NCT03909100

Study ID: CMO-MA-PLS-0602

Title: International CoolSculpting: Prospective, Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks (iCool)

Protocol Date: November 20, 2019

CLINICAL INVESTIGATION PLAN

International CoolSculpting: Prospective, Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks (iCOOL)

Protocol Number:	CMO-MA-PLS-0602
Protocol Amendment Number:	2
Investigational Product:	CoolSculpting®
Phase:	Post-Marketing
Sponsor:	Allergan Sales, LLC 5 Giralda Farms Madison, NJ 07940 USA
Protocol Date:	20 November 2019
Protocol Version:	Version 3.0

1 PROTOCOL APPROVAL SIGNATURE

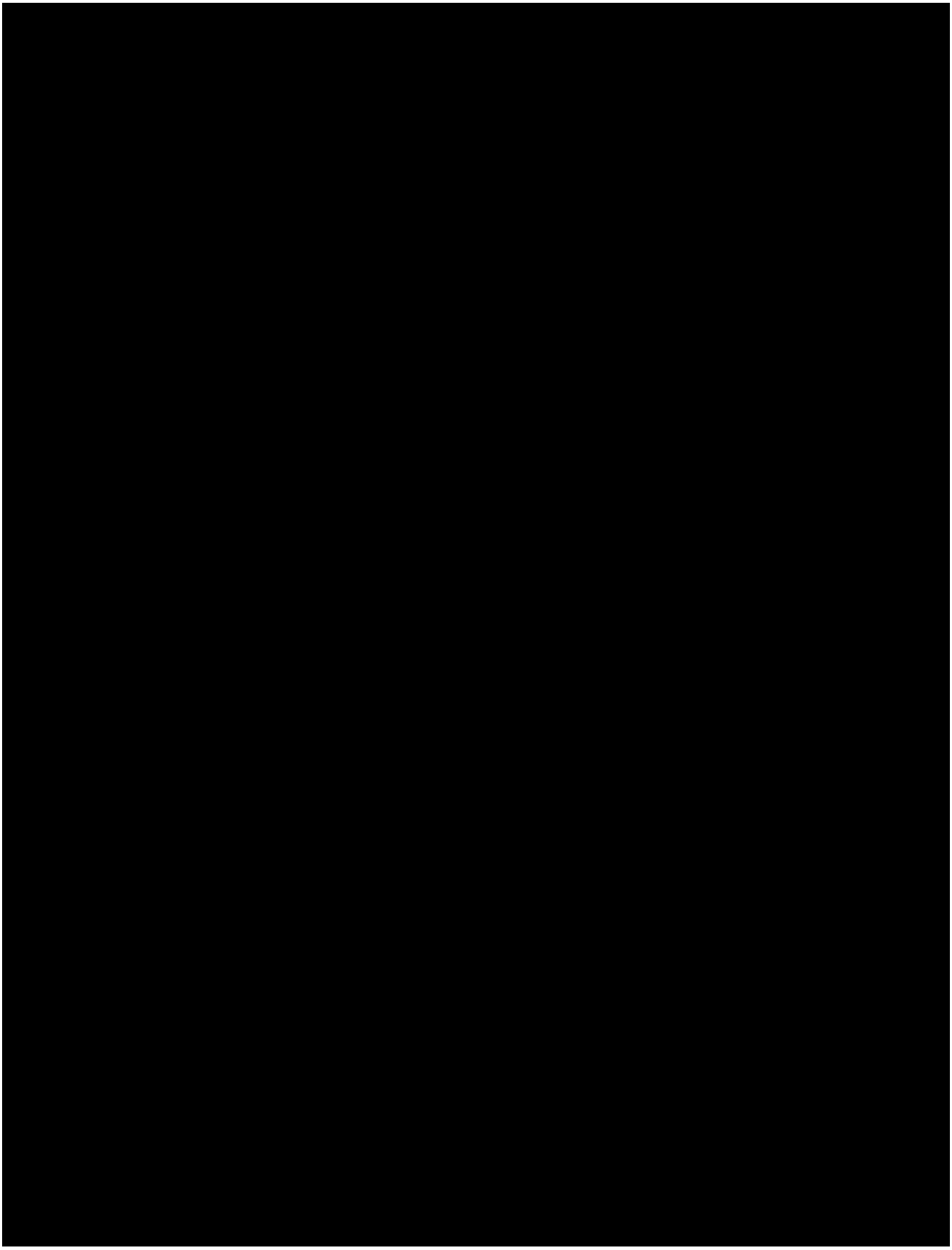
Protocol Title: International CoolSculpting: Prospective, Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks (iCOOL)

Protocol Number: CMO-MA-PLS-0602

Amendment Number: 2

This study will be conducted in compliance with the clinical study protocol (and amendments), ISO 14155(2011), guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

[redacted]



3 SYNOPSIS

Protocol Number: CMO-MA-PLS-0602

Title:

International CoolSculpting: Prospective, Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks (iCOOL)

Investigational Product:

CoolSculpting®

Study Sites:

Approximately 8 study sites

Phase:

Post-marketing

Objectives:

Primary Objective:

To evaluate overall patient satisfaction for non-invasive fat reduction in CoolSculpting subjects.

Secondary Objectives:

1. To evaluate overall satisfaction for non-invasive fat reduction in abdomen alone, flank alone, and abdomen and flanks combined in CoolSculpting subjects.
2. To evaluate overall satisfaction for non-invasive fat reduction in CoolSculpting subjects by number of treatment cycles.
3. To evaluate overall satisfaction for non-invasive fat reduction in CoolSculpting subjects by body mass index (BMI) (normal: 18.5 to < 25, overweight: 25 to ≤ 30).
4. To evaluate change in volume of fat after CoolSculpting treatment(s) using three-dimensional (3D) photography.
5. To determine frequency of adverse events (AEs) including serious AEs (SAEs); and adverse device effect (ADEs) including serious ADEs (SADEs).

[redacted]

Study Design:

Study CMO-MA-PLS-0602 is a multi-country, multi-center, non-randomized, open-label, single-arm, medical device post-marketing study.

Number of Subjects:

Approximately 100 subjects will be enrolled at approximately 8 sites.

Treatment:

Subjects will undergo CoolSculpting treatment session(s) in an outpatient clinical setting. A treatment session is comprised of timed segments of cooling (treatment cycles) followed by 2 minutes of manual massage. Treatments will be administered according to the User Manual CoolSculpting System.

Study Duration:

The study will be up to 20 weeks with up to 2 treatments sessions 8 weeks apart and final follow-up 12 weeks after the final treatment session (measured at Week 12 for subjects who receive 1 treatment session, or Week 20 for 2 treatment sessions).

Study Population:

Inclusion Criteria

1. Subject (healthy volunteers) has read and signed the study written informed consent form (ICF).
2. Male or female ≥ 22 years and ≤ 65 years of age.
3. Subject has clearly visible fat in the flanks and/or abdomen, which in the investigator's opinion, may benefit from the treatment.
4. Subject has not had weight change fluctuations exceeding 4.5 kg (or 5% of body weight) in the preceding month.
5. Subject has a BMI of 18.5 to 30. A BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2).
6. Subject agrees to maintain weight (ie, within 5% of body weight) by not making any changes in diet or exercise routine during the course of the study.
7. Subject agrees to have photographs taken of the treatment area(s) during the scheduled time periods.

Exclusion Criteria

1. Subject has had liposuction, or another surgical procedure(s) or mesotherapy in area of intended treatment.
2. Subject has had a non-invasive fat reduction and/or body contouring procedure in the area(s) of intended treatment within the past 12 months.
3. Subject needs to administer, or has a known history of subcutaneous injections into the area(s) of intended treatment (eg, cortisone, heparin, insulin) within the past 6 months.
4. Subject is pregnant or intending to become pregnant.
5. Subject is lactating or has been lactating in the past 6 to 9 months.
6. Subject is unable or unwilling to comply with study requirements.

7. Subject is currently enrolled in a clinical study of any unapproved investigational device, investigational product, or any other type of medical research judged not to be scientifically or medically compatible with this study.
8. Subject has an active implanted device such as a pacemaker, defibrillator, or drug delivery system or any other metal containing implant.
9. Subject with known history of cryoglobulinemia, cold agglutinin disease, or paroxysmal cold hemoglobinuria.
10. Subject with known sensitivity to cold or has any condition with a known response to cold exposure that limits blood flow to the skin such as cold urticaria or Raynaud's disease, or Chilblains (pernio).
11. Subject with known sensitivity or allergy to fructose, glycerin, isopropyl alcohol, or propylene glycol.
12. Subject with impaired peripheral circulation in the area(s) to be treated
13. Subject with neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy.
14. Subject with impaired skin sensation.
15. Subject with open or infected wounds.
16. Subject with bleeding disorder, or concomitant use of blood thinners, or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
17. Subject with recent surgery or scar tissue in the area(s) to be treated.
18. Subject has history of hernia in or adjacent to the treatment area(s) site.
19. Subject with skin conditions such as eczema, dermatitis, or rashes in the area(s) to be treated.
20. Subject has any dermatological conditions, such as moderate to excessive skin laxity, or scars in the location of the treatment sites that may interfere with the treatment or evaluation (stretch marks is not an exclusion).
21. Subject is taking or has taken diet pills or supplements within the past 6 months.
22. Any other condition or laboratory value that would, in the professional opinion of the investigator, potentially affect the subject's response or the integrity of the data or would pose an unacceptable risk to the subject.
23. Subject diagnosed with fibrosis.

Primary Endpoint:

The primary endpoint will be Cryolipolysis Satisfaction Questionnaire (CSQ) Item #1 measured at Week 12 for subjects who receive 1 treatment session and at Week 20 for subjects who receive 2 treatment sessions.

The analysis on the primary endpoint will be the proportion of subjects with "satisfied" or "very satisfied" on CSQ Item #1.

Secondary Endpoints

All secondary endpoints will be measured at Week 12 for subjects who receive 1 treatment session and at Week 20 for subjects who receive 2 treatment sessions, except for AEs, which will be assessed for all scheduled visits. The analyses on the secondary endpoints will include:

1. Proportion of subjects by treated area(s) (abdomen alone, flanks alone, and both abdomen and flanks) with "satisfied" or "very satisfied" on CSQ Item #1.
2. Proportion of subjects by number of treatment cycles who receive 1 or 2 treatment sessions with "satisfied" or "very satisfied" on CSQ Item #1.
3. Proportion of subjects by BMI categories with "Satisfied" or "Very Satisfied" on CSQ Item #1.
4. Mean change in volume of fat from baseline as measured by 3D photography.
5. Frequency of AEs including SAEs; and ADEs including SADEs.

[redacted]

Efficacy

The evaluable patient population will be the analysis population for efficacy summary.

Safety

Frequency of AEs including SAEs and ADEs including SADEs will be summarized.

Statistical Analysis

The primary endpoint of the study will be the overall patient satisfaction based on the CSQ Item #1 at 12 weeks after the final treatment session (measured at Week 12 for subjects who receive 1 treatment session, Week 20 for 2 treatment sessions) for non-invasive fat reduction in CoolSculpting subjects who receive treatment in abdomen alone, flanks alone, or both abdomen and flanks. Subjects who have reported 'Very satisfied' and 'Satisfied' will be categorized as 'Satisfied.' The counts and percentage will be summarized and the 95% confidence interval (CI) on the percentage will be calculated with normal approximation.

