TITLE PAGE

Protocol Number: C-17-TS14

Protocol Title: Open-label, Prospective, Multicenter Pivotal Study of the Cutera truSculpt™ Radiofrequency Device for Wrinkle Reduction

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Principal Investigators:
[redacted]

[redacted]

Version, Date: Version 2.0, August 10th, 2017

Statement of Compliance
The study will be conducted in accordance with the design and specific provisions of this IRB 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 Institutional Review Board. 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-17-TS14

Study Title: Open-label, Prospective, Multicenter Pivotal Study of the Cutera truSculpt™ Radiofrequency Device for Wrinkle Reduction

Protocol Version 2.0, Dated August 10th, 2017

I have received and read the protocol dated **August 10th, 2017** 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 Institutional Review Board, 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 Institutional Review Board (IRB) requirements. I agree to commence this study only after documented IRB approval is obtained.

Principal Investigator

_____ _____

Signature Date

_____

Printed Name

Table of Contents

Protocol Summary

Title	Open-label, Prospective, Multicenter Pivotal Study of the Cutera truSculpt™ Radiofrequency Device for Wrinkle Reduction
Objective	To evaluate the safety and efficacy of the Cutera truSculpt radiofrequency device for Wrinkle Reduction
Study Design	A prospective multi-center, uncontrolled study
Enrollment	Approximately 40 subjects
[redacted]	[redacted]
[redacted] **Endpoints**	• **Principal Investigator's assessment of improvement at 12 weeks post-final treatment (Physician's Global Assessment)** • [redacted]
Safety Endpoint	Incidence and severity of adverse events during the study period, including subject pain level at follow ups
Subject Population	Female and male subjects, **age 25 to 65 years**, Fitzpatrick Skin Type Classification I-VI
Planned Schedule	First subject enrolled: August 2017 Last subject last visit: April 2018

1 PURPOSE

The purpose of this investigation is to evaluate the safety and efficacy of the truSculpt radiofrequency (RF) device for wrinkle reduction and improvement of skin quality.

2 BACKGROUND INFORMATION

Non-invasive treatment options to improve one's appearance are in high demand by patients wanting to avoid surgical intervention. Due to this demand, patients have a variety of options for non-invasive wrinkle-reduction treatment, from laser and light-based treatments to devices that utilize ultrasound and radiofrequency. By delivering energy into the skin in the form of light, ultrasound or radio waves, thereby causing heat generation in the sub layers, these treatment modalities can be used to improve wrinkles and skin laxity [1-24].

Ultrasound and radiofrequency (RF) devices are increasingly utilized for non-invasive tissue tightening due to the ability of these technologies to penetrate the dermis at greater depths, as compared to light-based devices [25-27]. When collagen is heated sufficiently, intramolecular bonds sensitive to heat are broken and the collagen fibril transforms form a highly-organized structure to a random, gel-like state. Immediate collagen contraction occurs as a result of unwinding of the triple helix structure and the residual tension of the heat-resistant intermolecular bonds [30]. The effect of collagen denaturation from tissue heating is dependent on a number of factors, including maximum temperature reached, exposure time, concentration and orientation of the collagen fibers, and the hydration level of the tissue [30]. Many studies have examined histology of post-treatment skin biopsy samples, which demonstrated increased collagen deposition in the weeks to months following device treatments that cause thermal-induced wound healing. In addition, histology samples have demonstrated collagen fibers aligned in a horizontal orientation parallel to the plane of the epidermis. Some studies have demonstrated dermal and epidermal thickening [31]. Uniform volumetric heating of the epidermal, dermal and sub-dermal layers of the skin results in a primary effect of immediate collagen contraction and a secondary effect of fibroblast proliferation and the production of new collagen and elastic over time as a result of inflammation and the wound healing response. [22, 27-29].

RF, which is the most studied device in the non-ablative category, uses electrical current rather than light energy. Unlike light energy, radio waves can penetrate deeper depending on the frequency of operation. RF can be used with all Fitzpatrick skin types without jeopardizing epidermal integrity [33].

RF devices generate heat in the form of thermal energy as a result of electrical current delivered to the tissue. There is a natural resistance to the movement of electrons within the RF field when electrical current is applied [25]. This resistance will dictate the amount of thermal energy generated within the tissue according to Ohm's Law, which states the amount of energy generated is dependent on the electrical current, the tissue impedance and the time of application. Ohm's Law is expressed as an equation, where *I* is the amount of current (in Amps), *Z* is the tissue impedance (in Ohms) and *t* is the time current is applied (in seconds) [25, 30, 32]:

$$Energy\ (Joules) = I^2 x\ Z\ x\ t$$

RF may be delivered in three different ways: 1) Monopolar when energy is applied as current between a single electrode tip and a grounding plate. 2) Bipolar when energy is applied between two points on the

tip of a probe. 3) Unipolar when energy is delivered as the emission of electromagnetic radiation (EMR) rather than current and no grounding pad is necessary. This could be achieved by capacitive, inductive or resonant electrical coupling with the tissue.

