histories (medical chart and CRFs). Included in the description should be the nature of the sign or symptom, the date of onset, date of resolution (duration), the severity, anticipated or unanticipated, the relationship to study treatment or other therapy, the action taken (if any), and the outcome.

All SADEs, anticipated or unanticipated, must be reported to Cutera immediately but not later than 5 working days. The SADE must be recorded in: (1) the AE CRF and (2) a written report must be submitted to Cutera within five (5) working days after the investigator first learns of the event and is to include a full description of the event and sequelae, in the format detailed by the Cutera Serious Adverse Device Effect Form.

7.3 Follow-up of Subjects after ADEs and SADEs:

All reported ADEs/SADEs should be followed until resolution or until the subject's participation in the study ends. Resolutions of ADEs/SADEs are to be documented on the appropriate CRFs. All ADEs that result in permanent discontinuation from this clinical trial, whether serious or not, should also be reported on the subject Non-Completion of Study Form.

8 POTENTIAL RISKS / BENEFITS

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8.2 Potential Benefits

The subjects may or may not benefit from the treatment with the study device. Potential benefit of laser treatment for tattoos is lightening or complete removal of tattoo. There is no guarantee of success.

9 RISK MANAGEMENT

The investigator participating in this study was chosen based on extensive and safe experience with the use of lasers in dermatology applications. This is the most critical element in managing subject risk. In addition, study investigators will be trained on the use of the Cutera enlighten laser system by a representative of Cutera.

10 DATA ANALYSIS PLAN

10.1 Sample Size

Up to 10 subjects will be enrolled in this safety and efficacy study.

10.2 Demographics and Subject Characteristics at Baseline

Subject demographics, medical history, concomitant medications will be tabulated and summarized descriptively.

10.3 Statistical Analysis Methods

10.3.1 Analysis Sets

The efficacy analysis set will include all subjects who received at least one laser treatment session and complete the follow-up visit. The safety analysis set will include all subjects enrolled in the study who had at least one laser treatment session.

Missing data will not be imputed for efficacy or safety endpoints.

10.3.2 Analysis of Primary Endpoint

Formal statistical analysis is not planned for this study. The primary efficacy endpoint data, degree of tattoo clearing at 6 weeks post-final treatment as assessed by the Investigator (Physician's Global Assessment), will be summarized descriptively.

[redacted]

10.3.4 Safety Analyses

Safety variables will be analyzed descriptively.

The safety variables for this study are:

1. Subject discomfort (pain) during and after treatment (to be descriptively displayed).
2. Incidence and severity of adverse effects during study duration (to be displayed descriptively as counts and frequency distributions).

Device-related and procedure-related adverse effects (AEs) and subjects who prematurely terminate from the study due to an adverse device effect, including the treatment-related pain ratings, as reported on case report forms will be tabulated and analyzed. For a given AE term, counting will be done by subject, not by event, i.e. for a subject reporting the same AE more than once, the event will be counted only once, at the most severe and most-related occurrence. The number and percentage of subjects experiencing each AE Term will be descriptively summarized. Statistical hypothesis testing will not be performed for safety data.

[redacted]

12 STUDY MANAGEMENT AND ADMINISTRATIVE PROCEDURES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.3 Protocol Compliance

The principal investigator must comply with all terms of the protocol.

12.3.1 Protocol Amendments

Neither the principal investigator nor the sponsor will modify or alter this protocol without first obtaining the concurrence of the other party (with the exception of amendments which involves mitigating a medical emergency or immediate health risk to the subject). The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the sponsor and the principal investigator. IRB/EC approval must be obtained before implementation of an amendment.

12.3.2 Protocol Deviations

All protocol deviations must be clearly described on the case report form (i.e., Cutera Protocol Deviation Form). Deviations from the protocol may include but are not limited to subject's failure to attend scheduled visit during a visit window, use of out of range treatment parameters and incomplete or incorrect study procedures. Any medical emergency or immediate health risk to the subject which results in a protocol deviation and must be reported to the sponsor within 5 working days

Significant protocol deviations must be reported to the IRB/EC according to their policies.

[redacted]

[redacted]

12.5 Disclosure of Financial Interest

Each investigator [principal and sub-investigator(s)] is required to disclose sufficient accurate financial information to the sponsor, to allow sponsor to submit complete and accurate certification or disclosure statements.