Secondary efficacy endpoints related to overall patient satisfaction rate on CSQ Item #1 at 12 weeks after the final treatment session will also be summarized along with 95% CIs. Descriptive summary statistics for change in volume of fat from baseline and [redacted]

Safety endpoints will be presented as summary tables describing frequency and type of events.

Sample Size

The sample size will be based on providing reasonable precision for the estimate of the overall satisfaction rate.

Previous studies conducted on subjects undergoing flank or abdominal fat reduction using CoolSculpting products reported moderately high overall satisfaction rate. The mean overall satisfaction rate was 65.8% from the study (Protocol: ZA15-004) based on 19 subjects, and 63.3% from another study (Protocol: ZA10-001) based on 60 subjects. The weighted average of rates from the 2 studies, which is 63.9%, is now used as the initial estimate of the mean overall satisfaction rate for this planned study. A sample size of 98 subjects would provide a 10% margin of error (associated with 95% CI) for the estimate of the 63.9% expected rate. Allowing a 10% dropout during the study period, approximately 108 subjects will be needed for recruitment into the study.

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List of In-text Tables

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

LIST OF ABBREVIATIONS

3D	three-dimensional
AE	adverse event
ADE	adverse device effect
BMI	body mass index
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
CRF	case report form
CSQ	Cryolipolysis Satisfaction Questionnaire
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
ISO	International Organization for Standardization
PRO	patient-reported outcome
SADE	serious adverse device effect
SAE	serious adverse event

5 INTRODUCTION

5.1 Background

CoolSculpting is a nonsurgical (cryolipolysis procedure) clinically proven treatment that selectively reduces unwanted fat using a patented cooling technology. CoolSculpting works by gently cooling targeted fat cells in the body to induce a natural, controlled elimination of fat cells without affecting surrounding tissue. The hypothesis behind the mechanism of action is that tissue-specific cold injury can be used for reducing subcutaneous fat without injuring the overlying skin. The resulting effect is that adipose tissue is more preferentially sensitive to cold injury than skin and other tissues (eg, skin, muscle, and nerves) and the crystallization of cytoplasmic lipids in adipocytes occurs at temperatures well above the freezing point of water (Epstein, 1970; Beacham, 1980; Manstein et al, 2008).

Cryolipolysis first received US Food and Drug Administration (FDA) clearance in 2010 for non-invasive fat-layer reduction in the flank followed by clearance for the abdomen in 2012 (Bernstein et al, 2014). Further approvals were gained in the following indications: visible fat bulges in the submental and submandibular area, thigh, along with bra fat, back fat, underneath the buttocks (also known as "banana roll"), and upper arm. Approval for the abdomen and flank has been gained in all markets with CoolSculpting clearance (more than 70 countries). Also, a retrospective chart review has shown that the majority of CoolSculpting treatments were performed on the abdominal and flank regions (Stevens et al, 2013).

Although there are numerous clinical studies that have been conducted at US sites, only a limited number of subjects have been treated and studied at international sites (Dierickx et al, 2013) with less data generated in other ethnicities (Shek et al, 2012). There is also insufficient information regarding patient-centric outcomes related to the CoolSculpting procedure and the psychosocial impact of localized fat. Patient-reported outcomes (PROs) are key in describing the experience of treatment as viewed through the eyes of subjects (ie, those receiving treatment). Measuring PROs provides practical evidence in all conditions, but it is even more important in aesthetics for which subjects are the main decision makers for these elective treatments.

A literature search was performed to assess psychosocial impact tools for body contouring, which revealed a limited number of instruments, none of which were applicable for CoolSculpting. Based on the review of 191 abstracts/studies sourced from 4 different databases, 10 PROs were identified. However, of the 5 available PRO instruments, none were found to be suitable for use in their original format in this CoolSculpting study due to limitations of items and concepts with each of the instruments. Therefore, for the purpose of this study, a questionnaire was developed de novo to capture psychosocial impact using a well-designed instrument based on patient qualitative research.

[redacted]

[redacted]

Previous studies have demonstrated patient satisfaction after CoolSculpting treatment (User Manual, CoolSculpting System, 2017). The CSQ (Appendix 17.6) used in this study was created by modifying the original satisfaction questionnaires used in these previous studies. From the original satisfaction questionnaire, 3 versions were created to address treatment satisfaction with abdomen only, flank only, and abdomen and flank together. [redacted] Additional qualitative patient research was conducted on both questionnaires to ensure content validity (instruments are comprehensive, appropriate in the targeted population, and subjects interpret the questions in a way that was intended).

By generating data that convey subjects' experiences, and thus PROs, this study will provide insights for CoolSculpting providers to better inform the subjects about expected outcomes and support a more patient-centric consultation before treatment.

5.1.1 Abdominal Only Studies

Cryolipolysis received US FDA clearance for the reduction of fat in the abdomen in 2012 (Klein et al, 2017). Four studies described below, have been published that describe the safety and efficacy of this treatment in this area.

The first-ever published CoolSculpting multicenter study assessing safety, tolerability, and patient satisfaction was a retrospective study in France and Belgium of 518 subjects (73% female and 27% male). Twenty-eight percent of the 891 areas treated were on the abdomen. Side effects from the cryolipolysis treatment were minor; erythema was reported in 100% of the cases. Additional side effects observed immediately after treatment included rare vasovagal reaction (2.1%) after anterior abdominal area treatment and varying levels of pain, reported as minimal to tolerable in 96% of subjects. Severe pain was reported in 4% of subjects, occurring only during the initial 5 minutes of cryolipolysis, with no interruption of treatment required. There were 11 cases of transient increased sensitivity in subjects who underwent treatment on the abdomen, and all cases resolved in 3 weeks or less. All but 1 patient, a fitness instructor, was able to resume his/her normal daily activities. Efficacy was assessed by grading pre-treatment and 3-month post-treatment photographs (n=49): 73% of the subjects displayed reduction of fat thickness in the treated area, while 85.5% of subjects showed improvement in the abdomen and flank sites; 82% of subjects would recommend the procedure to others (Dierickx et al, 2013).

Another retrospective chart review was conducted on 403 females and 125 males (n = 528) who underwent cryolipolysis treatment from January 2010 to December 2012. Subjects were primarily Caucasian (67%), followed by Latino (15%), Middle Eastern (6%), African American (5%), Asian (4%), Mediterranean (1%), and other (1%). The lower and upper abdomen consisted of 28% and 11% of the treatment sites, respectively. Only 3 cases of side effects were noted in the patient charts, and all were reports of mild to moderate pain or neuralgia, which resolved in 4 days or less. No AEs were reported. While patient surveys were not conducted for this study, the follow-up visits with the physician assistant allowed subjects to express concerns and

dissatisfaction; 2 subjects requested refunds, and 4 subjects who were initially dissatisfied with their fat reduction received follow-up cryolipolysis treatments without charge and were subsequently satisfied with their results. The investigators believe this represents a high level of patient satisfaction (Stevens et al, 2013).

A retrospective chart review study was conducted on 27 males and 98 females (n = 125) who received 554 cryolipolysis treatment cycles at the Washington Institute of Dermatologic Laser Surgery. Subjects who received cryolipolysis treatment during a 12-month consecutive period (September 1, 2013 to August 29, 2014) were evaluated. Treatment sites included the lower (n = 203, 36.6%) and upper abdomen (n = 66, 11.9%), flanks, back, thighs, and chest. Once the treatment applicator was positioned on the patient, the 60-minute treatment cycle was initiated. Subjects were noted as developing delayed post-treatment pain if the patient experienced at least 2 of the following symptoms after cryolipolysis: neuropathic symptoms such as stabbing, burning, and shooting pain within treatment areas; increased pain causing sleep disruption; and discomfort unresponsive to analgesic medications. Females (mean age of 39 years) undergoing abdominal cryolipolysis were at greatest risk of experiencing delayed post-treatment pain, which developed, on average, 3 days after treatment and was self-limited and resolved completely without long-term sequelae within 11 days. The number of treatment cycles did not impact whether a patient developed delayed post-treatment pain. (Keaney et al, 2015).

In a Chinese population study, investigators compared the clinical efficacy and patient satisfaction of a novel cryolipolysis device (ZELTIQ®) for body contouring after a single treatment and after 2 treatments in a commercial setting. Twenty-one subjects received a single treatment lasting 60 minutes, and 12 subjects received 2 treatments lasting 60 minutes each, on average of 3 months apart. The thickness of fat at the treatment site is measured using a calliper, as well as standardized clinical photos, that were collected at baseline and 2 months post-treatment. There was a significant improvement ($p < 0.0001$) in the first group of subjects and after both treatments compared to the baseline in the second group of subjects for treatment on the abdomen. Fifty-seven percent of patients thought the treatment reached or exceeded their expectations, whereas 43% expected a more dramatic effect. Subjectively, 80% felt satisfied to very satisfied, and the rest were indifferent. Eighty-six percent would consider having non-invasive cryolipolysis performed on another part of their body and would consider recommending this treatment to family and friends (Shek et al, 2012).

Based on these studies, cryolipolysis is well tolerated, has a high patient satisfaction, and is effective in reducing fat in the abdominal region.

5.1.2 Flank Only Studies

Cryolipolysis received US FDA clearance for the reduction of fat in the flank area in 2010 (Klein et al, 2017).

In addition to the Klein et al, 2017 and Dierickx et al, 2013 papers described above, there are 2 other flank studies that describe safety and efficacy of cryolipolysis.

To test the safety and efficacy of a new sharply contoured cryolipolysis vacuum applicator, a study was conducted that treated 20 flanks on female subjects, with 2 treatment cycles

(60 minutes each) delivered sequentially to each flank. Efficacy was evaluated 12 weeks post-treatment by physicians performing a blinded, independent review of clinical photographs. Safety was assessed by the treating physician who monitored subjects for side effects and AEs. Four blinded, independent physician reviewers properly identified the pre- and post-treatment photographs 94.4% of the time. Improvement results, scored from 0 (none) to 10 (complete), showed an average score of 4.3 points (43%). Side effects were limited to erythema, edema, bruising, and numbness or tingling at the treatment site and resolved without intervention before the 12-week follow-up visit (Bernstein et al, 2014).

Another study investigated whether fat reduction in humans caused by cold exposure is associated with alteration in local sensory function or nerve fibers. Ten subjects were treated with a prototype cooling device on 1 of their flanks, and the other side was left untreated as a control. Fat reduction was assessed in 9 of the 10 subjects via ultrasound before treatment and at the 2- and 6-month follow-up visits. Clinical observations documented immediately after treatment were consistent with those anticipated for local inflammation (eg, edema, minor pain, erythema), the majority of which resolved within a few days after treatment; no clinical findings were reported for any of the treatment sites at the 2- or 6-month follow-up visits. Treatment resulted in a normalized fat-layer reduction of 20.4% at 2 months after treatment and 25.5% at 6 months after treatment. While transient reduction in sensation occurred in 6 of 9 subjects assessed by neurologic evaluation, all sensation returned by a mean of 3.6 weeks after treatment; biopsies showed no long-term change in nerve fiber structure. There were no lasting sensory alterations or observations of skin damage in any of the evaluated subjects (Coleman et al, 2009).

Based on these studies, cryolipolysis is well tolerated and is effective in reducing fat in the flank region.