[redacted]

3 STUDY OBJECTIVES

The objectives of this study are to evaluate the efficacy and safety of treatment with the Cutera truSculpt RF device for wrinkle reduction and improvement in skin quality with handpiece sizes 9cm^2, 12cm^2, and 16cm^2.

4 STUDY DESIGN

This is multi-center, pivotal study with approximately 40 subjects, age 25 to 65 years, who desire RF treatment for wrinkle reduction and improvement in skin quality. Subjects will receive [redacted] RF treatments [redacted]) and will be followed at [redacted]) and 12 weeks [redacted]) post-treatment.

4.1 STUDY ENDPOINTS

4.1.1 Efficacy Endpoints

[redacted]

[redacted] ***Efficacy Endpoints***

- Principal Investigator's assessment of improvement at 12 weeks post-final treatment (Physician's Global Assessment)

[redacted]

4.2 Study Duration

Subjects enrolled in this trial will be asked to participate for approximately six to seven months and will complete up to five visits: one screening visit, [redacted] RF treatment visits, [redacted] follow-up visits post final treatment; [redacted] at 12 weeks [redacted].

The screening and first RF treatment may be combined into one visit provided that the informed consent process has been completed (see Section 6) and *the subject has signed the IRB-approved Informed Consent Form prior to the commencement of any study related procedures and device treatments*. If the subject does not receive the first study treatment on the same day as screening, the subject must complete their first treatment within 7 days of their screening visit date.

4.3 Study Assessments

4.3.1 Effectiveness Assessment

[redacted]

[redacted]

4.3.1.2 Physician's Global Assessment of Improvement

Principal Investigators will be asked to rate the degree of improvement of the treated area at 12 weeks post-treatment as compared to the subject's baseline photos using the Physician's Global Assessment of Improvement Scale:

4 = Very Significant Improvement [redacted]
3 = Significant Improvement [redacted]
2 = Moderate Improvement [redacted]
1 = Mild Improvement [redacted]
0 = No Change [redacted]

[redacted]

[redacted]

[redacted]

4.3.1.5 Treatment-related Discomfort

Subjects will be asked after each procedure (2 total treatments) to rate the average amount of discomfort experienced during RF treatment using the Pain Rating Scale found in Appendix 3.

4.3.2 Safety Assessments

4.3.2.1 Incidence and Severity of Adverse Events:

Following the first RF 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.

4.4 Photographs

Standardized digital photographs will be taken of each subject's face and submental region. Photographs will be taken at baseline, prior to all RF treatments, and at each follow-up visit. Photographs will be obtained from at least three angles: 1) with the subject facing forward, 2) 45° to the right, and 3) 45° to the left. 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 should remain the same for all photographs and the highest resolution settings should be utilized.

4.5 Study Discontinuation

The study sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, unsatisfactory subject enrollment or the incidence or severity of adverse events in this study, or other studies with the study device, indicates a potential health hazard to subjects.

4.6 Investigator Selection

Investigators will be invited to participate in the study based on their medical specialty, experience conducting clinical research studies and experience in the use of energy based devices for aesthetic indications. The site's access to potential study subjects and ability to cooperate with study requirements will also be considered.

5 STUDY POPULATION

5.1 Study Subject Recruitment and Selection

Up to 40 male or female subjects, ages 25 to 65, with Fitzpatrick Skin Type I-VI who desire RF treatment for wrinkle reduction. Subjects will be recruited to participate from those patients who present themselves to the site requesting treatment, or from those patients who respond to advertisement. Only subjects who meet all Inclusion and Exclusion Criteria and 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.	Must be able to understand and provide written informed consent and release of health information
2.	Male or Female, 25 to 65 years of age (inclusive)
3.	Fitzpatrick Skin Type I – VI (Appendix 4)
4.	Has visible wrinkles or skin laxity in the treatment area
5.	On the Fitzpatrick Classification Wrinkle Classification System subject has a pre-treatment score of 4-9 (inclusive) (Appendix 5)
6.	No use of tobacco products for at least 6 months and willing to refrain from use for the duration of the study
7.	Subject must agree to not undergo any other cosmetic procedure(s) area, or start topical retinol products in the treatment area during the study period
8.	Subject must be willing to adhere to the follow-up schedule and study instructions
9.	Subject must be willing to adhere to the same diet and/or exercise routine throughout the study, and agree to maintain the same weight throughout the study, within 10% of baseline weight measurement
10.	Willing to have digital photographs taken of the treatment area and agree to use of photographs for presentations, educational, and/or marketing purposes
11.	For female subjects: not pregnant or lactating and is either post-menopausal, 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

