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Study ID: MED-MA-PLS-0633

Title: CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Statistical Analysis Plan Date: October 2, 2019

[redacted]

Statistical Analysis Plan for Interventional Studies

Protocol Number: MED-MA-PLS-0633
Protocol Title: CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Investigational Product: CoolSculpting®

Phase: Post-marketing

Sponsor: Allergan Sales, LLC
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USA

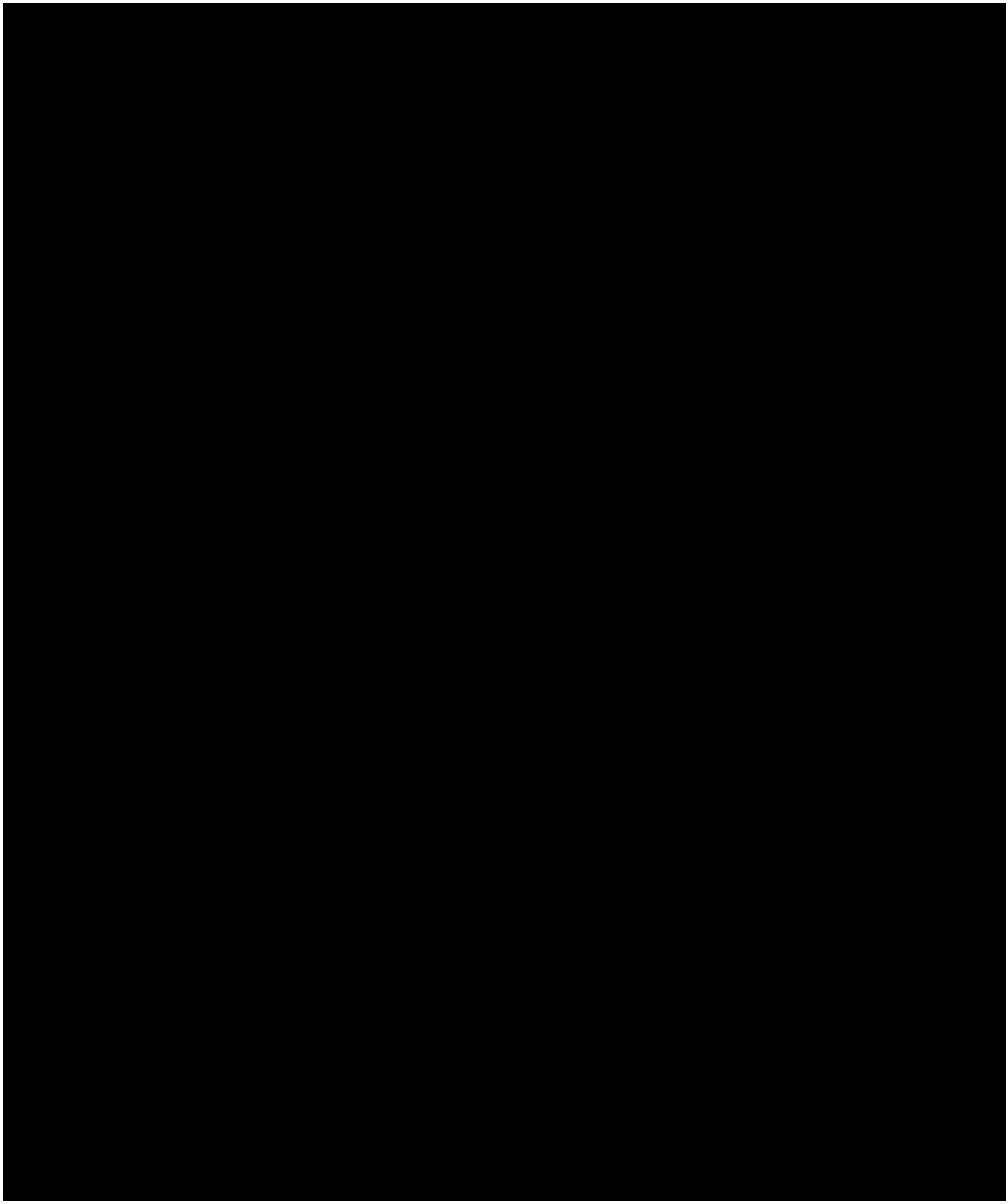
Protocol Version and Date: Version 1.0, 02-Oct-2019

[redacted]

Authors: [redacted]

Revision History

Version #	**Date** (DD-Mmm-YYYY)	**Document Owner**	**Revision Summary**



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1. Glossary of Abbreviations

Abbreviation	Description
ADE	Adverse Device Event
AE	Adverse Event
AT	As-Treated
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CTMS	Clinical Trial Management System
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
NIFR	Non-Invasive Fat Reduction
PP	Per-Protocol
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UADE	Unanticipated Adverse Device Effect
WHO DD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. All analyses included within this plan will be descriptive in nature; there are no plans for statistical hypothesis testing or comparisons between groups.

2.1. Responsibilities

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and effectiveness is planned after all participants complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

3. Study Objectives

The objective of this study is to evaluate the safety and effectiveness of the Allergan CoolSculpting system using CoolAdvantage and CoolAdvantage Petite applicators for non-invasive fat reduction (NIFR) of the upper arms and inner thighs in participants of Chinese descent.

3.1. Brief Description

This is a multi-center, prospective, open-label, nonrandomized, interventional cohort, medical device post-marketing study.

The purpose of this study is to collect meaningful clinical data for the use of CoolSculpting in participants of Chinese descent (to be conducted in Canada) using the current CoolAdvantage and CoolAdvantage Petite applicators for the upper arm and inner thigh body areas.

Participants will undergo a CoolSculpting treatment in an outpatient clinical setting. A treatment is comprised of timed segments of cooling. 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, is a non-invasive cooling device that applies controlled cooling to a treatment site on the participant's skin.

Approximately 42 participants will be enrolled at approximately 2-3 sites.

Screening (8 days), enrollment, and follow-up is expected to take approximately 3 months in total for each participant.