5.1.3 Abdominal and Flank Studies

A study of 8 adult males and 27 females (n = 35) assessed multiple same-day treatments on the lower abdomen and 2 flanks and effects on serum lipid levels and liver tests. Treatment consisted of 1 cycle each to the lower abdomen and simultaneous treatment of both flanks. The time between the abdomen and flanks procedures was not to exceed 30 minutes. Erythema, numbness, and edema were experienced by the majority of subjects immediately after the procedures. In most cases, these signs and symptoms were considered by the investigator to be minor or moderate in severity, and, in all cases, they resolved without treatment. At the Week 12 examination, all treatment sites appeared normal, and no subjects reported any associated symptoms. Immediately after the procedures, the mean pain score was 4 on a scale of 1 to 10. There were no reports of late-onset pain. There were no clinically meaningful changes from baseline to any subsequent time point in either the serum lipid tests or liver tests. Three subjects experienced AEs, all judged by the investigator to be unrelated to the procedures. Therefore, multiple cycles of same-day cryolipolysis treatment of the lower abdomen and both flanks are well tolerated and safe (Klein et al, 2017).

5.2 Rationale

Most clinical studies on CoolSculpting have been conducted at US sites; therefore, only a limited number of subjects have been treated and studied at international sites. There is also insufficient

information regarding patient-centric outcomes related to the CoolSculpting procedure and the psychosocial impact of localized fat. A literature search was performed to assess psychosocial impact tools for body contouring, but nothing relevant was found. Therefore, Allergan has developed a de novo research instrument, [redacted] to assess the psychosocial impact of treating subjects with CoolSculpting on the abdomen and flank.

5.2.1 Benefit and Risks

5.2.1.1 Benefits

Fat reduction in the treatment area is anticipated to provide an aesthetic benefit and the use of this non-invasive system will eliminate the need for an invasive procedure that requires anesthesia or recovery time.

5.2.1.2 Risks

Although this study presents minimal risks to the subject, there is the potential for some risk when any medical procedure is performed.

Anticipated Device Effects

These are known effects of the CoolSculpting Procedure, previously recorded in prior studies as transient and/or temporary effects related to the cold application and/or vacuum pressure inherent in the treatment. Anticipated effects of the device which will not be considered AEs include:

- inflammation of the subcutaneous fat layer, which is a desired effect of the procedure;
- sensations of coldness, stinging, burning, pinching, or pressure associated with placement of the applicator and the initiation of the cold treatment;
- known skin effects (eg, blanching; erythema, bruising, purpura, petechiae, swelling, discomfort, tenderness, or soreness at the treatment site, all mild to moderate in nature), which are temporary effects that resolve spontaneously shortly after the procedure; and
- localized sensory changes (eg, numbness, tingling) at the treatment area resolving within 12 weeks of the procedure.

If the severity of these anticipated effects causes disruption to the subject's daily activities, then they will be evaluated as a potential adverse effect.

Potential Adverse Effects

Potential Adverse Effect	Description
Severe Bruising	The appearance of bruising (purple discoloration); purpura (purple colored spots or patches); or petechiae (pin point red dots) that is rated as severe by the investigator.
Prolonged Bruising	Bruising lasting longer than 1 month.
Severe Erythema	The appearance of erythema (redness) that is rated as severe by the investigator.
Prolonged erythema	Erythema lasting longer than 2 weeks.
Severe Swelling	The appearance of swelling (edema) that is rated as severe by the investigator.
Prolonged swelling	Swelling lasting longer than 1 month.
First Degree Burn	Skin damage from burns may be due to hot or cold. A first degree burn is superficial and causes local inflammation of the skin. The inflammation is characterized by pain, redness, and mild swelling. The skin may be very tender to touch.
Second Degree Burn	Second degree burns are deeper and, in addition to the pain, redness, and inflammation, there is also blistering of the skin.
Third Degree Burn	Third degree burns are deeper still, involving all layers of the skin. Because the nerves and blood vessels are damaged, third degree burns appear white, leathery, and tend to be relatively painless.
Cold-induced Panniculitis	Severe inflammation which requires medical or surgical intervention.
Skin Pigment Changes	The appearance of hyperpigmentation or hypopigmentation in the treatment area.
Infection	Infection at the treatment site, diagnosed by a physician and requiring medical intervention.
Discomfort During Procedure	Discomfort reported during the procedure that is intolerable to the subject and results in an interruption or discontinuation of the procedure.
Discomfort Post Procedure	Significant discomfort, pain, cramping, tenderness, soreness, muscle spasm following the procedure which results in medical intervention (physician visit and/or prescription pain reliever).
Prolonged Sensory Alteration Post Procedure	Sensory changes (numbness, tingling, burning sensation) that are prolonged (ie, lasting longer than 12 weeks).
Sensory Alteration Requiring Medical Intervention	Sensory changes (pain, burning, stinging, hypersensitivity) with a severity warranting medical intervention.
Vasovagal Symptoms	The occurrence of symptoms of anxiety, light-headedness, dizziness, nausea, sweating, near syncope, or syncope (fainting).
Gastrointestinal Symptoms	Nausea, bloating, or diarrhea temporally related to the procedure (within the first few hours after the procedure).
Contour Irregularity	Significant indentation or contour irregularity in the treatment area that would require surgical intervention.
Allergic/Irritant Contact Dermatitis	Itchy rashes and skin peeling that may result from prolonged exposure to gel pad or applicator pressure.
Subcutaneous Induration	Hardness within the treatment area, either as general firmness or discrete nodules.
Paradoxical Hyperplasia	Visibly enlarged tissue volume within the treatment area which may develop 2-5 months after treatment.
Hernia	Creation or exacerbation of hernia. Hernia is defined as a protrusion of an organ or the fascia of an organ through the wall of the cavity that normally contains it.
Other	Any other untoward medical event determined by the investigator to be an AE, regardless of the relationship to the device or treatment.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Objectives

Primary Objective

To evaluate overall patient satisfaction for non-invasive fat reduction in CoolSculpting subjects.

Secondary Objectives

1. To evaluate overall satisfaction for non-invasive fat reduction in abdomen alone, flank alone, and abdomen and flanks combined in CoolSculpting subjects.
2. To evaluate overall satisfaction for non-invasive fat reduction in CoolSculpting subjects by number of treatment cycles.
3. To evaluate overall satisfaction for non-invasive fat reduction in CoolSculpting subjects by BMI (normal: 18.5 to < 25, overweight: 25 to ≤ 30).
4. To evaluate change in volume of fat after CoolSculpting treatment(s) using 3D photography.
5. To determine frequency of AEs including SAEs; and ADEs including SADEs.

[redacted]

6.2 Endpoints

Primary Endpoint

The primary endpoint will be CSQ Item #1 measured at Week 12 for subjects who receive 1 treatment session and at Week 20 for subjects who receive 2 treatment sessions.

The analysis on the primary endpoint will be the proportion of subjects with “satisfied” or “very satisfied” on CSQ Item #1.

Secondary Endpoints

All secondary endpoints will be measured at Week 12 for subjects who receive 1 treatment session and at Week 20 for subjects who receive 2 treatment sessions, except for AEs, which will be assessed for all scheduled visits. The analyses on the secondary endpoints will include:

1. Proportion of subjects by treated area(s) (abdomen alone, flanks alone, and both abdomen and flanks) with "satisfied" or "very satisfied" on CSQ Item #1.
2. Proportion of subjects by number of treatment cycles who receive 1 or 2 treatment sessions with "satisfied" or "very satisfied" on CSQ Item #1.
3. Proportion of subjects by BMI categories with "Satisfied" or "Very Satisfied" on CSQ Item #1.
4. Mean change in volume of fat from baseline as measured by 3D photography.
5. Frequency of AEs including SAEs; and ADEs including SADEs.

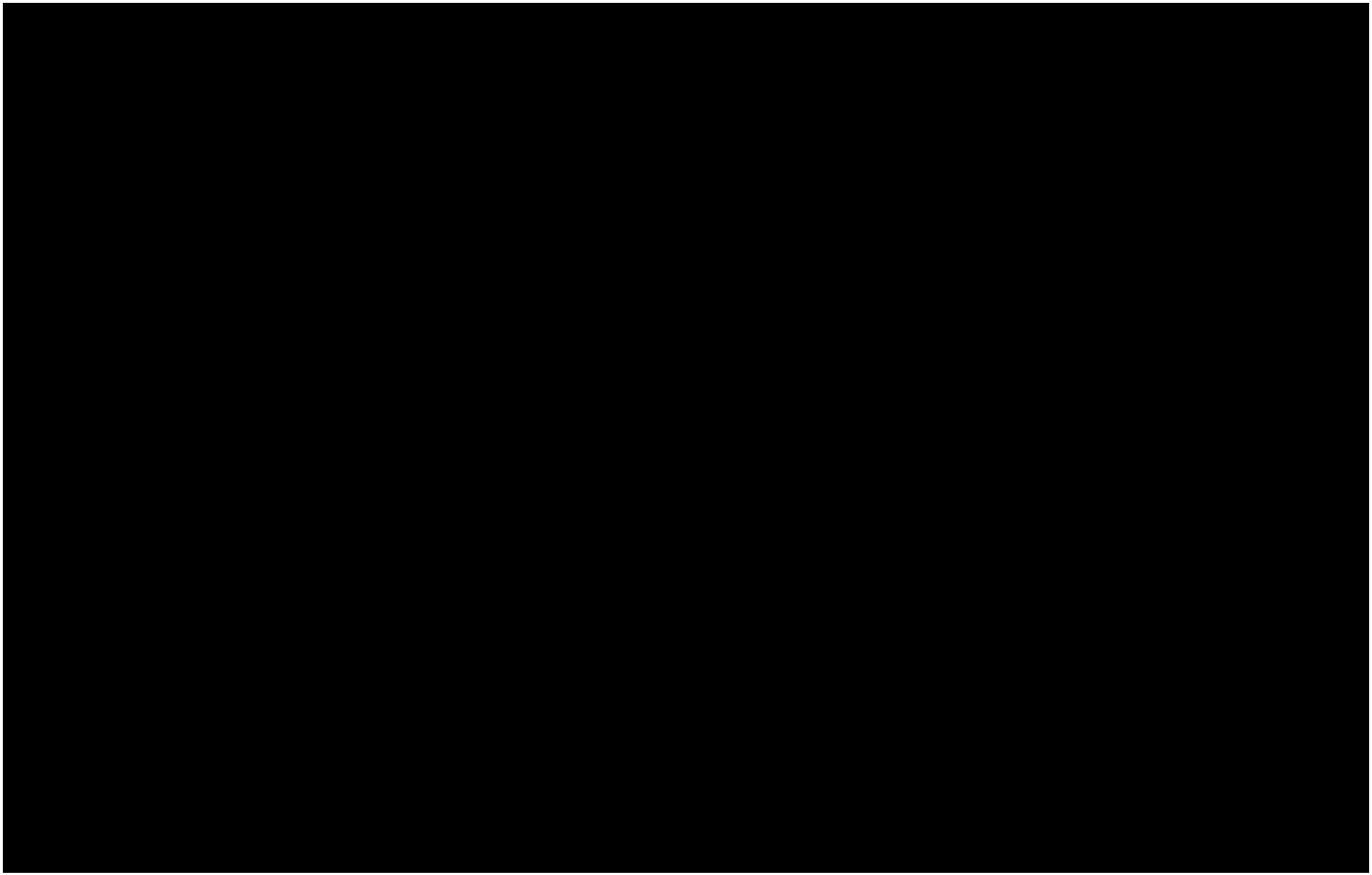
[redacted]

All individual items and the total score are transformed to a 0 (no impact) to 100 (highest impact) point scale.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

Study CMO-MA-PLS-0602 is a multi-country, multi-center, non-randomized, open-label, single-arm, medical device post-marketing study. See Table 1 Schedule of Assessments.