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 within 3 months of study participation, or during the study.
2.	Any type of prior cosmetic treatment to the target area within 12 months of study participation e.g., radiofrequency, cryolipolysis, deoxycholate injection, or light-based treatments
3.	Prior injection of botulinum toxin, collagen, hyaluronic acid filler, or other dermal filler, and medium-depth to deep chemical peels, to the treatment area within 6 months of study participation
4.	History of systemic steroid use within 3 months; history of topical steroid use in the target area within 2 months
5.	History of systemic retinoid (isotretinoin) and therapeutic dose of Vitamin A within 6 months of study participation
6.	Has a pacemaker, internal defibrillator, implantable cardioverter-defibrillator, nerve stimulator implant, cochlear implant or any other electronically, magnetically or mechanically activated implant

7.	Has metal implant(s) within the body that are local to the treatment area, such as surgical clips, plates and screws (metal tooth fillings or crowns will not exclude subject participation), or has , artificial heart valves or artificial joints
8.	Clinically significant concurrent illness, such as diabetes mellitus, cardiovascular disease, peripheral vascular disease or pertinent neurological disorders that in the opinion of the Investigator will confound participation in the study
9.	Diagnosed or documented immune system disorders
10.	History of any disease or condition that could impair wound healing
11.	History of diseases stimulated by heat, such as recurrent herpes zoster in the treatment area, unless treatment is conducted following a prophylactic regimen
12.	History of keloid formation, hypertrophic scarring or abnormal/delayed wound healing
13.	Infection, dermatitis, rash or other skin abnormality in the target area
14.	Currently undergoing systemic chemotherapy or radiation treatment for cancer, or history of treatment in the target area within 3 months of study participation
15.	Anticipated or planned need for surgery or hospitalization during the duration of the study
16.	Pregnant, nursing, or planning a pregnancy during the trial; or is a woman of child bearing potential but is not willing to use an acceptable method of contraception as determined by the Investigator
17.	As per the Investigator's discretion, any physical or psychological condition which might make it unsafe for the subject to participate in this study

5.2 Subject Numbering

Each site will be assigned an ID number by the sponsor, and each consented (enrolled) subject will be assigned a subject ID number, comprised of a sequential number assigned for each subject, and the subject's initials. The subject's initials will be comprised of the first letter of the first and last name (example: Site ID/Subject ID/Subject's Initials; 01-01MH).