Participants who do not comply with the protocol or who withdraw consent will not be replaced. Participants who stop study treatment for any other reason will not be replaced.

3.2. Participant Selection

To be eligible to participate, participants must meet all of the inclusion criteria and none of the exclusion criteria listed below.

3.2.1. Inclusion Criteria

The inclusion criteria are detailed in section 6.3.2 of the protocol.

3.2.2. Exclusion Criteria

The exclusion criteria are detailed in section 6.3.3 of the protocol.

3.3. Determination of Sample Size

In this study, both arms and thighs will be evaluated by independent raters. The independent raters' evaluations will be combined into one clinical judgement on each arm and thigh. The evaluations on arms and thighs will be considered as independent.

A previous study described that the rate of correct identification was 83%. Using 75% as the lower bound of the two-sided exact 95% confidence interval (CI), the ½-width of the two-sided exact 95% CI will be 8%.

Based on these assumptions, we will need 60 evaluable arms or 32 evaluable participants for the arm evaluations with the assumption that less than 10% of participants have only one arm evaluation available. The same number of participants for thigh evaluations will be needed.

With an assumption that only 80% of all participants will have both arms and thighs treated, we will need 38 evaluable participants in total for the study. Adding a 10% attrition rate, we will need to enroll 42 participants in the study.

3.4. Treatment Assignment & Blinding

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

This is an open-label study. Blinding will only be employed for photograph review by an independent panel of physician reviewers with expertise in the areas of dermatology and/or plastic surgery.

3.5. Administration of Study Medication

Participants will undergo CoolSculpting treatment(s) in an outpatient clinical setting using CoolAdvantage and/or CoolAdvantage Petite applicators. Each participant will undergo a single treatment session that comprises timed segments of cooling followed by 2 minutes of manual massage. Each treated arm will have up to two timed segments (or cycles) in the treatment session, each treated thigh will have one timed segment (or cycle) in the treatment session. Treatments will be administered according to the Canadian CoolSculpting System User Manual.

3.6. Study Procedures and Flow chart

Participants will provide written informed consent before any study-related procedures are performed.

Participants who meet all of the inclusion criteria and none of the exclusion criteria shall be eligible to participate in the study and the first treatment will be scheduled.

All participants will be asked to maintain their weight by not making any major changes to their diet or exercise routine during the course of the study. If the weight change is more than 5% of total body weight at 12 weeks after the treatment, the participant's data will be excluded from the primary effectiveness analyses (but the participant will continue in the study).

4. Endpoints

4.1. Primary Endpoint

Correct identification of baseline versus 12-week treatment images of the upper arms by at least two out of three blinded, independent reviewers. Success will be defined as at least 75% correct identification of the pre-treatment images.

4.2. Secondary Endpoints

1. Correct identification of baseline versus 12-week treatment images of the inner thighs by at least two out of three blinded, independent reviewers.
2. Participant response of 'satisfied' or 'very satisfied' for question 1 (overall satisfaction) on the following CoolSculpting participant questionnaires at the 12-week visit:
    a. Upper arms
    b. Inner thighs
3. Fat reduction using caliper measurements at 12-weeks compared to baseline for the following areas:
    a. Upper arms
    b. Inner thighs

4.3. Safety Endpoints

1. Adverse Events (AEs), including Serious Adverse Events (SAEs); and Adverse Device Events (ADEs), including Serious Adverse Device Events (SADEs).

[redacted]

5. Populations for Analyses

5.1. Enrolled Population

All screened participants who provide informed consent, receive participant ID, and provide demographic and/or baseline screening information, regardless of the participant's randomization and treatment status in the study.

5.2. Safety (SAF) Population

The safety population will consist of all the treated participants.

5.3. Per Protocol (PP) Population

The PP population will consist of all treated participants followed for 12 weeks and with weight change of no more than 5% of total body weight at the time the 12-week images are taken.

6. General Aspects for Statistical Analysis

6.1. General Methods

- [redacted] will be used to produce all listings, summaries, and analyses described in this document.
- Unless otherwise specified, summaries will be presented for each treatment area and overall.
- Continuous variables will be summarized using the number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max). Categorical variables will be summarized using number of observations (n), frequency and percentages of participants.
- All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings.
- Unscheduled assessments for visit based parameters will be listed but not summarized or analyzed; only data recorded on the nominal study visits will be included in summaries and analyses.
- Medical history data will be listed for the Enrolled Population sorting by participant number, start date (placing missing and partial dates first) and end date, then alphabetically by System Organ Class (SOC) and Preferred Term (PT) within SOC.
- Prior and concomitant medications will be listed for the Enrolled Population, sorted by participant number, start date (placing missing and partial dates first) and end date, alphabetically by Anatomic Therapeutic Chemical (ATC) level 2 category and then by preferred name within ATC level 2 category.
- All AEs will be listed, sorting by participant number, start date (placing missing and partial dates first) and end date, alphabetically by SOC, and then by PT within SOC. AE duration in days will be calculated as (end date - start date + 1) and included in the data listings.

6.2. Key Definitions

Day 1 is the study day on which CoolSculpting procedure is first performed. The study day of an assessment will be calculated as date of assessment - date of study day 1+1. Baseline assessments will be defined as the last assessments before performing CoolSculpting procedure.

6.3. Missing Data

No imputation of missing data will be made for any of the outcome variables.

For the purpose of assigning treatment-emergent AEs (TEAEs), prior and concomitant medications, and concomitant procedures, the followings rules will be applied for partial or missing start dates:

- If the day is missing, the first day of the given month will be used unless the month and year are the same as the month and year of enrollment, in which case the date of enrollment will be used.
- If the day and month are missing, the 1st of January will be used unless the year is the same as the year of enrollment, in which case the date of enrollment will be used.

- If the whole date is missing, the date of enrollment will be used.

Imputed dates will not be displayed in data listings.

Other dates will not be imputed.

6.4. Visit Windows

Data collected at unscheduled visits that occurred outside the time windows specified in the protocol (e.g., post-dose laboratory tests done on days not specified in the protocol) will be included in the data listings but will not be included in the analyses.