7.2 Discussion of Study Design

The background and rationale that led to the study design is described in Section 5.1.

7.3 Selection of Study Population

7.3.1 Number of Planned Subjects

Approximately 100 subjects will be enrolled at approximately 8 sites.

Refer to the statistical considerations on which the numbers are based in Section 10.1.

7.3.2 Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Subject (healthy volunteers) has read and signed the study written ICF as described in Section 14.4.
2. Male or female ≥ 22 years and ≤ 65 years of age.
3. Subject has clearly visible fat in the flanks and/or abdomen, which in the investigator's opinion, may benefit from the treatment.
4. Subject has not had weight change fluctuations exceeding 4.5 kg (or 5% of body weight) in the preceding month.
5. Subject has a BMI of 18.5 to 30. A BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2).
6. Subject agrees to maintain weight (ie, within 5% of body weight) by not making any changes in diet or exercise routine during the course of the study.
7. Subjects agree to have photographs taken of the treatment area(s) during the scheduled time periods.

7.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criteria are applicable:

1. Subject has had liposuction, or another surgical procedure(s) or mesotherapy in area of intended treatment.
2. Subject has had a non-invasive fat reduction and/or body contouring procedure in the area(s) of intended treatment within the past 12 months.

3. Subject needs to administer, or has a known history of subcutaneous injections into the area(s) of intended treatment (eg, cortisone, heparin, insulin) within the past 6 months.
4. Subject is pregnant or intending to become pregnant.
5. Subject is lactating or has been lactating in the past 6 to 9 months.
6. Subject is unable or unwilling to comply with study requirements.
7. Subject is currently enrolled in a clinical study of any unapproved investigational device, investigational product, or any other type of medical research judged not to be scientifically or medically compatible with this study
8. Subject has an active implanted device such as a pacemaker, defibrillator, or drug delivery system or any other metal containing implant.
9. Subject with known history of cryoglobulinemia, cold agglutinin disease, or paroxysmal cold hemoglobinuria.
10. Subject with known sensitivity to cold or has any condition with a known response to cold exposure that limits blood flow to the skin such as cold urticaria or Raynaud's disease, or Chilblains (pernio).
11. Subject with known sensitivity or allergy to fructose, glycerin, isopropyl alcohol, or propylene glycol.
12. Subject with impaired peripheral circulation in the area(s) to be treated
13. Subject with neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy.
14. Subject with impaired skin sensation.
15. Subject with open or infected wounds.
16. Subject with bleeding disorder, or concomitant use of blood thinners, or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
17. Subject with recent surgery or scar tissue in the area(s) to be treated.
18. Subject has history of hernia in or adjacent to the treatment area(s) site.
19. Subject with skin conditions such as eczema, dermatitis, or rashes in the area(s) to be treated.
20. Subject has any dermatological conditions, such as moderate to excessive skin laxity, or scars in the location of the treatment sites that may interfere with the treatment or evaluation (stretch marks is not an exclusion).

21. Subject is taking or has taken diet pills or supplements within the past 6 months.
22. Any other condition or laboratory value that would, in the professional opinion of the investigator, potentially affect the subject's response or the integrity of the data or would pose an unacceptable risk to the subject.
23. Subject diagnosed with fibrosis.

7.3.4 Removal of Subjects from Therapy or Assessments

Notification of early participant discontinuation from the study and the reason for discontinuation will be provided to the sponsor and will be clearly documented on the appropriate case report form (CRF).

Reasons for discontinuation from the study may include the following:

- Completed
- Other
- Physician decision
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by subject
- Lost to follow-up

Subjects who do not comply with the protocol or who withdraw consent will not be replaced. Subjects who stop study treatment for any other reason will not be replaced. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the CRF.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the CoolSculpting procedure or the company occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

Pregnancy

Female patients will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator, who fill out a provided pregnancy surveillance form. The form needs to be sent to the sponsor within 24 hours of awareness of a confirmed pregnancy to the following contact information:
CoolSculptingProductSurveillance@allergan.com

Once pregnancy is confirmed, the subject will be immediately withdrawn from the study. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery using the second page of the pregnancy surveillance form.

Full details will be recorded on the withdrawal page of the CRF.

7.4 CoolSculpting System

7.4.1 CoolSculpting Description

Patients will undergo CoolSculpting treatment in an outpatient clinical setting. A treatment session on any given day(s) comprises one or more timed segments of cooling called treatment cycles, which overall comprise the treatment plan for the patient. Treatments will be administered according to the User Manual CoolSculpting System that has been prepared for specific countries. The CoolSculpting System, also labelled as the ZELTIQ System or the ZELTIQ Breeze System (system), is a non-invasive cooling and heating device that applies controlled cooling to a treatment site on the patient's skin.

Uses of the system in cooling mode include:

- Fat-layer reduction through cold-assisted lipolysis.
- Minimizing pain and thermal injury during laser and dermatological treatments.
- Acting as a local anesthetic for procedures that induce minor local discomfort.

The system can also provide localized thermal therapy (hot or cold) to minimize pain for post-traumatic and/or post-surgical pain and to temporarily relieve minor aches and pains and muscle spasms.

The massage function can also be used for temporary:

- relief of minor aches and spasms
- improvement in local circulation
- reduction in the appearance of cellulite

The investigator or his/her designee is responsible for the following:

- explaining the procedure to the patient
- verifying that instructions are followed properly
- maintaining accurate records

7.4.2 Identity of CoolSculpting System

The CoolSculpting System is comprised of a control unit, a surface or vacuum applicator, and supplies such as cards, foam borders, gel pads, liners, pre-treatment skin wipes, and securement systems. The applicators, foam borders, gel, gel pads, liners, pre-treatment skin wipes, and securement systems are patient-applied parts.

During a treatment, the operator applies a gel/gel pad and applicator to the patient's skin. The vacuum applicator draws tissue into the applicator cup and holds the tissue against the cooling surfaces of the applicator; the surface applicator does not use vacuum pressure. The operator starts the treatment. Sensors in the cooling surfaces of the applicator monitor the skin surface, providing feedback that controls the rate of heat flux. The gel/gel pad protects the skin by providing thermal coupling at the interface between the cooling surfaces of the applicator and the skin. The card provides cycles and profiles for use with the system.

The CoolSculpting System operates at temperatures below 0°C, which can freeze tissue. Therefore, the system monitors tissue during cooling and employs multiple safety features, including the Freeze Detect system, to minimize the risk of damage to tissue. In spite of these multiple safety features, on rare occasions, a possible freeze condition may occur that can be detected by the Freeze Detect System.

The Freeze Detect system is comprised of several features, including thermal sensors and proprietary algorithmic software. Freeze Detect is an integral part of the CoolSculpting System and is automatically employed when a treatment is initiated. When the Freeze Detect system detects a possible freeze condition, it stops the treatment and displays a Z409 message. If this message is received, remove the applicator and gel pad or gel, and assess the tissue before taking further action. The current recommended practice is to wait at least 24 hours before retreating the area relating to a Z409 error message. Failure to follow instructions could result in injury to the participant, including first- or second-degree burns. Second-degree burns or complications of second-degree burns may result in hyperpigmentation.

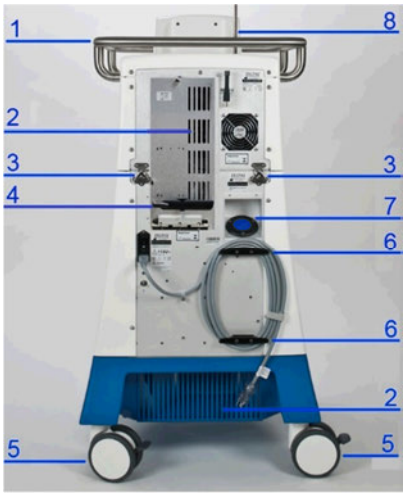
7.4.2.1 Control Unit

Control Unit - Front View

Components - Front View

1. Rail: When the applicator is resting on top of the control unit, the rail helps keep the applicator in place. In addition, the rail is used as a handle to move the system.
2. Vents: Vents provide airflow that reduces heat build-up inside the control unit. Ensure all vents are free from obstructions when the control unit is in operation.
3. Drawer: The drawer provides storage space for supplies and user documentation.
4. Casters and Locks: The control unit has four casters that swivel. Each caster has a lock. Always engage the locks on all four casters before you use the control unit.
5. Screen: The screen displays system controls, information about the status of the system, information about the treatment, and messages for the operator.

Control Unit - Rear View



Components: Control Unit, Rear View

1. Rail: When the applicator is resting on top of the control unit, the rail helps keep the applicator in place. In addition, the rail is used as a handle to move the system.
2. Vents: Vents provide airflow that reduces heat build-up inside the control unit. Ensure that all vents are free from obstructions when the control unit is in operation.
3. Latches: The latches lock the upper and lower modules of the control unit together.
4. Antenna: The antenna and data modem send data to ZELTIQ (availability and use of the data modem are subject to regional limitations).
5. Casters and locks: The control unit has four casters that swivel. Each caster has a lock. Always engage the locks on all four casters before you use the control unit.
6. Cleats: When the power cord is not in use, wrap it loosely around the cleats.
7. Chiller tank cap: The chiller tank cap provides access to the chiller tank for checking the coolant level and adding coolant.
8. Support Arm: Drape the applicator cable over the support arm to minimize drag on the connections and to keep the cable out of your way. Use the Velcro® straps to secure the cable to the support arm.

7.4.2.2 Applicator

The applicator delivers controlled cooling to the treatment site.

The applicator consists of the applicator connector, the applicator cable, and the applicator head.

The applicator is used with supplies provided by ZELTIQ, an Allergan affiliate.

7.5 [redacted]

[redacted]

7.6 Method of Assigning Subjects to Treatment Groups

At screening, after the study participant has signed the ICF, the study participant will be assigned a subject number sequentially based on the order in which the study participant is screened into the study. This subject number will serve as the study participant identification number on all study documents.

7.7 Blinding

This is an open-label study.

7.8 Prior and Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study.

7.9 Treatment Compliance

The study investigators are responsible for performing the study in compliance with the protocol. Non-adherence to the protocol is to be classified as a protocol violation, protocol deviation, or protocol exemption, as defined below.

Protocol Violation

A violation is any non-adherence to the protocol that may result in significant additional risk to the subject (eg, enrollment of a subject who does not meet the study criteria). A protocol violation can also be an event of non-adherence to Good Clinical Practices (GCPs) that may impact subject safety (eg, failure to obtain proper consent before performing study procedures). Violations should be reported to the study sponsor and the institutional review board (IRB) within 5 working days if they occur.

Protocol Deviation

A deviation is any non-adherence to study procedures that does not result in additional risk to the subject (eg, subject missed visit). Protocol deviations are not required to be reported to the IRB; however, they must be recorded on the study CRFs and may be reported and reviewed in conjunction with the progress report as part of the annual review process.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.3 Duration of Treatment

Each treatment session will comprise a number of treatment cycles, each lasting up to 45 minutes, depending on the applicator used. Subjects will have up to 2 treatment sessions, with the second treatment session approximately 8 weeks after the first one.

9 STUDY ASSESSMENTS

The planned schedule of assessments is in Section 7.1.1.

9.1 Efficacy Assessments

9.1.1 Patient-reported Outcomes

PROs to be conducted in this study are outlined below. A PRO questionnaire schedule for the study is provided in Appendix 17.2.