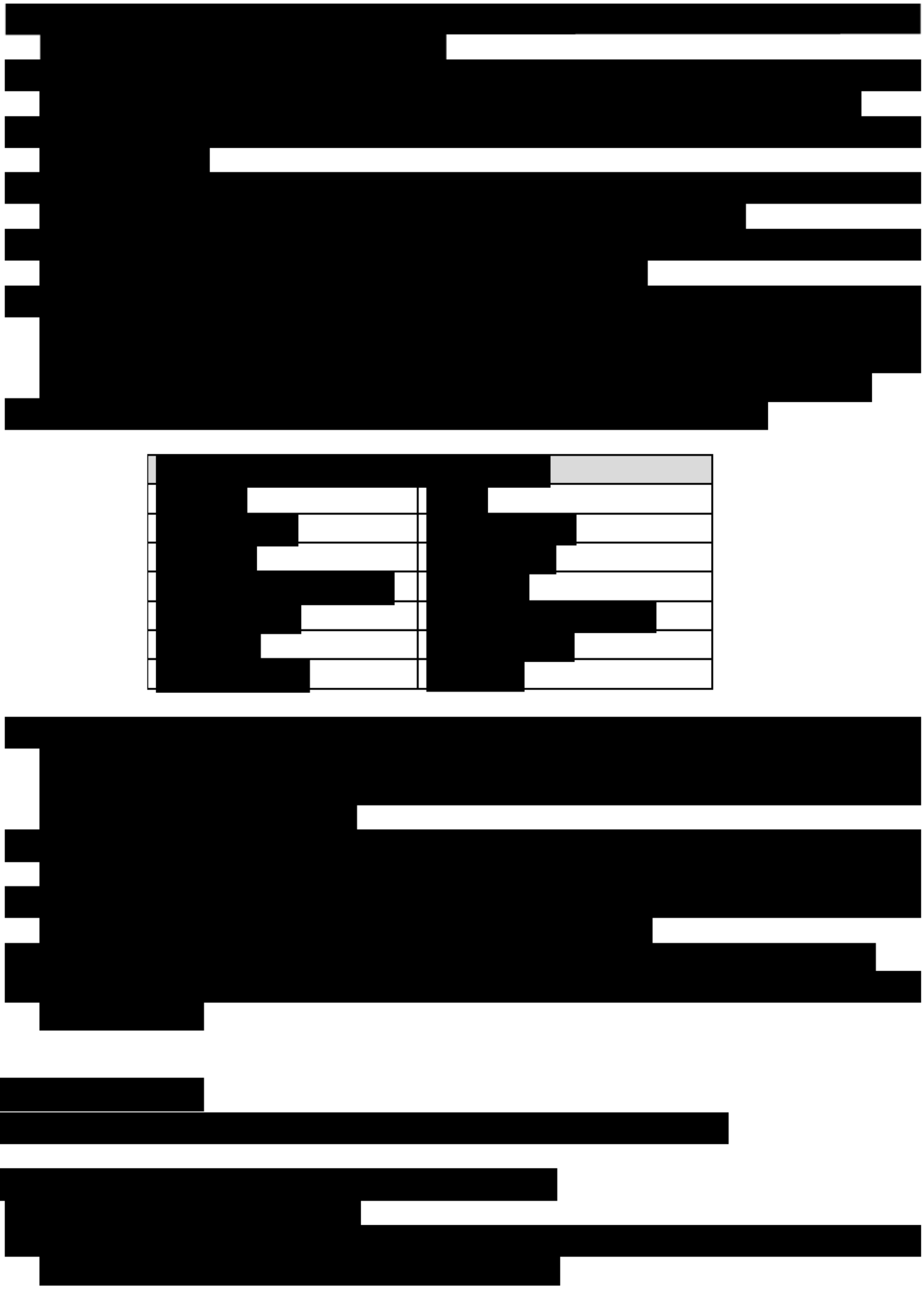
5.3 Subject Discontinuation Criteria

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. 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, or the study is stopped. In addition, subjects may be discontinued from the study if s/he develops any of the exclusion criteria during the study period. A subject will be considered lost to follow-up only after three unsuccessful, documented attempts to contact the subject have been made. Withdrawn subjects will not be replaced.

6 [redacted]

[redacted]

[redacted]



[redacted]