6.5. Pooling of Centres

Data from all investigational centers will be pooled for summaries and analyses.

6.6. Subgroups

Subgroup analyses will be described in section 10.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Participant Disposition and Withdrawals

The number of participants who have enrolled into the study, the number and percentage of participants who have had the procedure, the number and percentage of participants who have had all follow-up visits, and the number of participants who discontinued and the reasons for discontinuation will be summarized for Enrolled population.

Reasons for discontinuation from the study may include the following: Physician decision, Protocol deviation, Screen failure, Site terminated by sponsor, Study terminated by sponsor, Technical problems, Withdrawal by participant, Pregnancy, Adverse Even, and Other.

No formal statistical testing will be carried out on these data.

The number and percentage of participants included in each popution will be summarized. In addition, the number and percentage of participants excluded from PP population will be summarized descriptively by exclusion reason.

7.2. Demographic and Other Baseline Characteristics

The demographics (age, sex , race [including determination of 1st or 2nd generation Chinese descent]) of participants will be summarized descriptively.

The summary on height, weight, and Body Mass Index (BMI) will be also provided. The number and percentage of participants by BMI category (normal >=18.5 to <25, overweight >=25 to <=30) will also be provided.

Age at Day 1 = (Day 1) visit date - date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg) / [Height(m)^2]

Demographic data will be summarized for the safety and PP populations.

7.3. Medical History

Medical history will initially be coded using Medical Dictionary for Regulatory Activities (MedDRA) V22.1 or higher.

Medical history data will be summarized for the Safety Population. System organ class (SOC) terms are sorted using alphabetical order and preferred terms (PT) are sorted in decreasing frequency within SOC based on the number of participants.

7.4. Prior and Concomitant Medication

Prior medication is defined as any medication that was started and stopped before the date of first CoolSculpting procedure.

Concomitant medicationis defined as any medication that was taken on or after the date of first CoolSculpting procedure.

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Global (WHO DD Global) B3 September 2019.

Prior and concomitant medications will be summarized for the Safety Population by presenting the count and percentage of participants treated with each type of medication. Medications will be classified according to ATC categories (ATC Level 2) and the preferred name (generic name) sorted by the decreasing overall frequency of ATC level 2 category and then alphabetically by the preferred name within ATC level 2 category.

Missing/partial dates will not be imputed and listing/table will distinguish concomitant versus prior medications.

7.5. Concomitant Procedures

All concomitant procedures will be listed.

7.6. Protocol Deviations and Violations

Major protocol deviations (PDs) will be determined before database lock.

A deviation is any non-adherence to study procedures that does not result in additional risk to the participant (eg, participant missed a visit). Protocol deviations may or may not be required to be reported to the Institutional Review Board (IRB); however, they must be recorded on the source documentation as well as in the Clinical Trial Management System (CTMS) and may be reported and reviewed in conjunction with the progress report as part of the annual review process.

The process of recording and reporting PDs must be agreed with the sponsor before data collection starts.

PDs will be tracked in CTMS. The following CTMS PD categories will be utilized:

- Inclusion / Exclusion Criteria
- Informed Consent / data privacy: ICF not signed or signed late
- Study procedure: Site staff authorization, delegation, training
- Study procedure: missed procedure or visit

The protocol Deviations Report will be reviewed monthly during internal clinical team meetings as well as monthly during sponsor team meetings to identify any trends and action needed, if applicable.

8. Effectiveness Analyses

Photography: A series of baseline and follow-up photographs of the treatment areas will be taken using standardized set up, lighting, and camera settings to ensure consistency. Image files will be stored electronically by Allergan in addition to vendor and indexed by participant identifier. Copies of participant photographic data will be filed at the clinical site. Photos will be reviewed by a blinded independent panel of physician reviewers with expertise in the areas of dermatology and/or plastic surgery. All photographs will be blinded by removing the participant identification and dates of the photographs. The reviewers will be presented with two series of photographs for each treatment area, the pre-treatment and the post-treatment series, and asked to select the series representing the pre-treatment photographs. The order in which the photographs are presented will be randomized by participant. The order in which the pre- and post-treatment series are presented will also be randomized. The reviewers will be asked to select the baseline photograph series for each treatment area and record their data on individual data collection forms provided by the Sponsor.

Participant Satisfaction: Participant satisfaction data will be collected via written questionnaires at the final 12-week follow-up visit. These questionnaires have been developed based on questions used in previous CoolSculpting studies and modified to pertain to specific body areas treated (upper arms and inner thighs). One or two questionnaires will be provided depending on the body areas treated (upper arms and/or inner thighs). For the upper arm participant satisfaction questionnaire, see Appendix 20.1. For the inner thigh participant satisfaction questionnaire, see Appendix 20.2

Caliper Measurements: Caliper measurements of the treatment areas will be taken at baseline and at 12-weeks post treatment. After the treatment area is identified and marked, the thickness of the fat layer will be measured using a caliper at the middle of the fat bulge. For each treatment area, three measurements will be taken and recorded. The average of the three measurements will be calculated.

The primary effectiveness analysis will be based on the PP population.

8.1. Primary Effectiveness Analysis

The number and proportion of arms with correct identification of baseline vs. 12-week images of the upper arms by at least two out of three blinded, independent reviewers. Success will be defined as at least 75% correct identification of the pre-treatment images. The corresponding two-sided exact 95% CI of the proportion of arms with correct identification will be summarized.

8.2. Secondary Effectiveness Analysis

The number and proportion of thighs with correct identification of baseline vs. 12-week images of the inner thighs by at least two out of three blinded, independent reviewers and the corresponding two-sided exact 95% CI of the proportion of thighs with correct identification will be summarized.

Participants who have reported ‘Very satisfied’ or ‘Satisfied’ on each of the CoolSculpting participant questionnaires (upper arms and inner thighs) for question #1 (overall satisfaction) will be categorized as ‘Satisfied.’ The numbers and proportions of ‘Satisfied’ at 12-weeks visit will be summarized and two-sided exact 95% CI of the proportions will be provided for arms and thighs, respectively.