9.1.1.1 Cryolipolysis Satisfaction Questionnaire (CSQ) Subject Satisfaction Patient-Reported Outcome Survey

The CSQ is a 4-item PRO instrument that measures patient satisfaction with CoolSculpting treatment of the flank and abdomen. The questionnaire assesses patient satisfaction with treatment, visible fat reduction, improvement in fit of clothing, and overall effect of treatment. The CSQ consists of 3 versions: CSQ-Abdomen (Appendix 17.4), CSQ-Flank (Appendix 17.5), and CSQ-Abdomen and Flank (Appendix 17.3). Initial draft of the questionnaire was developed based on questions used in previous CoolSculpting studies and was revised based on hybrid concept elicitation and cognitive debriefing interviews with 6 patients.

The CSQ will be administered during office visits before treatment at Week 8 (Visit 4a) and during follow-up/exit visits at Weeks 12 (Visit 6, for patients who receive 1 treatment session) and 20 (Visit 7, for patients who receive 2 treatment sessions). Patients with abdomen only treatment will only be administered the CSQ-Abdomen version. Patients with flank only treatment will only be administered the CSQ-Flank version. Patients with both abdomen and flank treatment will be administered all 3 CSQ versions: CSQ-Abdomen, CSQ-Flank, and CSQ-Abdomen and Flank.

[redacted]

[redacted]

9.1.2 Assessment for 3D Volumetric Loss

The 3D [redacted] system will be used to obtain a 360° stitched image of the body. The system is composed of a 3D stereoscopic camera, tripod, and a turntable that gently rotates, stopping at one-eighth increments (45° angle rotation), to obtain 8 images of the body. The 8 images are then reconstructed to obtain a 360° image of the body and allowing quantification of the abdomen and flank areas.

To obtain optimal results, proper subject conditioning, camera orientation using the tripod, room organization, and standard backgrounds are all critical to minimize volume variations due to natural variability of the anatomy. In addition, each site will be provided with a detailed Image Procedure document, a training video, on-site training, and qualifications to ensure strict adherence to the imaging aspects of the study.

A [redacted]mera will acquire a 3D representation of the anatomical surface of the body. The skin surface is "textured" and the color and intensity patterns on its surface enable the stereoscopic 3D reconstruction methods to be applied.

[redacted] matching technology uses a 2-step matching algorithm process. First, the baseline and post-treatment images are matched to the overall global area. Next, to quantify the volume variation, a trained technician defines a Region of Interest on the baseline surface, defined as a cylinder on the shape of the 3D contour. The defined cylinder enclosed on the baseline surface and the follow-up surface on the other side is used to determine the actual volume.

The volume change is provided in cubic centimeters (cc) units and is illustrated by an Elevation Color Map. The following color codes are used to indicate the magnitude of volume change: gray is no change, smaller negative volumes in light blue, larger negative volumes in dark blue, smaller positive volumes in yellow, and larger positive volumes in red.

9.2 Safety Assessments

9.2.1 Adverse Events

Throughout the course of the study, all AEs will be reported and monitored on an AE CRF, including event name, duration, seriousness, relatedness, severity, action taken, and outcome. If AEs occur, the first concern will be the safety of the study participants.

All events and device deficiencies are to be recorded on the corresponding CRF for the patient upon the site becoming aware of said event.

AEs will be collected throughout the study once there is a signed ICF. At each visit, the investigator or designated study staff will solicit and assess the patient for AEs. Previously recorded AEs and changes in therapy/concomitant medications are to be updated as necessary. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate electronic CRF (eCRF).

Adverse Event Definition

An AE is defined in accordance with International Organization for Standardization (ISO) 14155 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, if related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. Disease signs and symptoms that existed before the study treatment are not considered AEs unless the condition recurs after the participant has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

AEs will be monitored throughout the study once the subject has signed the informed consent form. At each post-baseline visit, the investigator will begin querying for AEs by asking each participant a general, non-directed question such as “Have you had any changes to your condition since your last visit?” Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.

Adverse Device Effect

An ADE is defined in accordance with ISO 14155 as “an AE related to the use of an investigational medical device.” This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

Device Deficiency or Complaints

A device deficiency is defined in accordance with ISO 14155 as inadequacy of a medical device including issues with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

If a device deficiency occurs, the investigator will notify Allergan using the CRF. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. The Clinical Trial Site will enter all the information regarding device deficiency into the appropriate CRFs. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. These shall be reported to the regulatory authorities and IRBs as required by Federal regulations.

Assessment of Severity

Severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE will be assigned a category by the investigator as follows:

Mild	An AE that is easily tolerated by the subject, causes minimal discomfort, may require only minimal treatment and does not interfere with everyday activities.
Moderate	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed, but poses no significant or permanent risk of harm.
Severe	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Relationship to a device refers to a determination of the relationship (if any) between an AE and the device. A causal relationship is present if the investigator determines that there is a reasonable possibility that the AE may have been caused by the device.

An AE could be considered procedure-related when, in the judgment of the investigator, it is reasonable to believe that the event is associated with the procedure, regardless of the relationship to the study device. Procedure-related causes that contribute to the occurrence of the event can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the device and/or study procedure. Causality should be assessed using the categories presented in the following table:

Not related	Clinical event of which the relationship to the device and/or procedure can be excluded, such as if the event is incompatible time relationship to study procedure and/or use of the device, involves a body part or organ not expected to be affected by the device or procedure, could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study device, and is not due to use error.
Unlikely	Clinical event whose time relationship to use of the device and/or study procedure makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible	Clinical event with a reasonable time relationship to the use of the device and/or study procedure, but that could also be explained by concurrent disease or other drugs or chemicals. Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	Clinical event with a reasonable time relationship to the use of the device and/or study procedure, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Causal relationship	Clinical event with plausible time relationship to the use of the device and/or study procedure, is a known side effect of the product category the device belongs to or of similar devices and procedures; follows a known response pattern to the medical device; involves a body-site or organ that the device or procedures are applied to and/or influence; harm is due to error in use, and that cannot be explained by concurrent disease or other drugs or chemicals.

Follow-up of Adverse Events

All investigators should follow up with subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE in the appropriate CRF fields:

- Description of the symptom event.
- Classification of ‘serious’ or ‘not serious.’
- Severity.
- Date of first occurrence and date of resolution (if applicable).
- Action taken.

- Causal relationship.
- Outcome of event.

9.2.1.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is defined as an AE that:

- led to death
- led to serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury; or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization; or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
    - if a subject becomes pregnant, then spontaneous abortion, fetal distress, fetal death, or a congenital abnormality or birth defect is considered an SAE

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Serious Adverse Device Effect (SADE)

An ADE that resulted in a SAE or that might have led to any SAE consequences if a suitable action had not been taken or intervention had not been made.

All device or surgical related SAEs must be entered into the electronic data capture (EDC) system within 24 hours of being notified of the event. The sponsor will be notified by EDC system once the SAE electronic form has been submitted.

- The relationship of the clinical event to the devices and procedure should be reported on the Form and will be determined by the investigator.
- Following evaluation of each SAE, the responsible ethics committee will be notified as appropriate based on national regulations.

- All SAEs that occur from the time the ICF is signed through to their final study visit must be reported to the sponsor. In addition to entering the information into the EDC system, the investigator must:
    - Notify the sponsor immediately (within 24 hours) by emailing the Allegan Product Surveillance team at: CoolSculptingProductSurveillance@allergan.com using SAE form.

The following SAE information should be provided:

- Description of the symptom event (including treatment dates, areas treated, event description, etc.)
- Applicator(s) and Serial Number used during treatment
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event Report as much information within 24 hours regardless of the amount of information available, although the investigator is expected to provide as much information as possible.

Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.

Provide the sponsor with a complete, written case history (AE report form) that includes a statement as to whether the event was or was not related to the use of the investigational device or procedure.

The sponsor (or its representative) will report all SAEs associated with the use of the study device to the regulatory agencies (Ethics Committee, Competent Authorities) as appropriate according to relevant standard operating procedures and to the national laws of the country where the trial is performed.

In every SAE, appropriate measures should be taken to treat/resolve and monitor the subject. The investigator should keep Allergan closely informed of the progress as related to the SAE. Any subjects who are withdrawn from the study due to an AE shall still be followed until the outcome is resolved.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 7.3.4.

9.2.1.2 Unanticipated Serious Adverse Device Effect

Unanticipated Serious Adverse Device Effect Definition

An unanticipated serious ADE is a SADE effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

9.2.2 Warnings and Precautions

Unauthorized modification or repair of the control unit, its components, or supplies may result in unsafe conditions and/or impaired performance. No modification of this equipment is allowed without express authorization from ZELTIQ. Any unauthorized modification or repair will void the warranty.

CoolSculpting System use has not been studied in children, those who are pregnant or lactating, or who have:

- Known sensitivity to cold such as cold urticaria, Raynaud's disease, or Chilblains (pernio)
- Known sensitivity or allergy to fructose, glycerine, isopropyl alcohol, or propylene glycol
- Impaired peripheral circulation in the area to be treated
- Neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy
- Impaired skin sensation
- Open or infected wounds
- Bleeding disorders or concomitant use of blood thinners
- Recent surgery or scar tissue in the area to be treated
- Hernia in or adjacent to the treatment site
- Skin conditions such as eczema, dermatitis, or rashes in the area to be treated

9.2.3 Other Laboratory Variables

Screening for pregnancy will be performed (urine β-HCG at Screening, Treatment 1, and at Treatment 2 only).

9.3 Data Safety Monitoring Board

Not applicable.

9.3.1 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

10 STATISTICAL METHODS

The purpose of the study is to obtain PROs and have more subjects treated and studied at international sites. There is no statistical hypothesis to prove in this study. More details on the methods of statistical analysis, on statistical summary, and on the derivation of some statistical variables can be found from the statistical analysis plan.

10.1 Determination of Sample Size

The primary objective of this Phase IV study is to estimate the overall satisfaction rate, which is the proportion of subjects who report overall satisfaction with CoolSculpting treatment in real-world clinical settings. Consequently, the sample size will be based on providing reasonable precision for the estimate of overall satisfaction rate.

Previous studies conducted on subjects undergoing flank or abdominal fat reduction using CoolSculpting products reported moderately high overall satisfaction rate. The mean overall satisfaction rate was 65.8% from the study (protocol: ZA15-004) based on 19 subjects, and 63.3% from another study (Protocol: ZA10-001) based on 60 subjects. The weighted average of rates from the 2 studies, which is 63.9%, is now used as the initial estimate of the mean overall satisfaction rate for this planned study. A sample size of 98 subjects would provide a 10% margin of error (associated with 95% CI) for the estimate of the 63.9% expected rate. Allowing a 10% dropout during the study period, approximately 108 subjects will be needed for recruitment into the study.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Evaluable	All participants who sign the ICF, have at least one of the procedures conducted, and also report the CSQ Item #1 at 12 weeks after the final treatment (measured at Week 12 for participants who receive 1 treatment session and at Week 20 for participants who receive 2 treatment sessions).
Safety	All participants who have at least one of the procedures conducted.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses. This section is a summary of the planned statistical analyses of the primary, secondary endpoints, exploratory endpoints, and safety parameters.

10.3.1 Disposition, Baseline and Study Information

In general, the disposition data, patient baseline and characteristics data, and concomitant therapy data will be summarized descriptively. The categorical variables will be presented with

count and percentage and the continuous variables will be presented with mean, standard deviation, median, minimum, and maximum.