7 ADVERSE EVENTS

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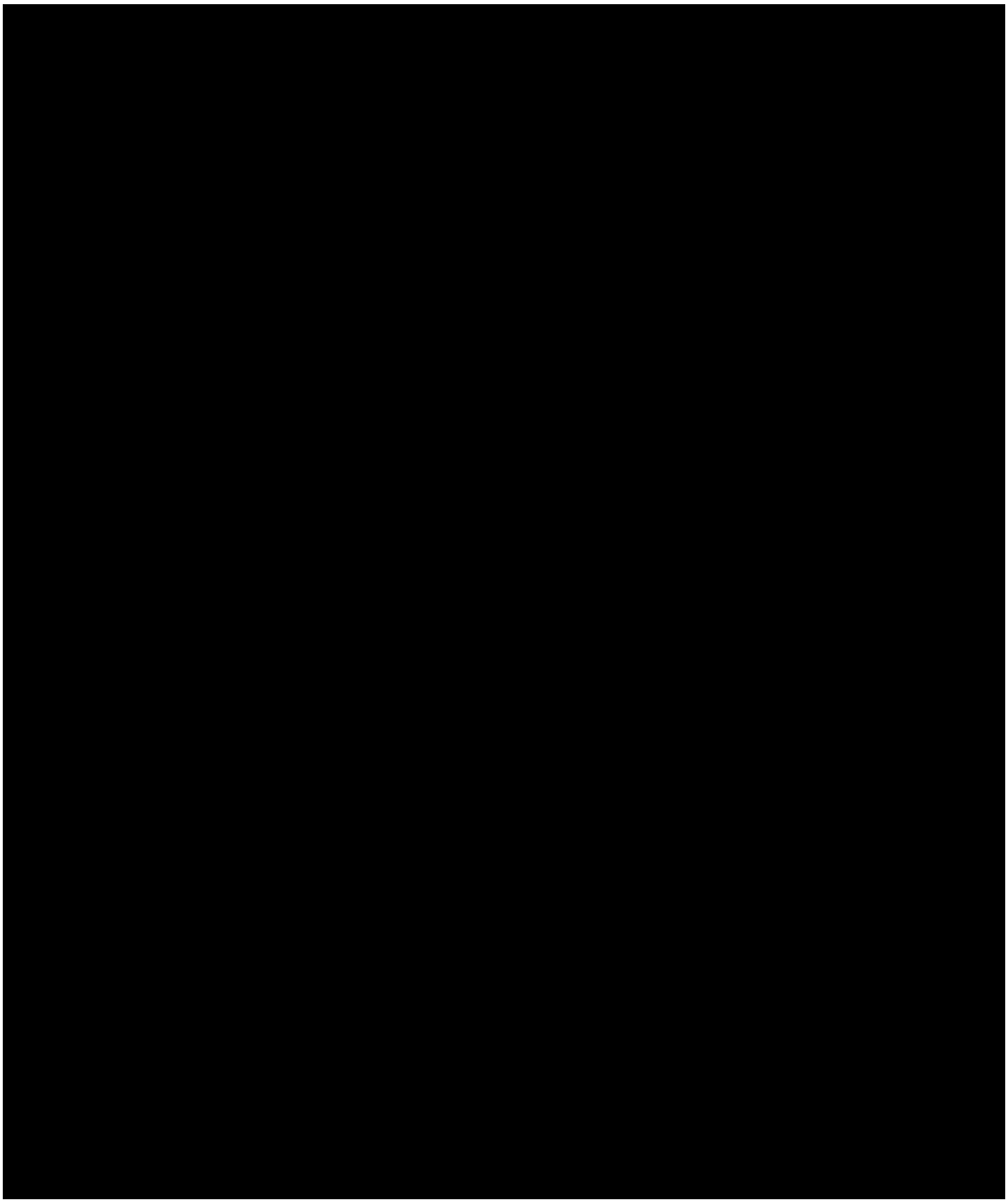


[redacted]

[redacted]

[redacted]

All potential AEs and ADEs will be evaluated and must be recorded in the subject's medical chart and in the study case report forms. AEs and ADEs will be monitored and tracked from the time of the first RF treatment.

At each contact with the subject, the Investigator will seek information on AEs by specific questioning and, as appropriate, by examination. AEs 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 (both expected and unexpected), regardless of severity or frequency, will be recorded in the (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, whether the event was expected or unexpected (anticipated or unanticipated), the relationship to study treatment or other therapy, the action taken (if any), and the outcome.

All SAEs and UADEs must be reported according to Cutera and IRB requirements.