[redacted]

[redacted]

13 SUBJECT CONFIDENTIALITY

[redacted]

14 PUBLICATION POLICY

The investigator shall have the right to publish the results of the study. Unless mutually agreed upon in writing, prior to submission for publication of any manuscript, poster, presentation, abstract or other written or oral material describing the results of the study, the investigator shall allow sponsor to review manuscript, poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any patentable information is disclosed. At the sponsor's request, the investigator shall withhold any publication or presentation to permit sponsor to seek patent protection and to remove any confidential information from all publications.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. It is the responsibility of the sponsor to register this trial in ClinicalTrials.gov. Any clinical trial starting enrollment after September 27, 2007 must be registered either on or before the onset of patient enrollment.

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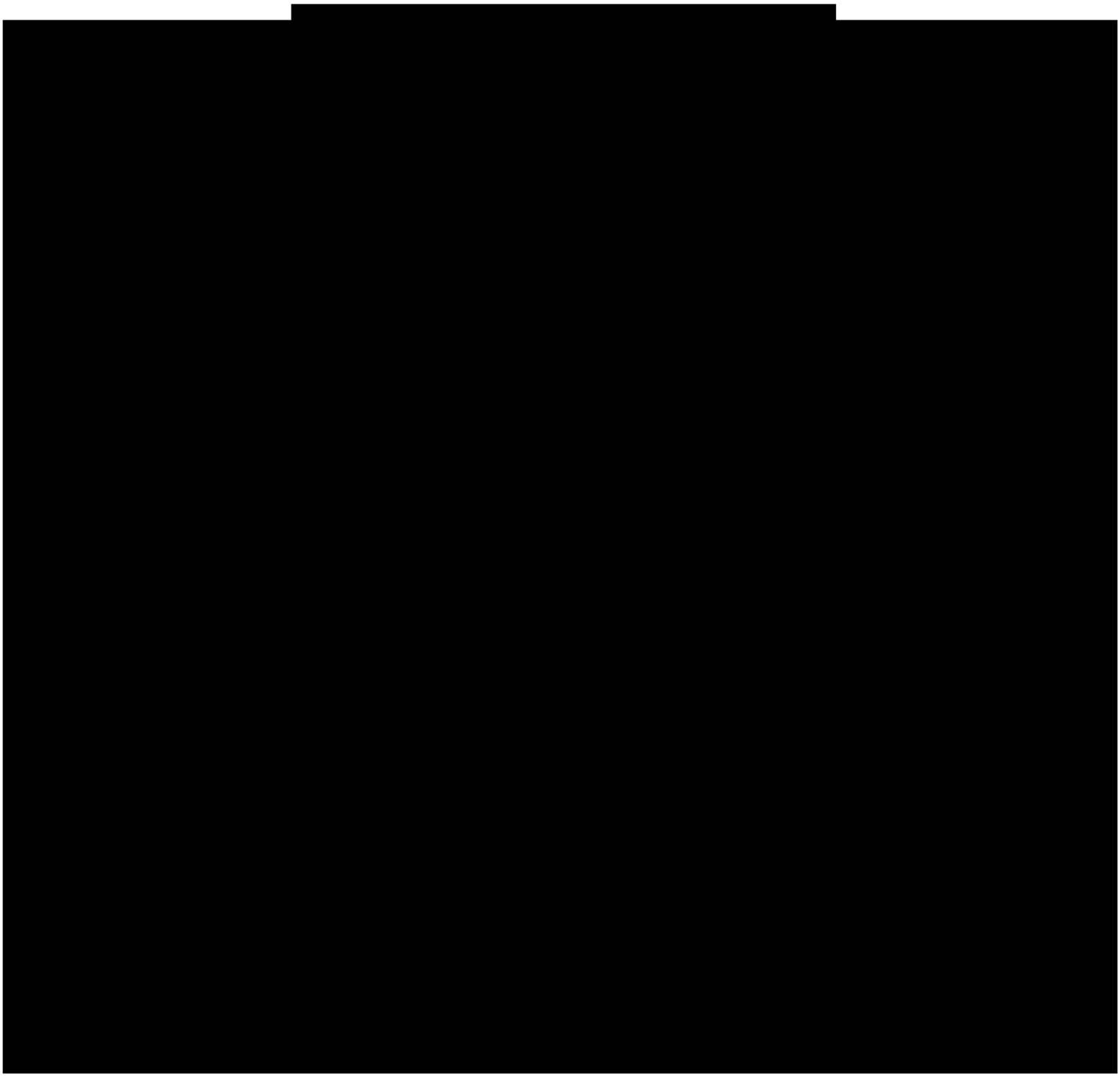

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