10.3.1.1 Patient Disposition

The number of subjects who have enrolled into the study, the number and percentage of subjects who have had the procedure, and the number and percentage of subjects who have had all follow-up visits will be summarized.

The number and percentage of subjects who are evaluable and the number of subjects who are in safety population will be also summarized.

10.3.1.2 Patient Baseline and Characteristics

Demographics (age, sex, and race) of subjects will be summarized.

A summary on height, weight, and BMI will be also provided. The number and percentage of subjects by BMI category (18.5 to < 25; 25 to ≤ 30) will also be provided.

10.3.1.3 Concomitant Therapy

Concomitant therapy that a patient has during the study will be recorded and summarized.

10.3.1.4 Treatment Compliance

Treatment compliance will not be applicable in the study.

10.3.2 Efficacy Analyses

The evaluable patient population will be the analysis population used for efficacy.

10.3.2.1 Primary Analyses

The primary endpoint will be CSQ Item #1 measured at Week 12 for subjects who receive 1 treatment session and at Week 20 for subjects who receive 2 treatment sessions.

Subjects who have reported ‘Very satisfied’ and ‘Satisfied’ will be categorized as ‘Satisfied.’ The counts and percentage will be summarized and the 95% CI on the percentage will calculated with normal approximation.

10.3.2.2 Secondary Analyses

All secondary endpoints will be measured at Week 12 for subjects who receive 1 treatment session and at Week 20 for subjects who receive 2 treatment sessions. The analyses on the secondary endpoints will include:

- Proportion of subjects by treated area(s) (abdomen alone, flanks alone, and both abdomen and flanks) with “satisfied” or “very satisfied” on CSQ Item #1.

- Proportion of subjects by number of treatment cycles who receive 1 or 2 treatment sessions with "satisfied" or "very satisfied" on CSQ Item #1.
- Proportion of subjects by BMI categories (18.5 to < 25; 25 to ≤ 30) with "Satisfied" or "Very Satisfied" on CSQ Item #1.
- Mean change in volume of fat from baseline as measured by 3D photography.

Subjects who have reported 'Very satisfied' and 'Satisfied' will be categorized as 'Satisfied.' The count and percentage of patients with the same categories as the primary endpoint for CSQ Item #1 will be summarized and the 95% CIs for the percentages will be calculated. Descriptive summary statistics of change in volume of fat from baseline will be provided.

[redacted]

10.3.3 Safety Analyses

The safety population will be the analysis population used for safety analyses.

Frequency of AEs including SAEs and ADEs including SADEs will be summarized.

10.3.4 Subgroup Analyses

Subgroup analysis for the primary and secondary endpoints will be summarized by selected race groups. Additional subgroup analyses will be discussed in the study statistical analysis plan.

10.3.5 Interim Analyses

No interim analyses are planned for this study.

10.4 Protocol Deviations

The incidence of major protocol deviations will be summarized for the evaluable population.

Major protocol deviations will be determined before database lock. Details can be found in the statistical analysis plan.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion

12.2 Monitoring

Data for each subject will be recorded on a CRF. Data collection must be completed for each subject who signs an ICF and is administered study treatment.

In accordance with current GCP and, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the independent ethics committee (IEC)/IRB, the sponsor's internal auditors, and representatives from regulatory authority's direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs

12.3 Data Management and Coding

The sponsor or sponsor's agent will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of sponsor or agent.

Study centers will enter data directly into an EDC system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA Code of Federal Regulations 21 Part 11 compliant.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

13 RECORDS AND SUPPLIES

13.1 Device Accountability

Not applicable.

13.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the sponsor and investigator's site.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s). The study subjects will be informed about this new information and reconsent will be obtained.

14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

16 REFERENCES

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17 APPENDICES

17.1 Investigator Signature Page

Protocol Title: International CoolSculpting: Prospective, Multi-Country, Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks
Protocol Number: CMO-MA-PLS-0602

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant regulatory guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Allergan and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Allergan and IEC/IRB, and approval will be obtained before any amendments are implemented.

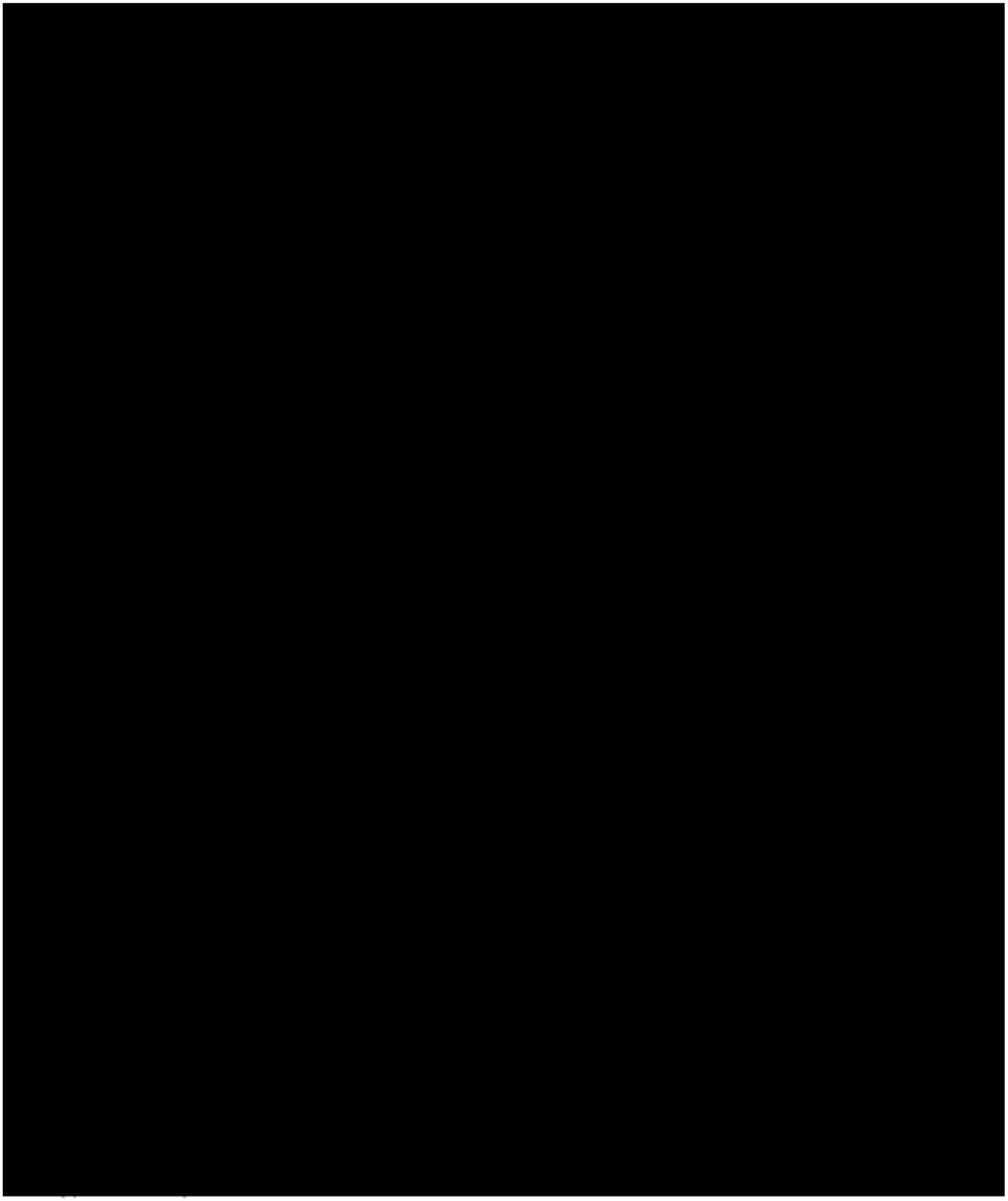
I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

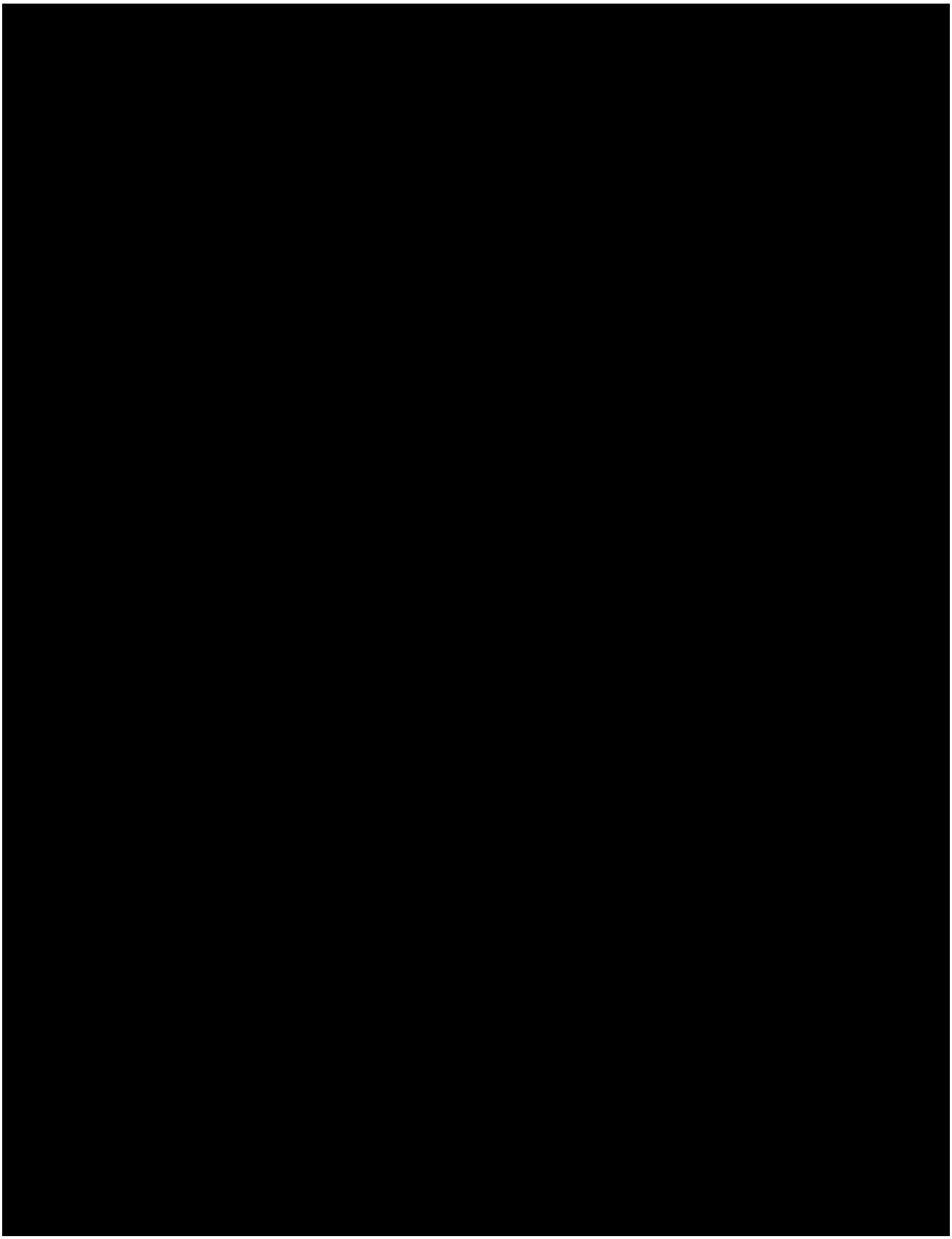
Information developed in this clinical study may be disclosed by Allergan, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