Fat reduction using caliper measurements at 12-weeks compared to baseline for upper arms and inner thighs will be summarized descriptively using the change from baseline to week 12 for arms and thighs,

respectively. Also, two-sided 95% CI of the mean change from baseline vs. Week 12 will be provided for arms and thighs, respectively.

9. Safety

The population used for safety analyses will be the Safety Population (SAF).

Safety will be assessed on the basis of adverse event (AE) or adverse device event (ADE), and other safety assessments.

The numbers and proportions of participants with TEAEs, Serious TEAEs, ADEs, SADEs, unanticipated ADEs, and unanticipated SADEs will be summarized. The numbers and proportions of participant-reported pain scores (0 to 10 scale) will be summarized.

9.1. Treatment Compliance

The treatment compliance will not be applicable in this study.

9.2. Adverse Events

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device or the comparator device. This definition includes events related to the procedures involved.

An SAE is defined as an AE that:

- led to death
- led to serious deterioration in the health of the participant, 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 participant becomes pregnant, then spontaneous abortion, fetal distress, fetal death, or a congenital abnormality or birth defect is considered an SAE

AEs will be coded using MedDRA V22.1 or higher.

AEs will be defined as treatment-emergent if they start after the first treatment. AEs with missing or partial dates will be handled according to Section **Error! Reference source not found.** with respect to assigning treatment-emergence. As a conservative approach, AEs are considered treatment-emergent unless there is clear indication that the event occurred before the first treatment in the study. In general, only TEAEs will be included in the summary tables, but all AEs will be included in the listings.

The number of participants and the number of TEAEs will be tabulated by SOC and PT, sorted by the decreasing overall frequency of SOC and then by PT in decreasing frequency within each SOC. For summaries by SOC, PT, and maximum severity, a participant will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, participants will only contribute once to each PT and once to each SOC level. Severity will be assessed as mild, moderate, or severe. For summaries by SOC, PT, and maximum

relationship (to study device or to study procedure), a participant will be counted once at the highest causality level for which the event occurred at the SOC level, and the highest causality level for each unique PT within that SOC level. Therefore, participants will only contribute once to each PT and once to each SOC level. Causality will be assessed in relation to the study device and the study procedure as not related, unlikely, possible, probable, or causal relationship.

An TEAE will be defined as device-related or procedure-related if it is assessed as unlikely, possible, probable, or causal relationship.

The following tables will be produced:

- An overall summary of the number and percentage of participants reporting TEAEs, device-related TEAEs, procedure-related TEAEs, and SAEs, including the total number of device-related TEAEs, procedure-related TEAEs, and TESAEs by overall.
- TEAEs, overall and by SOC and PT.
- TEAEs by maximum severity, overall and by SOC and PT.
- TESAEs, overall and by SOC and PT.

Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

9.3. Adverse Device Event

An ADE is any AE related to the use of an investigational medical device, including those events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

A serious adverse device event (SADE) is an ADE that resulted in any of the consequences characteristic of an SAE (all device or surgical related).

The number of participants and the number of ADEs will be tabulated by SOC and PT, sorted by decreasing overall frequency of SOC and then by PT within SOC.

The following tables will be produced:

- ADEs, overall and by SOC and PT.
- SADEs , overall and by SOC and PT.
- ADEs with maximum severity , overall and by SOC and PT.

All ADEs will be listed, sorting by participant number, start date (placing missing and partial dates first) and end date, alphabetically by SOC, and then by PT within SOC. ADE duration in days will be calculated as (end date - start date + 1) and included in the data listings.

9.4. Device Deficiencies or Complaints

Device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, such as malfunctions, misuse or use errors, and inadequate labeling.

The number and percentage of participants with at least one device deficiency that could have led to an SADE, along with the numbers of these events, will be summarized by overall for the safety population. For participants with at least one device deficiency that could have led to a SADE, the reasons for these deficiencies will be summarized. Device deficiencies will also be listed.

9.5. Laboratory Evaluations

Screening for pregnancy (urine β-HCG) will be performed at the Screening and Treatment visits. The pregnancy test results will be listed.

9.6. [redacted]

[redacted]

10. Subgroup Analyses

All efficacy and key safety will be presented for the following subgroups as appropriate:

- Investigational site.
- Generation

The number and proportion of arms with correct identification of baseline vs. 12-week images of the upper arms by at least two out of three blinded, independent reviewers. Success will be defined as at least 75% correct identification of the pre-treatment images. The corresponding two-sided exact 95% CI of the proportion of arms with correct identification will be summarized by generation (1st and 2nd generation).

The number and proportion of thighs with correct identification of baseline vs. 12-week images of the inner thighs by at least two out of three blinded, independent reviewers and the corresponding two-sided exact 95% CI of the proportion of thighs with correct identification will be summarized by generation (1st and 2nd generation).

Participants who have reported 'Very satisfied' or 'Satisfied' on each of the CoolSculpting participant questionnaires (upper arms and inner thighs) for question #1 (overall satisfaction) will be categorized as 'Satisfied.' The numbers and proportions of 'Satisfied' at 12-weeks visit will be summarized and two-sided exact 95% CI of the proportions will be provided for arms and thighs, respectively summarized by generation (1st and 2nd generation).

Fat reduction using caliper measurements at 12-weeks compared to baseline for upper arms and inner thighs will be summarized descriptively using the change from baseline to week 12 for arms and thighs, respectively summarized by generation (1st and 2nd generation).

An overall summary of the number and percentage of participants reporting TEAEs, device-related TEAEs, procedure-related TEAEs, and SAEs, including the total number of device-related TEAEs, procedure-related TEAEs, and TESAEs, by site and by generation (1st and 2nd generation).

In addition, TEAEs by SOC and PT will be produced by site and by generation (1st and 2nd generation).

11. Interim Analyses

No interim analyses are planned for this study.