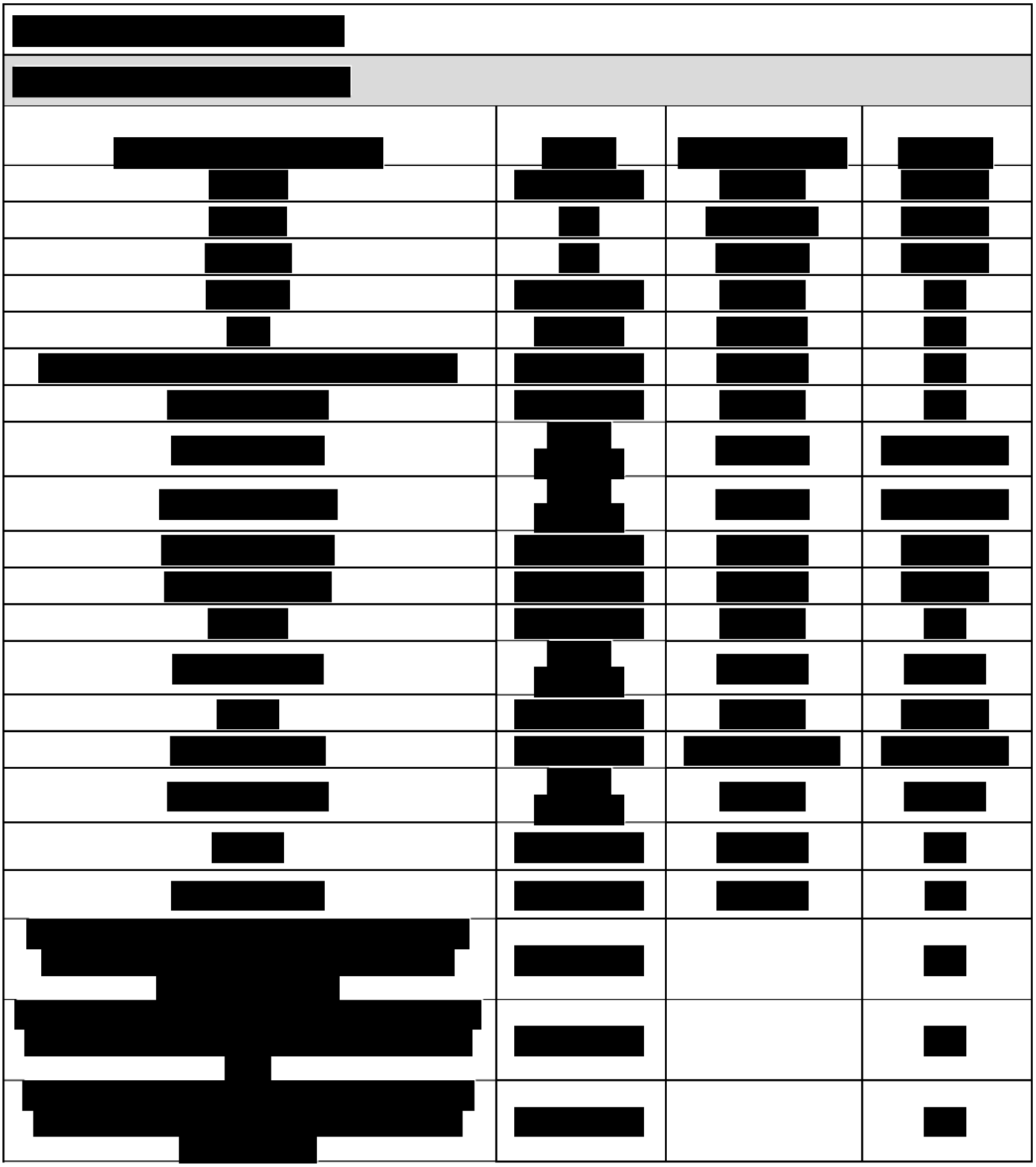
7.3 Follow-up of AEs and ADEs

All reported AEs and ADEs should be followed until resolution or until the subject's participation in the study ends. Resolutions of such events are to be documented on the appropriate CRF pages. All AEs and ADEs that result in permanent discontinuation from this clinical trial, whether serious or not, will also be reported on the Subject Non-Completion of Study Form.

8 POTENTIAL RISKS / BENEFITS

[redacted]

Table 04 Potential Study Risks



8.2 Potential Benefits

The subjects may or may not benefit from the treatment. Potential benefits include improved appearance of the wrinkles and sagging skin treated in the face or submental region. There is no guarantee of success.

8.3 Risk Management

The Investigator chosen for this study will have extensive and safe experience with the use of RF systems in dermatology applications. This is the most critical element in managing subject risk. In addition, the Investigators will be trained on the use of the Cutera RF device and any investigational handpieces.

9 DATA ANALYSIS PLAN

9.1 Sample Size

The primary objective is to [redacted] is statistically greater than 50%. Under the assumption that the true population response rate is 76%, 35 subjects will provide 80% power to reject the primary hypothesis. To allow for up to a 10% dropout rate, 39 subjects will be enrolled. The planned sample size of up to 35 subjects was determined based on clinical judgment to provide sufficient information to evaluate safety and efficacy of RF treatment for wrinkle reduction in the face and/or submentum region.

9.2 Analysis Sets

The efficacy analysis set will include all enrolled subjects who complete one RF treatment session using the study device.

The safety analysis set will include all subjects enrolled in the study who start the RF treatment session using the study device.

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

9.3 Analysis of Efficacy Endpoints

9.3.1 [redacted]

[redacted]

9.3.2 [redacted] Endpoint Analyses

[redacted] efficacy endpoints will be analyzed descriptively.

- Principal Investigator's assessment of improvement at 12 weeks post-final treatment (Physician's Global Assessment)

- [redacted]

9.4 Safety Analyses

Device-related and procedure-related adverse device effects (ADEs) and subjects who prematurely terminate from the study due to an adverse device effect, including the treatment-related pain ratings, will be tabulated and analyzed. For a given ADE term, counting will be done by subject, not by event, i.e. for a subject reporting the same ADE more than once, the event will be counted only once, at the most severe and longest duration. The number and percentage of subjects experiencing each ADE Term will be descriptively summarized. Subject pain ratings during treatment will also be summarized descriptively.