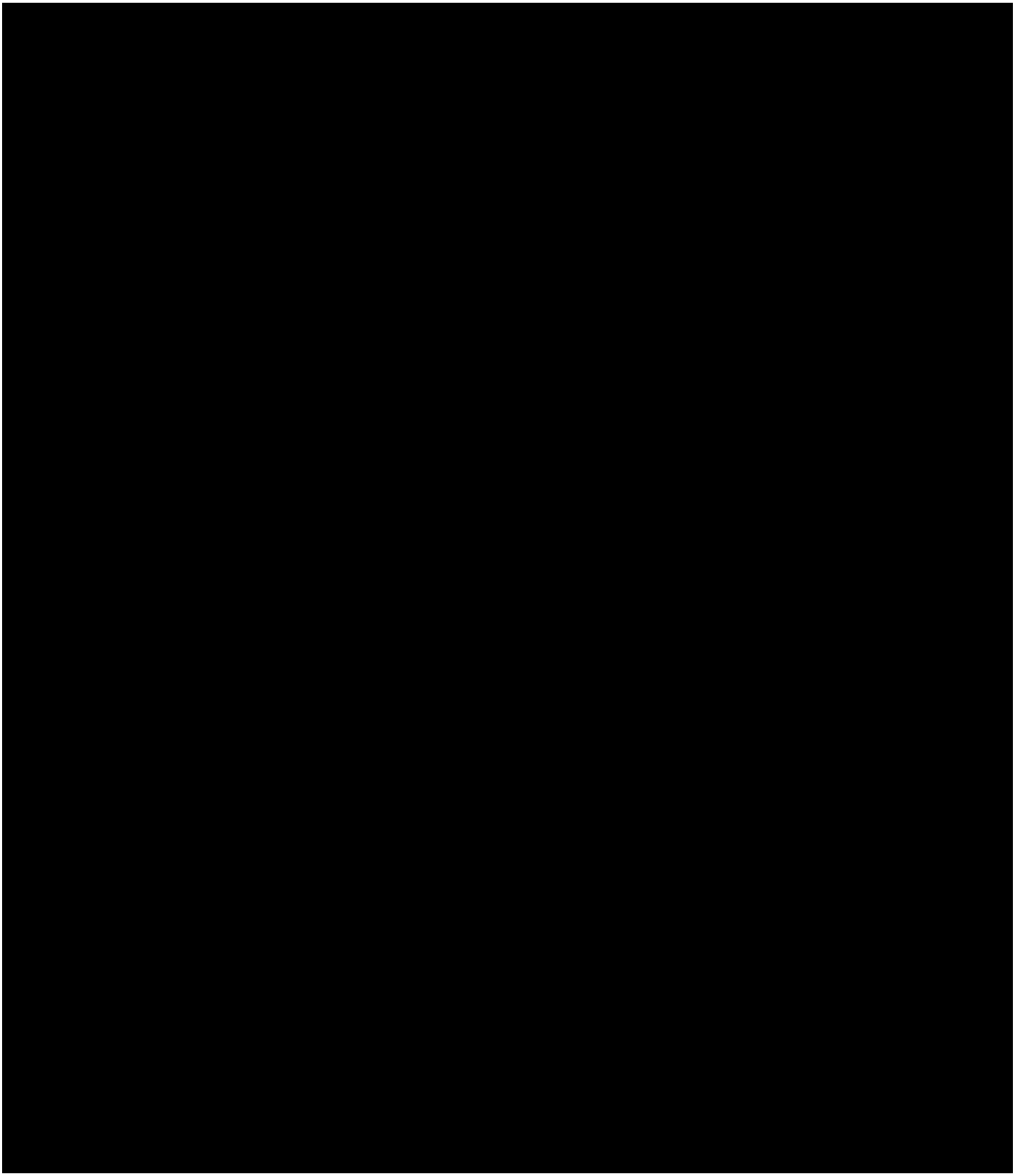
_____ _____
Investigator Signature Date

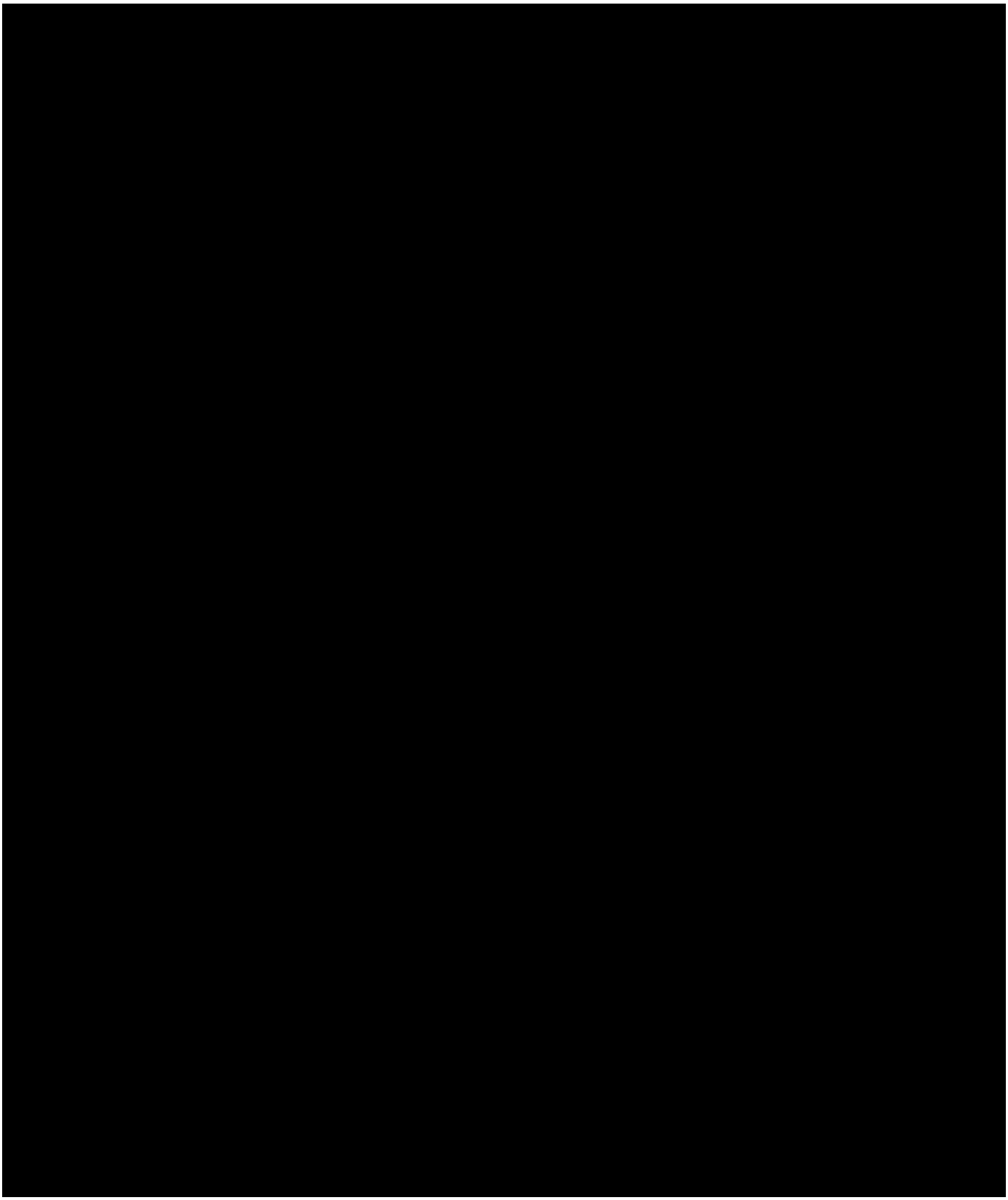
_____
Printed Name

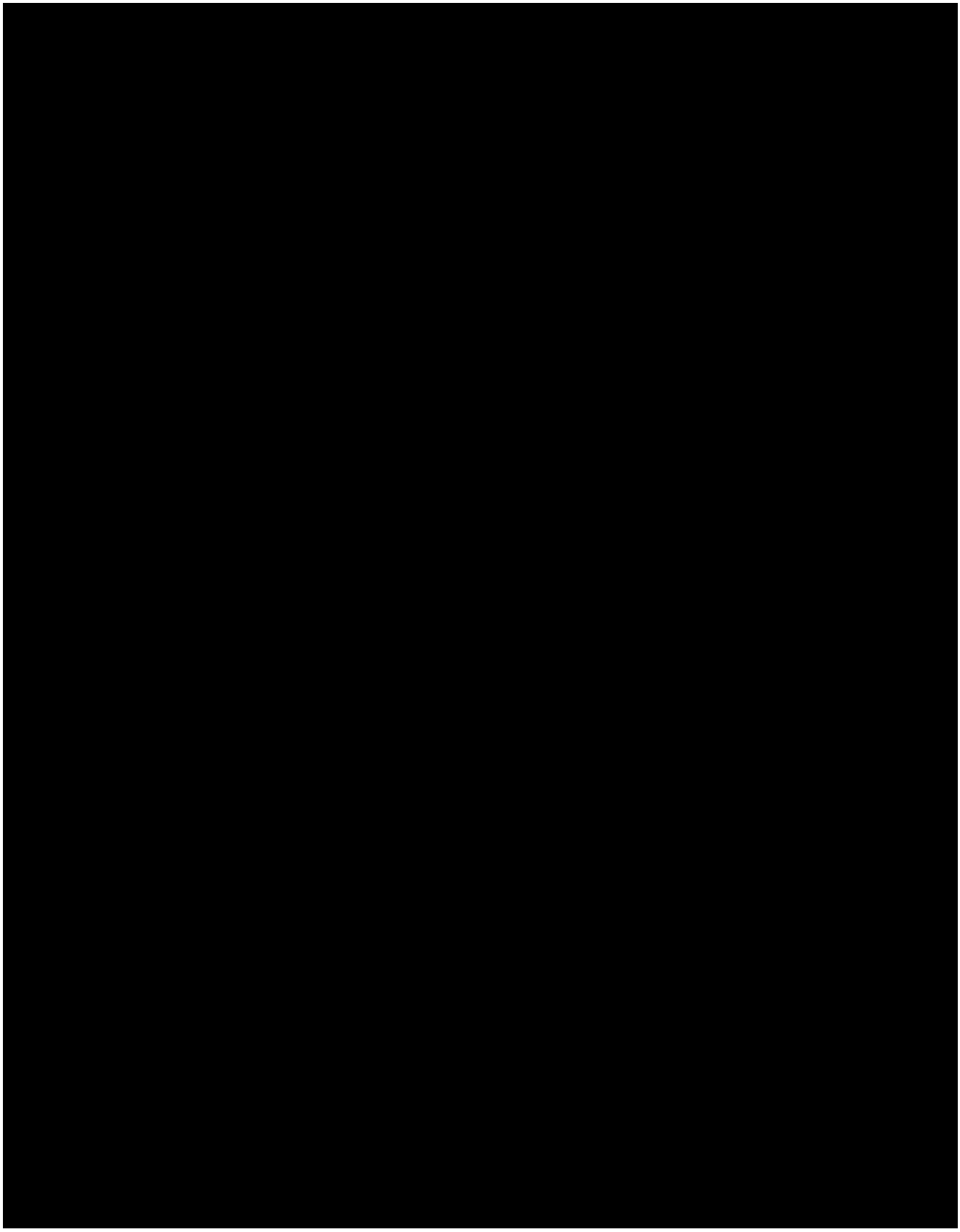
_____
Institution