12. Changes from Analysis Planned in Protocol

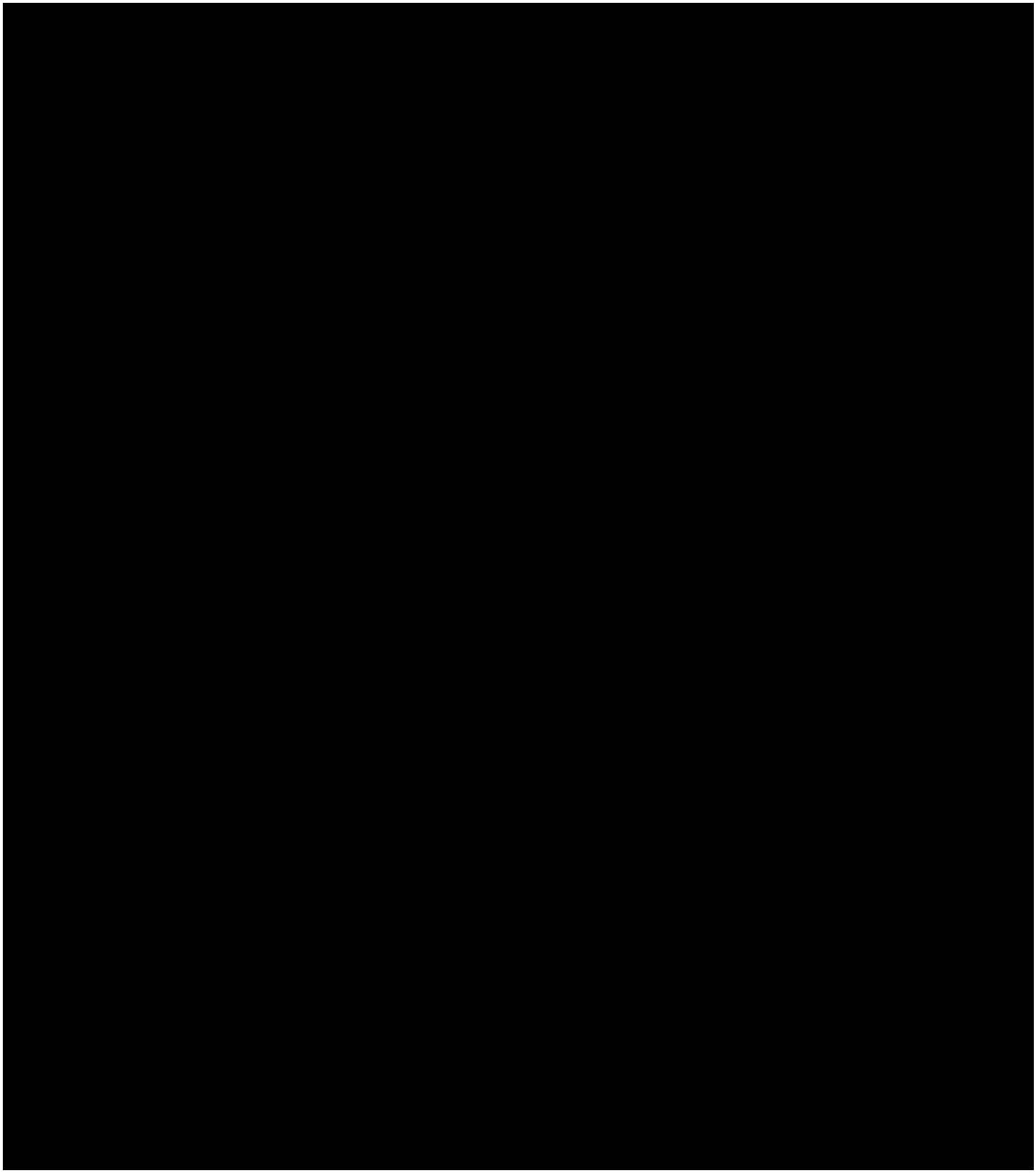
1. 'Day 1' is used in this SAP for the study day where 'Day 0' is used in the protocol.