10 SUBJECT PAYMENT

[redacted].

11 STUDY MANAGEMENT AND ADMINISTRATIVE PROCEDURES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

11.3 Protocol Compliance

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

11.3.1 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 approval must be obtained before implementation of an amendment.

11.3.2 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 IRB according to their policies.

11.4 Study Personnel

Prior to the start of the study, the investigator must supply the sponsor with a list of the names and curricula vitae that describe the professional backgrounds of the clinically responsible study investigators (principal, sub-investigators), research nurses, and other possible participants (e.g. medical doctor, nurse, etc.).

11.5 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]

[redacted]

[redacted]

[redacted]

[redacted]

11.7 Subject Confidentiality

This study preserves the confidentiality of all subjects under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. The following safeguards will be in place to protect the privacy of the individuals who are the subjects of the health information to be used in the research and the confidentiality of that information:

The subjects will be informed by the investigator or the investigator's designee that their medical records will be kept as confidential as possible but may be subject to review by: (1) Cutera, or its representative; (2) reviewing IRB; and/or (3) by appropriate regulatory bodies (e.g. the US Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies).

[redacted]

11.8 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.

[redacted]

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[1] Digital Photographs will be taken PRIOR to all treatments and at follow-up visits.

[redacted]

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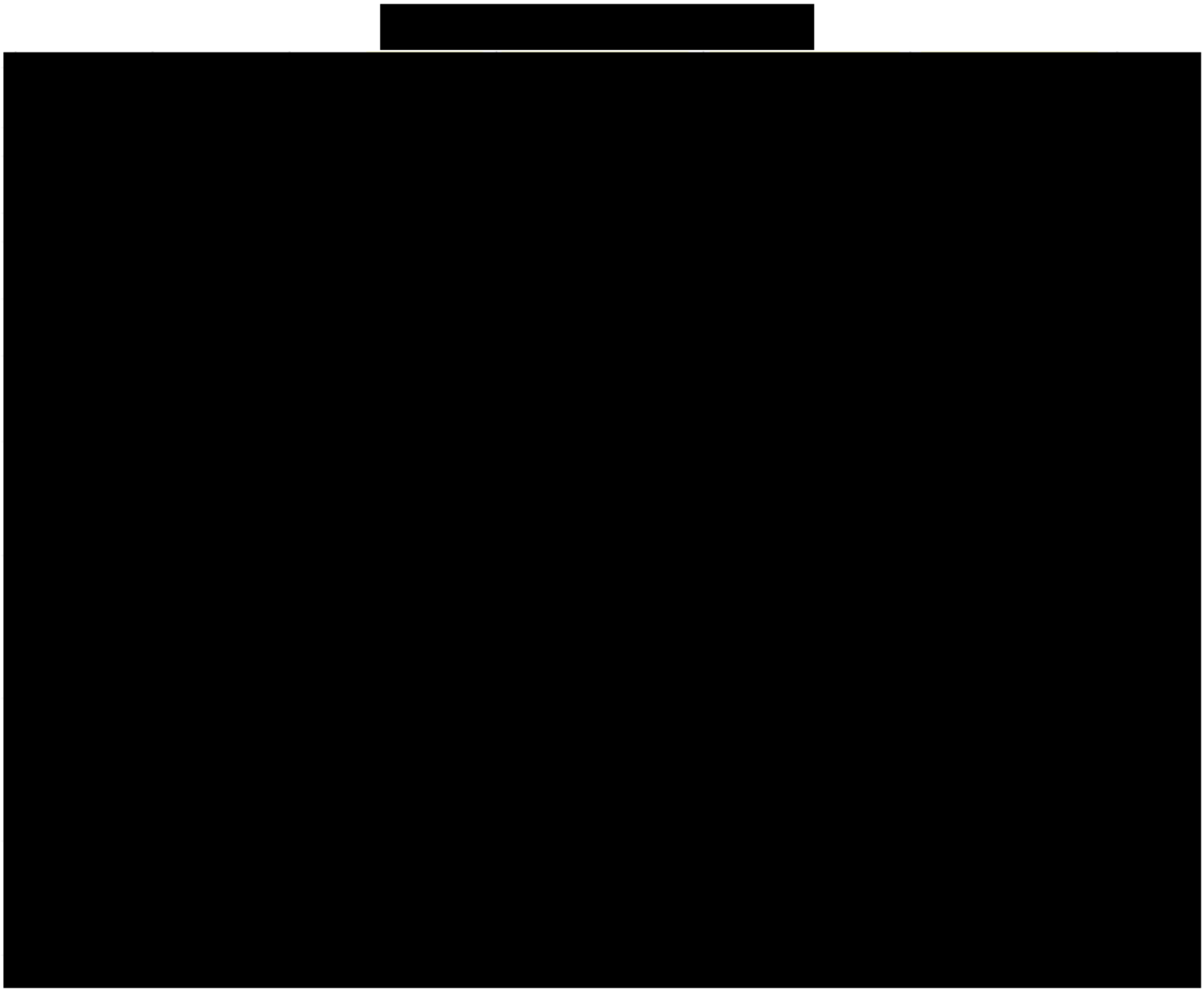