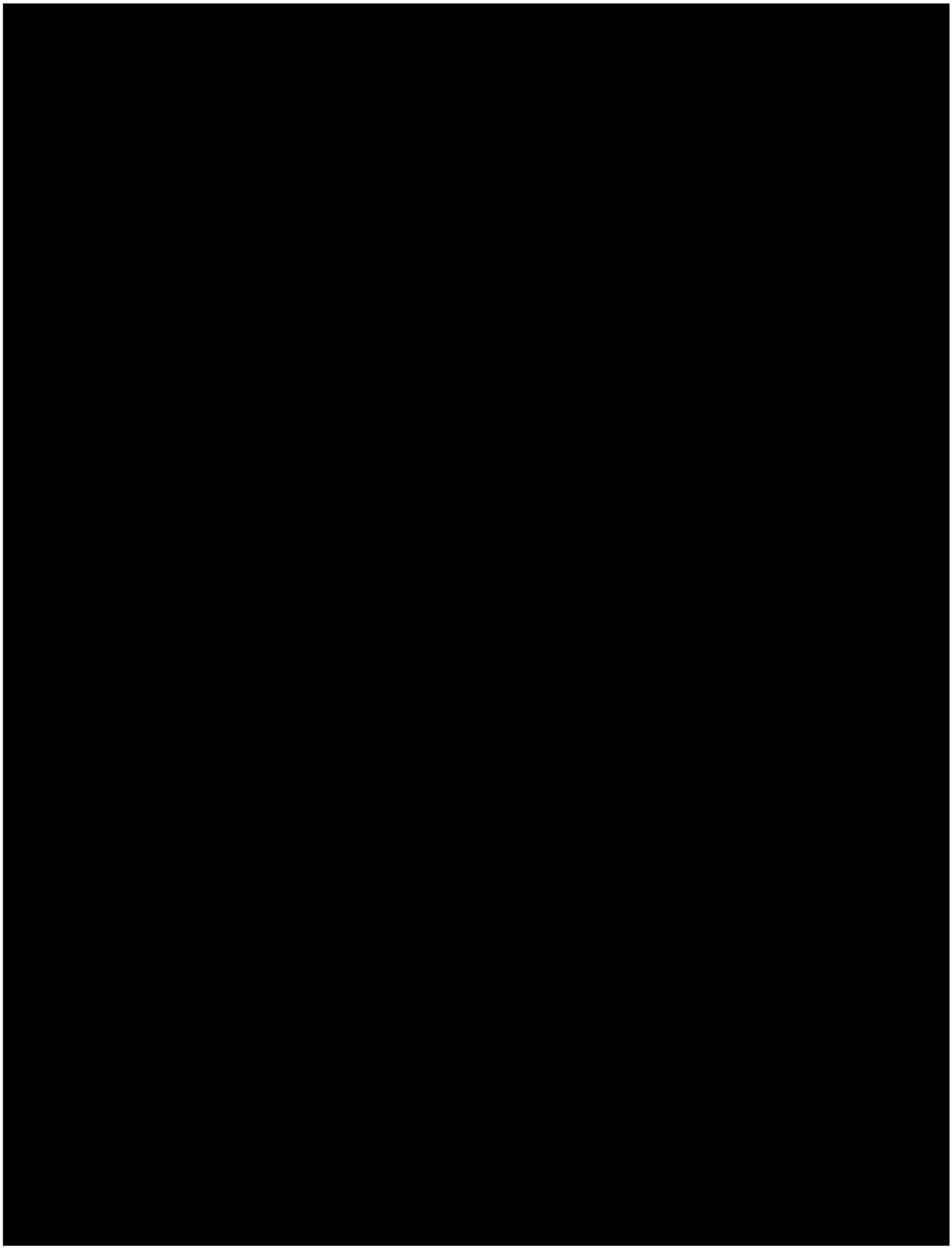


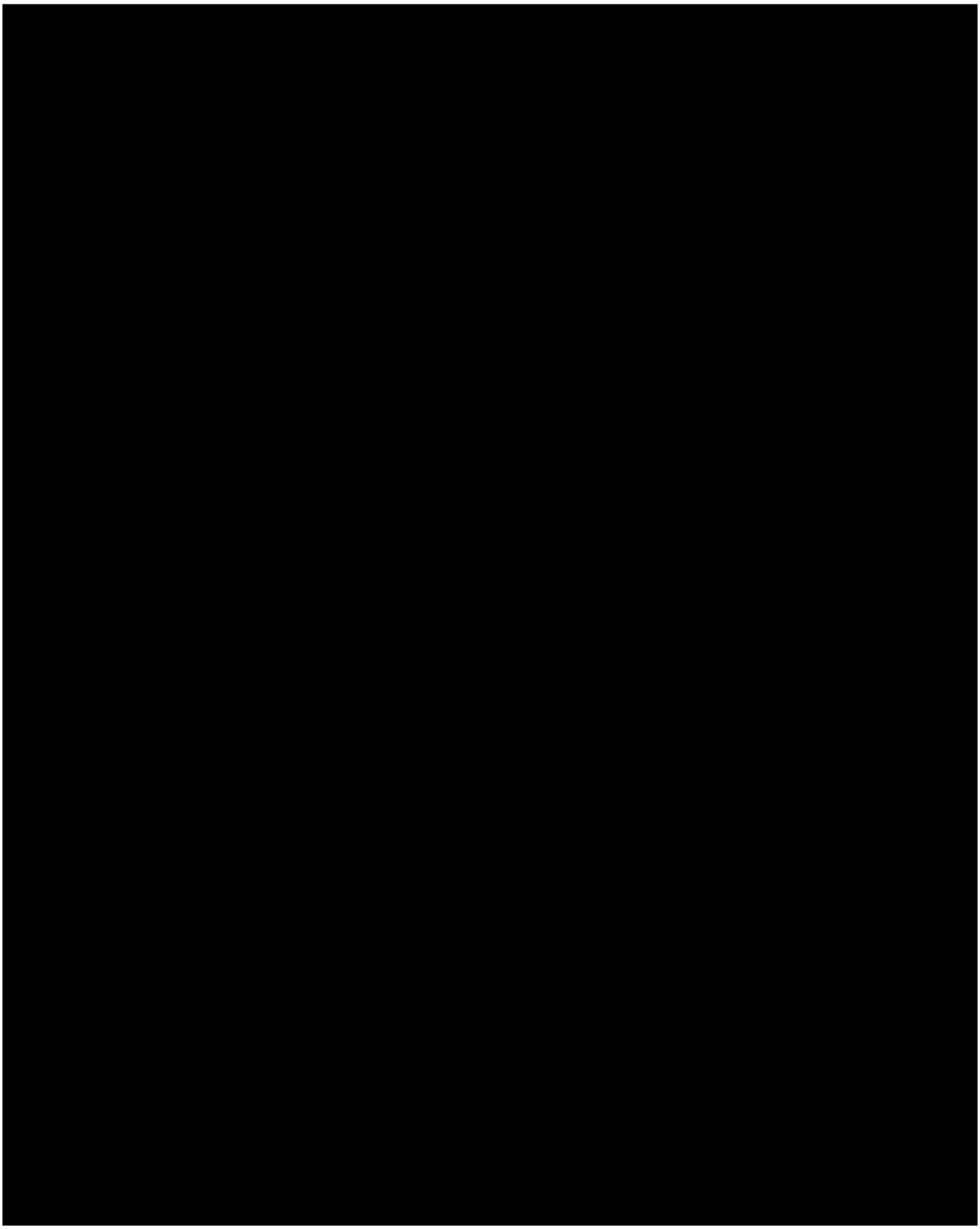


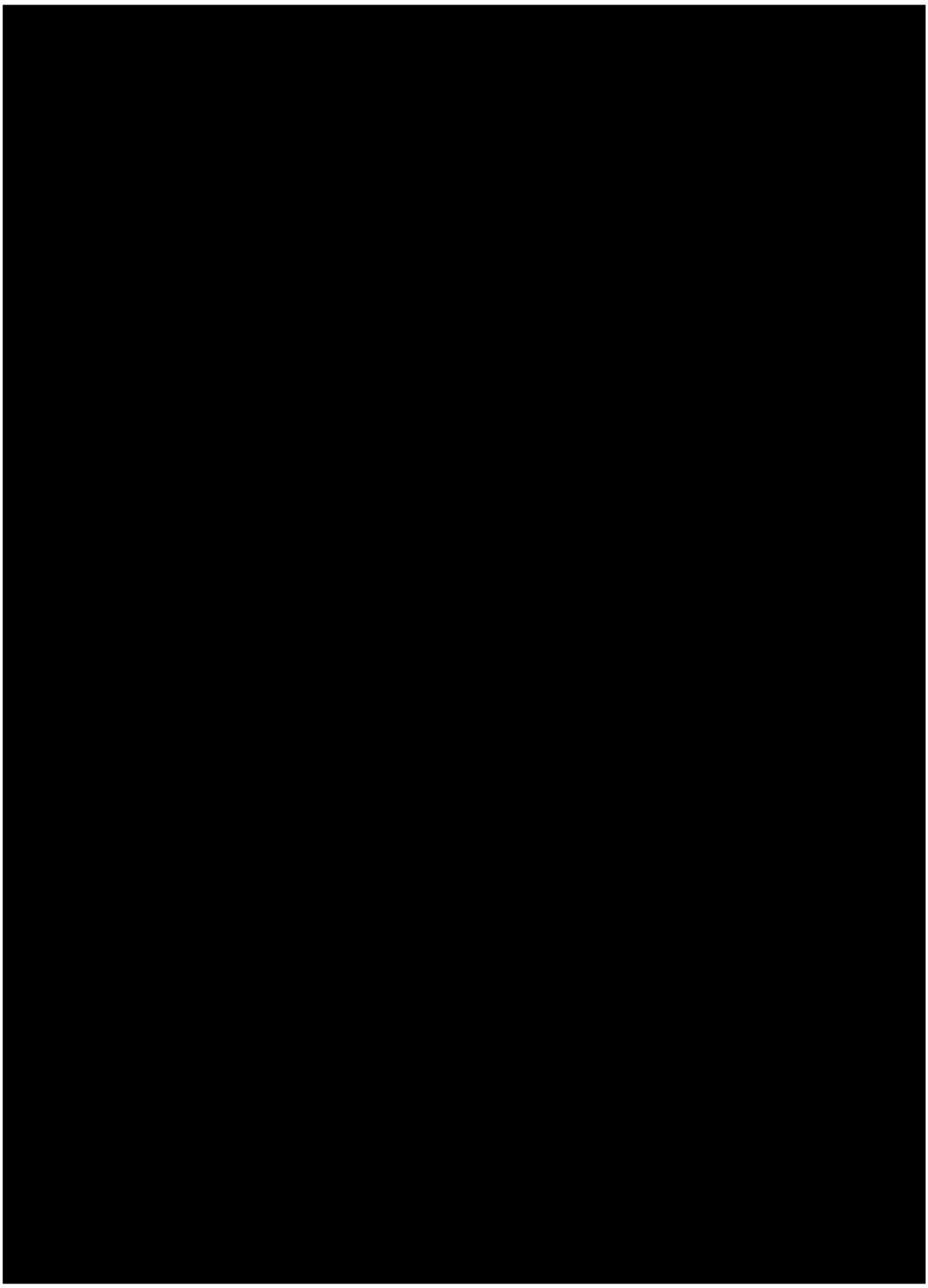












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