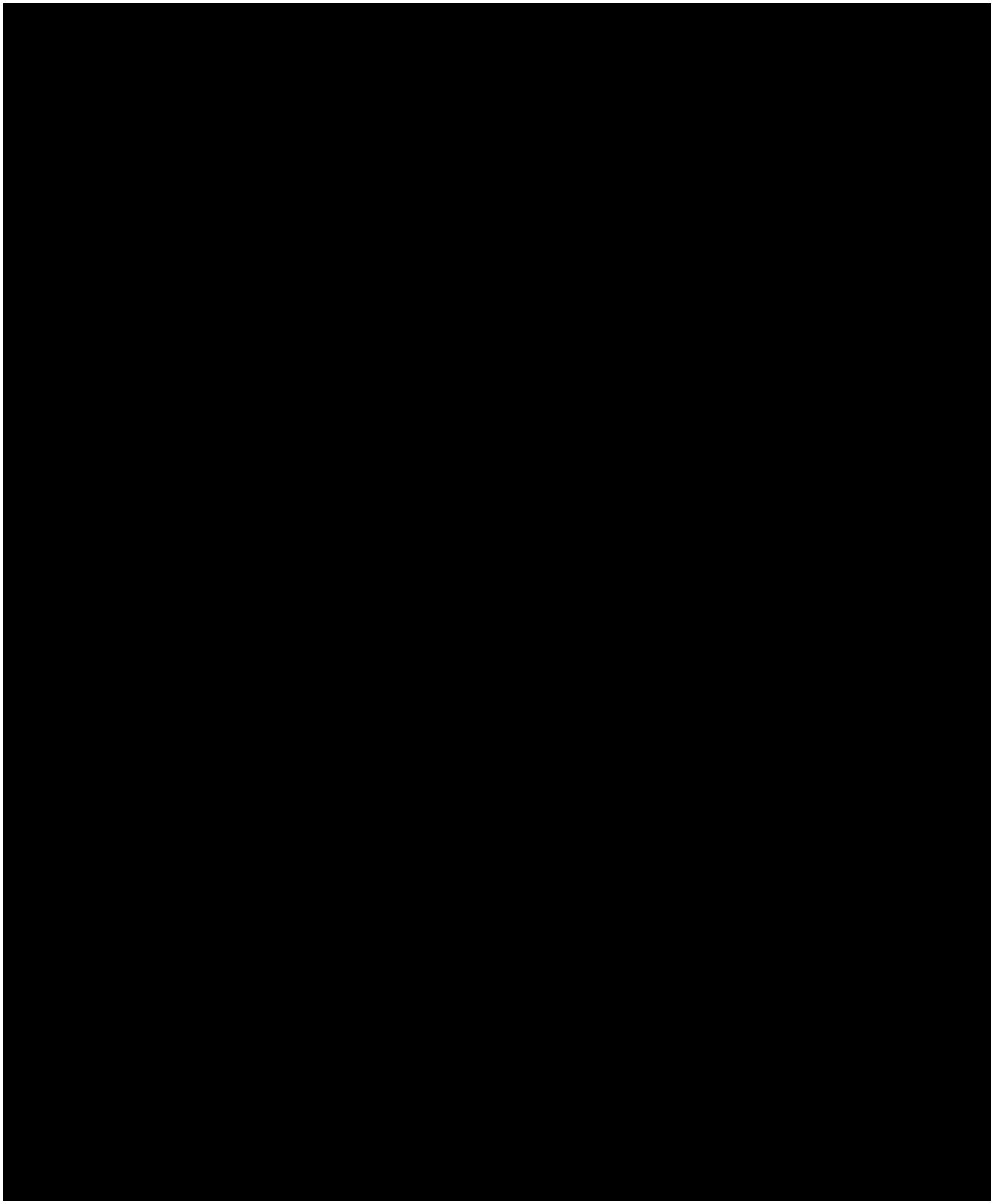
2. As per section 9.2 of the protocol, safety population was defined as 'The safety population will consist of all the treated participants with at least one safety evaluation after the treatment'; AT was defined as 'The AT population will consist of all treated participants regardless of weight change, etc.'. These two populations will consist same participants . Therefore, in the SAP, only one of them is defined as 'The safety population will consist of all the treated participants'.

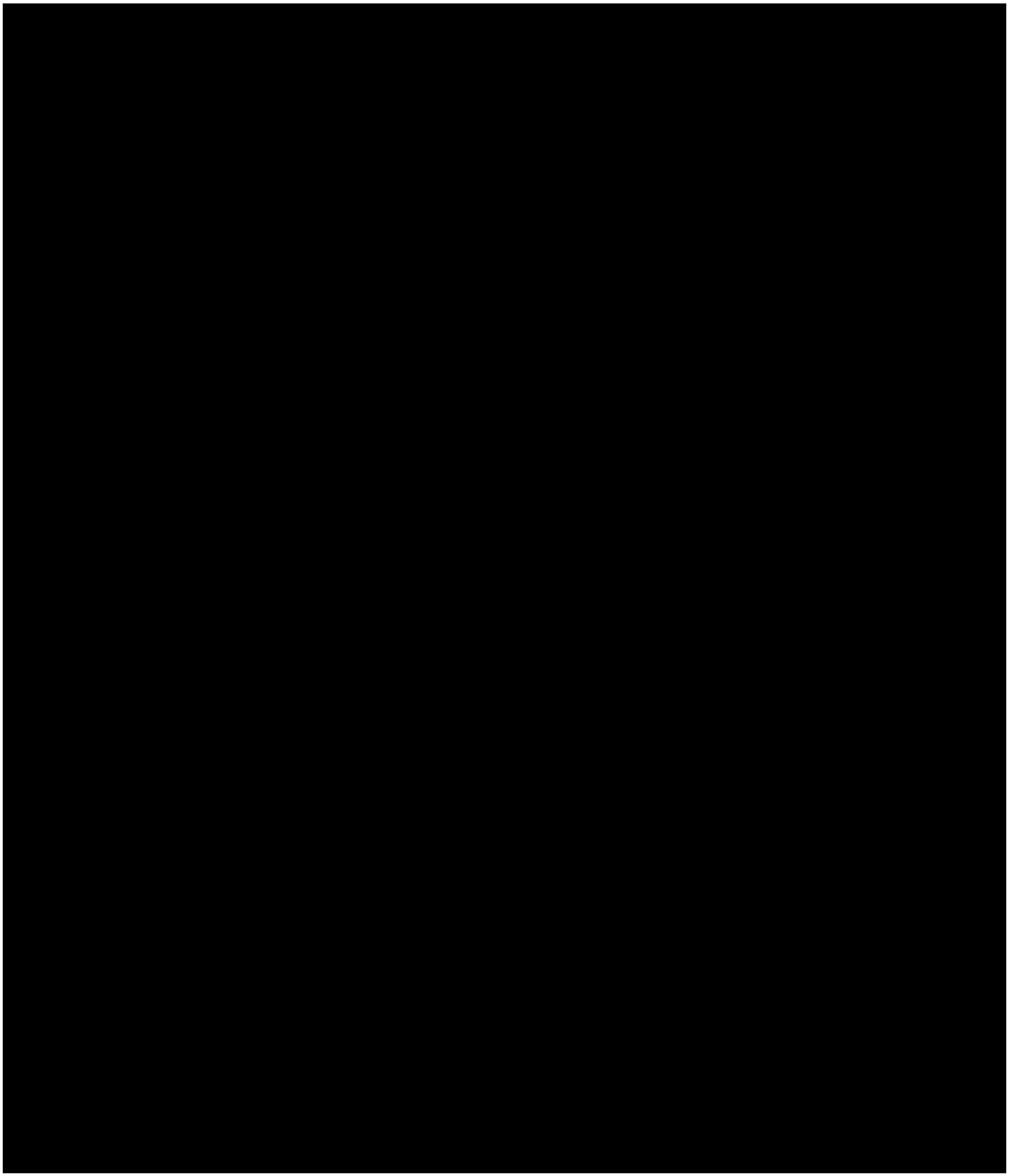
3. Sample size is calculated based on number of arms. 'participants' is a typo in the protocol. So, the term 'participants' is replaced by 'arms' appropriately. Similarly, 'participants' is a typo in the protocol for primary and secondary effectiveness analyses. The term 'participants' is replaced by 'arms' or 'thighs', respectively. These are administrative changes.