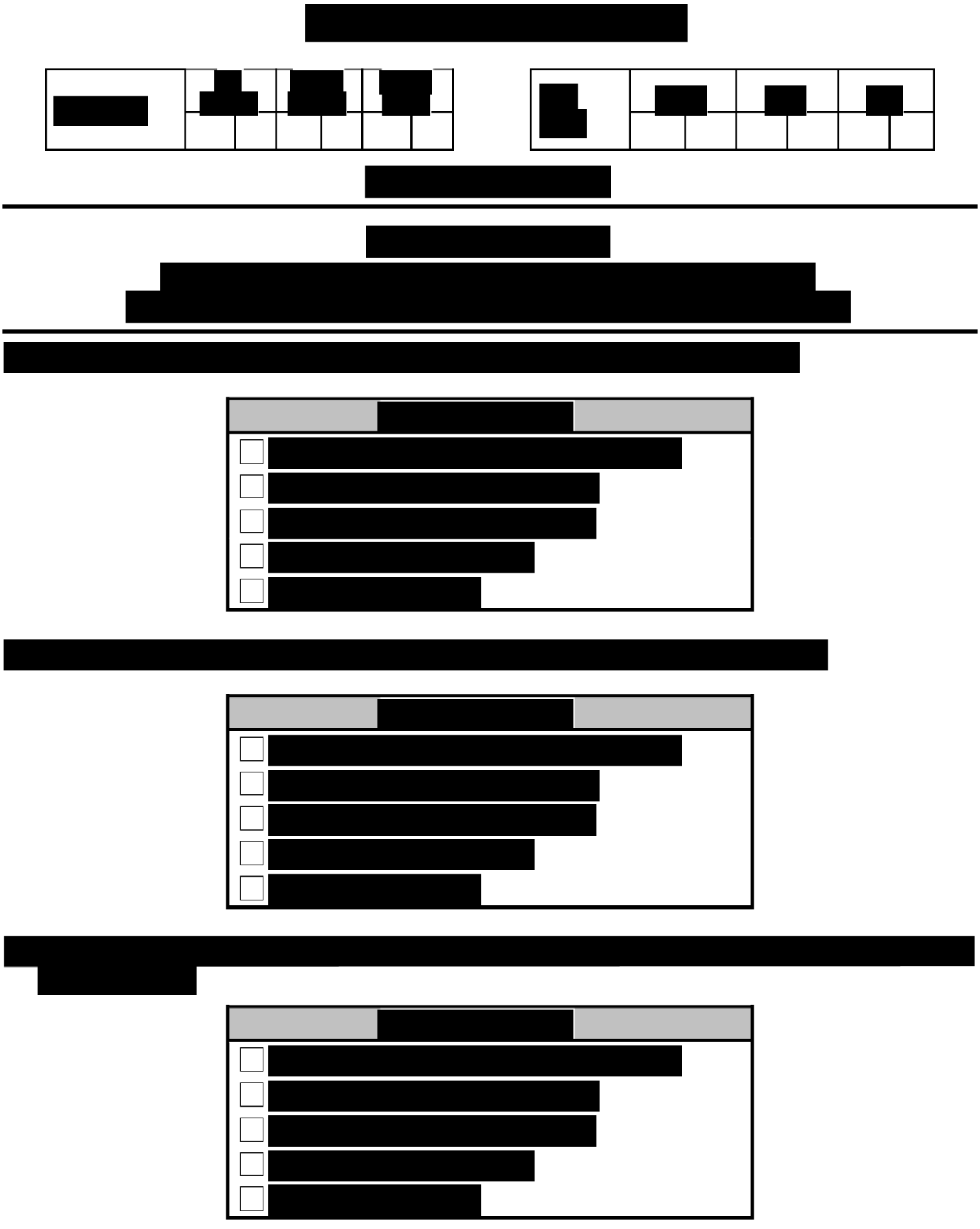

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