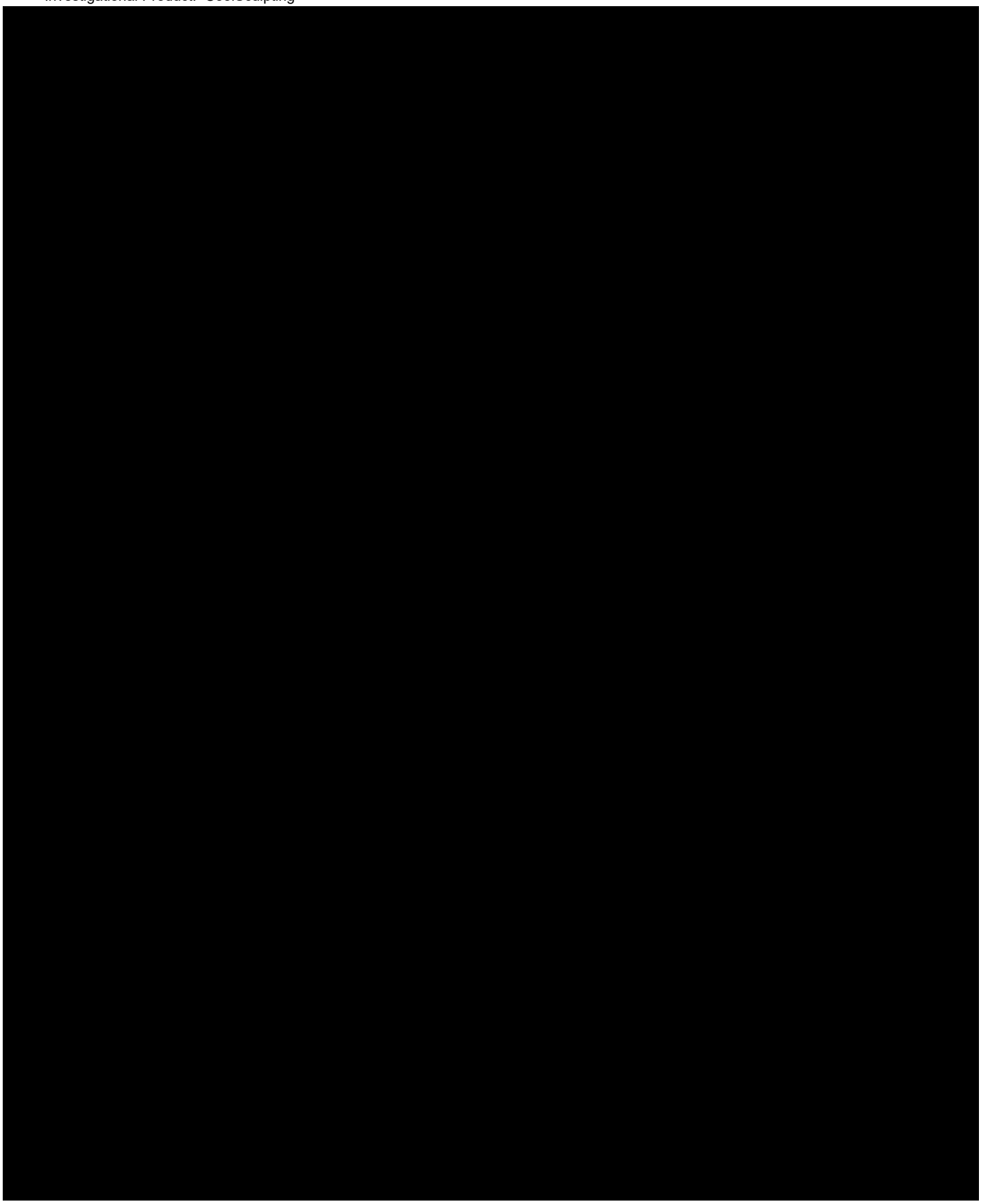
13. Reference List

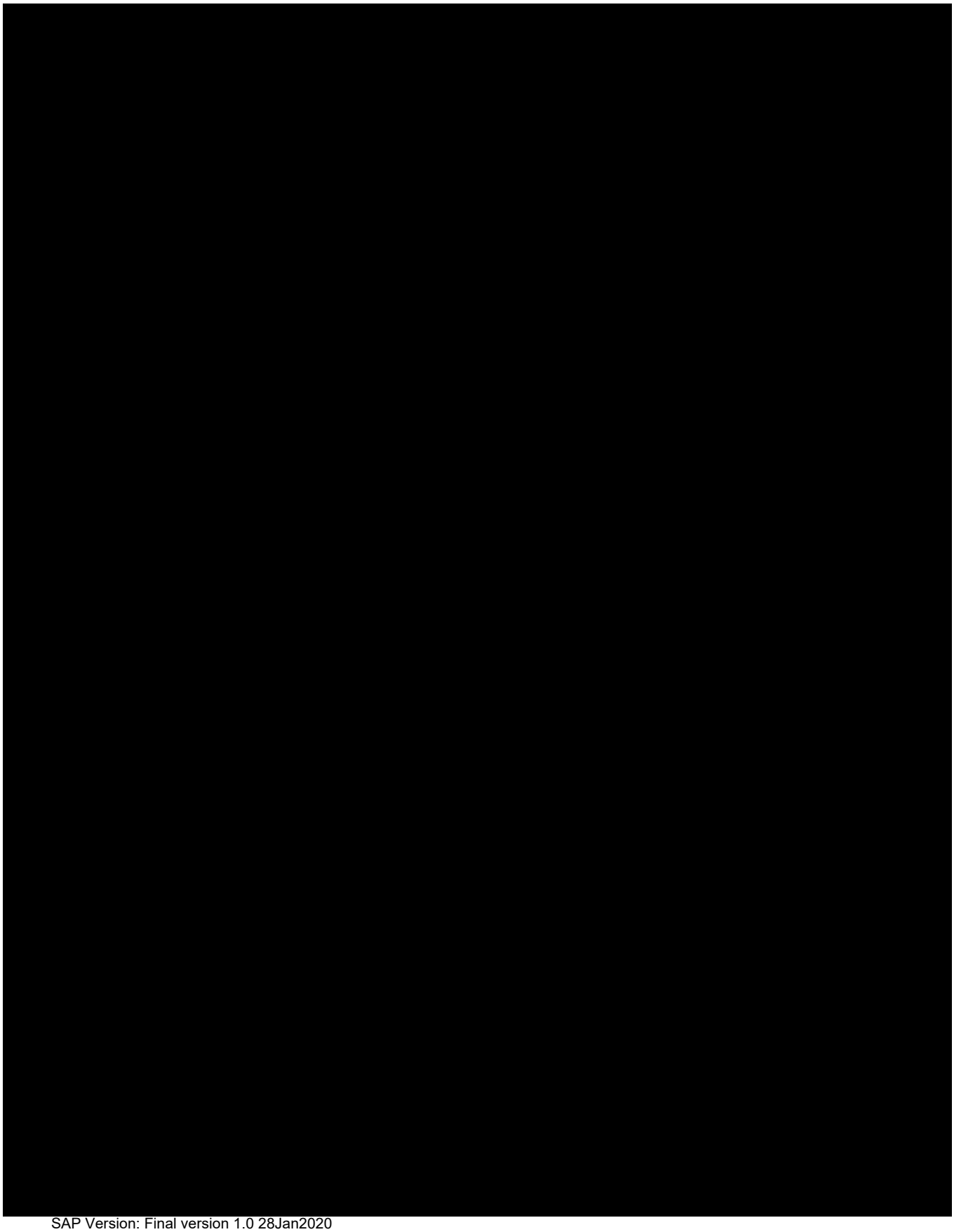
To be updated.

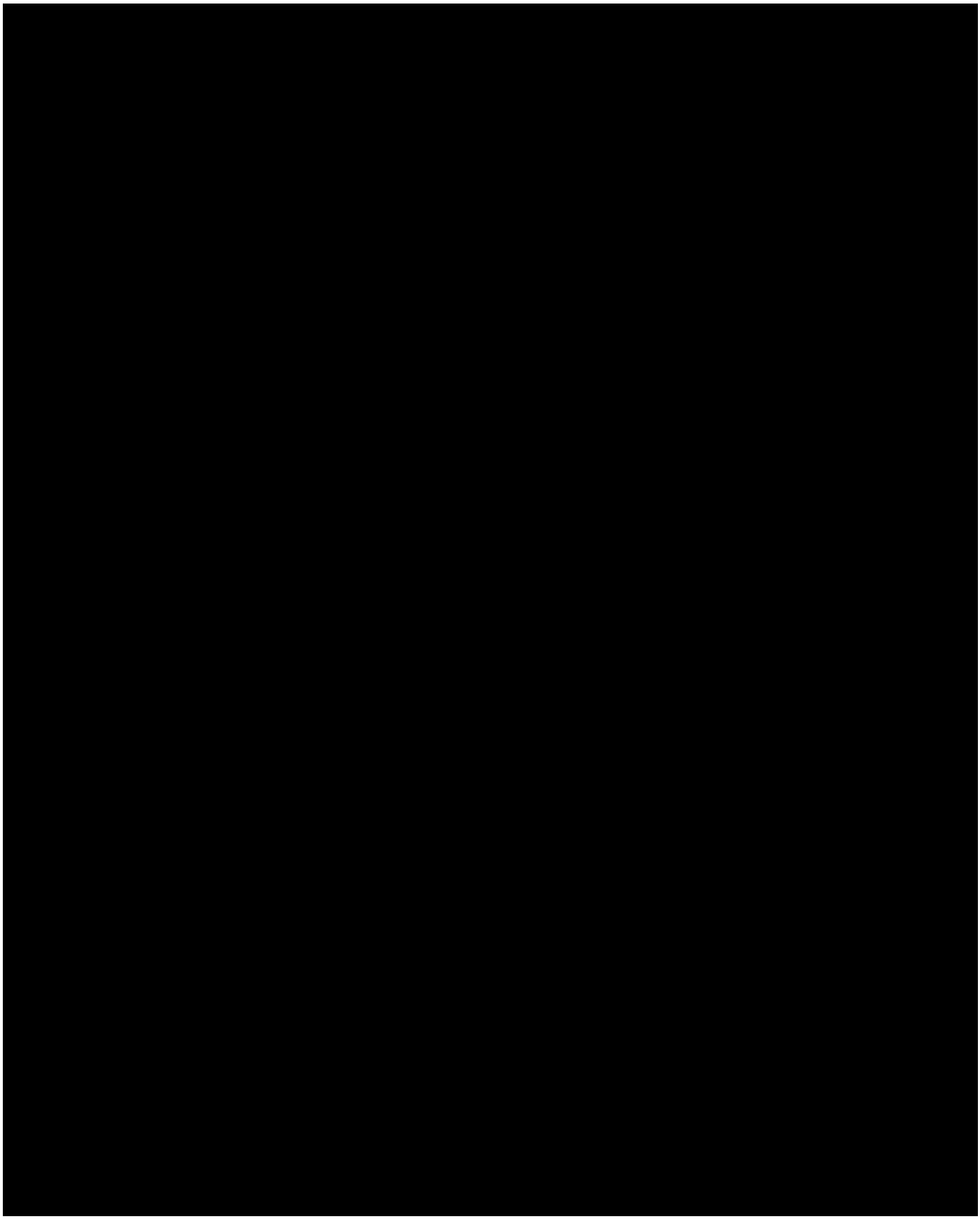












17. Index of Figures

No Figures

19. Table, Listing, and Figure Shells

This table, figure and listing shells will be provided as a separate document.